British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

Asthma: diagnosis, monitoring and chronic asthma management (update)

Cost-utility analysis: Step-up therapy for management of uncontrolled asthma

BTS/NICE/SIGN collaborative guideline NG245

Economic analysis report

November 2024

Final

Developed by BTS, NICE and SIGN

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1 Introduction

The committee identified pharmacological management of asthma as an area of high priority for economic modelling, particularly around the use of MART to step up treatment for patients with uncontrolled asthma. Three scenarios of step-up treatment with MART were identified as requiring further economic evidence, given uncertainty regarding their cost-effectiveness: escalation to low-dose MART in adults, escalation to moderate-dose MART in adults, and escalation to low-dose MART in children.

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2 Methods

2.1 Model overview

A cost-utility analysis was undertaken where quality-adjusted life years (QALYs) and costs from a current UK NHS (English NHS setting in the base case and Scottish NHS setting in a sensitivity analysis) and personal social services perspective were considered over a 5-year time horizon. The analysis was run separately for each of the three research questions and followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects.(National Institute for Health and Care Excellence, 2014) The only deviation from the NICE reference case was the shorter time horizon. An incremental analysis was undertaken.

2.1.1 Comparators

The following comparators were included in the analyses:

1. Escalation to low-dose MART in adults
    1. Low-dose MART
    2. Low/moderate-dose ICS/LABA +SABA prn
2. Escalation to moderate-dose MART in adults
    1. Moderate-dose MART
    2. Moderate/high-dose ICS/LABA +SABA prn
3. Escalation to low-dose MART in children
    1. Paediatric low-dose MART
    2. Paediatric low-dose ICS/LABA +SABA prn
    3. Paediatric moderate-dose ICS +SABA prn

In the base-case for each analysis the interventions and comparators were pooled if there were more than one inhaler option or dose available in that category, for example moderate-dose ICS/LABA could be either budesonide with formoterol or fluticasone with salmeterol. Scenario analyses were explored where the modelled treatment aligned with the specific study inputs selected (e.g. replicating each study).

2.1.2 Population

The analysis was conducted for three separate review questions with different populations.

For the analysis of escalation to low-dose MART in adults, the population was adults who had uncontrolled asthma on initial management with low-dose ICS/LABA.

For the analysis of escalation to moderate-dose MART in adults, the population was adults who had uncontrolled asthma on low-dose MART.

For the analysis of escalation to paediatric low-dose MART in children, the population was children who had uncontrolled asthma on initial management with paediatric low-dose ICS + SABA prn.

2.2 Approach to modelling

2.2.1 Model structure

A life-table model was developed, adjusted for asthma-specific mortality, where costs and quality of life were attached to symptom status and severe exacerbations were associated

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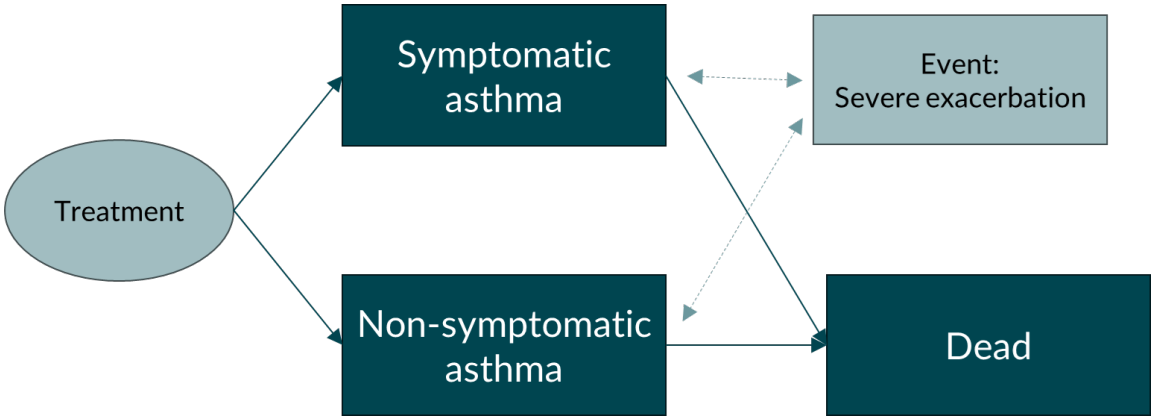
with costs and disutility. People in the model can either be alive with symptomatic asthma, alive with non-symptomatic asthma, or dead, and people with or without symptoms can experience severe exacerbation events. The proportion of people who are symptomatic and non-symptomatic remains constant over the time horizon and is dependent on treatment arm.

Figure 1: Model structure



The time horizon in this model was chosen to be 5 years in the model base-case as the committee agreed that it would be more suitable to use a shorter time horizon to capture the short-term outcomes rather than increase the uncertainty of the results by extrapolating. Also the limited data around referrals after severe exacerbations and treatment switching would limit any longer-term models. Different time horizons were explored in sensitivity analyses.

2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times for the base case and 1,000 times for each sensitivity analysis – and results were summarised.

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis we checked for convergence in the incremental costs, QALYs and net monetary benefit at a threshold of £20,000 per QALY gained for ICS/LABA versus MART in each of the three analyses. This was done by plotting the number of runs against the mean outcome at that point (see example for analysis 1 in Figure 2) for the base-case analysis. Convergence was assessed visually and the specified outcomes in all three analyses had stabilised by 3000 runs.

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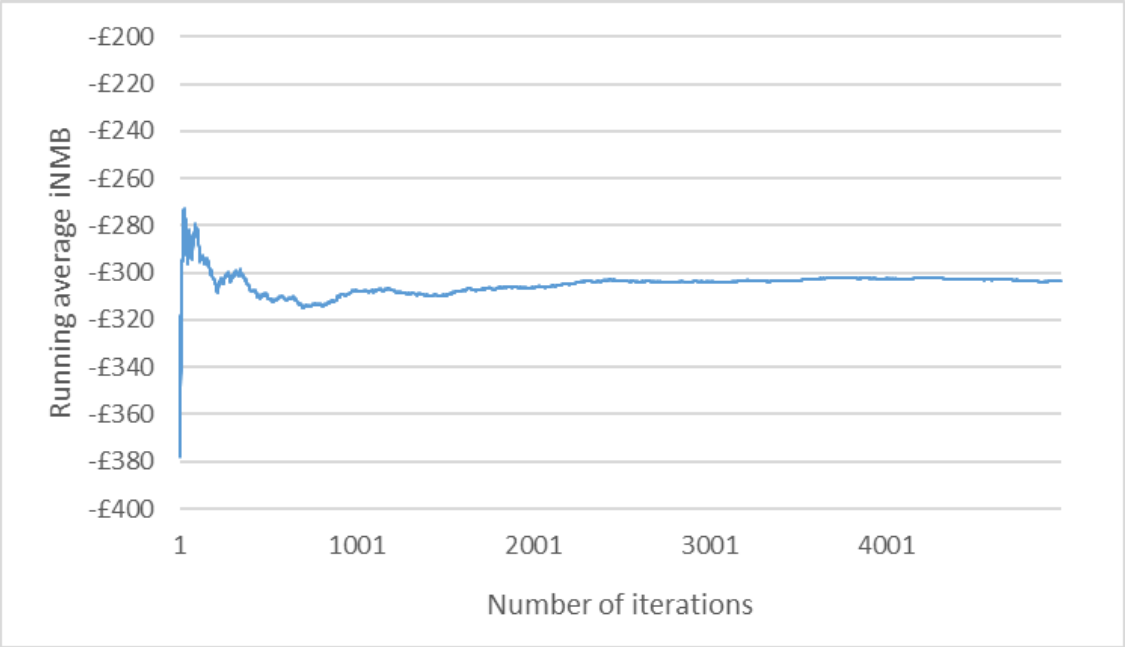
Figure 2: Checking for convergence: incremental NMB (ICS/LABA vs MART, analysis 1)



Abbreviations: iNMB, incremental net monetary benefit.

The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
% males Asthma control days (% of time) % type of follow-up for severe exacerbation	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: • Alpha = (events) • Beta = (sample size) − (events)
Mortality hazard ratio Exacerbation rate ratio Baseline age	Lognormal	The natural log of the mean and standard error were calculated as follows: • Mean = ln(mean cost) − $SE^2/2$ • SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2) $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$ This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean.
Mean difference in asthma control days (% of time)	Normal	Allows for positive and negative values. The standard error was calculated as follows: • SE = [upper 95% CI − lower 95% CI]/(1.96×2)

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Parameter	Type of distribution	Properties of distribution
Utility multipliers General population utility	Beta	Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $mean^2 \times [(1-mean)/SE^2] - mean$ Beta = $alpha \times [(1-mean)/mean]$
Exacerbation event rate Utility decrements Duration of exacerbation	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows: • Alpha = $(mean/SE)^2$ • Beta = $SE^2/Mean$

Abbreviations: 95% CI = 95% confidence interval; SE = standard error; SMR = standardised mortality ratio.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- reliever use (due to a lack of data reported around this outcome)
- the cost of staff required to implement each strategy (assumed to be fixed according to national pay scales and programme content)
- drug prices

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 2.5 Sensitivity analyses.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 2 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table. Full details of all inputs and their probabilistic parameters is provided in the following sections and in Appendix C.

Table 2: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution
Comparators	Analysis 1 • Low-dose MART • Low-dose ICS/LABA + SABA Analysis 2 • Moderate-dose MART • Moderate/high-dose ICS/LABA + SABA		n/a

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Input	Data	Source	Probability distribution
	Analysis 3 • Paediatric low-dose MART • Paediatric low-dose ICS/LABA + SABA • Paediatric moderate-dose ICS + SABA		
Population	Analyses 1 and 2 • Adults with uncontrolled asthma Analysis 3 • Children with uncontrolled asthma		n/a
Perspective	UK NHS & PSS	NICE reference case (National Institute for Health and Care Excellence, 2014)	n/a
Time horizon	5 years		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case (National Institute for Health and Care Excellence, 2014)	n/a
Cohort settings			
Baseline age	Analysis 1 • 40.7 years Analysis 2 • 42.1 years Analysis 3 • 8.0 years	• Weighted average of Atienza, O'Byrne, and Rabe (Atienza, et al., 2013, O'Byrne, et al., 2005, Rabe, et al., 2006) • Weighted average of Bousquet, Patel, and Vogelmeier (Bousquet, et al., 2007, Patel, et al., 2013, Vogelmeier, et al., 2005) • Bisgaard (Bisgaard, et al., 2006)	n/a
% males	Analysis 1 • 38.5% Analysis 2 • 39.1% Analysis 3 • 71.1%	• Weighted average of Atienza, O'Byrne, and Rabe (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) • Weighted average of Bousquet, Patel, and Vogelmeier (Bousquet et al., 2007, Patel et al., 2013, Vogelmeier et al., 2005) • Bisgaard (Bisgaard et al., 2006)	Beta
Severe exacerbation data			

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Input	Data	Source	Probability distribution
Severe exacerbation rate (ICS/LABA)	Analysis 1 • 0.358 Analysis 2 • 0.316 Analysis 3 (MART) [a] • 0.080	• Pooled (Atienza, O'Byrne, and Rabe) (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) • Pooled (Bousquet, Patel, and Vogelmeier) (Bousquet et al., 2007, Patel et al., 2013, Vogelmeier et al., 2005) • Bisgaard (Bisgaard et al., 2006)	Gamma
Severe exacerbation rate ratio (MART vs ICS/LABA)	Analysis 1 • 0.570 Analysis 2 • 0.770 Analysis 3 [b] 0.190 (MART vs. ICS/LABA) 0.270 (MART vs ICS)	• Pooled (Atienza, O'Byrne, and Rabe) (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) • Pooled (Bousquet, Patel, and Vogelmeier) (Bousquet et al., 2007, Patel et al., 2013, Vogelmeier et al., 2005) • Bisgaard (Bisgaard et al., 2006)	Lognormal
Symptom status data			
Asthma control days (% of time, ICS/LABA)	Analysis 1 • 34.4% Analysis 2 • 39.1% Analysis 3 (MART) [a] • 57.0%	• Pooled (Atienza, O'Byrne, and Rabe) (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) • Bousquet (Bousquet et al., 2007) • Bisgaard (Bisgaard et al., 2006)	Beta
Mean difference in asthma control days (% of time)	Analysis 1 • -2.2% (ICS/LABA vs MART) Analysis 2 • -1.0% (MART vs ICS/LABA) Analysis 3 [b] • -4.0% (MART vs. ICS/LABA) 6.0% (MART vs ICS)	• Pooled (Atienza, O'Byrne, and Rabe) (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) • Bousquet (Bousquet et al., 2007) • Bisgaard (Bisgaard et al., 2006)	Normal
Reliever use data			
As-needed inhalations per day (MART)	Analysis 1 • 1.081 Analysis 2 • 0.771 Analysis 3 • 0.580	• Pooled (Atienza, O'Byrne, and Rabe) (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) • Pooled (Bousquet and Vogelmeier) (Bousquet et al., 2007,	n/a

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Input	Data	Source	Probability distribution
		Vogelmeier et al., 2005) • Bisgaard (Bisgaard et al., 2006)	
As-needed inhalations per day (SABA)	Analysis 1 • 1.312 Analysis 2 • 0.971 Analysis 3 • 0.760	• Pooled (Atienza, O'Byrne, and Rabe) (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) • Pooled (Bousquet and Vogelmeier) (Bousquet et al., 2007, Vogelmeier et al., 2005) • Bisgaard (Bisgaard et al., 2006)	n/a
As-needed inhalations per day (SABA [ICS only regimen])	Analysis 3 • 0.740	• Bisgaard (Bisgaard et al., 2006)	n/a
Health-related quality of life (utilities)			
Baseline utility	Analysis 1 and 2 • General population norms Analysis 3 • 0.96 (asthma with no exacerbation)	• Kind et al. 1999 (Kind, et al., 1998) • Willems et al. 2007 (Willems, et al., 2007)	Beta
Symptomatic asthma utility multiplier	Analysis 1 and 2 • 0.819 Analysis 3 • 1	• Health Survey for England 2018 (NHS Digital, 2019) • Assumption	Beta
Non-symptomatic asthma utility multiplier	Analysis 1 and 2 • 0.986 Analysis 3 • 1	• Health Survey for England 2018 (NHS Digital, 2019) • Assumption	Beta
Disutility of severe exacerbation	Analysis 1 and 2 • 0.134 Analysis 3 • 0.971	• Briggs et al. 2021 (Briggs, et al., 2021)	Gamma
Costs			
MART maintenance treatment cost per day	Analysis 1 • £0.47 Analysis 2 • £0.93 Analysis 3 • £0.23	• BNF (Joint Formulary Committee, 2024)	n/a
ICS/LABA maintenance treatment cost per day	Analysis 1 • £0.47 Analysis 2 • £1.05 Analysis 3	• BNF (Joint Formulary Committee, 2024)	n/a

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Input	Data	Source	Probability distribution
	• £0.23		
ICS maintenance treatment cost per day	Analysis 3 • £0.21	• BNF (Joint Formulary Committee, 2024)	n/a
MART reliever cost (one inhalation)	Analysis 1 • £0.23 Analysis 2 • £0.23 Analysis 3 • £0.23	• BNF (Joint Formulary Committee, 2024)	n/a
SABA reliever cost (one inhalation)	Analysis 1 • £0.07 Analysis 2 • £0.04 Analysis 3 • £0.07	• BNF (Joint Formulary Committee, 2024)	n/a
Annual monitoring cost	Analyses 1 and 2 • £27.26 Analysis 3 • £31.28	• NHS reference costs 2021/22 (NHS England, 2022) • PSSRU 2022 (Jones, et al.)	n/a
Cost of severe exacerbation	Analyses 1 and 2 • £178.52 Analysis 3 • £186.24	• BNF (Joint Formulary Committee, 2024) • NHS reference costs 2021/22 (NHS England, 2022) • PSSRU 2022 (Jones et al.) • SYGMA 2	Beta (proportion of population requiring each type of follow-up)

Abbreviations: BNF, British National Formulary; ICS, inhaled corticosteroids; ICS/LABA, inhaled corticosteroids with long-acting beta agonists; MART, maintenance and reliever therapy; PSSRU, Personal Social Services Research Unit; SABA, short-acting beta agonist.

(a) For analysis 3, MART was used as the reference for severe exacerbation rate.

(b) For analysis 3, the treatment effects described the change in effect from the comparator to MART, so the inverse of this effect was applied to the baseline event rate of MART to calculate the relative event rates of each comparator.

2.3.2 Clinical data

The key efficacy data used in the model was taken from the relevant studies identified in the clinical review of evidence.

Three studies were identified in the clinical review for the initial step-up treatment to low-dose MART in adults, with severe exacerbations reported as an outcome; Atienza 2013, O'Byrne 2005, and Rabe 2006. (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006) These were studies in adults who were previously uncontrolled on ICS plus SABA as needed.

Five studies were identified in the clinical review for the further step-up treatment to moderate-dose MART in adults, with severe exacerbations reported as an outcome; Bousquet 2007, Kuna 2007, Patel 2013, Takeyama 2014, and Vogelmeier 2005. (Bousquet et al., 2007, Kuna, et al., 2007, Patel et al., 2013, Takeyama, et al., 2014, Vogelmeier et al., 2005) These were studies in adults who were previously uncontrolled on ICS (with or without LABA) plus SABA as needed. The Kuna 2007 study included low-dose MART rather than moderate-dose MART in the comparison, so was not included in the economic analysis. The Takeyama 2014 study was also not included in the economic analysis, as it was a

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significantly smaller study with very few participants and events compared with the other studies.

One study was identified in the clinical review for the initial step-up treatment to paediatric low-dose MART in children previously uncontrolled on ICS plus SABA, with severe exacerbations reported as an outcome; Bisgaard 2006. (Bisgaard et al., 2006)

2.3.3 Initial cohort settings

The cohort starting age and proportion male were informed by the population of each of the published studies, and are presented in Table 3 - Table 5. The base-case for each analysis was the weighted average from the studies for that population.

Table 3: Baseline characteristics, analysis 1 (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006)

Study	Baseline age (years)	% male
Atienza 2013	45.7	32.4
O'Byrne 2005	35.5	44.4
Rabe 2006	42.5	39.4
Pooled (base-case)	40.7	38.5

Table 4: Baseline characteristics, analysis 2 (Bousquet et al., 2007, Patel et al., 2013, Vogelmeier et al., 2005)

Study	Baseline age (years)	% male
Bousquet 2007	39.5	38.4
Patel 2013	42.0	31.0
Vogelmeier 2005	45.0	41.1
Pooled (base-case)	42.1	39.1

Table 5: Baseline characteristics, analysis 3 (Bisgaard et al., 2006)

Study	Baseline age (years)	% male
Bisgaard 2006	8.0	71.1

2.3.4 Severe exacerbations

Event rates for severe exacerbations were extracted from the identified published studies. Where there were multiple studies, pooled analyses were conducted.

2.3.4.1 Analysis 1

The data used to inform severe exacerbations in the model for analysis 1 are presented in Table 6 and Figure 3. In the model base-case the pooled estimates were used for ICS/LABA event rate, and the rate ratio of MART vs ICS/LABA. The individual studies were explored in scenario analyses.

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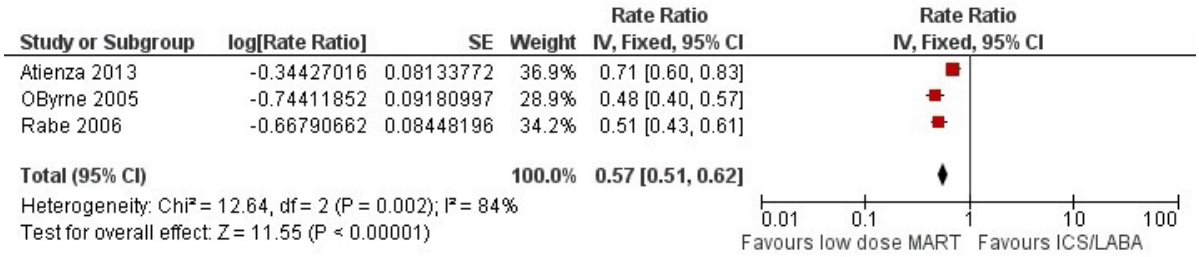
Table 6: Severe exacerbation data, analysis 1 (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006)

Study	Event/person/year ICS/LABA	Event/person/year MART	Rate ratio, MART vs ICS/LABA (95% CI)
Atienza 2013	0.307	0.214	0.71 (0.60, 0.83)
O'Byrne 2005	0.680	0.360	0.48 (0.40, 0.57)
Rabe 2006	0.370	0.190	0.51 (0.43, 0.61)
Pooled	0.358	-	0.570 (0.51, 0.62)

Figure 3: Forest plot, severe exacerbations analysis 1 (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006)



2.3.4.2 Analysis 2

The data used to inform severe exacerbations in the model for analysis 2 are presented in Table 7 and Figure 4. In the model base-case the pooled estimates were used for ICS/LABA event rate, and the rate ratio of MART vs ICS/LABA. The individual studies were explored in scenario analyses.

Table 7: Severe exacerbation data, analysis 2 (Bousquet et al., 2007, Patel et al., 2013, Vogelmeier et al., 2005)

Study	Event/person/year ICS/LABA	Event/person/year MART	Rate ratio, MART vs ICS/LABA (95% CI)
Bousquet 2007	0.310	0.250	0.81 (0.69, 0.94)
Patel 2013	0.970	0.530	0.55 (0.42, 0.72)
Vogelmeier 2005	0.230	0.190	0.83 (0.69, 1.00)
Pooled	0.316	-	0.77 (0.69, 0.85)

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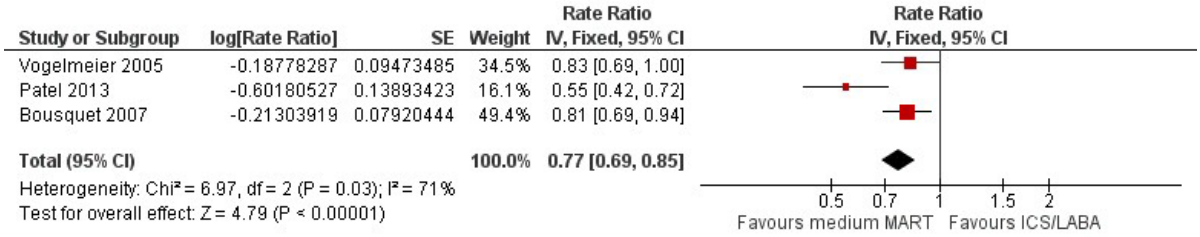
Figure 4: Forest plot, severe exacerbations analysis 2 (Bousquet et al., 2007, Patel et al., 2013, Vogelmeier et al., 2005)



2.3.4.3 Analysis 3

In the analysis for children, it was considered more appropriate to use the outcome reported by Bisgaard et al. of exacerbations requiring medical intervention, described as an exacerbation requiring hospitalization or emergency department treatment, treatment with oral steroids, an increase in ICS (via a separate inhaler), and/or other additional treatment.

The data used to inform exacerbations in the model for analysis 3 are presented in Table 8, Figure 5 and Figure 6.

Table 8: Severe exacerbation data, Bisgaard et al. 2006 (Bisgaard et al., 2006)

	Paediatric moderate dose ICS	Paediatric low dose ICS/LABA	Paediatric low dose MART
Event/person/year	0.307	0.214	0.093
Rate ratio compared with MART (95% CI)	0.27 (0.13, 0.57)	0.19 (0.09, 0.39)	-

Figure 5: Forest plot, severe exacerbations (MART vs ICS/LABA, analysis 3) (Bisgaard et al., 2006)

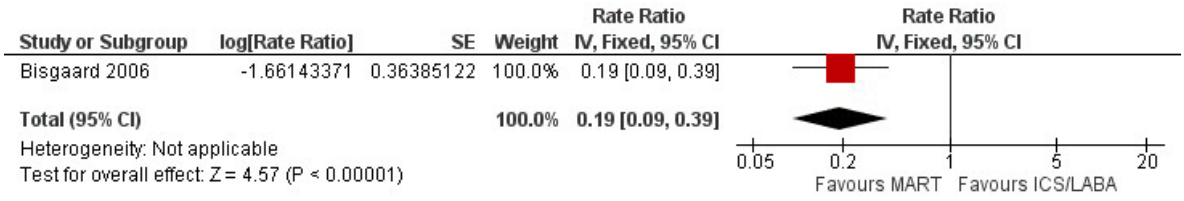
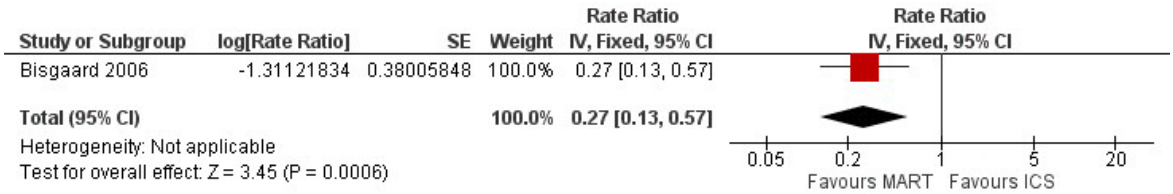


Figure 6: Forest plot, severe exacerbations (MART vs ICS, analysis 3) (Bisgaard et al., 2006)



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2.3.5 Symptom status

To account for asthma-specific quality of life when not having an exacerbation, the proportion of patients who were symptomatic vs non-symptomatic was used. This proportion was informed using a measure reported in the published studies of asthma control days (%), defined as the proportion of days without symptoms and no as-needed reliever use.

Where there were multiple studies, pooled analyses were conducted.

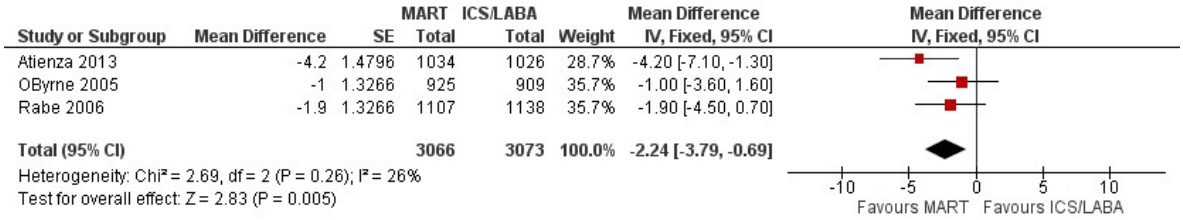
2.3.5.1 Analysis 1

The data used to inform symptom status in the model for analysis 1 are presented in Table 9 and Figure 7. In the model base-case the pooled estimates were used for ICS/LABA asthma control days, and the mean difference of ICS/LABA vs MART. The individual studies were explored in scenario analyses.

Table 9: Symptom status data, analysis 1 (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006)

Study	Asthma control days ICS/LABA	Asthma control days MART	Mean difference [%] (95% CI) ICS/LABA vs MART
Atienza 2013	31.6%	35.8%	-4.2 (-7.1, -1.3)
O'Byrne 2005	44.0%	45.0%	-1.0 (-3.6, 1.6)
Rabe 2006	29.3%	31.2%	-1.9 (-4.5, 0.7)
Pooled	34.42%	-	-2.24 (-3.79, -0.69)

Figure 7: Forest plot, % asthma control days, analysis 1 (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006)



2.3.5.2 Analysis 2

Only Bousquet et al. reported % control days for the population in analysis 2, and this data is presented in Table 10 and Figure 8. Given the uncertainty in the mean difference estimate (with the confidence interval crossing the line of no effect), a scenario was explored where the effect of symptom status was excluded from the model. This outcome was not reported in the Patel or Vogelmeier studies, so for the scenario analyses where only data from those trials was used, this outcome was informed by the Bousquet data.

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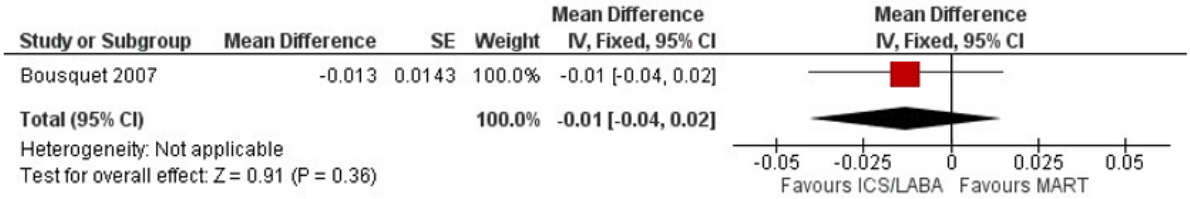
Table 10: Symptom status data, analysis 2 (Bousquet et al., 2007)

Study	Asthma control days ICS/LABA	Asthma control days MART	Mean difference [%] (95% CI) MART vs ICS/LABA
Bousquet 2007	39.1%	-	-1.0 (-4.0, 2.0)

Figure 8: Forest plot, % asthma control days, analysis 2 (Bousquet et al., 2007)



2.3.5.3 Analysis 3

The data on symptom status for analysis 3 is presented in Table 11, Figure 9 and Figure 10. In this analysis the reference proportion of asthma control days is that of MART, and the mean difference is given compared with MART.

Table 11: Symptom status data, analysis 3, Bisgaard 2006 (Bisgaard et al., 2006)

Asthma control days MART	Mean difference [%] (95% CI) ICS/LABA vs MART	Mean difference [%] (95% CI) ICS vs MART
57.0%	-4.0 (-5.0, -2.0)	6.0 (5.0, 7.0)

Figure 9: Forest plot, % asthma control days, analysis 3 ICS/LABA vs MART (Bisgaard et al., 2006)

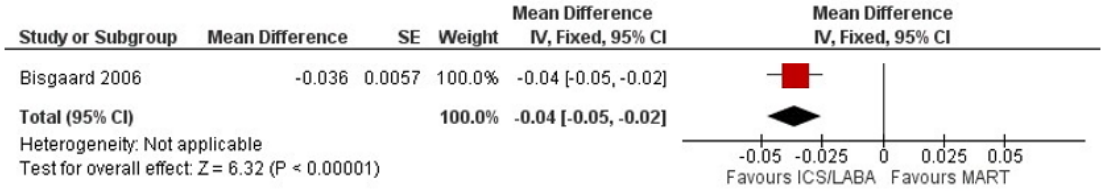
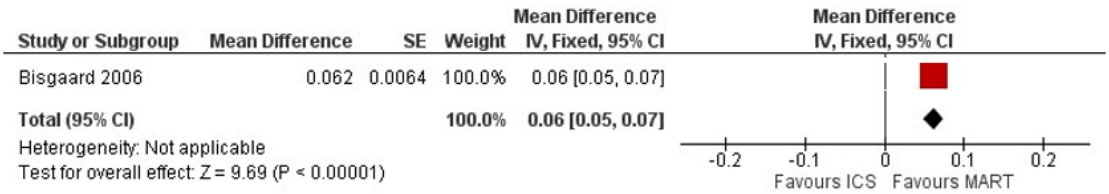


Figure 10: Forest plot, % asthma control days, analysis 3 ICS vs MART (Bisgaard et al., 2006)



2.3.6 Reliever use

Data informing reliever use was taken directly from the published studies, which generally reported as-needed inhalations per day for each regimen.

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2.3.6.1 Analysis 1

The data on reliever use for analysis 1 is presented in Table 12. In the base-case a weighted average of the three sources was used, and the data from individual studies was explored in scenario analyses.

Table 12: Reliever use, analysis 1 (Atienza et al., 2013, O'Byrne et al., 2005, Rabe et al., 2006)

Source	As-needed inhalations per day (n)	
	MART	SABA
Atienza 2013	1.21 (1034)	1.46 (1026)
O'Byrne 2005	1.01 (925)	1.21 (909)
Rabe 2006	1.02 (1107)	1.26 (1138)
Weighted average	1.081	1.312

2.3.6.2 Analysis 2

The data on reliever use for analysis 2 is presented in Table 13. In the base-case a weighted average of the two sources was used, and the data from individual studies was explored in scenario analyses. Reliever use was not reported in the Patel study, so in the scenario analysis using Patel data only the pooled estimates for reliever use were used.

Table 13: Reliever use, analysis 2 (Bousquet et al., 2007, Vogelmeier et al., 2005)

Source	As-needed inhalations per day (n)	
	MART	SABA
Bousquet 2007	0.95 (1144)	1.01 (1145)
Vogelmeier 2005	0.58 (1067)	0.93 (1076)
Weighted average	0.771	0.971

2.3.6.3 Analysis 3

The data on reliever use for children is reported in Table 14.

Table 14: Reliever use, analysis 3 (Bisgaard et al., 2006)

Source	As-needed inhalations per day (n)		
	MART	SABA (ICS/LABA regimen)	SABA (ICS regimen)
Bisgaard 2006	0.58 (118)	0.76 (117)	0.74 (106)

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2.3.7 Life expectancy

General population mortality data from the National Life Tables for England (Office for National Statistics, 2021) were used, and adjusted using asthma-specific hazard ratios from published literature, presented in Table 15. A sensitivity analysis using Scottish general population mortality data was also conducted.(Office for National Statistics, 2021) The model assumed that symptom status as defined in the model would not have an impact on mortality, as these symptoms would be controlled with reliever use.

Table 15: Asthma-specific mortality

	Asthma-specific mortality HR (95% CI)	Source
Adults	1.250 (1.05, 1.49)	Lemmetyinen 2018 (Lemmetyinen, et al., 2018)
Children	1.770 (1.30, 2.40)	Fleming 2019 (Fleming, et al., 2019)

2.3.8 Utilities

2.3.8.1 Symptom status utility

General population utility norms from Kind et al. were used in the model and were adjusted using asthma-specific utility multipliers.(Kind et al., 1998) The Health Survey for England (2018) reported utility multipliers based on symptom status and symptom control in adults, as presented in Table 16.(NHS Digital, 2019)

Table 16: HSE utility multipliers

Population	Utility multiplier
People on medication and symptomatic *(analysed to remove those not on medication)*	0.819 (0.105)
People on medication and not symptomatic	0.986 (0 .093)

Willems et al. 2007 reported a utility value of 0.960 for children with asthma and no exacerbation, which was used in the base-case for analysis 3 in the absence of symptom-related utility data in children.(Willems et al., 2007) A scenario analysis was conducted where the HSE utility multipliers were applied to the population utility norm for children, assumed to be 1.00.

2.3.8.2 Exacerbation quality of life

A quality of life decrement was included in the model for severe exacerbation events. For adults the data informing this decrement was taken from Briggs et al. 2021, where data was reported over four observation periods following a severe exacerbation, and an average decrement was calculated from these data presented in Table 17. No relevant studies were identified to inform this data for children, so in the base-case the Briggs et al. data was used, with an assumption applied for a shorter duration of disutility. A scenario analysis was considered for children, aligning with the EINSTEIN study which used utility data from a study in an adult population with moderate or severe asthma, and an assumption for the duration of exacerbation. These data are presented in Table 18.

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Table 17: EQ-5D-3L data for severe exacerbations, Briggs et al. (Briggs et al., 2021)

Observation period since exacerbation	Utility decrement	Standard error
7 days	0.163	0.0118
14 days	0.132	0.0096
21 days	0.125	0.0095
28 days	0.115	0.0090

Table 18: Exacerbation quality of life

Event	Disutility	Duration in days (range)	Source
Adults	0.134	28 (20 – 42)	Briggs et al., 2021 (Briggs et al., 2021)
Children (base-case)	0.134	20	Briggs et al. and assumption (Briggs et al., 2021)
Children (scenario)	0.2	7	EINSTEIN

2.3.9 Resource use and costs

2.3.9.1 Drugs

Drug costs in the model were sourced from the British National Formulary (BNF) for each of the treatments used in the published studies.(Joint Formulary Committee, 2024)

2.3.9.1.1 Analysis 1

In the base-case for analysis 1 an average cost per day was calculated for each maintenance treatment and dose as per the three published studies, using information from the BNF.(Joint Formulary Committee, 2024) Scenario analyses were conducted using the cost data matching the individual study treatments and doses. The full breakdown of drug costs is detailed in Appendix B.

Table 19: Maintenance therapy costs, analysis 1

	Cost per day	Source
Low-dose MART	£0.47	Table 41 - Average of MART arm costs for studies Atienza, O'Byrne, and Rabe
Low-dose ICS/LABA	£0.47	Table 41 - Average of ICS/LABA arm costs for studies Atienza, O'Byrne, and Rabe

Table 20: Reliever therapy costs, analysis 1

	Cost per inhalation	Source
Low-dose MART	£0.23	Table 42 - Average of MART arm costs for studies Atienza, O'Byrne, and Rabe
SABA (ICS/LABA regimen)	£0.07	Table 43 - Average of ICS/LABA arm costs for studies Atienza, O'Byrne, and Rabe

2.3.9.1.2 Analysis 2

In the base-case for analysis 2 an average cost per day was calculated for each maintenance treatment and dose as per the three published studies, using information from the BNF. Scenario analyses were conducted using the cost data matching the individual

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study treatments and doses, and the maximum and minimum drug costs available for each type of therapy. The full breakdown of drug costs is detailed in Appendix B.

Table 21: Maintenance therapy costs, analysis 2

	Cost per day	Source
Moderate-dose MART	£0.93	Table 41 - Average of MART arm costs for studies Bousquet, Patel, and Vogelmeier
Moderate/high-dose ICS/LABA	£1.05	Table 41 - Average of ICS/LABA arm costs for studies Bousquet, Patel, and Vogelmeier

Table 22: Reliever therapy costs, analysis 2

	Cost per inhalation	Source
Moderate-dose MART	£0.23	Table 42 - Average of MART arm costs for studies Bousquet, Patel, and Vogelmeier
SABA (ICS/LABA regimen)	£0.04	Table 43 - Average of ICS/LABA arm costs for studies Bousquet, Patel, and Vogelmeier

2.3.9.1.3 Analysis 3

Information from the BNF was used to inform the drug costs used for each treatment in analysis 3. Scenario analyses were conducted using the maximum and minimum drug costs available for each type of therapy. The full breakdown of drug costs is detailed in Appendix B.

Table 23: Maintenance therapy costs, analysis 3

	Cost per day	Source
Paediatric low-dose MART	£0.23	Table 41 – MART arm for Bisgaard study
Paediatric low-dose ICS/LABA	£0.23	Table 41 – ICS/LABA arm for Bisgaard study
Paediatric moderate-dose ICS	£0.21	Table 44 – Average of all ICS options

Table 24: Reliever therapy costs, analysis 3

	Cost per inhalation	Source
Paediatric low-dose MART	£0.23	Table 42 – MART arm for Bisgaard study
SABA (ICS/LABA regimen)	£0.07	Table 43 – Bisgaard study cost
SABA (ICS regimen)	£0.07	Table 43 – Bisgaard study cost

2.3.9.2 Monitoring

The average annual monitoring cost was calculated using committee assumption of the type and amount of monitoring activities required, presented in Table 25, and the unit costs in Table 26.

For adults the annual cost of monitoring used in the model was £27.26, and for children was £31.28.

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Table 25: Monitoring resource use

Monitoring requirement	Proportion required	Source
1 practice nurse visit per year	80%	Committee assumption
2 practice nurse visits per year	15%	Committee assumption
1 outpatient visit per year	5%	Committee assumption

Table 26: Monitoring unit costs

Activity	Unit cost	Source
Practice nurse visit	£16.37	PSSRU 2022 (Jones et al.)
Practice nurse visit (Scotland scenario)	£17.26	PSSRU 2022 (Jones et al.) adjusted using NHS Scotland pay scales {British Medical Association, 2024 #3095}
Outpatient visit (adults)	£185.07	NHS reference costs 2021/22: Outpatient attendance service code 340, respiratory medicine service (NHS England, 2022)
Outpatient visit (children)	£265.54	NHS reference costs 2021/22: Outpatient attendance service code 258, paediatric respiratory medicine service (NHS England, 2022)

2.3.9.3 Severe exacerbations

The average cost of a severe exacerbation was calculated using the proportions of patients requiring each type of follow-up as per SYGMA 2, detailed in Table 27, and the unit costs in Table 28.(Bateman, et al., 2018) It was assumed that the follow-up visits with a GP or practice nurse would be 50% with each type of staff member. The SYGMA 2 trial was in people aged 12 years or older, but it was assumed in the absence of other information that the resource use for follow up of severe exacerbations would be equivalent.

For adults the cost of severe exacerbation used in the model was £178.52, and for children was £186.24.

Table 27: Severe exacerbation resource use (SYGMA 2, (Bateman, et al., 2004, Bateman, et al., 2014, Bateman et al., 2018))

Follow up type	Proportion required
GP visit	100%
Systemic glucocorticoids (prednisolone) and a GP/nurse visit	80.2%
A&E visit and a GP/nurse visit	12.7%
Hospitalisation and a GP/nurse visit	7.1%

Table 28: Severe exacerbation activity unit costs

Activity	Unit cost	Source
GP visit	£38.00	PSSRU 2022 (Jones et al.)
GP visit (Scotland scenario)	£38.31	PSSRU 2022 (Jones et al.) adjusted using NHS Scotland pay scales {British Medical Association, 2024 #3095}
Practice nurse visit	£16.37	PSSRU 2022 (Jones et al.)

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Activity	Unit cost	Source
Practice nurse visit (Scotland scenario)	£17.26	PSSRU 2022 (Jones et al.) adjusted using NHS Scotland pay scales {British Medical Association, 2024 #3095}
Prednisolone, adult dose (40mg daily for 7 days)	£1.88	BNF - prednisolone 28 x5mg tablets £0.94. (accessed 17/12/23) (Joint Formulary Committee, 2024)
Prednisolone, child dose (30mg daily for 3 days)	£0.60	BNF - prednisolone 28 x5mg tablets £0.94. (accessed 17/12/23) (Joint Formulary Committee, 2024)
A&E attendance	£113.46	NHS reference costs 2021/22 (NHS England, 2022)
Hospitalisation (adults)	£1,181.18	NHS reference costs 2021/22 (NHS England, 2022)
Hospitalisation (children)	£1,223.27	NHS reference costs 2021/22 (NHS England, 2022)

2.4 Computations

The model was constructed in Microsoft Excel and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality using national life tables. Baseline utility was also time dependent and was conditional on the cohort age. Mortality and utility were adjusted for the asthmatic population using HR and utility multiplier data from the literature.

Patients start in cycle 0 in either the symptomatic asthma or the non-symptomatic asthma health state, defined by the proportion of people who were symptomatic for each treatment as discussed in section 2.3.4. Patients moved to the dead health state at the end of each cycle as defined by the general population mortality adjusted with the asthma-specific hazard ratios in section 2.3.6. The ratio of symptomatic to non-symptomatic was kept constant over the short time-horizon.

Mortality rates were converted into transition probabilities before inputting into the Markov model using the following formulae:

$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (1 year)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in the symptomatic or non-symptomatic states of the model was weighted by a utility value that is dependent on the cohort age and the symptom status. The disutility associated with exacerbation events was subtracted from the total QALYs in each cycle. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). The total discounted QALYs were the sum of the discounted QALYs in each cycle within the time-horizon.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

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$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

2.5 Sensitivity analyses

In addition to the probabilistic sensitivity analysis, scenario analyses were also run to explore the impact of specific parameters on the cost-effectiveness results.

2.5.1 Analysis 1

The scenarios considered in analysis 1 are detailed in Table 29, and results of these scenarios are presented in Table 34.

Table 29: Scenario analyses, analysis 1

Parameter	Base-case	Scenarios
Baseline data	• Pooled – all	• Atienza 2013 • O'Byrne 2005 • Rabe 2006
Efficacy data	• Pooled – all	• Atienza 2013 • O'Byrne 2005 • Rabe 2006
All data	• Pooled - all	• Atienza 2013 • O'Byrne 2005 • Rabe 2006
Time horizon	• 5 years	• 3 years • 10 years
Symptom status	• Included	• Excluded
General population mortality and PSSRU costs	• England	• Scotland

2.5.2 Analysis 2

The scenarios considered in analysis 2 are detailed in Table 30, and results of these scenarios are presented in Table 37.

Table 30: Scenario analyses, analysis 2

Parameter	Base-case	Scenarios
Baseline data	• Pooled – all	• Bousquet 2007 • Patel 2013 • Vogelmeier 2005
Efficacy data	• Pooled – all	• Bousquet 2007 • Patel 2013 • Vogelmeier 2005
All data	• Pooled – all	• Bousquet 2007 • Patel 2013 • Vogelmeier 2005
Drug cost strategy	• As per study (average)	• Minimum available costs • Maximum available costs
Time horizon	• 5 years	• 3 years • 10 years

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Parameter	Base-case	Scenarios
Symptom status	• Included	• Excluded
General population mortality and PSSRU costs	• England	• Scotland

2.5.3 Analysis 3

The scenarios considered in analysis 3 are detailed in Table 31, and results of these scenarios are presented in Table 40.

Table 31: Scenario analyses, analysis 3

Parameter	Base-case	Scenarios
Time horizon	• 5 years	• 3 years • Until 15-years old
Drug cost strategy	• As per study (average)	• Minimum available costs • Maximum available costs
Exacerbation QoL	• Briggs assumption	• EINSTEIN study
HS utility approach	• Willems et al.	• HSE multipliers
General population mortality and PSSRU costs	• England	• Scotland

2.6 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist; this included systematic checking of the model calculations.

2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost effective if:
- ICER < Threshold

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2.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money. (National Institute for Health and Care Excellence, 2014, National Institute for Health and Clinical Excellence, 2008) In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

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3 Results

3.1 Analysis 1: Escalation to low-dose MART in adults

3.1.1 Base-case

The results of the deterministic and probabilistic base-case analysis (English NHS perspective) for the escalation to low-dose MART in the adult model are presented in Table 32 and Table 33, respectively. In both cases, low-dose MART was associated with increased costs and increased QALYs compared with low/moderate-dose ICS/LABA + SABA, and a deterministic ICER of £6,338. The probabilistic results were similar, with an ICER of £6,382.

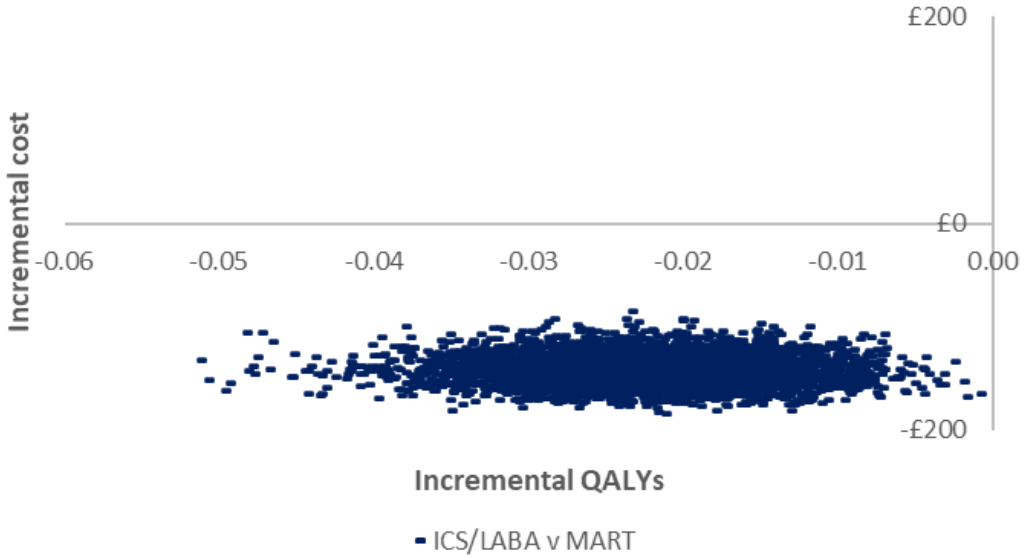
Table 32: Deterministic base-case results

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER
Low/moderate-dose ICS/LABA + SABA	£1,325	3.549	-	-	-
Low-dose MART	£1,467	3.571	£142	0.022	£6,338

Table 33: Probabilistic base-case results

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER	% CE
Low/moderate-dose ICS/LABA + SABA	£1,327	3.549	-	-	-	1.0%
Low-dose MART	£1,468	3.571	£141	0.022	£6,382	99.0 %

Figure 11: Cost-effectiveness plane, analysis 1



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3.1.2 Sensitivity analyses

The results of the scenario analyses listed in section 2.5.1 are presented in Table 34. The results of the model were fairly stable in most of the analyses, with the only scenario with a substantially different ICER was when the option to use different utility values based on symptom status was excluded, with an ICER of £20,710.

Table 34: Probabilistic scenario analysis results, analysis 1

Scenario	Absolute costs		Absolute QALYs		ICER (MART vs ICS/LABA)	% CE
	MART	ICS/LABA	MART	ICS/LABA		MART
Base-case	**£1,468**	**£1,327**	**3.571**	**3.549**	**£6,382**	**99.00%**
Baseline data: Atienza	£1,464	£1,323	3.337	3.315	£6,589	99.20%
Baseline data: O'Byrne	£1,469	£1,328	3.598	3.575	£6,319	98.80%
Baseline data: Rabe	£1,466	£1,325	3.468	3.446	£6,417	99.00%
Efficacy data: Atienza	£1,528	£1,301	3.564	3.531	£6,871	98.10%
Efficacy data: O'Byrne	£1,430	£1,348	3.627	3.611	£5,162	86.00%
Efficacy data: Rabe	£1,432	£1,328	3.536	3.514	£4,774	94.60%
All data: Atienza	£1,525	£1,298	3.332	3.301	£7,239	98.30%
All data: O'Byrne	£1,432	£1,349	3.659	3.642	£4,793	89.50%
All data: Rabe	£1,430	£1,326	3.437	3.416	£4,974	94.00%
Time horizon: 3 years	£912	£825	2.234	2.220	£6,301	99.10%
Time horizon: 10 years	£2,689	£2,429	6.354	6.314	£6,553	99.00%
Symptomatic split excluded	£1,467	£1,326	3.571	3.564	£20,710	41.30%
Scotland general population mortality and costs	£1,472	£1,331	3.571	3.548	£6,195	99.30%

3.2 Analysis 2: Escalation to moderate-dose MART in adults

3.2.1 Base-case

The results of the deterministic and probabilistic base-case analysis (English NHS perspective) for the escalation to moderate-dose MART in adults model are presented in Table 35 and Table 36, respectively. In both cases, moderate/high-dose ICS/LABA + SABA was associated with slightly increased costs and increased QALYs compared with moderate-dose MART, and a deterministic ICER of £5,147. The probabilistic results were similar, with an ICER of £4,769.

Table 35: Deterministic base-case results

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER
Moderate-dose MART	£2,144	3.478	-	-	-

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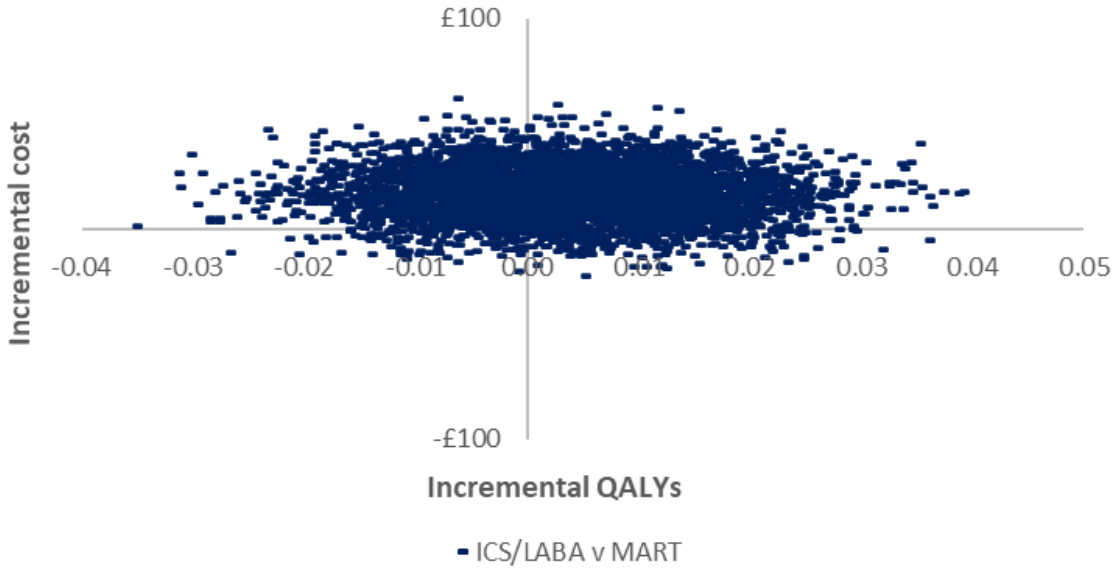
Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER
Moderate/high-dose ICS/LABA + SABA	£2,161	3.482	£17	0.003	£5,147

Table 36: Probabilistic base-case results

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER	% CE
Moderate-dose MART	£2,144	3.478	-	-	-	40.56%
Moderate/high-dose ICS/LABA + SABA	£2,161	3.482	£16	0.003	£4,769	59.44%

Figure 12: Cost-effectiveness plane, analysis 2



3.2.2 Sensitivity analyses

The results of the scenario analyses listed in section 2.5.2 are presented in Table 37. Due to the very small incremental costs and incremental QALYs, the ICER for this model varied more between each scenario. A key driver of the cost-effectiveness estimates in this population are the source of efficacy data used in the model. The Bousquet study is more favourable for ICS/LABA given it was the only study that reported the asthma control outcome in which MART had fewer control days, and the Patel study is more favourable for MART, given the much larger difference in exacerbation rate between the two arms. Drug costs also had a large impact on the ICER, given the small incremental costs and QALYs in the base-case.

A key scenario included was where symptom status was removed from the model, as for this population this aspect was only informed by the Bousquet study. The committee considered this scenario important as they had discussed some limitations with the Bousquet study and felt that it was important to explore how this affected the model results. The key limitation was that the dose of ICS/LABA in the ICS/LABA + SABA arm was much higher than other studies and the committee had not recommended that large a dose, and that this high dose is likely the reason for the ICS/LABA + SABA arm having better symptom control. Another limitation of the Bousquet data for symptom status was that this outcome had a high p-value, indicating uncertainty. The committee felt that the result of this scenario (MART being

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dominant over ICS/LABA) was feasible, given the limitations of the data informing symptom status in this population, and that their view was that severe exacerbations were a more important outcome than symptom status.

Table 37: Probabilistic scenario analysis results, analysis 2

Scenario	Absolute costs		Absolute QALYs		ICER (ICS/LABA vs MART)	% CE
	MART	ICS/LABA	MART	ICS/LABA		MART
Base-case	**£2,144**	**£2,161**	**3.478**	**3.482**	**£4,769**	**40.56%**
Baseline data: Bousquet	£2,146	£2,163	3.605	3.608	£5,350	40.50%
Baseline data: Patel	£2,146	£2,162	3.507	3.511	£4,199	36.70%
Baseline data: Vogelmeier	£2,141	£2,157	3.342	3.345	£4,488	39.40%
Efficacy data: Bousquet	£2,225	£2,158	3.479	3.483	ICS/LABA dominant	23.70%
Efficacy data: Patel	£2,375	£2,683	3.466	3.453	MART dominant	97.50%
Efficacy data: Vogelmeier	£2,026	£2,090	3.480	3.485	£14,151	45.20%
All data: Bousquet	£2,228	£2,279	3.602	3.607	£9,874	39.90%
All data: Patel	£2,379	£2,464	3.493	3.480	MART dominant	87.00%
All data: Vogelmeier	£2,023	£2,192	3.343	3.347	£37,534	67.60%
Drug costs: minimum	£2,145	£1,920	3.477	3.480	ICS/LABA dominant	9.10%
Drug costs: maximum	£2,144	£2,343	3.481	3.484	£58,680	74.40%
Time horizon: 3 years	£1,333	£1,343	2.213	2.215	£5,365	41.50%
Time horizon: 10 years	£3,929	£3,959	6.264	6.270	£4,968	39.90%
Symptomatic split excluded	£2,143	£2,160	3.469	3.465	MART dominant	100%
Scotland general population mortality and costs	£2,151	£2,168	3.480	3.484	£4,597	40.40%

3.3 Analysis 3: Escalation to low-dose MART in children

3.3.1 Base-case

The results of the deterministic and probabilistic base-case analysis (English NHS perspective) for the escalation to paediatric low-dose MART in children model are presented in Table 38 and Table 39, respectively. In both cases, paediatric low-dose MART was associated with lower costs and higher QALYs than the other interventions, i.e. MART was the dominant strategy.

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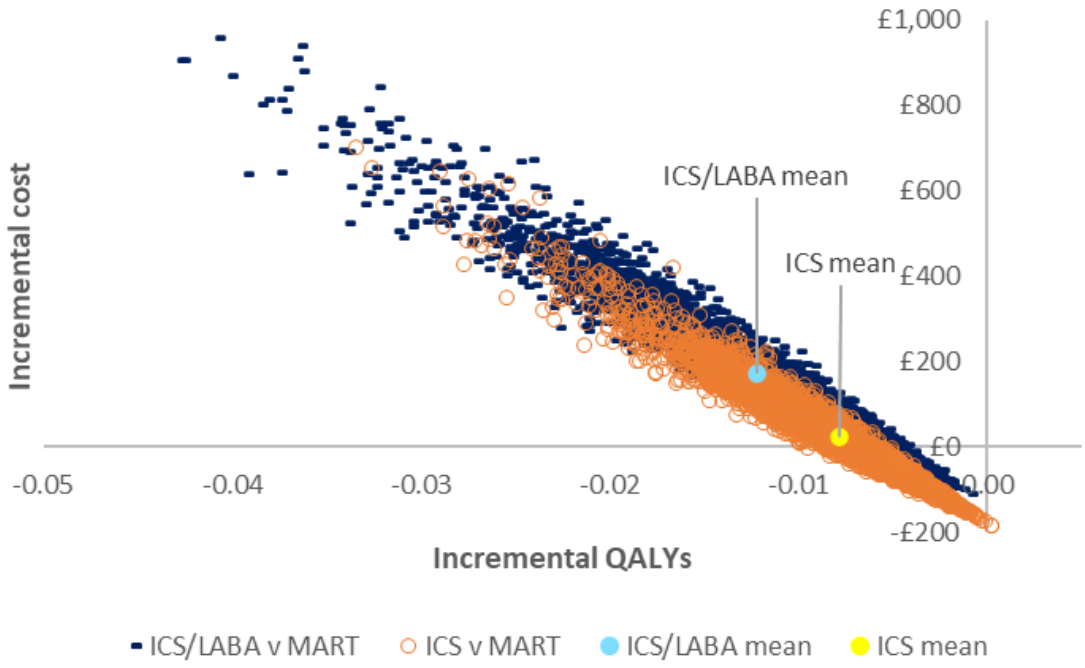
Table 38: Deterministic base-case results

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER
Paediatric low-dose MART	£816	4.331	-	-	-
Paediatric moderate-dose ICS + SABA	£820	4.323	£4	-0.007	Dominated
Paediatric low-dose ICS/LABA + SABA	£966	4.319	£150	-0.011	Dominated

Table 39: Probabilistic base-case results

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER	% CE
Paediatric low-dose MART	£816	4.329	-	-	-	84.90%
Paediatric moderate-dose ICS + SABA	£838	4.321	£22	-0.008	Dominated	14.46%
Paediatric low-dose ICS/LABA + SABA	£990	4.316	£174	-0.012	Dominated	0.64%

Figure 13: Cost-effectiveness plane, analysis 3



3.3.2 Sensitivity analyses

The results of the scenario analyses listed in section 2.5.3 are presented in Table 40. In the majority of scenarios, the cost-effectiveness results were stable, with MART being the dominant strategy over both ICS/LABA and ICS. In the two scenarios where MART was not dominant (when the minimum drug costs were used, and when the HSE utility multipliers were used) the ICER was below £20,000 per QALY for MART compared with either ICS/LABA or ICS.

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Table 40: Probabilistic scenario analysis results, population 3

Scenario	Absolute costs			Absolute QALYs			ICER (MART vs ICS/LABA)	ICER (MART vs ICS)	% CE	
	MART	ICS/LABA	ICS	MART	ICS/LABA	ICS			MART	ICS
Base-case	**£816**	**£990**	**£838**	**4.329**	**4.316**	**4.321**	**MART dominant**	**MART dominant**	**84.90%**	**14.46%**
Time horizon: 3 years	£507	£620	£522	2.686	2.679	2.682	MART dominant	MART dominant	85.10%	14.10%
Time horizon: until 15 years of age	£1,104	£1,343	£1,138	5.863	5.847	5.853	MART dominant	MART dominant	84.20%	15.30%
Drug costs: minimum	£816	£997	£744	4.329	4.316	4.321	MART dominant	£9,322	62.10%	37.20%
Drug costs: maximum	£816	£992	£861	4.333	4.321	4.326	MART dominant	MART dominant	88.20%	10.90%
Exacerbation QoL: EINSTEIN	£816	£986	£840	4.331	4.324	4.327	MART dominant	MART dominant	75.80%	22.70%
HS utility: HSE multipliers	£816	£991	£838	4.125	4.143	4.072	£9,749	MART dominant	22.00%	0.00%
Scotland general population mortality and costs	£820	£1,001	£845	4.332	4.320	4.324	MART dominant	MART dominant	83.70%	15.70%

4 Discussion

4.1 Summary of results

4.1.1 Analysis 1: Escalation to low-dose MART in adults

When low-dose MART was compared with low/moderate-dose ICS/LABA + SABA PRN in adults who had uncontrolled asthma, low-dose MART was found to have a probabilistic ICER of £6,382. The probabilistic results were consistent with the deterministic. Moreover, the ICER remained below £20,000 per QALY gained for the almost all scenario analyses. The only analysis with a substantially different ICER to the base-case was when data informing symptom status was excluded from the model, giving a probabilistic ICER of £20,710 when comparing low-dose MART with low/moderate-dose ICS/LABA + SABA PRN.

4.1.2 Analysis 2: Escalation to moderate-dose MART in adults

In the comparison between moderate-dose MART and moderate/high-dose ICS/LABA + SABA PRN, the MART regimen was found to have marginally lower costs and QALYs than ICS/LABA in the probabilistic base-case analysis, with ICS/LABA having an ICER of £4,769 compared with MART. The probabilistic results were consistent with the deterministic. Given the small incremental costs and QALYs, the resulting ICER is very sensitive to small changes in absolute costs and QALYs for example those seen in scenario analyses. The conclusions drawn from the ICER in this analysis are unstable to different assumptions explored in Section 3.2.2, particularly those where data from individual studies were used, where symptom status was excluded, and where drug costs were varied. A scenario of interest to the committee was that which excluded symptom status from the analysis given the limitations in the data informing this aspect, and this scenario resulted in MART being the dominant strategy.

4.1.3 Analysis 3: Escalation to paediatric low-dose MART in children

The analysis comparing paediatric low-dose MART with paediatric low-dose ICS/LABA + SABA PRN and with paediatric moderate-dose ICS + SABA PRN had consistent results in the base-case, probabilistic analysis and scenario analyses, with the MART regimen being dominant over both other strategies except in two scenarios. However, in these two scenarios, the ICER for MART remained below £20,000 per QALY gained.

4.2 Limitations and interpretation

The time horizon for the analysis was 5 years in the base-case, which a limitation as it would not be long enough to capture the patient's lifetime given the starting ages of 40, 42 and 8 years used in the respective analyses. However, the committee agreed that a shorter time horizon would avoid the uncertainty of extrapolating. Also the limited data around referrals after severe exacerbations and treatment switching would limit any longer-term models.

Only one study (Bousquet 2007) reported proportion of days without symptoms for the step-up to moderate-dose MART analysis, and this outcome had substantial uncertainty, as seen in Section 2.3.4.2, so this aspect of the model for analysis 2 was a limitation also highlighted by the committee. When making recommendations, the committee used the results of the base-case and the results of a scenario where symptom status was excluded from the model to inform their conclusions, and there was qualitative discussion on the treatment choices for this population.

Finally, the analyses in adults are based on indirect evidence as they are in populations with uncontrolled asthma following treatment with ICS plus SABA or ICS/LABA plus SABA, rather

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than a population uncontrolled on ICS/LABA as needed. There is uncertainty as to whether the efficacy of MART would be the same in these different populations.

4.3 Comparisons with published studies

Only one published study was identified as including the same comparison for the same question as this model; Wickstrom et al. 2009.(Wickstrom, et al., 2009) This analysis compared low and moderate dose MART regimens with various doses of ICS/LABA or ICS maintenance treatment and SABA as the as-needed reliever based on separate RCTs, and used a Danish perspective and Danish costs from 2007. Four of the five RCTs included in the Wickstrom analysis were also used as sources in the model developed for this guideline; Rabe et al. 2006 and O'Byrne et al. 2005 for the analysis of escalation to low-dose MART in adults, and Bousquet et al. 2007 and Vogelmeier et al. 2005 for the analysis of escalation to moderate-dose MART in adults. Wickstrom et al. conducted cost-effectiveness analyses rather than cost-utility, reporting number of severe exacerbations avoided as the outcome.

In the low-dose analysis or first treatment change, Wickstrom et al. found that low-dose MART had fewer severe exacerbations than low-dose ICS/LABA + SABA and MART was either dominant (based on O'Byrne et al.) or cost £82 per exacerbation avoided (based on Rabe et al.). In the guideline analysis, low-dose MART was more costly and more effective in the base-case, with an ICER of £6,338 per QALY gained, and MART had fewer severe exacerbations.

In the moderate-dose analysis or second treatment change, Wickstrom et al. found that moderate-dose MART was more costly and associated with fewer exacerbations, with a cost per exacerbation avoided of £868 and £458 based on Bousquet et al. and Vogelmeier et al., respectively. In the guideline analysis, moderate-dose MART had lower costs and fewer QALYs than moderate/high-dose ICS/LABA + SABA with the latter having a probabilistic ICER of £4,769 per QALY gained, but MART also had fewer severe exacerbations.

The guideline analysis gives some different results to that conducted by Wickstrom et al. however this study used Danish unit costs from 2007 rather than the updated UK NHS costs used in the guideline model. Additionally, the main outcome used in the Wickstrom et al. study was cost per severe exacerbation avoided, but the guideline analysis used cost per QALY gained.

4.4 Conclusions

The key findings of these analyses are that stepping up treatment to low-dose MART for adults or children (paediatric low-dose MART) who have uncontrolled asthma is likely to be a cost-effective use of resources compared with low/moderate-dose ICS/LABA + SABA PRN in adults, and with paediatric low-dose ICS/LABA + SABA PRN and paediatric moderate-dose ICS + SABA PRN in children.

The cost-effectiveness estimates for stepping up treatment to moderate-dose MART or moderate/high-dose ICS/LABA + SABA PRN were less certain, with the selected base-case analysis indicating ICS/LABA + SABA PRN to be more cost-effective, but a scenario that the committee thought was plausible given the quality of the evidence indicated that MART would be less costly and more effective.

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Appendices

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Appendix A Drug costs

The tables in this appendix detail the costs of the available treatments, and which of these treatments correspond to each clinical study.

Table 41: Drug costs, ICS/LABA used as maintenance treatment

Drug, formulation, dosing	Model	Study, arm	Cost per day	Details of calculation
Budesonide with formoterol Pressured inhalation 200/6 Two inhalations, twice daily	2	• Patel, md MART • Patel, m/hd ICS/LABA	£0.93	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23 Dose/day: 4
Budesonide with formoterol, Dry powder inhaler 80/4.5 One inhalation, twice daily	1	• O'Byrne, ld MART • O'Byrne, ld ICS/LABA	£0.47	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23 Dose/day: 2
Budesonide with formoterol, Dry powder inhaler 80/4.5 One inhalation	3	• Bisgaard, paediatric ld MART • Bisgaard, paediatric ld ICS/LABA	£0.23	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23 Dose/day: 1
Budesonide with formoterol, Dry powder inhaler 160/4.5 One inhalation, twice daily	1	• Atienza, ld MART • Atienza, ld ICS/LABA • Rabe, ld MART • Rabe, ld ICS/LABA	£0.47	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23 Dose/day: 2
Budesonide with formoterol, Dry powder inhaler 160/4.5 Two inhalations, twice daily	2	• Bousquet, md MART • Vogelmeier, md MART	£0.93	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23 Dose/day: 4
Budesonide with formoterol, Dry powder inhaler 200/6 Two inhalations, twice daily	2	• Patel, md MART • Patel, m/hd ICS/LABA	£0.93	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23 Dose/day: 4

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Drug, formulation, dosing	Model	Study, arm	Cost per day	Details of calculation
Fluticasone with Salmeterol, Dry powder inhaler 50/250 One inhalation, twice daily	2	• Vogelmeier, m/hd ICS/LABA	£1.13	Doses/pack: 60 Cost/pack: £33.95 Cost/dose: £0.57 Dose/day: 2
Fluticasone with Salmeterol, Dry powder inhaler 50/500 One inhalation, twice daily	2	• Bousquet, m/hd ICS/LABA	£1.09	Doses/pack: 60 Cost/pack: £32.74 Cost/dose: £0.55 Dose/day: 2

Abbreviations: md, moderate dose; m/hd, moderate/high dose; ld low dose.

Table 42: Drug costs, ICS/LABA used as reliever treatment

Drug, formulation, dosing	Model	Study, arm	Cost per inhalation	Details of calculation
Budesonide with formoterol, Pressured inhalation 200/6 One inhalation	2	• Patel, md MART	£0.23	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23
Budesonide with formoterol, Dry powder inhaler 200/6 One inhalation	2	• Patel, md MART	£0.23	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23
Budesonide with formoterol, Dry powder inhaler 80/4.5 One inhalation	1	• O'Byrne, ld MART	£0.23	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23
Budesonide with formoterol, Dry powder inhaler 160/4.5 One inhalation	1, 2, 3	• Atienza, ld MART • Bisgaard, paediatric ld MART • Bousquet, md MART • Rabe, ld MART • Vogelmeier, md MART	£0.23	Doses/pack: 120 Cost/pack: £28.00 Cost/dose: £0.23

Abbreviations: md, moderate dose; ld low dose.

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Table 43: Drug costs, SABA formulations

Drug, formulation, dosing	Model	Study, arm	Cost per inhalation	Details of calculation
Salbutamol, Pressurised inhalation 100 CFC free/evohaler	2	• Patel, ICS/LABA • Vogelmeier, ICS/LABA	£0.01	Doses/pack: 200 Cost/pack: £1.50 Cost/dose: £0.01
Salbutamol, Pressurised inhalation 100 easi-Breathe	2	• Patel, ICS/LABA • Vogelmeier, ICS/LABA	£0.03	Doses/pack: 200 Cost/pack: £6.30 Cost/dose: £0.03
Salbutamol, Pressurised inhalation 100 Autohaler	2	• Patel, ICS/LABA • Vogelmeier, ICS/LABA	£0.03	Doses/pack: 200 Cost/pack: £6.30 Cost/dose: £0.03
Salbutamol, Dry powder inhaler 100 Easyhaler	2	• Patel, ICS/LABA • Vogelmeier, ICS/LABA	£0.02	Doses/pack: 200 Cost/pack: £3.31 Cost/dose: £0.02
Salbutamol, Dry powder inhaler 100 Salbulin Novolizer	2	• Patel, ICS/LABA • Vogelmeier, ICS/LABA	£0.02	Doses/pack: 200 Cost/pack: £4.95 Cost/dose: £0.02
Salbutamol, Dry powder inhaler 100 Novolizer refill	2	• Patel, ICS/LABA • Vogelmeier, ICS/LABA	£0.01	Doses/pack: 200 Cost/pack: £2.75 Cost/dose: £0.01
Terbutaline, Inhalation powder 500 [(a)]	1,2,3	• Atienza, ICS/LABA • O'Byrne, ICS/LABA • Rabe, ICS/LABA • Bousquet, ICS/LABA • Bisgaard, ICS/LABA • Bisgaard, ICS	£0.07	Doses/pack: 120 Cost/pack: £8.30 Cost/dose: £0.07

(a) Terbutaline 500mcg results in a 400mcg actualised dose, aligning with the stated dose in the published studies.

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Table 44: Drug costs, ICS formulations

Drug, formulation, dosing	Model	Cost per day	Details of calculation
Budesonide, Dry powder inhaler 200 mcg	3	£0.23	Mcg/unit: 200 Units/pack: 100 Cost/pack: £14.25 Mcg/day: 320
Budesonide, Dry powder inhaler 200 mcg refill	3	£0.15	Mcg/unit: 200 Units/pack: 100 Cost/pack: £9.59 Mcg/day: 320
Budesonide, Dry powder inhaler 100 mcg	3	£0.23	Mcg/unit: 100 Units/pack: 200 Cost/pack: £14.25 Mcg/day: 320
Budesonide, Dry powder inhaler 400 mcg	3	£0.23	Mcg/unit: 400 Units/pack: 50 Cost/pack: £14.25 Mcg/day: 320

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Appendix B Probabilistic analysis input parameters

The table below summarises all probabilistic inputs in the model and the distribution parameters used.

Table 45: Probabilities, rate and utilities

Parameter	Mean	Standard error	95% CI lower	95% CI upper	Distribution	Distribution parameters (beta or gamma only)	
						alpha	beta
Adult asthma mortality HR	1.250	-	1.050	1.490	Lognormal	-	-
Child asthma mortality HR	1.770	-	1.300	2.400	Lognormal	-	-
% male (Atienza 2013)	32.38%	-	30.39%	34.40%	Beta	677	1414
% male (O'Byrne 2005)	44.44%	-	42.17%	46.72%	Beta	815	1019
% male (Rabe 2006)	39.35%	-	37.35%	41.38%	Beta	887	1367
% male (Bousquet 2007)	38.41%	-	36.44%	40.41%	Beta	887	1422
% male (Patel 2013)	31.02%	-	25.95%	36.34%	Beta	94	209
% male (Vogelmeier 2005)	41.06%	-	38.99%	43.15%	Beta	880	1263
% male (Bisgaard 2006)	71.06%	-	65.12%	76.67%	Beta	167	68
Low/moderate-dose ICS/LABA exacerbation rate (Atienza 2013)	0.307	0.00044	-	-	Gamma	481456.626	0.0000006
Low/moderate-dose ICS/LABA exacerbation rate (O'Byrne 2005)	0.400	0.00054	-	-	Gamma	551460.000	0.0000007
Low/moderate-dose ICS/LABA exacerbation rate (Rabe 2006)	0.370	0.00042	-	-	Gamma	761249.746	0.0000005
Exacerbation RR, low-dose MART vs low/moderate-dose ICS/LABA (Atienza 2013)	0.710	0.083	0.600	0.830	Lognormal	-	-
Exacerbation RR, low-dose MART vs low/moderate-dose ICS/LABA (O'Byrne 2005)	0.480	0.090	0.400	0.570	Lognormal	-	-
Exacerbation RR, low-dose MART vs low/moderate-dose ICS/LABA (Rabe 2006)	0.510	0.089	0.430	0.610	Lognormal	-	-
Exacerbation RR, low-dose MART vs low/moderate-dose ICS/LABA (pooled estimate)	0.570	0.050	0.510	0.620	Lognormal	-	-

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Parameter	Mean	Standard error	95% CI lower	95% CI upper	Distribution	Distribution parameters (beta or gamma only)	
						alpha	beta
Moderate/high-dose ICS/LABA exacerbation rate (Bousquet 2007)	0.310	0.00040	-	-	Gamma	597788.725	0.0000005
Moderate/high-dose ICS/LABA exacerbation rate (Patel 2013)	0.970	0.00112	-	-	Gamma	751944.000	0.0000013
Moderate/high-dose ICS/LABA exacerbation rate (Vogelmeier 2005)	0.230	0.00039	-	-	Gamma	346150.597	0.0000007
Exacerbation RR, moderate-dose MART vs moderate/high-dose ICS/LABA (Bousquet 2007)	0.830	0.095	0.690	1.000	Lognormal	-	-
Exacerbation RR, moderate-dose MART vs moderate/high-dose ICS/LABA (Patel 2013)	0.550	0.138	0.420	0.720	Lognormal	-	-
Exacerbation RR, moderate-dose MART vs moderate/high-dose ICS/LABA (Vogelmeier 2005)	0.810	0.079	0.690	0.940	Lognormal	-	-
Exacerbation RR, moderate-dose MART vs moderate/high-dose ICS/LABA (pooled estimate)	0.770	0.053	0.690	0.850	Lognormal	-	-
Paediatric low-dose MART exacerbation rate (Bisgaard 2006)	0.08	0.00229	-	-	Gamma	1221.043	0.00007
Exacerbation RR, paediatric low-dose MART vs paediatric low-dose ICS/LABA (Bisgaard 2006)	0.190	0.374	0.090	0.390	Lognormal	-	-
Exacerbation RR, paediatric low-dose MART vs paediatric moderate-dose ICS (Bisgaard 2006)	0.270	0.377	0.130	0.570	Lognormal	-	-
Asthma control proportion, low/moderate-dose ICS/LABA (Atienza 2013)	0.316	-	0.288	0.345	Beta	324.216	701.784
Asthma control proportion, low/moderate-dose ICS/LABA (O'Byrne 2005)	0.440	-	0.408	0.472	Beta	399.960	509.040
Asthma control proportion, low/moderate-dose ICS/LABA (Rabe 2006)	0.293	-	0.267	0.320	Beta	333.434	804.566
Mean difference in asthma control, low-dose MART vs low/moderate-dose ICS/LABA (Atienza 2013)	-0.042	0.015	-0.071	-0.013	Normal	-	-
Mean difference in asthma control, low-dose MART vs low/moderate-dose ICS/LABA (O'Byrne 2005)	-0.010	0.013	-0.036	0.016	Normal	-	-

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Parameter	Mean	Standard error	95% CI lower	95% CI upper	Distribution	Distribution parameters (beta or gamma only)	
						alpha	beta
Mean difference in asthma control, low-dose MART vs low/moderate-dose ICS/LABA (Rabe 2006)	-0.019	0.013	-0.045	0.007	Normal	-	-
Mean difference in asthma control, low-dose MART vs low/moderate-dose ICS/LABA (pooled estimate)	-0.02	0.008	-0.038	-0.007	Normal	-	-
Asthma control proportion, moderate/high-dose ICS/LABA (Bousquet 2007)	0.391	-	0.363	0.419	Beta	447.695	697.305
Mean difference in asthma control, moderate-dose MART vs moderate/high-dose ICS/LABA (Bousquet 2007)	-0.010	0.015	-0.040	0.020	Normal	-	-
Asthma control proportion, paediatric low-dose MART (Bisgaard 2006)	0.570	-	0.480	0.658	Beta	67.260	50.740
Mean difference in asthma control, paediatric low-dose MART vs paediatric low-dose ICS/LABA (Bisgaard 2006)	-0.040	0.008	-0.050	-0.020	Normal	-	-
Mean difference in asthma control, paediatric low-dose MART vs paediatric moderate-dose ICS (Bisgaard 2006)	0.060	0.005	0.050	0.070	Normal	-	-
Utility multiplier, medicated and symptomatic asthma	0.819	-	0.810	0.828	Beta	5421.252	1198.365
Utility multiplier, medicated and non-symptomatic asthma	0.986	-	0.974	0.995	Beta	430.049	5.886
Utility value, asthma without exacerbation, children	0.960	-	0.930	0.982	Beta	202.168	8.424
Exacerbation utility decrement (7 days observation)	0.163	0.0118	-	-	Gamma	190.814	0.0009
Exacerbation utility decrement (14 days observation)	0.132	0.0096	-	-	Gamma	189.063	0.0007
Exacerbation utility decrement (21 days observation)	0.125	0.0095	-	-	Gamma	173.130	0.0007
Exacerbation utility decrement (28 days observation)	0.115	0.0090	-	-	Gamma	163.272	0.0007

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Parameter	Mean	Standard error	95% CI lower	95% CI upper	Distribution	Distribution parameters (beta or gamma only)	
						alpha	beta
Duration of exacerbation (days)	28	16.309	20[(a)]	42[(a)]	Gamma	2.948	9.499

(a) Range of duration reported rather than 95% CI

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