National Guideline Centre

Final version

Chronic asthma management

Chronic asthma: management

NICE guideline NG80

Methods, evidence and recommendations

November 2017

In February 2020, this guideline was updated by an expert committee. They reviewed the evidence on increasing ICS treatment within supported self-management for children and young people.

See the NICE website for the guideline recommendations and the evidence review for the 2020 update.

This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2020.

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians · The Royal College of Surgeons of England · RCGP Royal College of General Practitioners · Royal College of Nursing · NGC National Guideline Centre · NICE accredited www.nice.org.uk/accreditation

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Update information
March 2018: Some of the algorithms were updated to clarify when actions should be taken and to show that medicines should be decreased once asthma is controlled.

Disclaimer
Healthcare professionals are expected to take NICE guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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Contents

Guideline Committee members

Name	Role
John Alexander (Chair)	Consultant in Paediatric Respiratory & Paediatric Intensive Care, Royal Stoke University Hospital
Noel Baxter	General Practitioner, NHS Southwark CCG
Andrew Bush	Professor of Paediatrics & Head of Section, Royal Brompton & Harefield NHS Foundation Trust
Susan Frost	Lead Respiratory Nurse Specialist, Birmingham Children's Hospital
Chris Griffiths	Principal in General Practice & Professor of Primary Care, Queen Mary University of London
Helen Haley	Pharmacist in Child Health, University Hospitals of North Midlands
Val Hudson	Patient Member
Matt Masoli	Consultant Respiratory Physician, Plymouth Hospitals NHS Trust
Nicola Mundy	Patient Member
Prunella Neale	Practice Nurse, Herschel Medical Centre
Ellen Nicholson	Senior Respiratory Nurse Specialist, Homerton University Hospital Foundation Trust
Stephen Scott	Consultant Respiratory Physician, Countess of Chester Hospital

NGC technical team members

Name	Role
Mikaela Bartlett	Document Editor/Process Assistant (until May 2016)
Katie Broomfield	Document Editor/Process Assistant (from May 2016)
Emily Davies	Senior Research Fellow (until January 2016)
James Gilbert	Senior Research Fellow
Alexander Haines	Senior Health Economist
Martin Harker	Health Economics Lead (from June 2017)
Bernard Higgins	Clinical Director
Samantha Jones	Project Manager (from September 2015)
Emma Madden	Research Fellow (until September 2015)
Ben Mayer	Research Fellow (from September 2015)
Abigail Moore	Specialist Trainee Adviser
Peter Rouse	Health Economist (until May 2016)
Sharon Swain	Senior Research Fellow (from February 2016 until June 2016)
Amelia Unsworth	Project Manager (until September 2015)
Claire Wallnutt	Information Specialist (until January 2017)

Co-optees

Name	Role
Lindsay Apps	Practitioner Health Psychologist, Leicester General Hospital
Charlotte Church	Physiotherapist in Asthma, University Hospital Southampton NHS Foundation Trust
Kevin Gruffydd-Jones	Principal in General Practice, Box Surgery

Acknowledgements

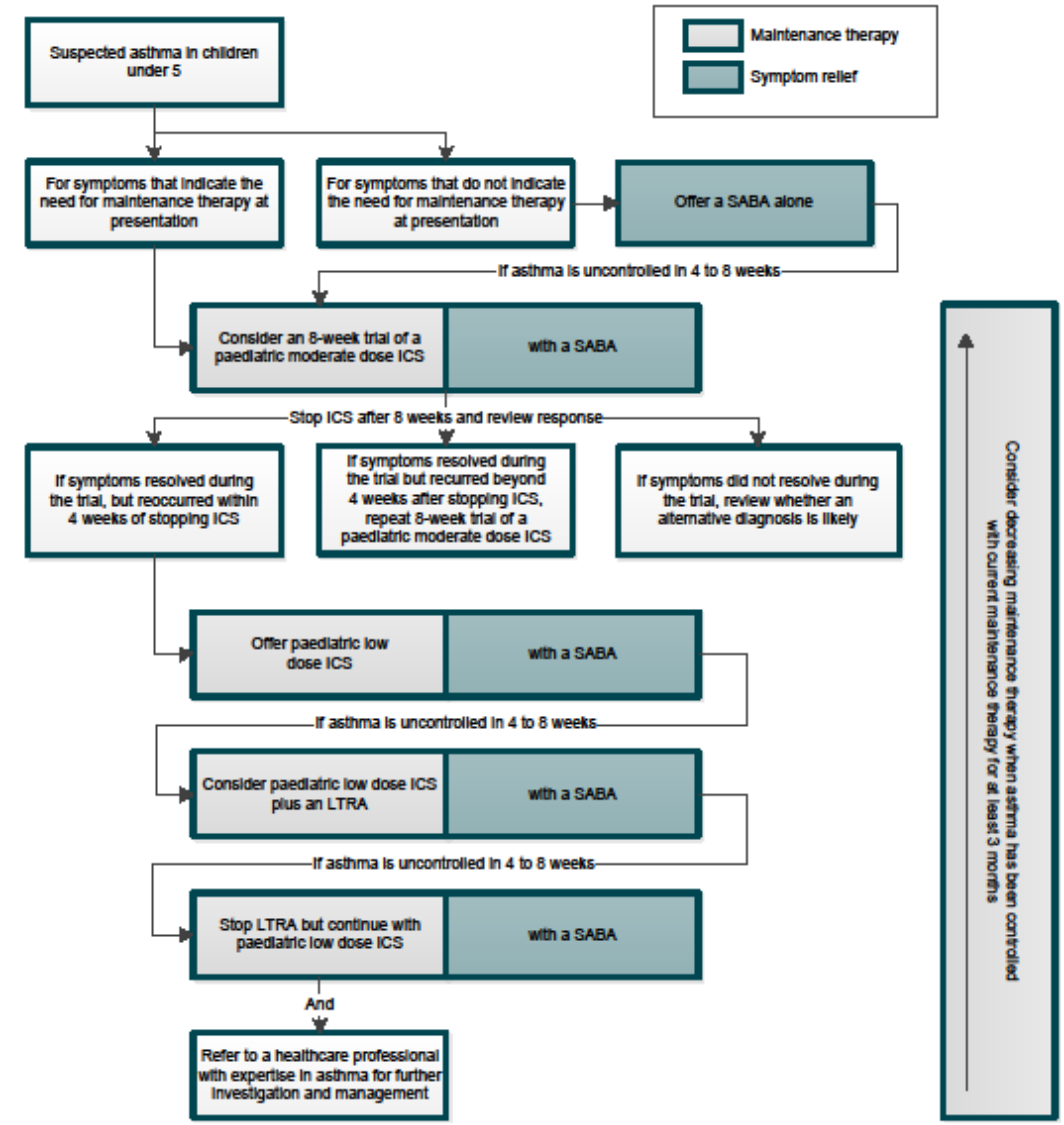
The development of this guideline was greatly assisted by the following people:

- Francesca Fasesin, Research Fellow, NGC
- Jill Cobb, Information Specialist, NGC
- Joseph Runicles, Information Specialist Assistant, NGC
- Martin Harker, Health Economics Lead, NGC
- Nancy Pursey. Senior Project Manager, NGC

1 Guideline summary

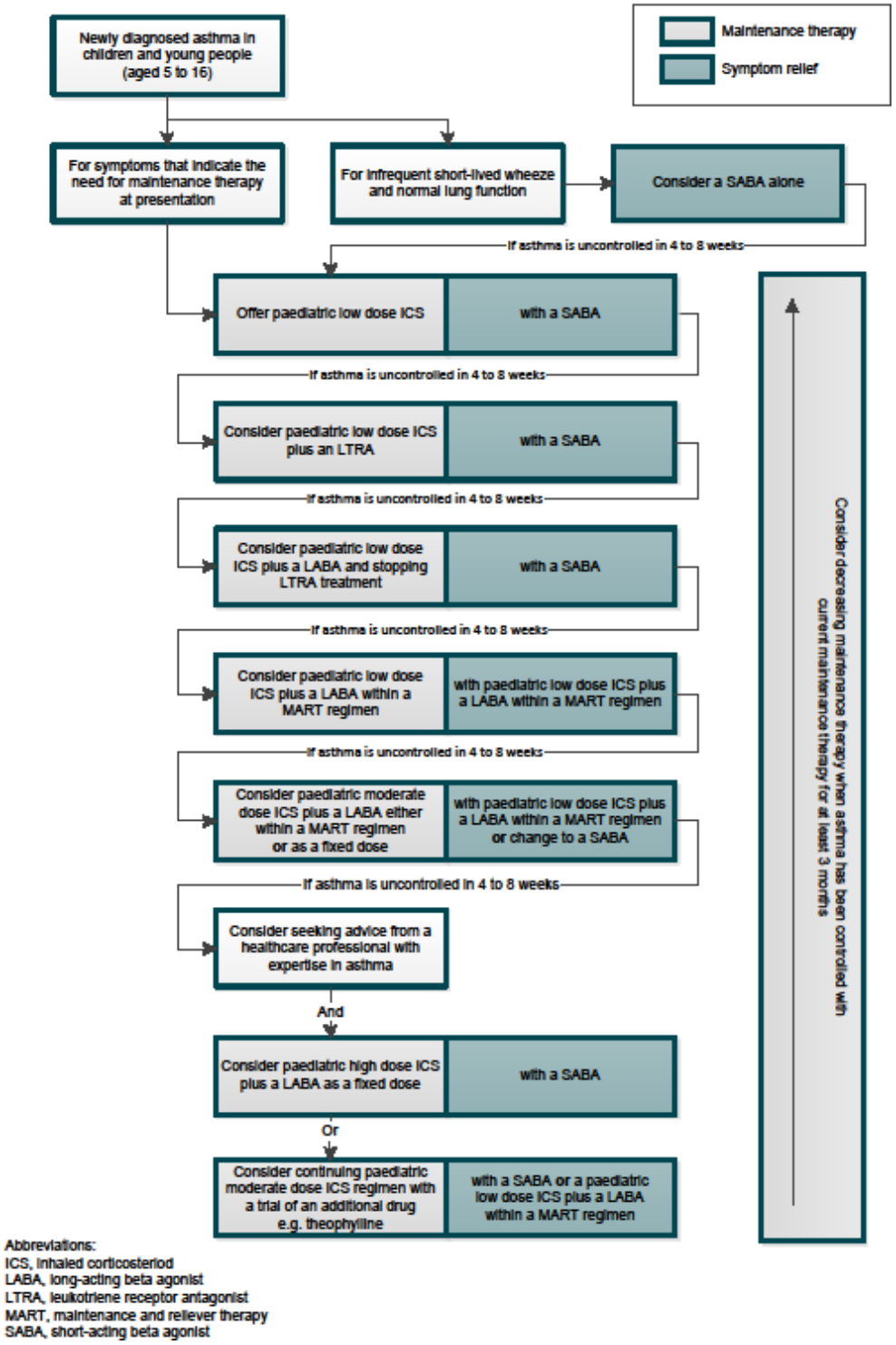
1.1 Algorithms

Algorithm A: Pharmacological treatment of chronic asthma in children under 5



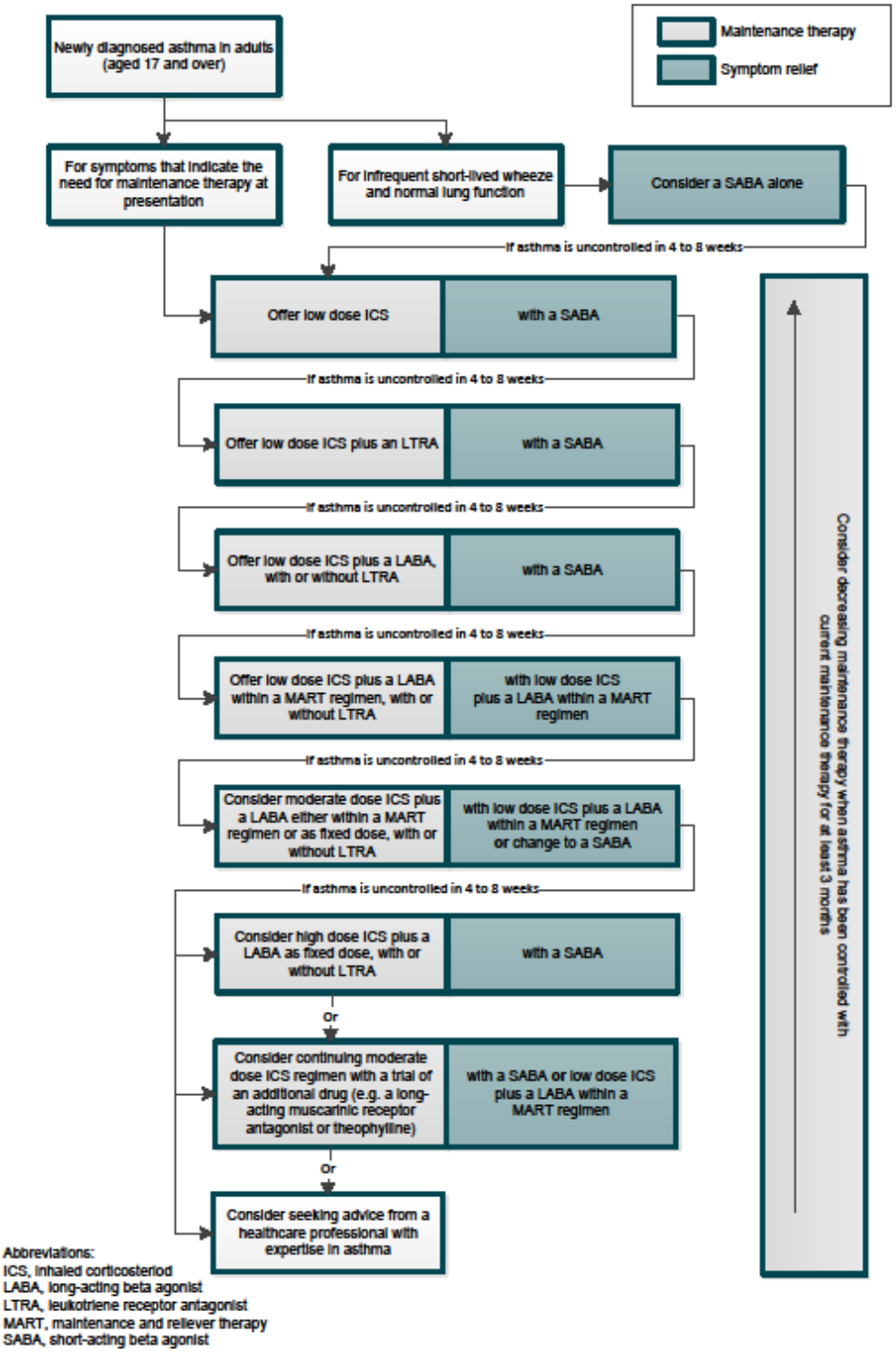
Abbreviations:
ICS, inhaled corticosteriod
LABA, long-acting beta agonist
SABA, short-acting beta agonist

Algorithm B: Pharmacological treatment of chronic asthma in children and young people aged 5 to 16



Abbreviations:
ICS, inhaled corticosteriod
LABA, long-acting beta agonist
LTRA, leukotriene receptor antagonist
MART, maintenance and reliever therapy
SABA, short-acting beta agonist

Algorithm C: Pharmacological treatment of chronic asthma in adults aged 17 and over



1.2 Full list of recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng80.

1.3 Key research recommendations

1.3.1 In adults, young people and children with asthma who have not been treated previously, is it more clinically and cost-effective to start treatment with a reliever alone (a short-acting beta2 agonist [SABA]) or with a reliever (a SABA) and maintenance therapy (such as ICS)? Are there specific prognostic features that indicate that one of these treatment options may be more appropriate for some groups?

1.3.2 Is maintenance therapy more effective with a paediatric low dose of ICS plus a leukotriene receptor antagonist (LTRA) or with a paediatric low dose of ICS plus a long-acting $beta_2$ agonist (LABA) in the treatment of asthma in children and young people (under 16) who have uncontrolled asthma on a paediatric low dose of ICS alone?

1.3.3 What is the clinical and cost effectiveness of offering additional maintenance therapy to adults, young people and children with asthma that is uncontrolled on a moderate dose of ICS plus LABA with or without LTRA?

1.3.4 What are the most clinically and cost-effective strategies to improve medicines adherence in adults, children and young people with asthma who are non-adherent to prescribed medicines?

1.3.5 In adults, children and young people with well controlled asthma, what are the objective measurements and prognostic factors that indicate that a decrease in regular maintenance treatment is appropriate?

2 Introduction

Asthma is the most commonly diagnosed long-term medical condition in the UK, affecting over 5 million people, of whom over 1 million are children (Asthma UK). The underlying pathology varies, but in general there is chronic inflammation of the lining of the airways that releases inflammatory mediators which trigger the smooth muscle of the airway to contract and narrow the air passages. The narrowing results in symptoms such as wheeze, cough, chest tightness and breathlessness. These symptoms can be measured by lung function tests that show evidence of airway obstruction and airway inflammation. A key feature of asthma is that the airway obstruction is reversible with medical treatment that relaxes the airway smooth muscle.

Most people with asthma have an episodic illness with periods of reasonable health interspersed with periods of increased symptoms that occasionally progress to an asthma attack. The increase in symptoms or asthma attack is usually caused by exposure to a trigger that the person is sensitive to. Triggers may be viral infections, environmental tobacco smoke, aeroallergens or exercise. The cause of asthma is unclear, but a combination of genetic and environmental factors is thought to make a person more susceptible to triggers that lead to airway narrowing.

The severity of asthma varies; some people have severe asthma that limits normal activities, whereas others are able to lead a relatively normal life. The illness fluctuates during the year and over time, so the level of treatment needs to be tailored to the person's current level of asthma severity. Many people with asthma, particularly children, seem to have fewer symptoms over time, and an important part of management is decreasing treatment if asthma is well controlled.

There is no cure for asthma, so management focuses on reducing exposure to known triggers if possible, relief of symptoms if there is airway narrowing, and reduction in airway inflammation by regular preventive treatment. Adherence to regular treatment reduces the risk of significant asthma attacks in most people with asthma. The focus of asthma management in recent years has been on developing guidelines that allow people with asthma and their healthcare professional to devise a personalised treatment plan that is effective and relatively easy to implement.

The aim of this guideline is to provide clear advice for healthcare professionals and people with asthma to develop a personalised action plan. The plan should support self-management of asthma , and ensure that the person is receiving the best possible treatment for their current level of illness.

The guideline covers children under 5, children and young people aged 5–16 and adults over 16 with suspected or diagnosed asthma. It focuses on the pharmacological management of chronic asthma, in particular the treatment pathway for people with uncontrolled asthma. It also covers adherence to treatment, risk stratification and self-management.

The guideline does not cover the management of acute asthma attacks.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services (NICE guideline CG138).

3 Development of the guideline

3.3 What is a NICE guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. These may also include elements of social care or public health measures. We base our guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a Guideline Committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGC and NICE produce a number of versions of this guideline:

- The 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence.
- The 'NICE guideline' lists the recommendations.
- 'Information for the public' is written using suitable language for people without specialist medical knowledge.
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.4 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NGC to produce the guideline.

The remit for this guideline is:

'to develop a clinical guideline on the management of asthma'.

3.5 Who developed this guideline?

A multidisciplinary Guideline Committee ('the committee') comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The committee was convened by the NGC and chaired by Dr John Alexander in accordance with guidance from NICE.

The group met approximately every 6–8 weeks during the development of the guideline. At the start of the guideline development process all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

3.3.1 What this guideline covers

This guideline will contain recommendations for the management of symptoms in adults, young people and children who have been diagnosed with asthma. Specific consideration will be given to subgroups based on age: children under 5 years; children aged 5–16 years; and adults and young people over 16 years of age.

The guideline will cover pharmacological management of chronic asthma, review of pharmacological therapy and non-pharmacological management of asthma (adherence, risk stratification, support self-management and breathing exercises only).

For further details please refer to the scope in Appendix A and the review questions in Section 4.1.

3.3.2 What this guideline does not cover

This guideline does not cover:

- Non-pharmacological treatment of asthma (except as specified: adherence, risk stratification, supported self-management and breathing exercises
- Biologics
- Comparison of drug-delivery services (inhalers)
- Bronchial thermoplasty
- Management of acute asthma attacks by a healthcare professional
- Service delivery for acute asthma attacks.

3.3.3 Relationships between the guideline and other NICE guidance

Related NICE technology appraisals:

- Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma. NICE technology appraisal guidance TA10 (2000).
- Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and older. NICE technology appraisal guidance TA138 (2008).
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisal guidance TA131 (2007).
- Inhaler devices for routine treatment of chronic asthma in older children (aged 5-15 years). NICE technology appraisal guidance TA38 (2002).
- Omalizumab for treating severe persistent allergic asthma. NICE technology appraisal guidance TA278 (2013).
- Mepolizumab for treating severe refractory eosinophilic asthma. NICE technology appraisal guidance TA431 (2017).

Related NICE interventional procedures guidance:

- Bronchial thermoplasty for severe asthma. NICE interventional procedure guidance IPG419 (2012).

Related NICE guidelines:

- Medicines adherence. NICE guideline CG76 (2009).

Related NICE guidance currently in development:

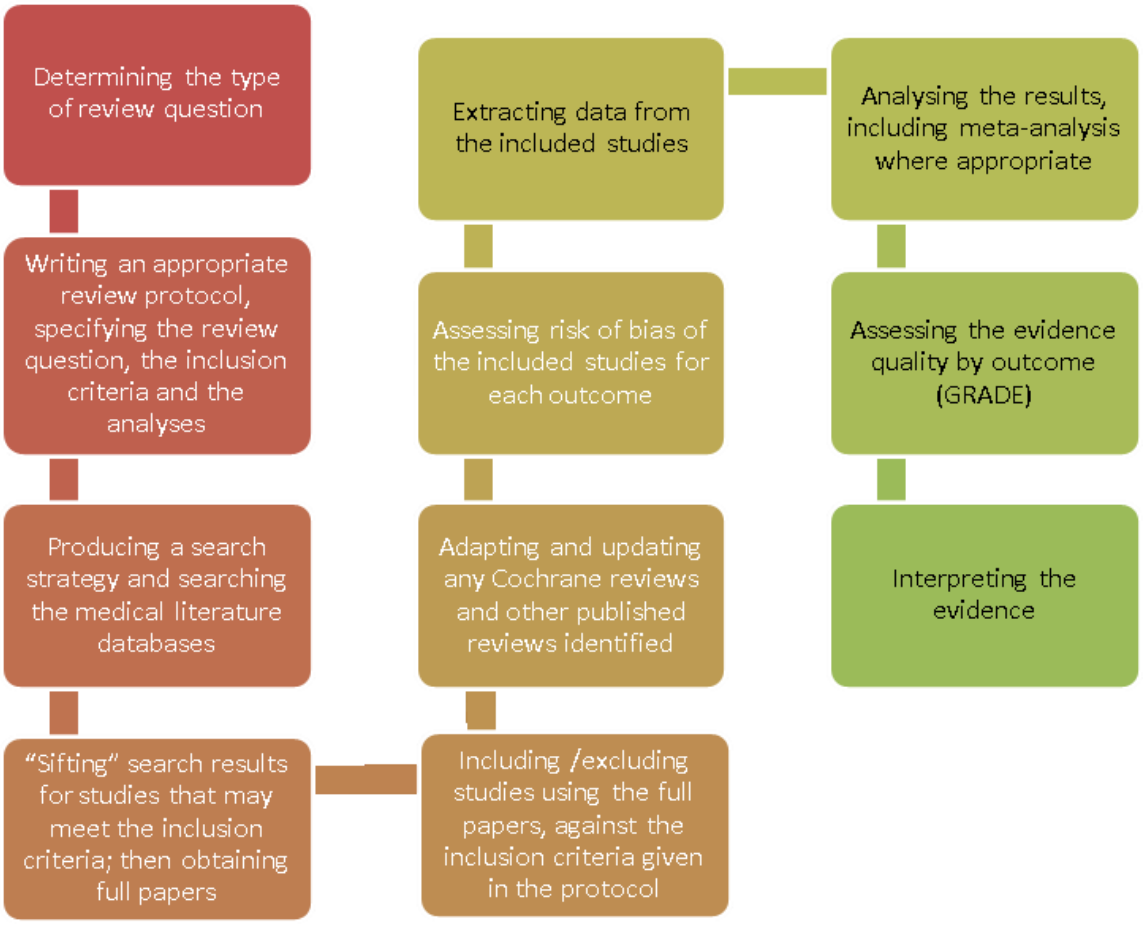
- Asthma diagnosis and monitoring. NICE guideline. Publication expected TBC.
- Acute medical emergencies. NICE guideline. Publication expected October 2017.

4 Methods

This chapter sets out in detail the methods used to review the evidence and to develop the recommendations that are presented in subsequent chapters of this guideline. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2012 and 2014 versions.[111]

Sections 4.1 to 4.3 describe the process used to identify and review clinical evidence (summarised in Figure 1), Sections 4.2 and 4.4 describe the process used to identify and review the health economic evidence, and Section 4.5 describes the process used to develop recommendations.

Figure 1: Step-by-step process of review of evidence in the guideline



4.3 Developing the review questions and outcomes

Review questions were developed using a PICO framework (population, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for diagnostic test accuracy reviews; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the committee. The review questions were drafted by the NGC technical team and refined and validated by the committee. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 12 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Minimum trial durations were specified for each outcome. Minimum durations were chosen by the committee as the first time points for which a clinically meaningful difference in the outcome would be observable. Rarer outcomes such as mortality and severe exacerbations therefore had longer minimum durations than more responsive outcomes like lung function and asthma control.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
5	Intervention	In children, young people and adults with asthma who have not been treated previously, is it more clinically and cost effective to start treatment with a reliever alone (SABA) or with a reliever (SABA) and a preventer (such as ICS)?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • SABA use • Lung function (FEV_1 or morning PEF) • Adverse effects ○ linear growth ○ infection ○ adrenal insufficiency
6	Intervention	What is the most clinically and cost effective first-line preventer drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are uncontrolled on SABA alone (preventer-naïve or no preventer for at least 1 month)?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever medication use • Lung function (FEV_1 or morning PEF) • Adverse events ○ linear growth ○ infection ○ adrenal insufficiency

Chapter	Type of review	Review questions	Outcomes
7	Intervention	In people with a clinician diagnosis of asthma who are uncontrolled on low dose ICS, what is the most clinically and cost-effective second-line preventer?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever medication use • Lung function (FEV_1 or morning PEF) • Adverse events ○linear growth ○all respiratory infections ○serious respiratory infections ○adrenal insufficiency
7	Intervention	What is the clinical and cost effectiveness of using ICS + LABA as preventer and reliever therapy compared to using ICS + LABA as preventer and a SABA as reliever therapy?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Total steroid dose • Reliever medication use • Lung function (FEV_1 or morning PEF) • Adverse events ○linear growth ○all respiratory infections ○serious respiratory infections ○adrenal insufficiency
7	Intervention	What is the most clinically and cost-effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking optimal preventer therapy beyond ICS low dose when this fails to provide adequate control?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever medication use • Lung function (FEV_1 or morning PEF) • Adverse events

Chapter	Type of review	Review questions	Outcomes
			○linear growth ○all respiratory infections ○serious respiratory infections ○adrenal insufficiency
8	Intervention	In children, young people and adults with asthma on ICS preventer therapy or requiring ICS, is intermittent ICS more clinically and cost effective than regular ICS?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever/rescue medication use • Lung function (FEV_1 or morning PEF) • Adverse events ○linear growth ○infection ○adrenal insufficiency
9	Intervention	What are the most clinically and cost-effective strategies to improve medicines adherence in children, young people and adults with asthma who are non-adherent to prescribed medicines?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life • Adherence **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever/rescue medication use • Lung function (FEV_1 or morning PEF) • Adverse events ○linear growth ○infection ○adrenal insufficiency
10	Intervention	What is the clinical and cost effectiveness of supported self-management (including self-management education, self-monitoring and a personalised asthma action plan, PAAP) in comparison to standard care (asthma review only), for improving outcomes for children, young people and adults with asthma?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever medication use • Lung function (FEV_1 or morning

Chapter	Type of review	Review questions	Outcomes
			PEF) • Adverse events: ○ linear growth ○ all respiratory infections ○ serious respiratory infections ○ adrenal insufficiency
11	Intervention	What is the optimal increase in ICS preventer therapy within supported self-management when control is lost?	**Critical outcomes:** • Subsequent asthma exacerbations • Treatment failures • Mortality • Quality of life **Important outcomes:** • Asthma control • Hospital admissions • Reliever medication use • Lung function (FEV_1 or morning PEF) • Adverse events ○linear growth ○infection ○adrenal insufficiency
12	Prognostic	What are the clinical features (symptoms and/or objective measures) which indicate that a step down in treatment is appropriate?	Step down successful (dichotomous outcome) – controlled according to BTS/SIGN guidelines after 4 weeks or more without the need to step back up or without asthma exacerbations Statistical outputs may include: Sensitivity, specificity, PPV, NPV, AUC OR/RR/HR
13	Intervention	Are breathing exercises clinically and cost effective for children, young people and adults with asthma?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever/rescue medication use • Lung function (FEV_1 or morning PEF)

Chapter	Type of review	Review questions	Outcomes
			• Adverse events ○linear growth ○infection ○adrenal insufficiency
14	Intervention	What is the clinical and cost effectiveness of delivering asthma care stratified according to risk of asthma attacks to improve outcomes for children, young people and adults with asthma?	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever/rescue medication use • Lung function (FEV_1 or morning PEF) •Adverse events: ○ linear growth ○ infections ○ adrenal insufficiency

4.4 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014.[111] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed. All searches were conducted in Medline, Embase, and The Cochrane Library. Additional subject-specific databases were used for some questions: Allied and Complementary Medicine (AMED). All searches were updated on 12 September 2016. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking committee members to highlight any additional studies. Searches were quality assured by a second information scientist before being run. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic

- Guidelines International Network database (www.g-i-n.net)

- National Guideline Clearing House (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- NHS Evidence Search (www.evidence.nhs.uk).

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken. The NGC and NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence considered by the committee for pharmaceutical interventions may be different from that considered by the MHRA and European Medicines Agency for the purposes of licensing and safety regulation.

4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to asthma in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment (HTA) database with no date restrictions (NHS EED ceased to be updated after March 2015). Additionally, the search was run on Medline and Embase using a health economic filter, from January 2014, to ensure recent publications that had not yet been indexed by the economic databases were identified. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in Appendix G. All searches were updated on 12 September 2016. No papers published after this date were considered.

4.5 Identifying and analysing evidence of effectiveness

Research fellows conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in Appendix C).
- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual.[113] Prognostic or qualitative studies were critically appraised using NGC checklists.
- Extracted key information about interventional study methods and results using 'Evibase', NGC's purpose-built software. Evibase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in Appendix H).
- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
    - Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.

- Prognostic data were meta-analysed where appropriate and reported in GRADE profile tables.

- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers and those for complex review questions (for example, prognostic reviews) were double-sifted by a senior research fellow and any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - correct methods were used to synthesise data
  - a sample of the risk of bias assessments.

4.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix L. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criteria were:

- Adults and children with asthma: the study was downgraded for indirectness if the diagnosis of asthma was not supported with objective tests
- For the pharmacological reviews assessing the best preventer to introduce when a person or child is uncontrolled on their previous preventers, at least 75% of the trial population had to meet the definition of uncontrolled. If sufficient information was provided to calculate this proportion, the study could be included. The definition of uncontrolled was taken from the literature as any one of the following:
  - Use of reliever medication on ≥3 days in a week
  - Presence of asthma symptoms on ≥3 days in a week
  - Awakening at night due to asthma symptoms ≥1 night in a week
- For the pharmacological reviews in which the population was restricted to those uncontrolled on previous specific preventers (in other words the restriction to be on no preventer for the first-line preventer review and only low dose ICS for the 2nd line preventer review), studies were only included where they specifically described the prior medication of their population. If criteria allowed for people with inappropriate prior medication to enter the trial and the study reported a breakdown of what proportion were using this medication, the committee agreed to include studies in which less than 10% of the population were using inappropriate preventers. If no breakdown was provided or more than 10% of the population were using inappropriate preventers, the study was excluded.
- For the pharmacological review of preventers beyond third line the committee chose to use less restrictive criteria due to the smaller evidence base.

Conference abstracts were not automatically excluded from any review. The abstracts were initially assessed against the inclusion criteria for the review question and further processed when a full publication was not available for that review question. If the abstracts were included the authors were contacted for further information. No relevant conference abstracts were identified for this guideline. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

4.3.2 Type of studies

Randomised trials, non-randomised intervention studies, and other observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. Crossover RCTs were not appropriate for the questions on long-term preventers, adherence or self-management as the interventions in question would be likely to have a long-term effect that would confound comparisons. If non-randomised intervention studies were considered appropriate for inclusion (for example, where no randomised evidence was available for critical outcomes) the committee stated a priori in the protocol that either certain identified variables must be equivalent at baseline or else the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion it was excluded. Please refer to the review protocols in Appendix C for full details on the study design of studies selected for each review question.

Where data from non-randomised studies were included, the results for each outcome were presented separately for each study or meta-analysed if appropriate.

4.3.3 Methods of combining clinical studies

4.3.3.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5)[147] software to combine the data given in all studies for each of the outcomes of interest for the review question.

All analyses were stratified by age (1 year old or younger, 1–5 years old, 5–16 years old, older than 16), which meant that different studies with predominant age-groups in different age strata were not combined and analysed together. For some questions additional stratification was used, and this is documented in the individual review question protocols (see Appendix C). When additional strata were used this led to substrata (for example, 2 stratification criteria leads to 4 substrata, 3 stratification criteria leads to 9 substrata) which were analysed separately.

Analyses comparing different ICS dose strategies were pooled into 3 categories: low, moderate and high dose. There were different cut-offs for these categories for adult and paediatric populations. The cut-offs were taken from the GINA guidance[57] available at the beginning of this guideline's development process. At the beginning of this guideline's development process, BTS/SIGN guidance[21] only distinguished 2 categories of ICS dose: above and below 800 µg per day of beclomethasone dipropionate (or equivalent), with cut-offs which differed in children and adults. The committee felt that the 3 categories provided greater resolution and would maintain the original analysis of the majority of studies better than using 2 categories, hence the decision to use the GINA guidance. The tables from the GINA guidance are reproduced with permission below, these tables are not meant to be exhaustive but were the basis for the stratification of evidence in the guideline.

Table 2: Low, moderate and high doses of inhaled corticosteroids: Adults and adolescents

Adults and adolescents	Low dose	Moderate dose	High dose
Beclometasone dipropionate (CFC)	200–500 µg	>500–1000 µg	>1000 µg

Adults and adolescents	Low dose	Moderate dose	High dose
Beclometasone dipropionate (HFA)	100–200 µg	>200–400 µg	>400 µg
Budesonide (DPI)	200–400 µg	>400–800 µg	>800 µg
Ciclesonide (HFA)	80–160 µg	>160–320 µg	>320 µg
Fluticasone propionate (DPI)	100–250 µg	>250–500 µg	>500 µg
Fluticasone propionate (HFA)	100–250 µg	>250–500 µg	>500 µg
Mometasone furoate	110–200 µg	>220–440 µg	>440 µg
Triamcinolone acetonide	400–1000 µg	>1000–2000 µg	>2000 µg

Table 3: Low, moderate and high doses of inhaled corticosteroids: Children

Children	Low dose	Moderate dose	High dose
Beclometasone dipropionate (CFC)	100–200 µg	>200–400 µg	>400 µg
Beclometasone dipropionate (HFA)	50–100 µg	>100–200 µg	>200 µg
Budesonide (DPI)	100–200 µg	>200–400 µg	>400 µg
Budesonide (nebules)	250–500 µg	>500–1000 µg	>1000 µg
Ciclesonide (HFA)	80 µg	>80–160 µg	>160 µg
Fluticasone propionate (DPI)	100–200 µg	>200–400 µg	>400 µg
Fluticasone propionate (HFA)	100–200 µg	>200–500 µg	>500 µg
Mometasone furoate	110 µg	≥220–≤440 µg	≥440 µg
Triamcinolone acetonide	400–800 µg	>800–1200 µg	>1200 µg

4.3.3.1.1 Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk, RR) for the binary outcomes, which included:

- mortality
- hospitalisation
- severe exacerbation
- adverse events

The absolute risk difference was also calculated using GRADEpro[59] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Continuous outcomes

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes included:

- health-related quality of life (HRQoL)
- lung function (by PEF or FEV_1)
- symptom scales (such as the ACT)
- reliever medication use

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of both); each different measure in each study was 'normalised' to the standard deviation value pooled between the intervention and comparator groups in that same study.

The means and standard deviations of continuous outcomes are required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals (95% CI) were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5)[147] software. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if a p value was reported as 'p≤0.001', the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied.

4.3.3.1.2 Generic inverse variance

If a study reported only the summary statistic and 95% CI the generic-inverse variance method was used to enter data into RevMan5.[147] If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[59] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported no absolute risk difference was calculated.

4.3.3.1.3 Heterogeneity

Statistical heterogeneity was assessed for each meta-analysis estimate by considering the chi-squared test for significance at $p<0.1$ or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating significant heterogeneity) as well as the distribution of effects. Where significant heterogeneity was present, predefined subgrouping of studies was carried out as per the subgroups specified in the review question protocols (see Appendix C).

If the subgroup analysis resolved heterogeneity within all of the derived subgroups, then each of the derived subgroups were adopted as separate outcomes (providing at least 1 study remained in each subgroup. For example, instead of the single outcome of '*missed diagnosis'*, this was separated into 2 outcomes '*missed diagnosis in people aged under 65'* and '*missed diagnosis in people aged 65 and over'*. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such is subject to uncontrolled confounding.

For some questions additional subgrouping was applied, and this is documented in the individual review question protocols (see Appendix C). These additional subgrouping strategies were applied independently, so subunits of subgroups were not created, unlike the situation with strata. Other subgrouping strategies were only used if the age category subgroup was unable to explain heterogeneity: then these further subgrouping strategies were applied in order of priority. Again,

once a subgrouping strategy was found to explain heterogeneity from all derived subgroups, further subgrouping strategies were not used.

If all predefined strategies of subgrouping were unable to explain statistical heterogeneity within each derived subgroup, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence interval around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the committee considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

4.3.3.1.4 Complex analysis

Network meta-analysis (NMA) was considered for the comparison of interventional treatments, but was not pursued because of insufficient data available for the relevant outcomes. The committee prioritised the outcomes of severe exacerbations and quality of life for NMA, however there was insufficient data for those outcomes when the studies were stratified by age and by previous preventer treatment.

Where studies had used a crossover design, paired continuous data were extracted where possible, and forest plots were generated in RevMan5[147] with the generic inverse variance function. When a crossover study had categorical data and the number of subjects with an event in both interventions was known, the standard error (of the log of the risk ratio) was calculated using the simplified Mantel-Haenszel method for paired outcomes. Forest plots were also generated in RevMan5[147]with the generic inverse variance function. If paired continuous or categorical data were not available from the crossover studies, the separate group data were analysed in the same way as data from parallel groups, on the basis that this approach would overestimate the confidence intervals and thus artificially reduce study weighting resulting in a conservative effect. Where a meta-analysis included a mixture of studies using both paired and parallel group approaches, all data were entered into RevMan5[147] using the generic inverse variance function.

4.3.3.2 Data synthesis for prognostic factor reviews

Odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs), with their 95% CIs, for the effect of the prespecified prognostic factors were extracted from the studies. Studies were only included if the confounders prespecified by the committee were either matched at baseline or were adjusted for in multivariate analysis. Prognostic accuracy data (sensitivity, specificity, AUC) were extracted from the studies.

Studies with lower risk of bias were preferred, taking into account the analysis and the study design. In particular, prospective cohort studies were preferred if they reported multivariable analyses that adjusted for key confounders identified by the committee at the protocol stage for that outcome.

Data were not combined in meta-analyses for prognostic studies.

4.3.4 Appraising the quality of evidence by outcomes

4.3.4.1 Intervention reviews

The evidence for outcomes from the included RCTs and, where appropriate, non-randomised intervention studies, were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[59]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 4.

Table 4: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an overestimate of the effectiveness of that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be taken into account. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

4.3.4.1.1 Risk of bias

The main domains of bias for RCTs are listed in Table 5. Each outcome had its risk of bias assessed within each study first. For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious'

rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weighting of studies according to study precision. For example if the most precise studies tended to each have a score of −1 for that outcome, the overall score for that outcome would tend towards −1.

Table 5: Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: • knowledge of that participant's likely prognostic characteristics, and • a desire for one group to do better than the other.
Performance and detection bias (lack of blinding of patients and healthcare professionals)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules. • Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

The assessment of risk of bias differs for non-randomised intervention studies, as they are inherently at high risk of selection bias. For this reason, GRADE requires that non-randomised evidence is initially downgraded on the basis of study design, starting with a rating of –2. This accounts for selection bias and so non-randomised intervention studies are not downgraded any further on that domain. Non-randomised evidence was assessed against the remaining domains used for RCTs in Table 3, and downgraded further as appropriate.

4.3.4.1.2 Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, each outcome had its indirectness assessed within each study first. For each study, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example in terms of population), indirectness was given a 'serious' rating of −1, but if there was indirectness in 2 or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of −1 each for that outcome, the overall score for that outcome would tend towards −1.

4.3.4.1.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in the underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (chi-squared $p<0.1$, or $I^2>50\%$), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of −1 if the I^2 was 50–74%, and a 'very serious' score of −2 if the I^2 was 75% or more.

If inconsistency could be explained based on prespecified subgroup analysis (that is, each subgroup had an $I^2<50\%$), the committee took this into account and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory factors. In such a situation the quality of evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

4.3.4.1.4 Imprecision

The criteria applied for imprecision were based on the 95% CIs for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either end of the 95% CI of the overall estimate of effect crossed one of the MID lines, imprecision was regarded as serious and a 'serious' score of −1 was given. This was because the overall result, as represented by the span of the confidence interval, was consistent with 2 interpretations as defined by the MID (for example, both no clinically important effect and clinical benefit were possible interpretations). If both MID lines were crossed by

either or both ends of the 95% CI then imprecision was regarded as very serious and a 'very serious' score of −2 was given. This was because the overall result was consistent with all 3 interpretations defined by the MID (no clinically important effect, clinical benefit and clinical harm). This is illustrated in Figure 2. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The position of the MID lines is ideally determined by values reported in the literature. 'Anchor-based' methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or 'anchoring' them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, a MID for an outcome could be defined by the minimum amount of change in that outcome necessary to make patients feel their quality of life had 'significantly improved'. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For binary variables, any MIDs reported in the literature will inevitably be based on expert consensus; as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, and so are not amenable to patient-centred 'anchor' methods.

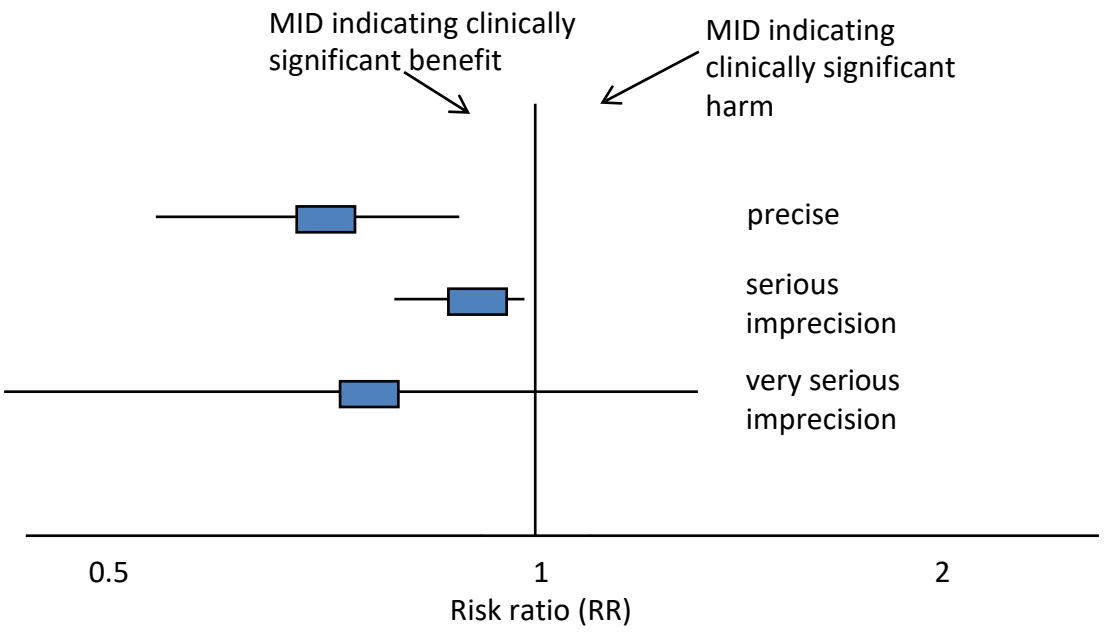
In the absence of values identified in the literature, the alternative approach to deciding on MID levels is the 'default' method, as follows:

- For categorical outcomes the MIDs were taken to be RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm.
- For mortality any change was considered to be clinically important and the imprecision was assessed on the basis of whether the confidence intervals crossed the line of no effect: that is, whether the result was consistent with both benefit and harm.
- For continuous outcome variables the MID was taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the minimum clinically significant benefit was positive for a 'positive' outcome (for example, a quality of life measure where a higher score denotes better health), and negative for a 'negative' outcome (for example, a visual analogue scale [VAS] pain score). Clinically significant harms will be the converse of these. If baseline values are unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.
- If standardised mean differences have been used, then the MID will be set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the 2 groups, and are thus effectively expressed in units of 'numbers of standard deviations'. The 0.5 MID value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the committee. If the committee decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, appropriate MIDs for continuous outcomes were found in the literature,[155] and so these were adopted. The committee decided that the MID level should be altered for the following dichotomous outcomes: severe exacerbations and hospitalisations (0.9 to 1.1). The committee noted that the impact of a severe exacerbation or hospitalisation is considerable for a person with asthma and therefore a lower threshold for importance would be appropriate. The 0.9 to 1.1 range was agreed by consensus.

Figure 2: Illustration of precise and imprecise outcomes based on the 95% CI of dichotomous outcomes in a forest plot (note that all 3 results would be pooled estimates, and would not, in practice, be placed on the same forest plot)



4.3.4.1.5 Overall grading of the quality of clinical evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. All RCTs started as High and the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 6. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Non-randomised intervention studies started at Low, and so a score of −1 would be enough to take the grade to the lowest level of Very Low. Non-randomised intervention studies could, however, be upgraded if there was a large magnitude of effect or a dose-response gradient.

Table 6: Overall quality of outcome evidence in GRADE

Level	Description

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.4.2 Prognostic reviews

The quality of evidence for prognostic studies was evaluated according to the criteria given in Table 7. If data were meta-analysed, the quality for pooled studies was presented. If the data were not pooled, then a quality rating was presented for each study.

Table 7: Description of quality elements for prospective studies

Quality element	Description of cases where the quality measure would be downgraded
Study design	Case–control studies rather than prospective cohort studies
Patient recruitment	If potential for selection bias
Validity of risk factor measure(s)	If non-validated and no reasonable face validity
Validity of outcome measure	If non-validated and no reasonable face validity
Blinding	If assessors of outcome not blinded to risk factor measurement (or vice versa)
Adequate duration of follow-up (or retrospective duration)	If follow-up (or retrospective) period inadequate to allow events to occur, or retrospective period so short that causality is in doubt because the outcome may have preceded the risk factor
Confounder consideration	If there is a lack of consideration of all reasonable confounders in a multivariable analysis
Attrition	If attrition is too high and there is no attempt to adjust for this
Directness	If the population, risk factors or outcome differ from that in the review question

4.3.4.2.1 Inconsistency

Inconsistency for association data was assessed as for intervention studies. Inconsistency for prediction data was assessed by inspection of the sensitivity and specificity (based on the primary measure) using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which it would be acceptable to recommend a test). For example, the committee might have set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (for example, 50–90% and 90–100%) and by 2 increments if the individual studies varied across 3 areas (for example, 0–50%, 50–90% and 90–100%).

4.3.4.2.2 Imprecision

In meta-analysed outcomes, or for non-pooled outcomes, the position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no

serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Imprecision for prediction data was assessed according to the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule (after discussion with the committee) a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

4.3.4.2.3 Overall grading

Because prognostic reviews were not usually based on multiple outcomes per study, quality rating was assigned by study. However if there was more than 1 outcome involved in a study, then the quality rating of the evidence statements for each outcome was adjusted accordingly. For example, if one outcome was based on an invalidated measurement method, but another outcome in the same study was not, the second outcome would be graded 1 grade higher than the first outcome.

Quality rating started at High for prospective studies, and each major limitation brought the rating down by 1 increment to a minimum grade of Very Low, as explained for interventional reviews. For prognostic reviews prospective cohort studies with a multivariate analysis are regarded as the gold standard because RCTs are usually inappropriate for these types of review for ethical or pragmatic reasons. Furthermore, if the study is looking at more than 1 risk factor of interest then randomisation would be inappropriate as it can only be applied to 1 of the risk factors.

4.3.5 Assessing clinical importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro[59] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The committee considered for most of the outcomes in the intervention reviews that if at least 10 more participants per 1000 (1%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For minor adverse events 50 events or more per 1000 (5%) represented clinical harm. For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this represented a clinical benefit or harm. For outcomes such as mortality any reduction or increase was considered to be clinically important.

This assessment was carried out by the committee for each critical outcome, and an evidence summary table was produced to compile the committee's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.6 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of

the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).
- A description of the overall quality of the evidence (GRADE overall quality).

4.4 Identifying and analysing evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[111] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

4.4.1 Literature review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual.[113]
- Extracted key information about the studies' methods and results into health economic evidence tables (included in Appendix I).
- Generated summaries of the evidence in NICE health economic evidence profile tables (included in the relevant chapter for each review question) – see below for details.

4.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published 15 years or more before the start of guideline; and studies from non-

OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see Table 8 below and the economic evaluation checklist (Appendix G of the 2012 NICE guidelines manual[113]) and the health economics review protocol in Appendix D.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

4.4.1.2 NICE health economic evidence profiles

NICE health economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each review chapter. The health economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[113] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See Table 8 for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[122]

Table 8: Content of NICE health economic evidence profile

Item	Description
Study	Surname of first author, date of study publication and country perspective with a reference to full information on the study.
Applicability	An assessment of applicability of the study to this guideline, the current NHS situation and NICE decision-making:[(a)] • Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study:[(a)] • Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet 1 or more quality criteria,

Item	Description
	and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (usually in £ per QALY gained).
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of the 2012 NICE guidelines manual[113]

4.4.2 Undertaking new health economic analysis

As well as reviewing the published health economic literature for each review question, as described above, new health economic analysis was undertaken by the health economist in selected areas. Priority areas for new analysis were agreed by the committee after formation of the review questions and consideration of the existing health economic evidence.

The committee identified pharmaceutical management as the highest priority area for original health economic modelling. Every individual with asthma will be on some form of pharmaceutical management and given the size of the asthma population this constitutes a large spend of the NHS budget. The systematic review of the clinical evidence found sufficient evidence to model what the optimal second line preventer should be for those who have failed on low dose inhaled corticosteroids. The committee felt other areas of pharmaceutical management would not benefit from original modelling because either sufficient economic evidence already existed or the clinical evidence was not found or too low in quality.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings.[111]
- The committee was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available expert opinion from the committee was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NGC.

Full methods for the cost-effectiveness analysis for optimal second line preventers are described in Appendix N.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money.[112] In general, an intervention was considered to be cost-effective (given that the estimate was considered plausible) if either of the following criteria applied:

- 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 cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[112]

4.4.4 In the absence of health economic evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.5 Developing recommendations

Over the course of the guideline development process, the committee was presented with:

- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables are in Appendices H and I.
- Summaries of clinical and health economic evidence and quality (as presented in Chapters 5–14).
- Forest plots (Appendix K).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix N).

Recommendations were drafted on the basis of the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the committee took into account the clinical benefits and harms when one

intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences), and the confidence the committee had in the evidence (evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the committee. The committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 4.5.1 below).

The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost-effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.2 in the 2014 NICE guidelines manual[111])

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance

- ethical and technical feasibility.

4.5.2 Validation process

This guidance was subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders were responded to in turn and posted on the NICE website.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.5.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

5 Treatment in patients not on regular preventers

5.3 Introduction

There has been consensus in widely used asthma guidelines (BTS/SIGN and GINA) about a stepwise approach to asthma management, and reliever therapy alone has been recommended for those with the mildest symptoms. Historically there has been a perception of a lack of risk for patients with symptoms less than 1–3 days per week. However, this view has been challenged. There is evidence of airway inflammation even in so-called "intermittent" asthma[183] and it can be argued that everyone with asthma should receive inhaled corticosteroids (ICS) because this underlying pathology is likely to respond to these agents. Even in mild asthma there is evidence that ICS can reduce the risk of severe exacerbations[129] (Pauwels 2003). However, this same evidence indicates that the absolute risk of severe exacerbations remains low in mild asthma when treated with reliever therapy alone.

The question we addressed in this review is whether it is clinically and cost-effective to start all those with newly diagnosed asthma on ICS, even if the presentation is of mild disease. It is assumed that people who present with severe symptoms or a severe exacerbation will require regular preventer therapy, and indeed such people could not ethically be randomised to a 'no treatment' study arm.

5.1.1 Review question: In children, young people and adults with asthma who have not been treated previously, is it more clinically and cost-effective to start treatment with a reliever alone (SABA) or with a reliever (SABA) and a preventer (such as ICS)?

For full details see review protocol in Appendix C.

Table 9: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma who are treatment-naïve. This population is likely to have very minimal or intermittent symptoms, or a new diagnosis of asthma. The population will primarily be primary and secondary care. People who have been off all asthma treatment (reliever and preventer) for at least 1 month will also be included as there will not be any lasting effects of the treatment. Also, very few people will be completely treatment-naïve, as people may have been put on treatments sporadically in their history, perhaps prior to an asthma diagnosis. Population strata: • Age: ○ <1 year ○ 1 to <5 years ○ 5 to <16 years ○ ≥16 years Exclusions: People already on either SABA alone or SABA plus a preventer treatment, or previous use of asthma medication within the last 1 month.
Intervention(s)	• SABA when required (salbutamol, terbutaline)

	• SABA when required + preventer (ICS: budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone; ICS+LABA: salmeterol, formoterol, vilanterol; LTRA: montelukast, zafirlukast; theophylline or aminophylline; cromolyns: sodium cromoglicate, nedocromil)
Comparison(s)	SABA when required (salbutamol, terbutaline) versus SABA when required + preventer (ICS: budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone; ICS+LABA: salmeterol, formoterol, vilanterol; LTRA: montelukast, zafirlukast; theophylline or aminophylline; cromolyns: sodium cromoglicate, nedocromil)

Outcomes	**Critical outcomes:**
	• Severe asthma exacerbations
	• Mortality
	• Quality of life
	
	Important outcomes:
	• Asthma control assessed by a validated questionnaire
	• Hospital admissions
	• SABA use
	• Lung function
	• Adverse events
	  ○ linear growth
	  ○ infection
	  ○ adrenal insufficiency

Study design	RCT Systematic review

5.1.1.1 Clinical evidence

No clinical evidence was identified that met the protocol for answering this review question.

5.1.1.2 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

5.1.1.3 Evidence statements

Clinical

No clinical evidence was identified that met the protocol for answering this review question.

Economic

No relevant economic evaluations were identified.

5.1.1.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80
Research recommendation	**1. In adults, young people and children with asthma who have not been treated previously, is it more clinically and cost-effective to start treatment with a reliever alone (a short-acting beta2 agonist [SABA]) or with a reliever (a SABA) and maintenance therapy (such as ICS)? Are there specific prognostic features that indicate that one of these treatment options may be more appropriate for some groups?**
Relative values of different outcomes	The committee considered the following outcomes as critical or important for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee also considered the following additional outcomes: asthma control (as assessed by a validated questionnaire), hospital admission, SABA use, lung function (FEV_1 or morning PEF) and adverse events. These outcomes were considered as important measures of asthma control for the patient. The committee agreed that the clinical effectiveness of the interventions would only be apparent after 6 months follow-up for the outcomes of severe exacerbations, hospital admissions and mortality, as these are rare events. However, the committee considered that a clinical benefit of any intervention would be apparent for the following outcomes after a shorter time period of 3 months: quality of life, asthma

	control, SABA use and lung function.
Trade-off between clinical benefits and harms	No clinical evidence addressing the question asked in this review was identified. The committee discussed the benefits and harms of starting all people with asthma on SABA as a reliever plus a regular preventer. It was agreed that this would be a change in current practice; although the majority of people are currently started on a preventer (usually ICS) plus SABA as a reliever, some will get SABA as a reliever alone. There was general consensus that most people would benefit from a preventer since this will treat the airway inflammation which underlies asthma and therefore reduce the risk of potentially serious exacerbations, as well as relieving symptoms. However, although ICSs are generally well tolerated they can have side effects, and they commit the person with asthma to taking an inhaler regularly, usually twice a day. This may not be a good trade-off for someone with very mild asthma who might need to use a SABA infrequently even if on no preventer. The committee agreed there is currently a lack of clinical evidence to support the use of a preventer as a first line intervention in all people with asthma, irrespective of the severity at presentation. The committee felt that it is important that people who need preventer therapy, because their asthma is uncontrolled without it, are started on it in a timely fashion. However the committee did not feel that the available evidence was strong enough to remove the option of SABA as a reliever alone from management of asthma across the whole population. Taking into account the lack of evidence, their clinical experience and the current trends in asthma management, the committee chose to recommend that all people newly diagnosed with asthma are provided with SABA as a reliever. The committee also recommended that for some people with very mild symptoms, this may be all that is required but that should they have more severe symptoms at presentation or persistently meet the committee's criteria for uncontrolled asthma whilst using a SABA alone they should immediately start preventer therapy.
Economic considerations	No economic studies were included in this review. The committee noted that starting people on SABA alone would likely cost less than starting everyone on low dose ICS straight away. However, there was no evidence to reflect on resource use and clinical outcomes and therefore the committee did not feel they could properly evaluate the cost effectiveness of the two treatment options.
Quality of evidence	No clinical evidence was identified.
Other considerations	The committee noted that there may be additional benefit from starting ICS early in the treatment pathway if it prevents long-term harmful effects of untreated inflammation. These benefits would be difficult to capture in any conventional RCTs. The population of interest for this recommendation was people with newly diagnosed asthma or people with asthma who are treatment naïve. People with asthma who had not received any treatment for the previous month were also included, as the committee acknowledged that people may have received asthma medication sporadically in the past or during a diagnosis of asthma. The committee did not consider studies in people with asthma who are already controlled on SABA treatment to be relevant for this review. This population would be pre-selecting people who already have good asthma control on SABA alone, and therefore may not gain much further benefit from receiving additional preventer treatment.

The committee recognised that there is ongoing research into the treatment of different asthma phenotypes, and that certain groups (such as people with high FeNO) may be shown to benefit from starting on both SABA and ICS rather than SABA alone. The committee felt that this was an area where a research recommendation is appropriate.

See recommendations 8 and 9 in section 6 for guidance on first-line maintenance therapy in adults (aged 17 and over), children and young people (aged 5 to 16).

6 Choice of first-line preventer in patients with poor asthma control

6.1 Introduction

Asthma is generally driven by type 2 inflammation, with therapeutic strategies aimed at controlling this response. There is also bronchial hyper-responsiveness and airflow obstruction, which may be in part related to inflammation. Reliever medications; that is, short-acting beta agonists, are aimed at symptom relief through airway smooth muscle relaxation. Patients may be prescribed short- acting beta agonists to relieve symptoms but this does not treat the underlying inflammatory condition. We are considering here those treatments that would be termed preventers as the next step. If adequate control of symptoms and risk reduction in asthma cannot be achieved by very intermittent use of short-acting beta agonists, the next step is a reliever medication to address the (usually presumptively diagnosed) underlying airway inflammation.

6.1.1 Review question: What is the most clinically and cost effective first-line preventer drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are uncontrolled on SABA alone (preventer-naïve or no preventer for at least 1 month)?

For full details see the review protocol in Appendix C.

Table 10: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma who are uncontrolled on a SABA alone and have never been prescribed preventer medication for their asthma (for example ICS) or people who have been free from preventer medication for at least 1 month. Population strata: • <1 year • 1 to <5 years • 5 to <16 years • ≥16 years
Intervention(s)	• Placebo/no treatment • Regular 'low dose' ICS • Regular 'moderate dose' ICS • Regular 'high dose' ICS • ICS+LABA • ICS+LABA (regular ICS+LABA with SABA when required) • ICS+LABA (formoterol) used as maintenance and reliever therapy (for example SMART or MART therapy) • Leukotriene receptor antagonist • Theophylline or aminophylline • Cromolyns
Comparisons	First-line preventer versus placebo/usual care Any listed intervention versus another

Outcomes	**Critical outcomes:**
	• Severe asthma exacerbations
	• Mortality
	• Quality of life
	Important outcomes:
	• Asthma control assessed by a validated questionnaire
	• Hospital admissions
	• Reliever medication use
	• Lung function (change in FEV_1 or morning PEF)
	• Adverse events
	  ○ linear growth
	  ○ infection
	  ○ adrenal insufficiency

Study design	RCT Systematic review of RCTs

6.1.1.1 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of preventer drugs as first line treatment for patients with asthma who are uncontrolled on SABA therapy alone. The review population was people who have never been prescribed preventer medication for their asthma or people who have been free from preventer medication for at least 1 month. The latter allows for people who have been prescribed preventer medication during diagnosis or in the past. The committee agreed that the effects of the preventer would be expected to have worn off after a period of 1 month. Studies recruiting a mix of people with asthma on different stages of treatment were only included if at least 90% of people included in the study were on SABA alone at inclusion. Studies were included that recruited people with asthma who were uncontrolled in line with BTS/SIGN guidelines (using SABA three times a week or more; symptomatic three times a week or more; or waking one night a week or more). Studies recruiting a mix of people with asthma, including both people who were controlled and uncontrolled, were only included if at least 75% of people included in the study were uncontrolled on SABA alone. While the committee agreed that asthma diagnosis in children under 1 is imprecise, the inclusion of those with persistent wheeze and recurrent cough (as defined in the NICE guideline on asthma diagnosis and management)[110] satisfied the inclusion criteria.

Thirty-six studies from thirty-seven publications were included in the review; [10 14 18 26 27 31 33 35 48 56 71 77 81 85 87 101 103 109 114 116 117 132 133 140 137 145 146 152 154 158 161 165 169 170 197 199] these are summarised in Table 11 below. A variety of preventer drugs were used. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 12, Table 13, Table 14, Table 15, Table 16, Table 17, Table 18, Table 19, Table 20, Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, Table 27, Table 28,Table 29, Table 30, Table 31, Table 32, Table 33, Table 34, Table 35,Table 36, Table 37, Table 38, Table 39, Table 40 and Table 41). See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Table 11: Summary of studies included in the review

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
Berger 2002[10]	ICS low dose (n=198) Placebo (n=210)	Stratum: ≥16 years Age - Mean (range): FP: 33 (12–74) Placebo: 33 (12–69) At baseline mean rescue-free days was 13.4% (SD 22.11) therefore the mean rescue-using days was 86.6%, and the probability of any one patient having >43% (3/7) of their days with rescue use=97.6%	• Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 12 weeks	Population determined as uncontrolled using baseline data
Boonsawat 2008[14]	ICS + LABA (n=149) ICS low dose (n=154) Placebo (n=155)	Stratum: ≥16 years Age - mean (range): 34.02 (12–73) Pre-bronchodilator PEF >80% of predicted during run-in, diagnosis of asthma with positive BDR (increase in PEF of ≥15% following 400 ug salbutamol), day-time symptom score of >1 on 3–6 of last 7 days.	• Rescue use (% free days) • FEV_1 (L) • Morning PEF (L/min) Reported at 12 weeks	
Bousquet 2005[18]	ICS low dose (n=320) LTRA (n=325)	Stratum: ≥16 years Age - mean (SD): 36.3 (14.1) Mild persistent asthma as defined by GINA, aged 18–80, with a history of asthma for at least 4 months, baseline FEV_1 80% of predicted and either β-agonist reversibility of 12% or positive exercise challenge test. Daytime symptoms and reliever medication use on at least 2 days of the first week of 2-week run-in period.	• AQLQ • Rescue use (%days) • FEV_1 (% of predicted) • Morning PEF (L/min)	
Busse 2001[26]	ICS low dose (n=271)	Stratum: ≥16 years	• Rescue use (puffs/day)	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
	LTRA (n=262)	Age - Mean (range): 34.9 (15–83) At randomisation, patients were required to demonstrate that additional asthma therapy was warranted using the following criteria: an unmedicated FEV_1 value of 50% to 80% of predicted normal that was within 15% of the FEV_1 value obtained at screening, use of salbutamol on 6 or more of the 7 days before randomisation, and an asthma symptom score of 2 or more (on a scale of 0–5) on 4 or more of the 7 days before randomisation.	• FEV_1 (L) • Morning PEF (L/min) Reported at 24 weeks	
Calhoun 2001[27]	ICS + LABA (n=211) LTRA (n=212)	Stratum: ≥16 years Age - Mean (range): FSC: 37 (16–72) Montelukast: 36 (15–66). Patients considered symptomatic and thus eligible if they required SABA on five or more days during the 7 days preceding randomisation, or if they had a symptom score of ≥2 on three or more days.	• Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 12 weeks	
Chavasse 2001[31]	ICS low dose (n=26) Placebo (n=26)	Stratum: <1 year Age - mean (SD): ICS: 9.8 months (2.6) Placebo: 8.9 months (2.9). Documented history of persistent wheeze (occurring on at least 3 days per week for 6 weeks), persistent cough (occurring on at least 3 nights per week for 6 weeks) or recurrent wheeze (occurring on at least 3 occasions for the previous 3 months).	• Rescue use (puffs/day) Reported at 12 weeks	Diagnosis by physician unclear: aged 3–12 months; documented history of persistent wheeze (occurring on at least 3 days per week for 6 weeks), persistent cough (occurring on at least 3 nights per week for 6 weeks) or recurrent wheeze (occurring on at least 3 occasions for the previous 3 months); personal history of eczema or family history of asthma

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
				or seasonal rhinitis in first degree relative.
Chuchalin 2008[33]	Placebo (n=315) ICS low dose (n=970) ICS+LABA (n=973)	Stratum: ≥16 years Age - Mean (range): Placebo: 35 (12–76); FP: 33.8 (12–76); SFC: 33.8 (12–75) Mild to moderate asthma with PEF ≥80% predicted, positive BDR (increase in PEF of ≥15% following 400 ug salbutamol), daytime asthma symptom score ≥1 on 3–6 of the previous 7 days.	• Morning PEF (L/min) • FEV_1 (L) Reported at 1 year	Insufficient data reported from placebo arm.
Connet 1993[35]	Placebo (n=20) ICS high dose (n=20)	Stratum: 1 to <5 years Age - Mean (SD): 3.8 (1.3). Cough, wheeze, sleep disturbance, or limitation of activity recorded on at least 3 days per week for both run-in weeks.	• Rescue use (day-time) • Rescue use (night-time) Reported at 6 months	
Fish 1997[48]	LTRA (n=514) Placebo (n=218)	Stratum: ≥16 years Age - Range: 12–76. Considered symptomatic and thus eligible if they had a cumulative symptom score of at least 8 (scale 0–3) over 7 consecutive days during run in period.	• Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 13 weeks	
Garcia 2005[56]	LTRA (n=495) ICS low dose (n=499)	Stratum: 5 to <16 Age – Median (range): 9 (5–15) Increase in FEV_1 or PEF of >12% after SABA, decrease in >15% after	• QOL (AQLQ) • FEV_1 (%) • Rescue use (% of days)	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
		exercise challenge.	Reported at 1 year	
Hoshino 1998[71]	ICS moderate dose (n=15) Placebo (n=15)	Stratum: ≥16 years Age - Mean (range): ICS: 29 (16-44) Placebo: 27 (17-48). At baseline the mean reliever medication use per day was 5.05 (1.92). A threshold of 0.43 SABA puffs per day was agreed for the review as 'uncontrolled' and the probability of using >0.43 was calculated as 99%.	• Rescue use (puffs/day) • FEV_1 (% predicted) • Morning PEF (L/min) Reported at 6 months	Population determined as uncontrolled using baseline data.
Jones 1994[77]	ICS low dose (n=255) Placebo (n=85)	Stratum: ≥16 years Age - Mean (SD): Morning: 36 (16) Evening: 36 (17) BD: 36 (17) Placebo: 40 (18). Patients were considered symptomatic and thus eligible if they recorded reliever medication use and asthma symptoms on at least 2 of the last 5 run-in days.	• Rescue use (doses/day) • Rescue use (doses/night) • Morning PEF (L/min) • Respiratory infection Reported at 12 weeks	Three ICS low dose arms analysed separately in the study but combined for analysis in review (400 µg AM or PM, or 200 µg twice daily administration).
Kemp 2000[81]	ICS low dose (n=79) ICS moderate dose (n=153) Placebo (n=74)	Stratum: ≥16 years Age - Mean (SD): ICS 200 µg AM: 32 (15) ICS 400 µg AM: 29 (11) ICS 200 µg twice daily: 32 (14) Placebo: 32 (15). Required to have used salbutamol for the control of asthma at least 3 times per week during the run-in period. Reversibility of airway disease with FEV_1 increase of 12% or more of pre-bronchodilator value.	• Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 12 weeks	
Kerwin	ICS low dose (n=212)	Stratum: ≥16 years	• Rescue use	Two ICS+LABA arms

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
2008[85]	ICS+LABA (n=420) Placebo (n=212)	Age - range: 12–85 During the 7 days prior to randomisation: symptom score (combined daytime and night time) of ≥2 or used SABA on ≥4 days, an evening PEF between 50% and 90% of predicted, and demonstrated an FEV_1 within ±15% of the pre-bronchodilation screening FEV_1.	(puffs/day) • FEV_1 (L) • Morning PEF (L/min) • Upper respiratory tract infection Reported at 12 weeks	analysed separately in the study but combined for analysis in review (evening or twice daily administration).
Kooi 2008[87]	ICS low dose (n=25) LTRA (n=18) Placebo (n=20)	Stratum: 1 to <5 years Age - Mean (SD): 3.8 (1.3). Required to have asthma symptoms on at least 4 days during the two-week run-in period.	• Rescue use (% rescue free days) • Upper respiratory tract infection Reported at 3 months	Diagnosis was children aged 2–5 with asthma-like symptoms (wheeze, cough and/or shortness of breath) of sufficient severity to justify the use of prophylactic asthma treatment.
Maspero 2008[101]	ICS + LABA (n=281) LTRA (n=267)	Stratum: 5 to <16 years Age - Mean (SD): SFC: 9.3 (2.2) MON: 9.3 (2.1) Unmedicated FEV_1 of 55–80% of predicted, use of SABA or symptoms on at least 4 of the 7 days during 2-week run-in. Diagnosis of asthma with positive BDR (increase in FEV_1 of ≥12%).	• QOL (Paediatric AQLQ) • Rescue use (rescue-free 24-hour periods) Reported at 12 weeks	
Meltzer 2002[103]	ICS low dose (n=258) LTRA (n=264)	Stratum: ≥16 years Age - Mean (range): FP: 36.2 (15–73) Montelukast: 35.4 (15–77). During run-in period: unmedicated FEV_1 of 50–80% and within 15% of FEV_1 obtained at initial screen, use of salbutamol for at least 6 of the 7 days	• Severe asthma exacerbations • QOL (AQLQ) • Rescue use (puffs/day) • FEV_1 (L)	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
		before randomisation, asthma symptom score of 2 or more (0–5 scale) on at least 4 of 7 days before randomisation.	• Morning PEF (L/min) Reported at 24 weeks	
Nathan 1999[109]	ICS low dose (n=129) Placebo (n=129)	Stratum: ≥16 years Age - Mean (SD): Age (SE) - BDP: 29.9 (1.1), Placebo: 29.1 (1.1). Baseline data states that during the week before randomisation, the range of symptom free days was 17% to 20% (therefore all patients would have had symptoms three times a week or more at inclusion).	• Severe asthma exacerbations • Rescue use (% free days) • Rescue use (% free nights) • FEV_1 (L) Reported at 6 months	Population determined as uncontrolled using baseline data
Nayak 2002[114]	ICS low dose (n=120) ICS moderate dose (n=117)	Stratum: 5 to <16 years Age - Mean (SD): 9.2 (2).	• Rescue use (puffs/day) • FEV_1 (% predicted) • Upper respiratory tract infection • Adrenal insufficiency Reported at 12 weeks	
	Placebo (n=116)	Considered symptomatic if: FEV_1 of 50–80% of predicted, reversibility of airway obstruction shown as FEV_1 increase of at least 12% following 400 µg pirbuterol, and use of pirbuterol on 50% of the days during the 2-week run-in period.		
Nelson 2003[116]	ICS low dose (n=97) ICS+LABA (n=95)	Stratum: ≥16 years Age - Mean (range): 32.4 (12–77). Patients must have demonstrated a total 24-hour symptom score of 7 or	• Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min)	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
		higher during the 7 days before randomisation. The asthma symptom score was a 6 point scale ranging from 0 (no symptoms) to 5 (symptoms so severe that the patient could not go to work or perform normal daily activities).	Reported at 12 weeks	
OPTIMA trial: O'byrne 2001[117]	ICS low dose (n=228) ICS+LABA (n=231) Placebo (n=239)	Stratum: ≥16 years Age - Range of means: 30.6–31.2. Randomized patients demonstrated a need for two or more inhalations per week of rescue medication during the last 2 weeks of run-in (4 week placebo run-in). Demonstrated symptoms during run-in consistent with being "uncontrolled".	• Severe asthma exacerbations • Rescue use (puffs/day) • FEV_1 (% predicted) Reported at 1 year	
Pearlman 2002[132]	ICS+LABA (n=216) Placebo (n=216)	Stratum: ≥16 years Age - Mean (range): 35.5 (15–83) Use of salbutamol for at least 5 of the 7 days before randomisation during run-in, asthma symptom score of 2 or more (0–5 scale) on 3 or more of 7 days before randomisation.	• QOL (AQLQ) • Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 12 weeks	
Pedersen 1996 [133]	ICS low dose (n=29) ICS high dose (n=29) Theophylline (n=27)	Stratum: ≥16 years Age - Mean (SD): low-dose ICS: 46.8 (12.5) high-dose ICS: 46.1 (11.2) theophylline: 45.0 (13.7). Believed to require regular maintenance treatment due to attacks of dyspnoea, cough, and wheezing, in addition to signs of air flow variability.	• FEV_1 (% predicted) Reported at 9 months	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
Price 1997[140]	ICS low dose (n=52) Sodium Cromoglicate (n=70)	Stratum: 5 to <16 years Age - Mean (SD): FPr: 6.0 (1.4) SCG: 6.4 (1.6). On at least 6 days of the 2-week baseline period, eligible patients were to have experienced either PEF measurements less than 80% of their maximum, or daytime or night-time symptom scores or 1 or more (0–3 scale) and a requirement for extra SABA during the same 24-hour period.	• Severe asthma exacerbations • Morning PEF (L/min) • Growth velocity Reported at 1 year	No objective diagnosis. History of asthma with recurrent episode of wheeze or cough, satisfactory inhaler and peak flow technique, PEF <80% during run-in, daytime or night-time symptom scores of >1 (scale 0–3).
Price 2011[137]	ICS moderate dose (n=158) LTRA (n=148)	Stratum: ≥16 years Age - Mean (SD): LTRA: 47.6 (16.5) ICS: 44.1 (16.4). Symptoms deemed by physician to require asthma controller therapy; impaired asthma-related quality of life (score of <6 on miniAQLQ); or impaired asthma control (>1 on Asthma Control Questionnaire).	• Severe asthma exacerbations • QOL (miniAQLQ; EQ-5D) • Asthma control (ACQ) • Hospitalisations • Rescue use (puffs/day) • Rescue use (puffs/night) • Morning PEF (L/min) • Respiratory tract infection Reported at 2 years	Subset of data taken from Health Technology Assessment (Price 2011[136])
Reid 2008[145]	LTRA (n=14) Placebo (n=7)	Stratum: ≥16 years Age - Median (range): 41 (21–69).	• Rescue use (puffs/day) • FEV_1 (L) • Morning PEF	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
		Subjects needed a minimum cumulative symptom score (asthma severity score) of ≥10 (maximum 21), over the last seven days of the screening period using a daily three-point scale; 0=no symptoms, 1=mild symptoms not interfering with activities, 2=moderate symptoms interfering with some activities, 3=severe symptoms interfering with most activities.	(L/min) Reported at 12 weeks	
Renzi 2010[146]	ICS low dose (n=270) ICS+LABA (n=262)	Stratum: ≥16 years Age - Median (range): ICS/LABA: 34.8 (12-76); ICS: 34.3 (12-77). Patients included if during the last 7 days of the run-in period: asthma symptom score ≥2 on 3 days, disruptions of normal sleep patterns on ≥2 occasions, or use of rescue medication on ≥4 days.	• Mortality • Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 24 weeks	Diagnosis of asthma: Documented history of asthma treated with SABA only and FEV_1 ≥80% predicted. No objective diagnosis.
Rojas 2007[152]	ICS moderate dose (n=182) ICS+LABA (n=180)	Stratum: ≥16 years Age - Mean (range): ICS/LABA: 40 (15–78) ICS: 41 (12–74). Required to have a daytime symptom score of ≥2 on at least four days of the last 7 days run-in.	• Rescue use (number of people with 100% rescue free days) • Rescue use (number of people with 100% rescue free nights) • Morning PEF (L/min) Reported at 12 weeks	
Ruff 2003[154]	ICS low dose (n=108) ICS moderate dose (n=104)	Stratum: 5 to <16 years Age - Mean (SD): 9.6 (1.8).	• FEV_1 (% predicted) • Morning PEF (L/min)	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
	Placebo (n=107)	Requiring beta-agonist at least once a day on at least 10 of the last 14 days of the run-in period.	• Upper respiratory tract infection Reported at 12 weeks	
Schokker 2008[158]	ICS low dose (n=48) Placebo (n=48)	Stratum <5 years Age - Mean (SD): 2.65 (1.21) Considered symptomatic and thus eligible if GPs had considered prescribing ICS for asthma. Required to record symptoms on at least 7 of the 14 days during the run-in period.	• Rescue use (puffs/day) • Rescue use (puffs/night) Reported at 6 months	
Sheffer 1996[161]	ICS low dose (n=234) Placebo (n=73)	Stratum: ≥16 years Age - Mean (range): 29.5 (12-72) One or more days with more than 8 puffs of salbutamol during 7 run-in days, total weekly score of 7 or more on any asthma symptom.	• Rescue use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 12 weeks	Three ICS low dose arms analysed separately in the study but combined for analysis in review (25, 50 or 100 µg twice a day).
Stelmach 2005[165]	ICS moderate dose (n=16) ICS high dose (n=18) LTRA (n=17)	Stratum: 5 to <16 years Age - Mean (SD): 12.1 (1.1) At baseline the mean symptom score out of 9 was 7.1 (SD 1.38). A threshold of 6 was agreed for the review as 'uncontrolled' and the probability of scoring >6 was calculated as 78.73%. The baseline is the mean score over each day over the 4-week screening period. Daytime asthma symptom score and nocturnal awakenings were scored as follows: 0=no symptoms during day/night, 1=symptoms but they do not affect	• FEV_1 (% predicted) Reported at 6 months	Population determined as uncontrolled using baseline data.

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
		activities during the day/night sleep, 2=symptoms affect at least one daily activity/disturb night sleep, 3=symptoms affect two or more daily activities/disturb sleep all or most of the night. Use of beta agonists was scored 0=none, 1=once a day, 2=twice or three times a day, 3=more than three times a day. Minimum score for each day was 0, maximum score was 9.		
Teper 2004[169]	ICS low dose (n=11) ICS moderate dose (n=11) placebo (n=12)	Stratum <1 year Age - Mean (SD): Placebo: 11.9 months (6.4) FP100: 13.1 (5.2) FP250: 14.2 (5.7)	• Rescue use (number of days) Reported at 6 months	Patients were eligible if aged less than 2 years, asthmatic symptoms (3 or more episodes of wheeze) and a family history of asthma. Unclear if uncontrolled at baseline.
Teper 2005[170]	ICS moderate dose (n=16) placebo (n=15)	Stratum <1 year Age - Mean (SD): 13.4 months (4)	• Rescue use (% of days) Reported at 6 months	Patients were eligible if aged less than 2 years, asthmatic symptoms (3 or more episodes of wheeze) and a family history of asthma. Unclear if uncontrolled at baseline.
Zeiger 2005[197]	ICS low dose (n=191) LTRA (n=189)	Stratum: ≥16 years Age - Mean (SD): 35.2 (14.4) Symptoms or use of salbutamol on an average of 2–6 days a week during the two-week run-in period.	• QOL (AQLQ) • Rescue use (puffs/day) • FEV_1 (% predicted) • Morning PEF (L/min) Reported at 12 weeks	

Study	Intervention and comparison	Population (age and how the population was defined as 'uncontrolled')	Outcomes	Comments
Zielen 2006[199]	ICS moderate dose (n=37) Disodium Cromoglycate (n=41)	Stratum 1 to <5 years Age - Mean (SD): 18 months (5.5).	• Rescue use (puffs/day) Reported at 3 months	Infants with suspected asthma included if they had a history of 3 physician diagnosed exacerbations of dyspnoea associated with wheezing during the past 12 months, with at least one of these exacerbations in the 3 months immediately prior to enrolment. Unclear if uncontrolled at baseline.

Table 12: Clinical evidence summary: ICS (low dose) compared to Placebo in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with Placebo	Risk difference with ICS (low dose) (95% CI)
Exacerbations	467 (1 study) 1 years	LOW[a,c] due to risk of bias	RR 0.51 (0.33 to 0.77)	234 per 1000	115 fewer per 1000 (from 54 fewer to 157 fewer)
Morning PEF	1696 (6 studies) 12 weeks	VERY LOW[a,c,d] due to risk of bias, inconsistency, imprecision	-	Results given as mean difference of control versus intervention	The mean morning PEF in the intervention groups was 17.19 L/min higher (11.15 to 23.24 higher)
FEV_1 (% predicted)	467 (1 study) 1 years	LOW[a] due to risk of bias	-	Results given as mean difference of control versus intervention	The mean FEV_1 (% predicted) in the intervention groups was 2.25% higher (0.7 to 3.8 higher)
FEV_1 (L)	1067 (4 studies) 12 weeks	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	Results given as mean difference of control versus intervention	The mean FEV_1 (L) in the intervention groups was 0.16L higher

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (low dose) (95% CI)
					(0.11 to 0.22 higher)
Reliever medication use (puffs/day)	1534 (5 studies) 4.5 months	VERY LOW[a,c, d] due to risk of bias, inconsistency, imprecision	-	Results given as mean difference of control versus intervention	The mean reliever medication use (puffs/day) in the intervention groups was 0.76 lower (1.23 to 0.29 lower)
Reliever medication use - daytime	340 (1 study) 12 weeks	LOW[a] due to risk of bias	-	The mean change in reliever medication use - daytime in the control groups was -0.59 puffs	The mean reliever medication use - daytime in the intervention groups was 0.55 lower (1.05 to 0.05 lower)
Reliever medication use - night-time	340 (1 study) 12 weeks	LOW[a] due to risk of bias	-	The mean change in reliever medication use - night-time in the control groups was 0.13 puffs	The mean reliever medication use - night-time in the intervention groups was 0.41 lower (0.81 to 0.01 lower)
Infection	685 (2 studies) 12 weeks	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.59 (0.37 to 0.97)	125 per 1000	51 fewer per 1000 (from 4 fewer to 79 fewer)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because I^2 >50%, unexplained by subgroup analysis.
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Downgraded by 1 or 2 increments because the confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis

Table 13: Clinical evidence summary: ICS (moderate dose) compared to Placebo in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with ICS (moderate dose) (95% CI)
Exacerbations	258	VERY LOW[a,b]	RR 0.76	Moderate	

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with ICS (moderate dose) (95% CI)
	(1 study) 6 months	due to risk of bias, imprecision	(0.39 to 1.51)	132 per 1000	32 fewer per 1000 (from 81 fewer to 67 more)
Morning PEF	220 (2 studies) 4 months	LOW[a,b] due to risk of bias	-	Results given as mean difference of control versus intervention	The mean morning PEF in the intervention groups was 37.45 L/min higher (19.34 to 55.55 higher)
FEV_1 (% predicted)	33 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	-	The mean FEV_1 (% predicted) in the control groups was 68.5 % of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 5.2% higher (1.74 lower to 12.14 higher)
FEV_1 (L)	403 (2 studies) 4 months	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	Results given as mean difference of control versus intervention	The mean FEV_1 (L) in the intervention groups was 0.2L higher (0.08 to 0.32 higher)
Reliever medication use (puffs/day)	220 (2 studies) 4 months	LOW[a,c] due to risk of bias, inconsistency	-	Results given as mean difference of control versus intervention	The mean reliever medication use (puffs/day) in the intervention groups was 2.16 lower (4.49 to 0.17 lower)
Reliever medication use - rescue-free days (%)	258 (1 study) 6 months	MODERATE[a] due to risk of bias	-	Results given as mean difference of control versus intervention	The mean reliever medication use - rescue-free days (%) in the intervention groups was 12 higher (4.94 to 19.06 higher)
Reliever medication use - rescue-free nights (%)	258 (1 study) 6 months	MODERATE[a] due to risk of bias	-	Results given as mean difference of control versus intervention	The mean reliever medication use - rescue-free nights (%) in the intervention groups was 14 higher (4.54 lower to 32.54 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with ICS (moderate dose) (95% CI)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 or 2 increments because $I^2 > 50\%$, unexplained by subgroup analysis

Table 14: Clinical evidence summary: ICS + LABA compared to Placebo in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS + LABA (95% CI)
Exacerbations	470 (1 study) 1 years	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.63 (0.43 to 0.92)	Moderate 234 per 1000	87 fewer per 1000 (from 19 fewer to 133 fewer)
Morning PEF	1145 (2 studies) 12 weeks	LOW[a,c] due to risk of bias, imprecision	-	Results given as mean difference of control versus intervention	The mean morning PEF in the intervention groups was 25.53 higher (18.08 to 32.97 higher)
FEV_1 (% predicted)	470 (1 study) 1 years	LOW[a] due to risk of bias	-	Results given as mean difference of control versus intervention	The mean FEV_1 (% predicted) in the intervention groups was 4.08 higher (2.04 to 6.12 higher)
FEV_1 (L)	1145 (2 study) 12 weeks	LOW[a,c] due to risk of bias, imprecision	-	The mean change in FEV_1 (L) in the control groups was 0.18 Litres	The mean FEV_1 (L) in the intervention groups was 0.27 higher (0.21 to 0.33 higher)
Reliever medication use (puffs/day)	1102 (2 studies) 7.5 months	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.4 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.83 lower

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS + LABA (95% CI)
					(2.02 lower to 0.35 higher)
Reliever medication use (rescue free days [%])	289 (1 study) 12 weeks	MODERATE[a] due to risk of bias	OR 5.26 (3.12 to 8.85)	Event rate not reported	-
Infection	516 (1 study) 12 weeks	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.33 (0.61 to 2.9)	49 per 1000	16 more per 1000 (from 19 fewer to 93 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because I^2 >50%, unexplained by subgroup analysis
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: Clinical evidence summary: LTRA compared to Placebo in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with LTRA (95% CI)
Morning PEF	645 (2 studies) 12.5 weeks	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	The mean morning PEF in the control groups was 404.7 L/min	The mean morning PEF in the intervention groups was 4.88 higher (12.36 lower to 22.13 higher)
FEV_1 (L)	645 (2 studies) 12.5 weeks	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	The mean FEV_1 (L) in the control groups was 2.95 Litres	The mean FEV_1 (L) in the intervention groups was 0.16 higher (0.03 lower to 0.34 higher)
Reliever medication use (puffs/day)	645 (2 studies) 12.5 weeks	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	The mean reliever medication use (puffs/day) in the control groups was 3.91 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0 higher

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with LTRA (95% CI)
					(1.54 lower to 1.54 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because I^2 >50%, unexplained by subgroup analysis.
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence summary: ICS (moderate dose) compared to ICS (low dose) in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS (moderate dose) (95% CI)
Morning PEF	207 (1 study) 12 weeks	LOW[a, b] due to risk of bias, imprecision	-	Results given as mean difference of control versus intervention.	The mean morning PEF in the intervention groups was 32.2 higher (14.33 lower to 50.07 higher)
FEV_1 (L)	207 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	Results given as mean difference of control versus intervention.	The mean FEV_1 (L) in the intervention groups was 0.14 higher (0.01 lower to 0.29 higher)
Reliever medication use (puffs/day)	184 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean change in reliever medication use (puffs/day) in the control groups was -2.1 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.44 higher (1.78 lower to 2.66 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence summary: ICS (high dose) compared to ICS (low dose) in people over 16

Outcomes	Number of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with ICS (low dose)	Risk difference with ICS (high dose) (95% CI)
FEV_1 (% predicted)	58 (1 study) 9 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean FEV_1 (% predicted) in the control groups was 74%	The mean FEV_1 (% predicted) in the intervention groups was 8 higher (18.77 lower to 34.77 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 18: Clinical evidence summary: ICS + LABA compared to ICS (low dose) in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects: Risk with ICS (low dose)	Anticipated absolute effects: Risk difference with ICS + LABA (95% CI)
Exacerbations	459 (1 study) 1 years	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.24 (0.78 to 1.99)	118 per 1000	8 more per 1000 (from 26 fewer to 117 more)
Mortality	433 (1 study) 24 weeks	LOW[a,b] due to risk of bias, indirectness	Unable to calculate[d]	See comment	See comment
Morning PEF	3571 (5 studies) 22 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	Results given as mean difference of control versus intervention.	The mean morning PEF in the intervention groups was 4.58 higher (1.73 to 7.44 higher)
FEV_1 (% predicted)	459 (1 study) 1 years	LOW[a] due to risk of bias	-	Results given as mean difference of control versus intervention.	The mean FEV_1 (% predicted) in the intervention groups was 1.83 higher (0.26 to 3.4 higher)
FEV_1 (L)	3571	LOW[a,b]	-	Results given as mean difference of	The mean FEV_1 (L) in the intervention

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS + LABA (95% CI)
	(5 studies) 6 months	due to risk of bias, indirectness		control versus intervention.	groups was 0.07 higher (0.04 to 0.1 higher)
Reliever medication use (puffs/day)	1806 (4 studies) 6 months	LOW[a,b] due to risk of bias, indirectness	-	The mean change in reliever medication use (puffs/day) in the control groups was -1.5 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.22 lower (0.32 to 0.11 lower)
Reliever medication use (rescue free days [%])	289 (1 study) 12 weeks	MODERATE[a] due to risk of bias	OR 1.79 (1.12 to 2.84)	Event rate not provided	-
Infection	535 (1 study) 24 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.98 (0.82 to 4.77)	33 per 1000	32 more per 1000 (from 6 fewer to 124 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d No events in either arm

Table 19: Clinical evidence summary: LTRA compared to ICS (low dose) in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with LTRA (95% CI)
Exacerbations	395 (1 study) 24 weeks	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 1.11 (0.62 to 2)	96 per 1000	11 more per 1000 (from 36 fewer to 96 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with LTRA (95% CI)
AQLQ Scale from: 1–7	775 (2 studies) 18 weeks	LOW[a,c] due to risk of bias, indirectness	-	Results given as mean difference of control versus intervention.	The mean AQLQ in the intervention groups was 0.17 lower (0.33 to 0.01 lower)
Morning PEF	1726 (4 studies) 18 weeks	VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision	-	Results given as mean difference of control versus intervention.	The mean morning PEF in the intervention groups was 19.41 lower (30.67 to 8.15 lower)
FEV_1 (% predicted)	941 (2 studies) 12 weeks	MODERATE[a] due to risk of bias	-	Results given as mean difference of control versus intervention.	The mean FEV_1 (% predicted) in the intervention groups was 3.09 lower (4.18 to 2 lower)
FEV_1 (L)	776 (2 studies) 24 weeks	LOW[a,c] due to risk of bias, indirectness	-	The mean change in FEV_1 (L) in the control groups was 0.5 Litres	The mean FEV_1 (L) in the intervention groups was 0.17 lower (0.23 to 0.1 lower)
Reliever medication use (puffs/day)	1156 (3 studies) 20 weeks	VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision	-	The mean change in reliever medication use (puffs/day) in the control groups was -3.16 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.58 higher (0.05 lower to 1.2 higher)
Reliever medication use (% of days)	625 (1 study) 12 weeks	LOW[a,d] due to risk of bias, imprecision	-	Results given as mean difference of control versus intervention.	The mean reliever medication use (% of days) in the intervention group was 3.7 higher (1.32 lower to 8.72 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because I^2 >50%, unexplained by subgroup analysis.
c Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with LTRA (95% CI)

d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence summary: Theophylline compared to ICS (low dose) in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with Theophylline (95% CI)
FEV_1 (% predicted)	115 (1 study) 9 months	LOW[a,b] due to risk of bias, indirectness	-	The mean FEV_1 (% predicted) in the control groups was 75 % of predicted value	The mean FEV_1 (% predicted) in the intervention groups was the same (10.3 lower to 10.3 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population

Table 21: Clinical evidence summary: ICS + LABA compared to ICS (moderate dose) in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with ICS + LABA (95% CI)
Morning PEF	362 (1 study) 12 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	Results given as mean difference of control versus intervention.	The mean morning PEF in the intervention groups was 21 higher (11 to 31 higher)
Reliever medication use - participants with 100% rescue-free days	362 (1 study) 12 weeks	LOW[a,b] due to risk of bias, indirectness	RR 1.56 (0.99 to 2.44)	143 per 1000	80 more per 1000 (from 1 fewer to 206 more)
Reliever medication use - participants with 100% rescue-free nights	362 (1 study)	LOW[a,b] due to risk of bias,	RR 1.76 (1.19 to	170 per 1000	129 more per 1000 (from 32 more to 272 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with ICS + LABA (95% CI)
	12 weeks	indirectness	2.6)		

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 22: Clinical evidence summary: LTRA compared to ICS (moderate dose) in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with LTRA (95% CI)
Exacerbations	306 (1 study) 2 years	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	RR 1.42 (0.91 to 2.22)	171 per 1000	72 more per 1000 (from 15 fewer to 209 more)
AQLQ Scale from: 1–7	218 (1 study) 2 years	LOW[a,c] due to risk of bias	-	The mean AQLQ in the control groups was 5.65	The mean AQLQ in the intervention groups was 0.12 lower (0.31 lower to 0.23 higher)
EQ-5D Scale from: 0–1	275 (1 study) 2 years	VERY LOW[a, c] due to risk of bias, indirectness	-	The mean EQ-5D in the control groups was 0.881	The mean EQ-5D in the intervention groups was 0.06 lower (0.11 lower to 0.00 higher)
ACQ Scale from: 0–6	217 (1 study) 2 years	VERY LOW[a,c] due to risk of bias, indirectness	-	The mean ACQ in the control groups was 1.08	The mean ACQ in the intervention groups was 0.07 higher (0.18 lower to 0.32 higher)
Hospitalisations	302	VERY LOW[a,b,c]	RR 2.00	13 per 1000	13 more per 1000

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with LTRA (95% CI)
	(1 study) 2 years	due to risk of bias, indirectness, imprecision	(0.37 to 10.76)		(from 8 fewer to 129 more)
Morning PEF	306 (1 study) 2 years	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	-	The mean morning PEF in the control groups was 419.2 L/min	The mean morning PEF in the intervention groups was 6.8 lower (33.91 lower to 20.31 higher)
Reliever medication use - daytime	306 (1 study) 2 years	VERY LOW[a,c] due to risk of bias, indirectness	-	The mean reliever medication use - daytime in the control groups was 1.24 puffs	The mean reliever medication use - daytime in the intervention groups was 0.43 higher (0.08 to 0.78 higher)
Reliever medication use - night-time	296 (1 study)	VERY LOW[a,c] due to risk of bias, indirectness	-	The mean reliever medication use - night-time in the control groups was 0.48 puffs	The mean reliever medication use - night-time in the intervention groups was 0.04 higher (0.16 lower to 0.24 higher)
Infection	296 (1 study) 2 years	VERY LOW[a,b, c] due to risk of bias, imprecision, indirectness	RR 0.89 (0.71 to 1.11)	534 per 1000	59 fewer per 1000 (from 155 fewer to 59 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

Table 23: Clinical evidence summary: Theophylline compared to ICS (high dose) in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (high dose)	Risk difference with Theophylline (95% CI)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (high dose)	Risk difference with Theophylline (95% CI)
FEV_1 (% predicted)	56 (1 study) 9 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean FEV_1 (% predicted) in the control groups was 82% of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 7 lower (36.86 lower to 22.86 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 24: Clinical evidence summary: LTRA compared to ICS + LABA in people over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA	Risk difference with LTRA (95% CI)
AQLQ	354 (1 study) 12 weeks	MODERATE[c] due to imprecision	-	The mean change in AQLQ in the control groups was 1.7	The mean AQLQ in the intervention groups was 0.5 lower (0.74 to 0.26 lower)
Morning PEF	777 (2 studies) 12 weeks	LOW[a,b] due to risk of bias, indirectness	-	The mean change in morning PEF in the control groups was 86.1 L/min	The mean morning PEF in the intervention groups was 47.85 lower (59.35 to 36.34 lower)
FEV_1 (L)	780 (2 studies) 12 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean change in FEV_1 (L) in the control groups was 0.57 Litres	The mean FEV_1 (L) in the intervention groups was 0.28 lower (0.34 to 0.22 lower)
Reliever medication use (puffs/day)	780 (2 studies)	LOW[a,b] due to risk of bias,	-	The mean change in reliever medication use (puffs/day) in the	The mean reliever medication use (puffs/day) in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA	Risk difference with LTRA (95% CI)
	12 weeks	indirectness		control groups was -3.4 puffs/day	1.4 higher (0.99 to 1.81 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 25: Clinical evidence summary: ICS (low dose) compared to Placebo in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (low dose) (95% CI)
Morning PEF	445 (2 studies) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean change in morning PEF in the control groups was 5.5 L/min	The mean morning PEF in the intervention groups was 18.97 higher (9.96 to 27.97 higher)
FEV_1 (% predicted)	411 (2 studies) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean change in FEV_1 (% predicted) in the control groups was 3.2% of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 5.26 higher (2.94 to 7.58 higher)
Reliever medication use (puffs/day)	202 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.22 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.37 lower (0.73 to 0.01 lower)
Infection	417 (2 studies) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.99 (0.71 to 1.37)	256 per 1000	3 fewer per 1000 (from 74 fewer to 95 more)
Adrenal insufficiency	202	LOW[a,b]	OR 0.12	31 per 1000	27 fewer per 1000

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (low dose) (95% CI)
	(1 study) 12 weeks	due to risk of bias, imprecision	(0.01 to 1.19)		(from 31 fewer to 6 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Clinical evidence summary: ICS (moderate dose) compared to Placebo in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (moderate) (95% CI)
Morning PEF	204 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean change in morning PEF in the control groups was 5.5 L/min	The mean morning PEF in the intervention groups was 10.6 higher (0.34 lower to 21.54 higher)
FEV_1 (% predicted)	409 (2 studies) 12 weeks	LOW[a,c] due to risk of bias, inconsistency	-	The mean change in FEV_1 (% predicted) in the control groups was 3.2% of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 3.39 higher (2.09 lower to 8.88 higher)
Reliever medication use (puffs/day)	205 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.22 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.62 lower (0.98 to 0.26 lower)
Infection	416 (2 studies) 12 weeks	LOW[a,b] due to risk of bias, imprecision	RR 0.85 (0.6 to 1.2)	256 per 1000	38 fewer per 1000 (from 102 fewer to 51 more)
Adrenal insufficiency	205 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision	OR 0.32 (0.04 to 2.34)	31 per 1000	21 fewer per 1000 (from 30 fewer to 39 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (moderate) (95% CI)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c Downgraded by 1 or 2 increments because I^2 > 50%, unexplained by subgroup analysis.					

Table 27: Clinical evidence summary: ICS (moderate dose) compared to ICS (low dose) in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS (moderate) (95% CI)
Morning PEF	200 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-	The mean change in morning PEF in the control groups was 23.3 L/min	The mean morning PEF in the intervention groups was 7.2 lower (18.13 lower to 3.73 higher)
FEV_1 (% predicted)	418 (2 studies) 12 weeks	LOW[a,b] due to risk of bias, inconsistency	-	The mean change in FEV_1 (% predicted) in the control groups was 8.5% of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 1.85 lower (7.24 lower to 3.54 higher)
Reliever medication use (puffs/day)	213 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.59 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.25 lower (0.6 lower to 0.1 higher)
Infection	425 (2 studies) 12 weeks	LOW[a,c] due to risk of bias, imprecision	RR 0.85 (0.6 to 1.2)	255 per 1000	38 fewer per 1000 (from 102 fewer to 51 more)
Adrenal insufficiency	205 (1 study) 12 weeks	VERY LOW[a,c] due to risk of bias, imprecision	OR 6.67 (0.13 to 338.23)	0 per 1000	-
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high					

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS (moderate) (95% CI)
risk of bias b Downgraded by 1 or 2 increments because I^2 >50%, unexplained by subgroup analysis. c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 28: Clinical evidence summary: LTRA compared to ICS (low dose) in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with LTRA (95% CI)
Quality of life (AQLQ)	541 (1 study) 1 years	HIGH	-	The mean change in quality of life (AQLQ) in the control groups was 1.05	The mean quality of life (AQLQ) in the intervention groups was 0.13 lower (0.33 lower to 0.07 higher)
FEV_1 (%)	881 (1 study) 1 years	HIGH	-	The mean change in FEV_1 (%) in the control groups was 2.7%	The mean FEV_1 (%) in the intervention groups was 2.1 lower (3.65 to 0.55 lower)
Rescue use (% of days)	881 (1 study) 1 years	HIGH	-	The mean change in rescue use (% of days) in the control groups was -25.4%	The mean rescue use (% of days) in the intervention groups was 2.7 higher (0.58 to 4.82 higher)

Table 29: Clinical evidence summa ry: Cromolyn compared to ICS (low dose) in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with Cromolyn (95% CI)
Exacerbations	122 (1 study) 12 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.74 (0.23 to 2.43)	96 per 1000	25 fewer per 1000 (from 74 fewer to 137 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with Cromolyn (95% CI)
Morning PEF (% predicted)	60 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, indirectness	-	Results given as mean difference of control versus intervention.	The mean morning PEF (% predicted) in the intervention groups was 7.3 lower (11.43 to 3.17 lower)
Growth velocity	60 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, indirectness	-	The mean growth velocity in the control groups was 6 cm/year	The mean growth velocity in the intervention groups was 0.5 higher (0.3 to 0.7 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 30: Clinical evidence summary: ICS (high dose) compared to ICS (moderate dose) in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with ICS (high dose) (95% CI)
FEV_1 (% predicted)	33 (1 study) 6 months	MODERATE[a] due to risk of bias	-	The mean FEV_1 (% predicted) in the control groups was 93.4 % of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 0.4 lower (2.56 lower to 1.76 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 31: Clinical evidence summary: LTRA compared to ICS (moderate dose) in people aged 5–16 years

Outcomes	Number of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with ICS (moderate dose)	Risk difference with LTRA (95% CI)
FEV_1 (% predicted)	31 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	-	The mean FEV_1 (% predicted) in the control groups was 93.4 % of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 2.5 lower (4.59 to 0.41 lower)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 32: Clinical evidence summary: LTRA compared to ICS (high dose) in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with ICS (high dose)	Risk difference with LTRA (95% CI)
FEV_1 (% predicted)	34 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	-	The mean FEV_1 (% predicted) in the control groups was 93% of predicted value	The mean FEV_1 (% predicted) in the intervention groups was 2.1 lower (3.65 to 0.55 lower)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 33: Clinical evidence summary: LTRA compared to ICS+LABA in people aged 5–16 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with ICS + LABA	Risk difference with LTRA (95% CI)
Quality of life (PAQLQ)	548 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-	Results given as mean difference of control versus intervention.	The mean quality of life (PAQLQ) in the intervention groups was 0.09 lower (0.3 lower to 0.12 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA	Risk difference with LTRA (95% CI)
Rescue use (rescue-free 24-hour periods)	548 (1 study) 12 weeks	MODERATE[a] due to risk of bias	OR 0.31 0.20 to 0.48	Event rate not reported	

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 34: Clinical evidence summary: ICS (low dose) compared to Placebo in children aged 1–5 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (low dose) (95% CI)
Reliever medication use - daytime	88 (1 study) 6 months	HIGH	-	The mean change in reliever medication use - daytime in the control groups was 0.31 puffs	The mean reliever medication use - daytime in the intervention groups was 0.06 higher (0.19 lower to 0.31 higher)
Reliever medication use - night-time use	88 (1 study) 6 months	MODERATE[c] due to imprecision	-	The mean change in reliever medication use - night-time use in the control groups was 0.06 puffs	The mean reliever medication use - night-time use in the intervention groups was 0.05 higher (0.04 lower to 0.14 higher)
Infection	36 (1 study) 3 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 4.29 (0.57 to 32.01)	67 per 1000	220 more per 1000 (from 29 fewer to 1000 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 35: Clinical evidence summary: ICS (high dose) compared to Placebo in children aged 1–5 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (high dose) (95% CI)
Reliever medication use – daytime (doses)	36 (1 study) 6 months	MODERATE[a] due to risk of bias	-	The mean reliever medication use - daytime in the control groups was 1.5 doses	The mean reliever medication use - daytime in the intervention groups was 1.6 lower (1.99 to 1.21 lower)
Reliever medication use - night-time use (doses)	36 (1 study) 6 months	MODERATE[a] due to risk of bias	-	The mean reliever medication use - night-time use in the control groups was 1.2 doses	The mean reliever medication use - night-time use in the intervention groups was 1.7 lower (2.09 to 1.31 lower)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 36: Clinical evidence summary: LTRA compared to Placebo in children aged 1–5 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with LTRA (95% CI)
Infection	32 (1 study) 3 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 5.29 (0.72 to 39.11)	67 per 1000	287 more per 1000 (from 19 fewer to 1000 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 37: Clinical evidence summary: LTRA compared to ICS (low dose) in children aged 1–5 years

Outcomes	Number of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with ICS (low dose)	Risk difference with LTRA (95% CI)
Infection	38 (1 study) 3 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.24 (0.49 to 3.14)	286 per 1000	69 more per 1000 (from 146 fewer to 612 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 38: Clinical evidence summary: Cromolyn compared to ICS (moderate dose) in children aged 1–5 years

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with Cromolyn (95% CI)
Reliever medication use - puffs/day	78 (1 study) 3 months	MODERATE[a] due to risk of bias	-	The mean change in reliever medication use - puffs/day in the control groups was 0.35 puffs/day	The mean reliever medication use - puffs/day in the intervention groups was 0.13 higher (0.1 lower to 0.36 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 39: Clinical evidence summary: ICS (low dose) compared to Placebo in children under 1

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (low dose) (95% CI)
Reliever medication use - puffs/day	37 (1 study) 12 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean change in reliever medication use - puffs/day in the control groups was	The mean reliever medication use - puffs/day in the intervention groups was 0.34 lower

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (low dose) (95% CI)
				0.12 puffs/day	(0.88 lower to 0.2 higher)
Reliever medication use - number of days	20 (1 study) 6 months	HIGH	-	The mean reliever medication use - number of days in the control groups was 24.3 days	The mean reliever medication use - number of days in the intervention groups was 17.8 lower (18.75 to 16.85 lower)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 40: Clinical evidence summary: ICS (moderate dose) compared to Placebo in children under 1

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ICS (moderate dose) (95% CI)
Reliever medication use - days	46 (2 studies) 6 months	LOW[a,b] due to risk of bias, inconsistency	-	The mean reliever medication use - days in the control groups was 19.9 days	The mean reliever medication use - days in the intervention groups was 7.01 standard deviations lower (19.25 lower to 5.23 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because I^2 >50%, unexplained by subgroup analysis.
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 41: Clinical evidence summary: ICS (moderate dose) compared to ICS (low dose) in children under 1

Outcomes	Number of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with ICS (low dose)	Risk difference with ICS (moderate dose) (95% CI)
Reliever medication use - number of days	20 (1 study) 6 months	HIGH	-	The mean change in reliever medication use - number of days in the control groups was 6.5 days	The mean reliever medication use - number of days in the intervention groups was 2.6 higher (1.9 to 3.3 higher)

6.1.1.2 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review. [136] This is summarised in the economic evidence profile below (Table 42) and the economic evidence table in Appendix I.

See also the health economic article selection flow chart in Appendix F.

Unit costs

Full details of medication costs can be found in Appendix O.

Table 42: Economic evidence profile: ICS versus leukotriene receptor antagonist

Study	Applicability	Limitations	Other comments	Incremental cost (2-1)	Incremental effects (2-1)	Cost effectiveness	Uncertainty
Price 2011 [136] UK	Directly applicable	Potentially serious limitations[(a)]	CUA within-trial analysis (RCT) Population: Patient with diagnosed asthma not receiving steroids in the previous 12 weeks Two comparators: 1) ICS 2) Leukotriene receptor antagonist Time horizon: 2 years	**Total NHS costs (mean per patient):** £242	**QALYs (mean per patient):** -0.073	ICS dominates leukotriene receptor antagonist	Probability of LTRAs being cost effective at a £20,000 per QALY threshold: Less than 5%

Abbreviations: CUA: cost-utility analysis ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Although montelukast is now out of patent since the study was conducted, LTRAs would not be cost-effective, even at zero cost, at the reported level of effectiveness. However probabilistic results will be skewed against LTRAs because of this. The main concern is that the pragmatic nature of the RCT on which the evaluation is based may not reflect the true treatment effect sizes

(b) Adjusted for baseline values

6.1.1.3 Evidence statements

6.1.1.3.1 Clinical

ICS (low dose) compared to Placebo in people over 16

- ICS (low dose) compared to Placebo resulted in a clinically important benefit for number of asthma exacerbations (1 study, 467 patients, Very Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for morning PEF (6 studies, 1696 patients, Very Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for FEV_1 (% of predicted) (1 study, 467 patients, Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for FEV_1 (L) (4 studies, 1067 patients, Very Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for reliever medication use (puffs/day) (5 studies, 1534 patients, Very Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for reliever medication use (daytime) (1 study, 340 patients, Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for reliever medication use (night-time) (1 study, 340 patients, Low quality evidence)
- ICS (low dose) compared to Placebo resulted in a clinically important benefit for infection (2 studies, 685 patients, Very Low quality evidence)

ICS (moderate dose) compared to Placebo in people over 16

- ICS (moderate dose) compared to Placebo resulted in a clinically important benefit for number of asthma exacerbations (1 study, 258 patients, Very Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in a clinically important benefit for morning PEF (2 studies, 220 patients, Very Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in a clinically important benefit for FEV_1 (% of predicted) (1 study, 33 patients, Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in no clinically important difference for FEV_1 (L) (2 studies, 403 patients, Very Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in a clinically important benefit for reliever medication use (puffs/day) (2 studies, 220 patients, Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in no clinically important difference for reliever medication use (rescue-free days) (1 study, 258 patients, Moderate quality evidence)
- ICS (moderate dose) compared to Placebo resulted in no clinically important difference for reliever medication use (rescue-free nights) (1 study, 258 patients, Moderate quality evidence)

ICS + LABA compared to Placebo in people over 16

- ICS + LABA compared to Placebo resulted in a clinically important benefit for number of asthma exacerbations (1 study, 470 patients, Very Low quality evidence)
- ICS + LABA compared to Placebo resulted in a clinically important benefit for morning PEF (2 studies, 857 patients, Low quality evidence)
- ICS + LABA compared to Placebo resulted in no clinically important difference for FEV_1 (% of predicted) (1 study, 470 patients, Low quality evidence)

- ICS + LABA compared to Placebo resulted in a clinically important benefit for FEV_1 (L) (2 studies, 1145 patients, Moderate quality evidence)
- ICS + LABA compared to Placebo resulted in a clinically important benefit for reliever medication use (puffs/day) (2 studies, 1102 patients, Very Low quality evidence)
- ICS + LABA compared to Placebo resulted in a clinically important benefit for reliever medication use (rescue free days) (1 study, 289 patients, Moderate quality evidence)
- ICS + LABA compared to Placebo resulted in a clinically important harm for infection (1 study, 516 patients, Very Low quality evidence)

LTRA compared to Placebo in people over 16

- LTRA compared to Placebo resulted in no clinically important difference for morning PEF (2 studies, 645 patients, Very Low quality evidence)
- LTRA compared to Placebo resulted in no clinically important difference for FEV_1 (L) (2 studies, 645 patients, Very Low quality evidence)
- LTRA compared to Placebo resulted in no clinically important difference for reliever medication use (puffs/day) (2 studies, 645 patients, Very Low quality evidence)

ICS (moderate dose) compared to ICS (low dose) in people over 16

- ICS (moderate dose) compared to ICS (low dose) resulted in a clinically important benefit for morning PEF (1 study, 207 patients, Low quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (L) (1 study, 207 patients, Low quality evidence)

ICS (high dose) compared to ICS (low dose) in people over 16

- ICS (high dose) compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (% of predicted) (2 studies, 391 patients, Very Low quality evidence)

ICS + LABA compared to ICS (low dose) in people over 16

- ICS + LABA compared to ICS (low dose) resulted in a clinically important harm for number of asthma exacerbations (1 study, 459 patients, Very Low quality evidence)
- ICS + LABA compared to ICS (low dose) could not be calculated for mortality (1 study, 433 patients, Low quality evidence)
- ICS + LABA compared to ICS (low dose) resulted in no clinically important difference for morning PEF (3 studies, 3571 patients, Very Low quality evidence)
- ICS + LABA compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (% of predicted) (1 study, 459 patients, Low quality evidence)
- ICS + LABA compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (L) (5 studies, 3571 patients, Low quality evidence)
- ICS + LABA compared to ICS (low dose) resulted in no clinically important difference for reliever medication use (puffs/day) (4 studies, 1806 patients, Low quality evidence)
- ICS + LABA compared to ICS (low dose) resulted in a clinically important benefit for reliever medication use (rescue-free days) (1 study, 289 patients, Moderate quality evidence)
- ICS + LABA compared to ICS (low dose) resulted in a clinically important harm for infection (1 study, 535 patients, Very Low quality evidence)

LTRA compared to ICS (low dose) in people over 16

- LTRA compared to ICS (low dose) resulted in a clinically important harm for number of asthma exacerbations (1 study, 395 patients, Very Low quality evidence)
- LTRA compared to ICS (low dose) resulted in no clinically important difference for quality of life (AQLQ) (2 studies, 775 patients, Low quality evidence)
- LTRA compared to ICS (low dose) resulted in a clinically important harm for morning PEF (4 studies, 1726 patients, Very Low quality evidence)
- LTRA compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (% of predicted) (2 studies, 941 patients, Moderate quality evidence)
- LTRA compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (L) (2 studies, 776 patients, Low quality evidence)
- LTRA compared to ICS (low dose) resulted in no clinically important difference for reliever medication use (puffs/day) (3 studies, 1156 patients, Very Low quality evidence)
- LTRA compared to ICS (low dose) resulted in no clinically important difference for reliever medication use (% of days) (1 study, 625 patients, Low quality evidence)

Theophylline compared to ICS (low dose) in people over 16

- Theophylline compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (% of predicted) (1 study, 115 patients, Low quality evidence)

ICS + LABA compared to ICS (moderate dose) in people over 16

- ICS + LABA compared to ICS (moderate dose) resulted in a clinically important benefit for morning PEF (1 study, 362 patients, Very Low quality evidence)
- ICS + LABA compared to ICS (moderate dose) resulted in a clinically important benefit for reliever medication use (participants with 100% rescue-free days) (1 study, 362 patients, Low quality evidence)
- ICS + LABA compared to ICS (moderate dose) resulted in a clinically important benefit for reliever medication use (participants with 100% rescue-free nights) (1 study, 362 patients, Low quality evidence)

LTRA compared to ICS (moderate dose) in people over 16

- LTRA compared to ICS (moderate dose) resulted in a clinically important harm for number of asthma exacerbations (1 study, 306 patients, Very low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in no clinically important difference for quality of life (AQLQ) (1 study, 300 patients, Low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in no clinically important difference for asthma control (ACQ) (1 study, 300 patients, Low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in no clinically important difference for hospitalisations (1 study, 302 patients, Very Low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in no clinically important difference for morning PEF (1 study, 306 patients, Very Low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in no clinically important difference for reliever medication use (daytime) (1 study, 306 patients, Low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in no clinically important difference for reliever medication use (night-time) (1 study, 296 patients, Low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in no clinically important difference for infection (1 study, 296 patients, Very low quality evidence)

Theophylline compared to ICS (high dose) in people over 16

- Theophylline compared to ICS (high dose) resulted in no clinically important difference for FEV_1 (% of predicted) (1 study, 56 patients, Very Low quality evidence)

LTRA compared to ICS + LABA in people over 16

- LTRA compared to ICS + LABA resulted in a clinically important harm for quality of life (AQLQ) (1 study, 354 patients, Moderate quality evidence)
- LTRA compared to ICS + LABA resulted in a clinically important harm for morning PEF (2 studies, 777 patients, Low quality evidence)
- LTRA compared to ICS + LABA resulted in a clinically important harm for FEV_1 (L) (2 studies, 780 patients, Very Low quality evidence)
- LTRA compared to ICS (moderate dose) resulted in a clinically important harm for reliever medication use (puffs/day) (2 studies, 780 patients, Low quality evidence)

ICS (low dose) compared to Placebo in people aged 5–16

- ICS (low dose) compared to Placebo resulted in a clinically important benefit for morning PEF (2 studies, 445 patients, Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for FEV_1 (% of predicted) (2 studies, 411 patients, Low quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for reliever medication use (puffs/day) (1 study, 202 patients, Moderate quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for infection (2 studies, 417 patients, Very Low quality evidence)
- ICS (low dose) compared to Placebo resulted in a clinically important benefit for adrenal insufficiency (1 study, 202 patients, Low quality evidence)

ICS (moderate dose) compared to Placebo in people aged 5–16

- ICS (moderate dose) compared to Placebo resulted in no clinically important difference for morning PEF (1 study, 202 patients, Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in no clinically important difference for FEV_1 (% of predicted) (2 studies, 409 patients, Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in no clinically important difference for reliever medication use (puffs/day) (1 study, 205 patients, Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in no clinically important difference for infection (2 studies, 416 patients, Low quality evidence)
- ICS (moderate dose) compared to Placebo resulted in a clinically important benefit for adrenal insufficiency (1 study, 205 patients, Low quality evidence)

ICS (moderate dose) compared to ICS (low dose) in people aged 5–16

- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for morning PEF (1 study, 200 patients, Moderate quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (% of predicted) (2 studies, 418 patients, Low quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for reliever medication use (puffs/day) (1 study, 213 patients, Moderate quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for infection (2 studies, 425 patients, Low quality evidence)

- ICS (moderate dose) compared to ICS (low dose) resulted in a clinically important harm for adrenal insufficiency (1 study, 205 patients, Very Low quality evidence)

ICS (moderate dose) compared to ICS (low dose) in people aged 5–16

- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for morning PEF (1 study, 200 patients, Moderate quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (% of predicted) (2 studies, 418 patients, Low quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for reliever medication use (puffs/day) (1 study, 213 patients, Moderate quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in no clinically important difference for infection (2 studies, 425 patients, Low quality evidence)
- ICS (moderate dose) compared to ICS (low dose) resulted in a clinically important harm for adrenal insufficiency (1 study, 205 patients, Very Low quality evidence)

LTRA compared to ICS (low dose) in people aged 5–16

- LTRA compared to ICS (low dose) resulted in no clinically important difference for quality of life (1 study, 541 patients, High quality evidence)
- LTRA compared to ICS (low dose) resulted in no clinically important difference for FEV_1 (% of predicted) (1 study, 881 patients, High quality evidence)
- LTRA compared to ICS (low dose) resulted in no clinically important difference for reliever medication use (% of days) (1 study, 881 patients, High quality evidence)

Cromolyn compared to ICS (low dose) in people aged 5–16

- Cromolyn compared to ICS (low dose) resulted in a clinically important benefit for number of asthma exacerbations (1 study, 122 patients, Very Low quality evidence)
- Cromolyn compared to ICS (low dose) resulted in a clinically important harm for morning PEF (% of predicted) (1 study, 60 patients, Very Low quality evidence)
- Cromolyn compared to ICS (low dose) resulted in a clinically important benefit for growth velocity (1 study, 60 patients, Very Low quality evidence)

ICS (high dose) compared to ICS (moderate dose) in people aged 5–16

- ICS (high dose) compared to ICS (moderate dose) resulted in no clinically important difference for FEV_1 (% of predicted) (1 study, 33 patients, Moderate quality evidence)

LTRA compared to ICS (moderate dose) in people aged 5–16

- LTRA compared to ICS (moderate dose) resulted in a clinically important harm for FEV_1 (% of predicted) (1 study, 31 patients, Moderate quality evidence)

LTRA compared to ICS (high dose) in people aged 5–16

- LTRA compared to ICS (high dose) resulted in a clinically important harm for FEV_1 (% of predicted) (1 study, 34 patients, Low quality evidence)

LTRA compared to ICS + LABA in people aged 5–16

- LTRA compared to ICS + LABA resulted in no clinically important difference for quality of life (1 study, 548 patients, Moderate quality evidence)

- ICS + LABA compared to ICS (low dose) resulted in a clinically important harm for reliever medication use (rescue-free days) (1 study, 548 patients, Moderate quality evidence)

ICS (low dose) compared to Placebo in children aged 1–5

- ICS (low dose) compared to Placebo resulted in no clinically important difference for reliever medication use (daytime) (1 study, 88 patients, High quality evidence)
- ICS (low dose) compared to Placebo resulted in no clinically important difference for reliever medication use (night-time) (1 study, 88 patients, Moderate quality evidence)
- ICS (low dose) compared to Placebo resulted in a clinically important harm for infection (1 study, 36 patients, Very Low quality evidence)

ICS (high dose) compared to Placebo in children aged 1–5

- ICS (high dose) compared to Placebo resulted in a clinically important benefit for reliever medication use (daytime) (1 study, 36 patients, Moderate quality evidence)
- ICS (high dose) compared to Placebo resulted in a clinically important benefit for reliever medication use (night-time) (1 study, 36 patients, Moderate quality evidence)

LTRA compared to Placebo in children aged 1–5

- LTRA compared to Placebo resulted in a clinically important benefit for infection (1 study, 32 patients, Very Low quality evidence)

LTRA compared to ICS (low dose) in children aged 1–5

- LTRA compared to ICS (low dose) resulted in no clinically important difference for infection (1 study, 38 patients, Very Low quality evidence)

Cromolyn compared to ICS (moderate dose) in children aged 1–5

- Cromolyn compared to ICS (moderate dose) resulted in no clinically important difference for reliever medication use (puffs/day) (1 study, 78 patients, Moderate quality evidence)

ICS (low dose) compared to Placebo in children aged <1

- ICS (low dose) compared to Placebo resulted in no clinically important difference for reliever medication use (puffs/day) (1 study, 37 patients, Very Low quality evidence)
- ICS (low dose) compared to Placebo resulted in a clinically important benefit for reliever medication use (number of days) (1 study, 20 patients, High quality evidence)

ICS (moderate dose) compared to Placebo in children aged <1

- ICS (moderate dose) compared to Placebo resulted in a clinically important benefit for reliever medication use (days) (2 studies, 46 patients, Low quality evidence)

ICS (moderate dose) compared to ICS (low dose) in children aged <1

- ICS (moderate dose) compared to ICS (low dose) resulted in a clinically important harm for reliever medication use (number of days) (1 study, 20 patients, High quality evidence)

6.1.1.3.2 Economic

- One cost–utility analysis found that low dose ICS was dominant compared to LTRAs for treating individuals with asthma over 16 years of age (reduced costs and increased QALYs). This analysis was assessed as directly applicable with potentially serious limitations.

6.1.1.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80

Relative values of different outcomes	The committee considered the following outcomes as critical for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee considered the following outcomes as important: asthma control (as assessed by a validated questionnaire), hospital admission, reliever medication use, lung function (FEV_1 or morning PEF) and adverse events. No evidence was identified for mortality.
Trade-off between clinical benefits and harms	All the available evidence assessed and compared the effectiveness of preventer drugs as first-line treatment for patients with asthma who were uncontrolled on SABA therapy alone. <u>Adults over 16 years</u> Low dose ICS was seen to have a clinically important benefit for the outcomes severe exacerbations, and infection when compared to placebo. The committee compared the effects of first-line treatment with low dose ICS with use of higher doses of ICS, and with low dose ICS plus LABA. Although there were some outcomes where the group data showed greater benefit for these other first-line treatments, the magnitude of benefit was not judged sufficient to recommend these in preference to low-dose ICS. The committee reasoned that there would be a minority of subjects within these studies who would need more than low-dose ICS, but that the most efficient way of introducing treatment is to start with low-dose ICS, which will be effective in most, and escalate in those in whom this proves insufficient. The committee noted the biological implausibility of increased ICS dose leading to reduced respiratory infections and considered this finding to be due to the low quality of the evidence. LTRA and theophylline were not seen to be clinically effective as first-line preventer medication.

	5 to 16 age group The use of ICS (low dose) was again associated with a general clinical benefit in outcomes, although this was less clear-cut than in older subjects. ICS (moderate dose) and ICS (high dose) provided no additional clinically important benefit over ICS (low dose). In a comparison with cromolyns, there was a small disadvantage of ICS use in measures of growth velocity, but the committee noted that this was over a short time frame. They also recognised that cromolyns have a less convenient dosing regimen, and that options for treatment escalation, if required, are easier with ICS. LTRA again demonstrated inferior effectiveness as a first-line preventer. Children aged 1–5 years There were fewer data available. Reliever medication use and infection rate were recorded, yet there were no observed benefits in any outcome following treatment of ICS (low dose), LTRA, or cromolyn. There was no available evidence for severe asthma exacerbation, mortality, quality of life, asthma control, hospital admission, lung function or the two remaining adverse events. In the <1 year old population, reliever medication use was the only outcome reported. The limited evidence suggests that both low and moderate dose ICS provide benefit compared to placebo. A major problem in this age group, both in formal studies and in real-life practice, is that it is harder to obtain objective evidence of the diagnosis of asthma, and in particular to distinguish this from episodes of viral-induced wheeze. Based on consensus opinion and clinical experience, the committee recommended a continuation of current practice of initiating children with suspected asthma on paediatric moderate dose ICS as their first-line preventer for an 8-week period in order to ascertain if there is any response to ICS. If there is no response, the diagnosis of asthma should be questioned. This might involve further investigation for other conditions, beyond the scope of this guideline. If there is an apparent response to treatment the possibility still remains that this actually reflects natural resolution of a virus-induced episode of wheezing rather than asthma, and the committee therefore suggested withdrawing treatment to assess if symptoms recur. Should symptoms recur within 4 weeks, this would support the diagnosis of asthma and the committee therefore recommended continuing on ICS but at a paediatric low dose in order to minimise side effects. If symptoms recur but later than 4 weeks after withdrawal, the committee felt that this may represent a recurrence of viral infection or other trigger and therefore not necessarily support the diagnosis of asthma. In this case the committee felt that repeating a trial of ICS at a paediatric moderate dose would be appropriate. The overall aim for children under the age of 5, as for older age groups, is to maintain asthma control at the lowest possible dose of ICS. The committee emphasised that the recommendation to start at a paediatric moderate dose was driven by a need to confirm whether or not the symptoms were responsive to ICS at all.
Trade-off between net clinical benefits and costs	One health economic study was identified for this review question. The included study compared low-dose ICS to LTRA and showed ICS to be dominant, both cheaper and more effective, in an adult population. However this study was conducted when LTRA was still on patent, meaning the drug cost was considerably higher. The committee was presented with the most up-to-date costs for LTRA and low dose ICS. When the study was conducted the cost of LTRAs was £26.97 for a 28 tablet pack; a generic is now available which costs £1.90. The economic study showed that low-dose ICS provided an additional 0.05 QALYs

	compared to LTRAs over 2 years. At a £20,000 per QALY threshold LTRAs would need to save the NHS £2,000 over the two years to be deemed cost effective. Therefore even if the study was updated with present day drug costs low dose ICS would remain cost effective as the cost difference between LTRAs and low dose is around £26 per year, as shown in Appendix O. The study also reports lower healthcare utilisation for those taking low dose ICS, meaning the cost difference is even smaller. Although this economic paper was based on one trial, the clinical benefit of ICS over LTRA was supported in other papers included in the review. The committee's main concern with the study was that it was based on a pragmatic trial. Although they acknowledged the benefits of this approach they noted the limitations this may have on the clinical evidence presented. Although a pragmatic trial reflects what happens in reality, it is not blinded which may introduce biases. For example, in the trial the GP was allowed to change the individual's medication as appropriate. As LTRAs are not prevailing practice the GP may be more inclined to change their treatment compared with individuals who started on low dose ICS. Overall from drug cost alone the cost difference between low dose ICS and LTRA is not large at £27 per year, assuming adherence is 100%. This cost difference is even smaller when adherence decreases. The clinical evidence presented to the committee along with the one economic study appeared to show that it is highly likely that low dose ICS will provide enough benefit to be considered cost effective. No other economic studies were identified for the other relevant treatment comparisons. In the absence of evidence, unit costs of drugs and estimated annual use for each treatment option were presented. Based on the clinical evidence, the committee noted that the optimal clinical option, low dose ICS, also had the lowest annual drug cost in most cases. The cheapest option was shown to be theophylline, however the committee noted this was a very rarely prescribed treatment and would need good quality evidence of benefit to support its use over low dose ICS which has proven efficacy. The potential saving from using theophylline instead of low dose ICS was marginal. Although there were no economic studies available in a child population the committee felt the cost-effectiveness results could safely be extrapolated from an adult population as the same level of clinical benefit was also apparent.
Quality of evidence	The evidence for the majority of outcomes at each age group were Low or Very Low quality by GRADE criteria, due to risk of bias and imprecision. There were a number of exceptions with Moderate quality evidence in the 16 years and over group reported for quality of life, reliever medication use and lung function outcomes. For children and young people 5–16 years old the outcomes AQLQ, reliever medication use (puffs/day) and FEV_1 (% of predicted) also produce a set of Moderate quality evidence. Reliever medication use (daytime use) in the comparison between low dose ICS and placebo in children aged 1–5 produced High quality evidence. High quality evidence was again reported in the <1 strata in both the comparisons low dose ICS versus placebo, and moderate dose ICS versus low dose ICS for the outcome reliever medication use (number of days). However, only one study contributed to the evidence for each outcome found to produce Moderate or High quality evidence. The quality and breadth of the evidence in the under 5 stratum was low and limited. The recommendation in this population is consensus and experience driven.
Other considerations	The consensus of the committee was that a number of important principles applied to all changes to pharmacological therapy for asthma. First, that people should not have their maintenance therapy increased in intensity without healthcare

	professionals first considering all other possible reasons for worsening of asthma control. This may identify other possible solutions and also indicate how long a period any increase in maintenance therapy intensity is warranted for. Second, the committee consensus was that any increase in therapy should be reviewed to ensure it has helped improve asthma control. The timing of this review is dependent on the context of the change in medication but the consensus of the committee was that 4–8 weeks would generally be an appropriate time to review; this would allow time for additional medication to take effect but not leave a person with uncontrolled asthma for an unnecessary length of time. Third, the committee recommended that any healthcare professional who is changing a person's pharmacological asthma therapy should ensure that the person fully understands how to use any new devices that are being supplied. Fourth, the committee made a number of recommendations relating to the dose of ICS used throughout the guideline however they emphasised that the over-arching principle of ICS therapy was to use the minimum dose required in order to provide effective control. The committee felt that the subgroup of people with asthma who smoke may be under-represented in clinical trials. From the adult studies included, only 52.2% included non/ex-smokers, 39.1% did not state the population smoking status, while two studies (8.7%) included a mixed cohort of smokers, ex-smokers and non-smokers. The committee were aware that individuals with asthma who smoke may get less benefit from the introduction of low-dose ICS treatment.[177] However, although smokers are likely to need higher overall doses of ICS, there is no clear evidence to support a higher starting dose in all smokers. The committee had already decided to make a recommendation about reviewing the effect of any treatment change to ensure adequate benefit, and if carried out this will allow dose-adjustment in those who continue to smoke. The committee noted that the most recent BTS/SIGN guidance on asthma management includes a recommendation to use LTRAs as a first line preventer in children under the age of 5 who are unable to take ICS. The committee recommendations in this age group are based predominantly on consensus and extrapolation from adult evidence. The committee did not identify any evidence for meeting the protocol criteria for this review comparing LTRAs with placebo (or ICS) in this population. The consensus view of the committee was that based on their clinical experience and their awareness of the evidence referenced around this option in the BTS/SIGN guidance (two studies, one in a population whose asthma was not defined as uncontrolled and who had previously been using additional preventers and one in a population in which a significant proportion were using ICS during the trial) it was not appropriate to include a specific additional recommendation about LTRA as an alternative to ICS.

7 Escalating pharmacological treatment in patients poorly controlled on low dose ICS

7.1 Introduction

There are a number of treatment strategies aimed at reducing the airway inflammation driving the disease or providing longer acting bronchodilation, including increasing the dose of inhaled corticosteroids, long-acting beta agonists, combinations of inhaled steroids and long acting beta agonists delivered in fixed or variable dose regimens, leukotriene receptor antagonists, theophylline or aminophylline and cromolyns.

Asthma varies in severity and if a medication fails to control the disease then additional treatment should be considered following an assessment to ensure the medication is being used and also that the patient is able to use it effectively. Therefore adherence and inhaler technique should be checked. Following this and if asthma remains uncontrolled then asthma treatment should be escalated.

It is also important to consider the potential adverse effects of this treatment when considering the approach: linear growth, secondary infection and adrenal insufficiency. Choice of medication should therefore be based upon a balance of efficacy, fewer adverse effects and economic profile.

7.1.1 Review question: In people with a clinician diagnosis of asthma who are uncontrolled on low dose ICS, what is the most clinically and cost-effective second-line preventer?

For full details see review protocol in Appendix C.

Table 43: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma who are uncontrolled on low dose ICS and have not been prescribed a second-line preventer for at least a month prior to starting the intervention. Population strata: • <1 year • 1 to <5 years • 5 to <16 years • ≥16 years
Interventions	• Continuing on 'low dose' ICS • Regular 'moderate dose' ICS • Regular 'high dose' ICS • ICS+LABA with SABA when required • ICS+LABA (formoterol) used as maintenance and reliever therapy (for example SMART or MART therapy) • ICS + LAMA (tiotropium) • Leukotriene receptor antagonist +/- ICS • Theophylline or aminophylline +/- ICS • Cromolyns +/- ICS

Comparisons	Second-line preventer versus continuing on low dose ICS Any listed intervention versus another

Outcomes	**Critical outcomes:**
	• Severe asthma exacerbations
	• Mortality
	• Quality of life
	Important outcomes:
	• Asthma control assessed by a validated questionnaire
	• Hospital admissions
	• Reliever medication use
	• Lung function (change in FEV_1 or morning PEF)
	• Adverse events
	  ○ linear growth
	  ○ all respiratory infections
	  ○ serious respiratory infections
	  ○ adrenal insufficiency

Study design	RCT Systematic review of RCTs

7.1.1.1 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of preventer drugs as second-line treatment for patients with asthma who are uncontrolled on first-line preventer treatment (low dose ICS) alone. The review population was people who had only ever been prescribed first-line preventer treatment (low dose ICS) or had been free from additional preventer treatment in the previous month. The latter was to allow for people who have been prescribed additional preventer medication in the past. The committee agreed that the effects of the additional preventers would be expected to have worn off after a period of 1 month. Studies recruiting a mix of people with asthma on different stages of treatment were only included if at least 90% of people included in the study were on ICS alone at inclusion. If studies reported the mean ICS dose of their population, they were included in this review if the mean dose was in the low dose range.

Studies were included that recruited people with asthma who were uncontrolled in line with BTS/SIGN guidelines (using SABA three times a week or more; symptomatic three times a week or more; or waking one night a week or more). Studies recruiting a mix of people with asthma including both people who were controlled and uncontrolled were only included if at least 75% of people included in the study were uncontrolled.

Twenty one studies were included in the review;[6,13,15,41,61,72,90,92,94,96,99,102,108,115,117,123,130,136,137,151,179,195] these are summarised in Table 44 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 45, Table 46, Table 47, Table 48, Table 49, Table 50, Table 51, Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, Table 58, Table 59, Table 60 and Table 61).

See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Sixteen studies included a population over the age of 16. Five studies included a population between the ages of 5 and 16. No studies were identified that included a population under the age of 5.

Table 44: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Baraniuk 1999[6]	ICS (low dose) + LABA n=231 ICS (low dose) n=449	Stratum: >16 years Age – ICS + LABA mean 40, ICS (low dose) mean 40 Participants were included if they had previously been using ICS for 3 months, had an FEV_1 of 40-85% predicted and demonstrated reversibility of airway obstruction with ≥15% increase following salbutamol.	• Reliever medication use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 12 weeks	Fluticasone propionate and triamcinolone acetonide arms combined.
Bjermer 2003[13]	ICS (low dose) + LTRA n=747 ICS (low dose) + LABA n=743	Stratum: >16 years Age – ICS + LTRA mean 41.2, ICS + LABA mean 41.0 Participants were included if they had previously been using ICS and underwent a 4-week run-in period on low dose ICS Participants were included if during the run-in period they had an average use of one puff or more a day of SABA and met a pre-specified minimum biweekly daytime symptoms score	• Severe exacerbations (requiring OCS) • Quality of life (AQLQ) • Hospital admissions • FEV_1 • Morning PEF Reported at 48 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
Bouros 1999[15]	ICS (low dose) + LABA n=69 ICS (moderate dose) n=65	Stratum: ≥16 years Age – mean (SD) 43(14.9) Participants were included if they had previously been using ICS for 1 months and underwent a 2-week run-in period. Participants were included if they had a symptom score (day and night) of ≥2 on ≥4 of the 7 days during second week of run-in period and demonstrated airway reversibility.	• Morning PEF Reported at 12 weeks	
De Blic 2009[41]	ICS (low dose) + LABA n=160 ICS (moderate dose) n=161	Stratum: 5 to <16 years Age – ICS + LABA mean 8.0, ICS (moderate dose) mean 8.1 Patients were included if they had previously been using ICS (BDP or equivalent) 400 ug per day and underwent a run-in period on fluticasone propionate 200 ug per day Patients included if asthma was 'not controlled' for at least 2 of the 4	• Morning PEF (L/min) • Adherence (taking ≥75% of prescribed medication) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		weeks of the run-in period. Not controlled defined as either 1 or more night-time awakenings or having 2 or more of the following: symptoms on >2 days, SABA use on >2 days or morning PEF <80% predicted		
Greening 1994[61]	ICS (low dose) + LABA n=220 ICS (moderate dose) n=206	Stratum: ≥16 years Age – ICS + LABA mean 48, SD 15, ICS (moderate dose) mean 47, SD 15 Patients entered the trial continuing their previous dose of ICS (BDP) 400 ug per day Patients were included if they had symptoms on at least 4 of 7 days during the second baseline week	• Severe asthma exacerbations • Hospitalisations Reported at 6 months	
Ilowite 2004[72]	ICS (low dose) + LTRA n=743 ICS (low dose) + LABA n=730	Stratum: >16 years Age – ICS + LTRA mean 38.1, ICS + LABA mean 39.0 Participants were included if they had previously been using ICS and underwent a 4-week run-in period on low dose ICS Participants were included if during the run-in period	• Severe exacerbations (requiring OCS) • Quality of life (AQLQ) • Hospital admissions • Reliever medication use (puffs/day) • FEV_1 (L) • Morning PEF (L/min) Reported at 48 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		they had an average use of one puff or more a day of SABA and met a pre-specified minimum biweekly daytime symptoms score		
Kuna 2006[90]	ICS (low dose) + LABA n=409 ICS (low dose) n=207	Stratum: ≥16 years Age – ICS + LABA mean 43.9, ICS (low dose) mean 45.8 Patients had been receiving a daily ICS dose of 200–500 ug for at least 30 days before study entry Patients were included if "not optimally controlled" (not further defined). Mean baseline symptom-free day percentage (36.1–38.1%, no SD provided)	• Reliever medication use (% reliever free days) • Morning PEF (L/min) • Infections (all respiratory) Reported at 12 weeks	Two ICS+LABA arms analysed separately in the study but combined for analysis in review (once or twice daily administration, same total dosage).
Laviolette 1999[92]	ICS (low dose) + LTRA n=193 ICS (low dose) n=200	Stratum: ≥16 years Age – LTRA + ICS mean 40, ICS (low dose) mean 39 Patients had been treated with ICS (BDP equivalent) 400–500 ug for at least 6 weeks, were treated with 400 ug BDP per day during 4-week run-in Patients were incompletely	• Reliever medication use (puffs/day) • Morning PEF (L/min) • FEV_1 (L) • All respiratory infections Reported at 16 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		controlled during run-in period as defined by a minimum total daytime asthma symptom score of 64/336 and daily average SABA when required use of at least 1 puff per day during the last 2 weeks		
Lenney 2013[94]	ICS (low dose) + LTRA n=21 ICS (low dose) + LABA n=23 ICS (low dose) n=19	Stratum: 5 to <16 years Age – mean 10.4, range 6.5–14.7 4-week run-in period on fluticasone propionate 200 ug total daily dose Required 7 or more puffs of SABA in the past 7 days, excluded if asthma controlled after 4-week run-in period (absence of any symptoms or when symptoms had not interfered with usual activities in the last week)	• Severe exacerbations • Quality of life (PAQLQ) • Hospitalisations • PEF (L/min) • FEV_1 (% predicted) Reported at 48 weeks	
Lim 2000[96]	ICS (low dose) + theophylline n=49 ICS (high dose) n=52 ICS (low dose) n =54	Stratum: ≥16 years Age – range of means, 36.5 to 40.5 Patients had been treated with low dose ICS prior to screening Patients had symptoms on at	• Severe exacerbations • PEF (L/min) • Infections (all respiratory) Reported at 6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		least 3 of the last 7 days of the run-in period on low dose ICS		
Malone 2005[99]	ICS (low dose) + LABA n=101 ICS (low dose) n=102	Stratum: 5–16 years Age – range of means, 8 to 8.1 Patients had been treated with low to moderate dose ICS prior to screening, mean dose in the low dose range Daytime asthma symptom score of at least one (scale 0 to 5) on 3 or more days of the last 7 of the run-in period on their baseline ICS.	• Infection (all respiratory) Reported at 12 weeks	
Meltzer 2007[102]	ICS (moderate dose) n=97 ICS (low dose) n=100	Stratum: 5–16 years Age – range of means, 8.2 to 8.7 Patients had been treated with low to moderate dose ICS prior to screening, mean dose in the low dose range At baseline patients had mean SABA use per day of 1.54 to 1.88, with SD 0.18–0.19, probability of any one patient being uncontrolled	• Reliever medication use (puffs/day) • FEV_1 (% predicted) • PEF (L/min) • Infections (all respiratory) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		>75%.		
Nabil 2014[108]	ICS (low dose) + LABA n=30 ICS (high dose) n =30	Stratum: ≥16 years Age – range 20–60 Patients had been treated with low dose of ICS prior to screening, either budesonide or beclometasone 400 ug total daily dose Study reports patients' asthma was uncontrolled, no further details	• FEV_1 (% predicted) Reported at 6 months	
Nelson 2000[115]	ICS (low dose) + LTRA n=222 ICS (low dose) + LABA=225	Stratum: ≥16 years Age – ICS + LABA mean 40.2, SD 14.4, ICS + LTRA mean 43.0, SD 13.7 Patients were on low doses of ICS at screening and for preceding 30 days Patients were symptomatic (one of average SABA use of 4 or more puffs per day, symptom score of 2 or more on 3 or more days, 3 or more nights with awakening due to asthma) during the last 7 days of a run-in period on low dose ICS	• Reliever medication use (puffs/day) • PEF (L/min) • FEV_1 (L) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
O'Byrne 2001[117]	ICS (low dose) + LABA n=323 ICS (low dose)=312	Stratum: ≥16 years Age – range of means 30.6–38.1 Patients had been taking low dose ICS for at least 3 months Patients required two more inhalations per week of reliever medication during last 2 weeks of run-in, a >15% variability in PEF or a >12% increase in FEV_1 after terbutaline.	• Severe exacerbations • Hospitalisations Reported at 1 year	Study contained 4 arms: budesonide 200 ug/day, budesonide 400 ug/day, budesonide 200 ug/day + LABA, budesonide 400 ug/day + LABA. The ICS only arms were combined, as were the ICS + LABA arms, as both ICS doses fell in the ICS low dose range. Hospitalisation data taken from health economics paper of the O'Byrne trial.
Paggiaro 2016[123]	ICS (low dose) + LAMA=154 ICS (low dose)=155	Stratum: ≥16 years Patients had been taking low dose ICS for at least 4 weeks Symptomatic at screening and randomisation; mean ACQ-7 score of ≥1.5. FEV_1 reversibility of ≥12% after 400ug salbutamol.	• FEV_1% predicted • PEF (L/min) • ACQ-7 Reported at 12 weeks	
Pavord 2007[130]	ICS (low dose) + LABA n=33 ICS (low dose) + LTRA n=33	Stratum: ≥16 years Age – ICS + LABA mean 36.3, SD 8.11, ICS + LTRA mean 34.4, SD 7.71 Patients were receiving a stable dose of low dose ICS prior to the trial	• Reliever medication use (% reliever free nights) • FEV_1 (L) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		and underwent a run-in period on low dose ICS for 2 weeks Patients had at least one of symptoms on at least 4 of the last 7 days of the run-in period or SABA use on at least 2 different days during the last 7 days of the run-in period		
Price 2011[136,137]	ICS (low dose) + LTRA n=169 ICS (low dose) + LABA n=181	Stratum: ≥16 years Age – range of means 49.7–51.0 All patients had been previously prescribed ICS of any dose, mean baseline dose was in the low dose ICS range Patients had "symptoms requiring an increase in therapy"	• Severe exacerbations (requiring OCS) • Quality of life (miniAQLQ) • Quality of life (EQ5D) • Asthma control (ACQ) • Hospitalisations • PEF (L/min) • Rescue medication (puffs/day) • Rescue medication use (puffs/night) Reported at 2 years	
Ringdal 2003[151]	ICS (low dose) + LTRA n=369 ICS (low dose) + LABA n=356	Stratum: ≥16 years Age – ICS + LTRA mean 43, ICS + LABA mean 43 Patients had used ICS low dose prior to screening, underwent a 4-week run-in period on low dose ICS During the run-in	• Reliever medication use (reliever free days) • FEV_1 (L) • PEF (L/min) • Infections (all respiratory) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		period, cumulative symptoms score (day and night) of ≥8 during last 7 days, and symptoms on at least 4 of last 7 days.		
Vaessen-Verberne 2010[179]	ICS (low dose) + LABA n=78 ICS (moderate dose) n=80	Stratum: 5 to <16 years Age – ICS + LABA mean 9.4, SD 1.8, ICS moderate dose mean 9.3 (1.9) Patients had used ICS low dose prior to screening, underwent a 4-week run-in period on low dose ICS During the run-in period, had a cumulative symptom score of ≥14 over the last 14 days of the run-in period. Symptoms were scored separately for cough, wheeze and shortness of breath with a daily maximum score of 18	• Severe exacerbations • FEV_1 (%predicted) Reported at 26 weeks	
Yurdakul 2003[195]	ICS high dose n=25 LTRA (without ICS) n=25 Theophylline (without ICS) n=24	Stratum: ≥16 years Age – mean ICS 35.9, mean LTRA 34.3, mean theophylline 33.5 Patients had previously been	• Reliever medication use (puffs/day) • FEV_1 (%predicted) Reported at 3 months	Baseline calculator used to estimate breakdown of patients by control status

Study	Intervention and comparison	Population	Outcomes	Comments
		using low dose ICS for at least 2 months prior to study Patients mean baseline Reliever inhalations per day 0.7, SD 0.2		

7.1.1.1.1 Patients over the age of 16

Table 45: Clinical evidence summary: ICS high dose versus ICS low dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with ICS (low dose)	 Risk difference with ICS (high dose) (95% CI)
Severe exacerbations (requiring OCS)	106 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.76 (0.33 to 1.73)	204 per 1000	49 fewer per 1000 (from 136 fewer to 149 more)
PEF (L/min)	93 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	-	The mean change in PEF (L/min) in the control groups was 4.4 L/min	The mean change in PEF (L/min) in the intervention groups was 15.1 higher (2.66 lower to 32.86 higher)
Infections (all respiratory)	106 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.78 (0.29 to 2.09)	148 per 1000	33 fewer per 1000 (from 105 fewer to 161 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 46: Clinical evidence summary: ICS low dose + LABA versus ICS low dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with ICS (low dose)	 Risk difference with ICS + LABA (95% CI)
Severe exacerbations (requiring OCS)	1272 (1 study) 1 years	LOW[a,b] due to risk of bias, indirectness	RR 0.57 (0.46 to 0.72)	-[d]	-[d]
Hospitalisations	1233 (1 study)	VERY LOW[a,d] due to risk of bias,	RR 0.55 (0.19 to	15 per 1000	7 fewer per 1000

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS + LABA (95% CI)
	1 years	indirectness, imprecision	1.64)		(from 12 fewer to 9 more)
Reliever medication use (reliever free days)	616 (1 study) 12 weeks	HIGH	-	The mean % of reliever free days in the control groups was 55.1 %	The mean % of reliever free days in the intervention groups was 8.6 higher (4.21 to 12.99 higher)
Reliever medication use (puffs/ day)	680 (1 study) 12 weeks	LOW[b,c] due to indirectness, imprecision	-	The mean change in puffs/day in the control groups was -2.1 puffs/day	The mean change in puffs/day in the intervention groups was 0.80 lower (1.28 to 0.32 lower)
PEF (L/min)	1296 (2 studies) 12 weeks	MODERATE[c] due to imprecision	-	The mean change in PEF (L/min) in the control groups was 23.8 L/min	The mean change in PEF (L/min) in the intervention groups was 19.48 higher (13.74 to 25.21 higher)
FEV_1 (L)	680 (1 study) 12 weeks	LOW[b,c] due to indirectness, imprecision	-	The mean change in FEV_1 (L) in the control groups was 0.41 L	The mean change in FEV_1 (L) in the intervention groups was 0.17 L higher (0.10 to 0.24 higher)
Infections (all respiratory)	616 (1 study) 12 weeks	LOW[c] due to imprecision	RR 1.11 (0.72 to 1.73)	121 per 1000	13 more per 1000 (from 34 fewer to 88 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the majority of the evidence had indirect outcomes or population, by 2 increments if the majority of the evidence had very indirect outcomes or population

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS + LABA (95% CI)
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
d Actual event numbers not reported					

Table 47: Clinical evidence summary: ICS low dose + LTRA versus ICS low dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with LTRA + ICS (95% CI)
Reliever medication use (puffs/day, % change from baseline)	393 (1 study) 16 weeks	HIGH	-	The mean change in reliever medication use (puffs/day, % change from baseline) in the control groups was 6.04 %	The mean reliever medication use (puffs/day, % change from baseline) in the intervention groups was 11.55 lower (25.59 lower to 2.49 higher)
FEV_1 (L)	393 (1 study) 16 weeks	HIGH	-	The mean change in FEV_1 (L) in the control groups was 0.02 L	The mean change in FEV_1 (L) in the intervention groups was 0.12 higher (0.06 to 0.18 higher)
PEF (L/min)	393 (1 study) 16 weeks	HIGH	-	The mean change in PEF (L/min) in the control groups was 2.65 L/min	The mean change in PEF (L/min) in the intervention groups was 7.76 higher (2.06 to 13.46 higher)
Infections (all respiratory)	393 (1 study) 16 weeks	MODERATE[a] due to imprecision	RR 0.92 (0.71 to 1.18)	395 per 1000	32 fewer per 1000 (from 115 fewer to 71 more)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 48: Clinical evidence summary: ICS low dose + theophylline versus ICS low dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with Theophylline (95% CI)
Severe exacerbations (requiring OCS)	103 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	RR 0.3 (0.09 to 1.01)	204 per 1000	143 fewer per 1000 (from 185 fewer to 2 more)
PEF (L/min)	83 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	-	The mean change in PEF (L/min) in the control groups was 4.4 L/min	The mean change in PEF (L/min) in the intervention groups was 17.4 higher (1.47 lower to 36.27 higher)
Infections (all respiratory)	103 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.69 (0.24 to 1.96)	148 per 1000	46 fewer per 1000 (from 113 fewer to 142 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 49: Clinical evidence summary: ICS low dose + LAMA versus ICS low dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS (low dose) + LAMA (95% CI)
FEV_1 (% predicted)	306 (1 study) 12 weeks	MODERATE[a] due to imprecision	-	The mean change in FEV_1 (%) in the control groups was 4.3%	The mean FEV_1 (% predicted) in the intervention groups was 4.7 higher (2.54 to 6.86 higher)
PEF (L/min)	304 (1 study) 12 weeks	MODERATE[a] due to imprecision	-	The mean change in PEF (L/min) in the control groups was -2.5 L/min	The mean PEF (L/min) in the intervention groups was 25.6 higher (15.21 to 35.99 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS (low dose) + LAMA (95% CI)
Asthma control (ACQ, 0-6, lower is better))	306 (1 study) 12 weeks	HIGH	-	The mean change in ACQ-7 in the control groups was 1.38	The mean asthma control (ACQ, 0-6, lower is better)) in the intervention groups was 0.06 higher (0.07 lower to 0.19 higher)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 50: Clinical evidence summary: ICS low dose + LABA versus ICS moderate dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with ICS + LABA (95% CI)
Severe exacerbations (requiring OCS)	446 (1 studies) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.89 (0.48 to 1.64)	92 per 1000	10 fewer per 1000 from 48 fewer to 59 more)
Hospitalisations	446 (1 studies) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	OR 6.93 (0.14 to 350.17)	0 per 1000	-[c]
PEF (L/min)	134 (1 study) 12 weeks	VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	-	-[e]	The mean change in PEF (L/min) in the intervention groups was 20.36 higher (3.16 lower to 37.56 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c Unable to calculate absolute effects as control group event rate is 0

d Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with ICS + LABA (95% CI)
e Control group data not presented separately					

Table 51: Clinical evidence summary: LTRA alone versus ICS high dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (high dose)	Risk difference with LTRA (95% CI)
Reliever medication use (puffs/day)	50 (1 study) 3 months	LOW[a] due to risk of bias	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.6 puffs/day	The mean change in reliever medication use (puffs/day) in the intervention groups was 0 higher (0.11 lower to 0.11 higher)
FEV_1 (%predicted)	50 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	-	The mean change in FEV_1 (%predicted) in the control groups was 4.8%	The mean change in FEV_1 (%predicted) in the intervention groups was 3.9 lower (6.8 to 1 lower)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 52: Clinical evidence summary: ICS low dose + LABA versus ICS high dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (high dose)	Risk difference with ICS + LABA (95% CI)
FEV_1 (%predicted)	60 (1 study) 6 months	VERY LOW[a,b, c] due to risk of bias, imprecision, indirectness	-	The mean FEV_1 (%predicted) in the control groups was 62%	The mean FEV_1 (%predicted) in the intervention groups was 3.7 higher

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (high dose)	Risk difference with ICS + LABA (95% CI)
					(1.35 to 6.05 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population

Table 53: Clinical evidence summary: LTRA alone versus theophylline alone

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Theophylline	Risk difference with LTRA (95% CI)
Reliever medication use (puffs/day)	49 (1 study) 3 months	LOW[a] due to risk of bias	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.6 puffs/day	The mean change in reliever medication use (puffs/day) in the intervention groups was 0 higher (0.09 lower to 0.09 higher)
FEV_1 (%predicted)	49 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	-	The mean change in FEV_1 (%predicted) in the control groups was 0.5%	The mean change in FEV_1 (%predicted) in the intervention groups was 0.4 higher (1.66 lower to 2.46 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 54: Clinical evidence summary: ICS high dose versus ICS low dose + theophylline

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Theophylline	Risk difference with ICS (high dose) (95% CI)
Severe exacerbations (requiring OCS)	101 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.51 (0.71 to 8.93)	61 per 1000	92 more per 1000 (from 18 fewer to 486 more)
PEF (L/min)	86 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	-	The mean change in PEF (L/min) in the control groups was 21.8 L/min	The mean change in PEF (L/min) in the intervention groups was 2.3 lower (22.92 lower to 18.32 higher)
Infections (all respiratory)	101 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.13 (0.37 to 3.47)	102 per 1000	13 more per 1000 (from 64 fewer to 252 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 55: Clinical evidence summary: ICS high dose versus theophylline alone

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Theophylline	Risk difference with ICS (high dose) (95% CI)
Reliever medication use (puffs/day)	50 (1 study) 12 weeks	LOW[a] due to risk of bias	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.6 puffs/day	The mean change in reliever medication use (puffs/day) in the intervention groups was 0 higher (0.09 lower to 0.09 higher)
FEV_1 (%predicted)	49 (1 study)	VERY LOW[a,b] due to risk of	-	The mean change in FEV_1 (%predicted) in the control groups was	The mean change in FEV_1 (%predicted) in the intervention groups was 0.4 higher

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Theophylline	Risk difference with ICS (high dose) (95% CI)
	12 weeks	bias, imprecision		0.5 %	(1.66 lower to 2.46 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 56: Clinical evidence summary: ICS low dose + LTRA versus ICS low dose + LABA

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA	Risk difference with ICS + LTRA (95% CI)
Severe exacerbations (requiring OCS)	3294 (3 studies) 48–104 weeks	LOW[a,c] due to risk of bias, imprecision	RR 1.09 (0.94 to 1.26)	181 per 1000	15 more per 1000 (from 10 fewer to 44 more)
Quality of life (AQLQ/mini AQLQ, 1–7, higher is better outcome)	3260 (3 studies) 48–104 weeks	MODERATE[a] due to risk of bias	-	-[d]	The mean quality of life (mini AQLQ) in the intervention groups was 0.08 lower (0.15 lower to 0.01 higher)
Quality of life (EQ-5D, 0–1, higher is better outcome)	330 (1 study) 104 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean EQ-5D final value in the control groups was 0.798	The mean quality of life (EQ-5D) in the intervention groups was 0.01 higher (0.05 lower to 0.07 higher)
Asthma control (ACQ, 0–6, lower is better outcome)	296 (1 study) 104 weeks	LOW[a,b] due to risk of bias, indirectness	-	-[d]	The mean asthma control (ACQ) in the intervention groups was 0.06 lower (0.24 lower to 0.12 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA	Risk difference with ICS + LTRA (95% CI)
Hospitalisations	3287 (3 studies) 48–104 weeks	LOW[a,c] due to imprecision	OR 0.65 (0.31 to 1.37)	10 per 1000	4 fewer per 1000 (from 7 fewer to 4 more)
Reliever medication use (puffs/day)	2099 (3 studies) 12–104 weeks	MODERATE[a] due to risk of bias	-	-[d]	The mean reliever medication use (puffs/day) in the intervention groups was 0.41 higher (0.39 to 0.44 higher)
Reliever medication use (puffs/night)	162 (1 study) 104 weeks	VERY LOW[a,b] due to risk of bias, indirectness	-	The mean reliever medication use (puffs/night) in the control groups was 0.63 puffs/night	The mean reliever medication use (puffs/night) in the intervention groups was 0.06 higher (0.24 lower to 0.36 higher)
Reliever medication use (% reliever-free nights)	66 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-	-[d]	The mean % reliever-free nights in the intervention groups was 16.5 lower (33.87 lower to 0.87 higher)
Reliever medication use (reliever-free days during study period)	725 (1 study) 12 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 0.77 (0.61 to 0.97)	-[d]	-[d]
FEV_1 (L)	2728 (4 studies) 12-48 weeks	MODERATE[a] due to risk of bias	-	-[d]	The mean FEV_1 (L) in the intervention groups was 0.14 lower

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA	Risk difference with ICS + LTRA (95% CI)
					(0.14 to 0.13 lower)
FEV_1 (% predicted)	1473 (1 study) 48 weeks	HIGH	-	The mean change in FEV_1 (% predicted) in the control group was 5.12%	The mean FEV_1 (% predicted) in the intervention groups was 1.98 lower (2.95 to 1.01 lower)
PEF (L/min)	4316 (5 studies) 12-104 weeks	MODERATE[a] due to risk of bias	-	-[d]	The mean PEF (L/min) in the intervention groups was 11.97 lower (12.36 to 11.59 lower)
Infections (all respiratory)	1157 (2 studies) 12-104 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.89 (0.74 to 1.07)	251 per 1000	28 fewer per 1000 (from 65 fewer to 18 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d Adjusted control group event rates/final values/change scores not reported

7.1.1.1.2 Patients aged 5–16

Table 57: Clinical evidence summary: ICS moderate dose versus ICS low dose

Outcomes	Number of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with ICS (low dose)	Risk difference with ICS (moderate) (95% CI)
Reliever medication use (puffs/day)	197 (1 study) 12 weeks	HIGH	-	The mean change in reliever medication use (puffs/day) in the control groups was -0.49 puffs/day	The mean change in reliever medication use (puffs/day) in the intervention groups was 0.15 higher (0.31 lower to 0.61 higher)
FEV_1 (% predicted)	197 (1 study) 12 weeks	HIGH	-	The mean change in FEV_1 (% predicted) in the control groups was 5.74 % predicted	The mean change in FEV_1 (% predicted) in the intervention groups was 0.74 lower (5.35 lower to 3.87 higher)
PEF (L/min)	197 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean change in PEF (L/min) in the control groups was 25.8 L/min (change score)	The mean change in PEF (L/min) in the intervention groups was 10.0 lower (26.69 lower to 6.69 higher)
Infections (all respiratory)	197 (1 study) 12 weeks	LOW[b] due to imprecision	RR 0.52 (0.05 to 5.59)	20 per 1000	10 fewer per 1000 (from 19 fewer to 92 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 58: Clinical evidence summary: ICS low dose + LABA versus ICS low dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS + LABA (95% CI)
Severe exacerbations (requiring OCS)	26 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 3.67 (0.5 to 27.12)	91 per 1000	243 more per 1000 (from 45 fewer to 1000 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS + LABA (95% CI)
Quality of life (PAQLQ)	25 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision		-[d]	The mean quality of life (PAQLQ) in the intervention groups was 0.73 lower (1.75 lower to 0.29 higher)
Hospitalisations	26 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 6.08 (0.35 to 106.55)	0 per 1000	-[e]
FEV_1 (%predicted)	21 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	-[d]	The mean FEV_1 (%predicted) in the intervention groups was 8.58 higher (3.56 lower to 20.72 higher)
Infections (all respiratory)	245 (2 studies) 12-48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.84 (0.55 to 1.29)	273 per 1000	44 fewer per 1000 (from 123 fewer to 79 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d Adjusted final values/change scores not available

e Could not be calculated as no events in control group

Table 59: Clinical evidence summary: ICS low dose + LTRA versus ICS low dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS + LTRA (95% CI)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (low dose)	Risk difference with ICS + LTRA (95% CI)
Severe exacerbations (requiring OCS)	23 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.92 (0.06 to 12.95)	91 per 1000	7 fewer per 1000 (from 85 fewer to 1000 more)
Quality of life (PAQLQ)	22 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	-[d]	The mean quality of life (PAQLQ) in the intervention groups was 0.12 higher (0.94 lower to 1.18 higher)
Hospitalisations	23 (1 study) 48 weeks	LOW[a,b] due to risk of bias, indirectness	Unable to calculate[e]	See comment[e]	-
FEV_1 (%predicted)	23 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	-[d]	The mean FEV_1 (%predicted) in the intervention groups was 3.51 higher (9.22 lower to 16.24 higher)
Infections (all respiratory)	40 (1 study) 48 weeks	VERY LOW[a,b] due to risk of bias, indirectness, imprecision	RR 0.9 (0.39 to 2.1)	368 per 1000	37 fewer per 1000 (from 225 fewer to 405 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d Adjusted final values/change scores not available

e No events in either arm

Table 60: Clinical evidence summary: ICS low dose + LTRA versus ICS low dose + LABA

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA	Risk difference with ICS + LTRA (95% CI)
Severe exacerbations (requiring OCS)	27 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.25 (0.03 to 1.86)	333 per 1000	250 fewer per 1000 (from 323 fewer to 287 more)
Quality of life (PAQLQ)	27 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	-[d]	The mean quality of life (PAQLQ) in the intervention groups was 0.84 higher (0.1 lower to 1.78 higher)
Hospitalisations	27 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 0.15 (0.01 to 2.64)	133 per 1000	111 fewer per 1000 (from 132 fewer to 156 more)
FEV_1 (%predicted)	28 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	-[d]	The mean FEV_1 (%predicted) in the intervention groups was 5.07 lower (16.7 lower to 6.56 higher)
Infections (all respiratory)	44 (1 study) 48 weeks	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.85 (0.39 to 1.88)	391 per 1000	59 fewer per 1000 (from 239 fewer to 344 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Adjusted final values/change scores not available

Table 61: Clinical evidence summary: ICS low dose + LABA versus ICS moderate dose

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS (moderate dose)	Risk difference with ICS + LABA (95% CI)
Severe exacerbations (requiring OCS)	151 (1 study) 26 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.19 (0.69 to 6.98)	51 per 1000	60 more per 1000 (from 16 fewer to 303 more)
FEV_1 (%predicted)	158 (1 study) 26 weeks	MODERATE[a] due to risk of bias	-	-[c]	The mean FEV_1 (%predicted) in the intervention groups was 1.00 higher (2.2 lower to 4.2 higher)
PEF (L/min, change score)	265 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-	The mean PEF (L/min, change score) in the control groups was 18.4 L/min (change score)	The mean PEF (L/min, change score) in the intervention groups was 9.3 higher (3.28 to 15.32 higher)
Adherence	303 (1 study) 12 weeks	MODERATE[a] due to risk of bias	RR 0.98 (0.92 to 1.04)	920 per 1000	19 fewer per 1000 (from 75 fewer to 38 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c Adjusted control group values not provided

7.1.1.2 Economic evidence

Published literature

Three health economic studies were identified with the relevant comparison and have been included in this review. [78,94,136] These are summarised in the economic evidence profile below and the economic evidence tables in Appendix I.

One economic study relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations. [43] This is listed in Appendix M, with reasons for exclusion given.

See also the health economic article selection flow chart in Appendix F.

Unit costs

Full details on medication costs can be found in Appendix O.

Table 62: Economic evidence profile: low dose ICS versus ICS + LABA in adults

Study	Applicability	Limitations	Other comments	Incremental cost (2-1)	Incremental effects (2-1)	Cost effectiveness	Uncertainty
Jönsson 2004 [78] Sweden	Partially applicable [(a)]	Potentially serious limitations[(b)]	CEA within-trial analysis (RCT) Population: Group B from OPTIMA. Taking up to 400 µg per day of inhaled budesonide or equivalent for 3 months and a FEV_1 of ≥70% predicted normal Two comparators: 1) low dose ICS 2) low dose ICS + LABA Time horizon: 1 year	**Total costs (mean per patient):** £112	**Severe exacerbations (mean per patient):** -0.57 **Symptom free days (mean per patient):** 10	£196.50 per severe exacerbation avoided £11.20 per symptom free day	Applied unit costs from the UK and Spain to the entire population. This did not significantly change the overall results.

Abbreviations: CEA: cost-effectiveness analysis; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA; long-acting beta-adrenoceptor agonist
(a) Swedish healthcare system may not be reflective of UK NHS. Quality of life not included as an outcome
(b) Costs from published Swedish literature rather than national statistics/data. Sensitivity analysis only conducted around country of unit costs and not effectiveness parameters

Table 63: Economic evidence profile: ICS + LABA versus ICS + LTRA in adults

Study	Applicability	Limitations	Other comments	Incremental cost (2-1)	Incremental effects (2-1)	Cost effectiveness	Uncertainty
Price 2011 [136] UK	Directly applicable	Potentially serious limitations[(a)]	CUA within-trial analysis (RCT) Population: Patient with diagnosed asthma not receiving steroids in the previous 12 weeks Two comparators: 1) ICS + LABA	**Total NHS costs (mean per patient):** £113	**QALYs (mean per patient):** 0.053 Adjusted[(b)]: 0.009 **MiniAQLQ**	ICS+LTRA costs £11,919 per QALY gained compared to ICS+LABA using adjusted QALYs	Probability of LTRAs being cost effective at a £20,000 per QALY threshold: 55%

Study	Applicability	Limitations	Other comments	Incremental cost (2-1)	Incremental effects (2-1)	Cost effectiveness	Uncertainty
			2) ICS + LTRA Time horizon: 2 years		**(mean per patient):** 0.037 Adjusted I[(b)]: 0.034		

Abbreviations: CUA: cost-utility analysis ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Montelukast is now out of patent which reduces the price significantly since the date of study. This would increase the cost effectiveness of ICS+LTRA and possibly see it as cost-saving compared to ICS+LABA and therefore dominant. The main concern is that the pragmatic nature of the RCT on which the evaluation is based may not reflect the true treatment effect sizes

(b) Including imputed data and adjusted for baseline values

Table 64: Economic evidence profile: ICS + LABA versus ICS + LTRA in 5–16 year olds

Study	Applicability	Limitations	Other comments	Total cost	Health outcomes	Cost effectiveness	Uncertainty
Lenney 2013[94] UK	Partially applicable [(a)]	Potentially serious limitations[(b)]	CUA within-trial analysis (RCT) Population: Aged from 6 years to 14 years 11 months, uncontrolled on ICS defined as required 7 or more puffs of SABA in the past 7 days Three comparators: 1) Low dose ICS 2) ICS + LABA 3) ICS + LTRA Time horizon: 2 years	ICS: £144.75 ICS + LABA: £458.80 ICS + LTRA: £447.99	**QALYS:** ICS: 0.09 ICS + LABA: 0.12 ICS + LTRA: 0.13	**ICER:** ICS + LABA versus ICS: £12,054 ICS + LTRA versus ICS: £6,827 ICS + LTRA versus ICS + LABA: (ICS + LTRA dominates)	ICS + LTRA has an 80% probability of being cost-effective compared to ICS at £30,000 threshold.

Abbreviations: CUA: cost-utility analysis ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) QALYs estimated using PAQLQ as a proxy and converting onto a 0–1 scale rather than using a validated mapping algorithm.

(b) Number of study participants is very small meaning the clinical benefit is very uncertain.

7.1.1.3 Original cost-effectiveness analysis for the review question: in people with a clinician diagnosis of asthma who are uncontrolled on low dose ICS, what is the most clinical and cost-effective second-line preventer?

This section summarises how the cost-effectiveness analysis for this review question was conducted. A full, comprehensive breakdown of the model can be found in Appendix N.

Population

Adults (≥16 years) with a clinician diagnosis of asthma who are uncontrolled on an optimal first-line preventer (low dose ICS) and have never been prescribed second-line preventer medication. Note that a model for children was not built due to insufficient evidence. Therefore, the results and methods of this model should be viewed in the context of an adult population only.

Comparators

The four comparisons under consideration for this analysis were:

1. Low dose ICS + LABA
2. Low dose ICS + LTRA
3. Low dose ICS (do nothing approach)
4. Moderate dose ICS

All of the strategies included assume the use of SABAs for short-term symptom relief.

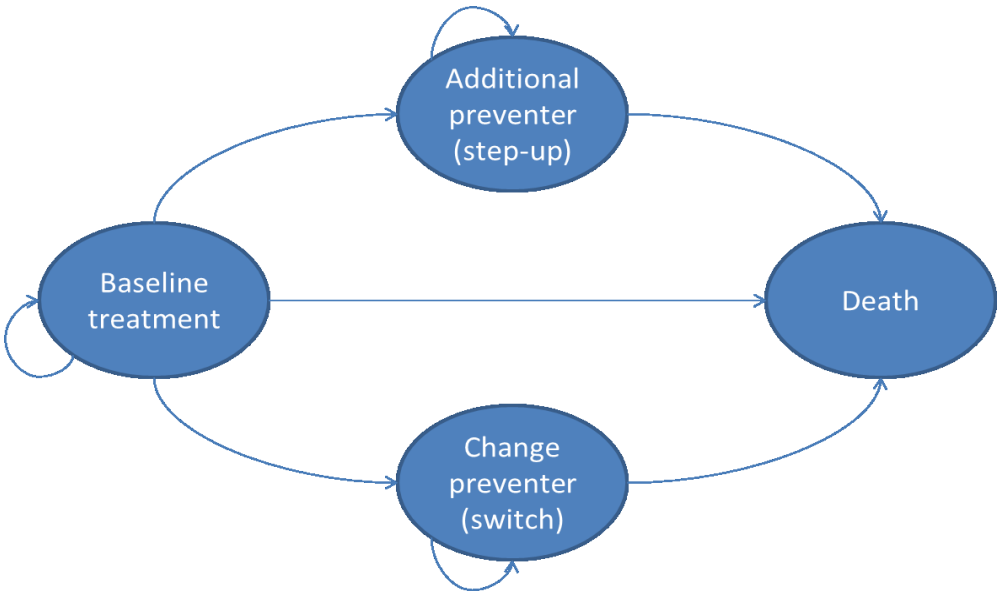
Once the cost effectiveness of these four comparisons was established the cost effectiveness of other comparators that did not have sufficient data to model was inferred.

Time horizon, perspective, discount rate used and uncertainty

The analysis followed the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects. A sensitivity analysis using a discount rate of 1.5% for costs and health effects was conducted. A lifetime time horizon was adopted and a 10-year time horizon was looked at in a sensitivity analysis. Using a shorter time horizon and decreasing the discount rate will assess whether the timing of costs and health outcomes is crucial in determining the cost effectiveness. The analysis was undertaken using an NHS/PSS perspective. The model was built probabilistically to take account of the uncertainty around input parameter point estimates. Model assumptions were also tested in various sensitivity analyses. These are outlined in the full model write-up in Appendix N. They are outlined in brief in Table 66.

Model structure

Figure 3: Markov model structure



Movement through the model

The model follows a simple Markov structure with four states: baseline treatment, stepped-up treatment, switched treatment and death. All individuals start in the baseline treatment state. As time goes on the individual either responds or does not respond to their treatment. If the individual responds well to the treatment, then they continue to stay on the baseline treatment until the model simulation ends. If the individual does not respond to treatment, then they either switch to another second line preventer or they have an additional second line preventer added onto their current therapy. In the model if the individual starts on low dose ICS+LTRA then they can either have LABA replace the LTRA (switch) or have a LABA added onto their therapy (step-up).An assumption was made that if the individual starts on a single ICS inhaler and their asthma remains uncontrolled they will always have an additional preventer added (step-up) as opposed to having their dose increased. This is in line with best practice. The Markov model runs using a 1-month cycle length; this cycle length was deemed necessary to capture the movement between health states, such as the probability of responding to treatment which is likely to occur soon after treatment is administered.

Health outcomes

Health outcomes used in the model are quality of life (utility) values, which are all dependent on the treatment assigned to the individual in the model. Utility values were derived from the clinical review for each treatment option and are discussed in the full model write up in Appendix N.

Utilities are adjusted by disutilities due to exacerbations, which are also dependent on treatment. These disutilities are calculated based on the number of exacerbations during one cycle and the disutility associated with each exacerbation event. The sources of data used to inform exacerbation rates are discussed in the full model write-up in Appendix N.

Costs

The costs experienced in each state mainly correspond to the treatment the individual is receiving, therefore if the individual experiences a treatment change they move to the corresponding health

state where the cost takes into account the new treatment cost. Additional costs are also added for resource utilisation such as unscheduled GP visits and costs associated with exacerbations. Exact details and breakdowns of these costs can be found in the full model write-up in Appendix N.

Results

The results below in Table 65 show that low dose ICS + LTRAs have the highest net monetary benefit and are therefore the most cost effective way of managing asthma for this patient population. Low dose ICS + LABAs produce the highest number of QALYs however are not deemed cost effective at a £20,000 per QALY threshold. Continuing on low-dose ICS produces the least QALYs and the highest cost. The results from the sensitivity analyses show that the cost-effectiveness rankings do not change across a wide range of changes to the model. A more detailed breakdown of how costs and QALYs changed for each sensitivity analysis can be found in the full model write-up in Appendix N.

Table 65: Base case results (probabilistic)

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold	Probability of being cost effective at £20,000 threshold
	QALYs	Cost				
ICS + LTRA	16.222	£3,923	£320,514	1	-	71%
Moderate dose ICS	16.221	£4,653	£319,764	3	Dominated	13%
ICS + LABA	16.234	£4,639	£320,049	2	£56,977	12%
Low dose ICS	16.113	£5,068	£317,191	4	Dominated	3%

Table 66: Sensitivity analyses

Sensitivity analysis	Cost-effectiveness ranking			
	Low dose ICS	Low dose ICS + LABA	Low dose ICS + LTRA	Moderate dose ICS
Use cheapest medication brand	4	2	1	3
Double length of exacerbations	4	2	1	3
Half the length of exacerbations	4	2	1	3
Decrease the disutility associated with exacerbations	4	2	1	3
Reduce the time horizon to 10 years	4	2	1	3
Assume no treatment switching for those taking low dose/moderate dose ICS	4	3	1	2
Assume equal treatment switching for those taking low dose/moderate dose ICS	4	2	1	3

Sensitivity analysis	Cost-effectiveness ranking			
	Low dose ICS	Low dose ICS + LABA	Low dose ICS + LTRA	Moderate dose ICS
Reduce hospitalisations for low dose ICS	4	2	1	3
Use 1.5% discount rate for costs and effects	4	2	1	3
Reduce exacerbation rate for ICS + LTRA	4	2	1	3
Increase the exacerbation rate for ICS + LTRA	4	2	1	3
Add an additional GP visit for those starting on ICS+LTRA	4	2	1	3
Increase the disutility from starting on ICS+LTRA	4	2	1	3

Summary of results

The results show that low dose ICS + LTRA is the most cost-effective treatment to start on for individuals whose asthma has remained uncontrolled on low dose ICS alone.

The clinical review highlighted that the main benefit of choosing ICS + LABA over ICS + LTRA was a reduction in the number of exacerbations. There was no evidence that it impacted hospitalised exacerbations, though due to the small number of hospitalisations a study would need thousands of participants to be adequately powered. Finally, there was some evidence that LABAs improved quality of life though this was only statistically significant in one study and even then did not pass the minimal important difference. However, in the model a small quality of life benefit was given to those who started on LABA as shown in the study by Price et al. These additional benefits lead to a 0.011 increase in QALYs for individuals starting on ICS + LABAs across a lifetime horizon when compared to those starting on ICS + LTRA. However, the NHS incurs an additional £730 across this period, meaning these additional benefits were not considered cost effective at a £20,000 per QALY threshold. All other treatment options in the model were dominated by ICS + LTRA. Indirect evidence showed that ICS + LTRA led to better outcomes than moderate or low dose ICS. Although low dose ICS costs less than ICS + LTRA, it became a dominated option when the additional costs of exacerbations were considered.

In all the sensitivity analyses ICS + LTRA remained the most cost-effective option. These sensitivity analyses aimed to test the robustness of the model's results. One sensitivity analysis explored the impact of extending the period of time the disutility lasts from an exacerbation to the highest plausible limit. Although this increased the amount of QALYs gained by choosing ICS + LABA, the most effective option, it did not make it cost effective. Likewise exploring a 'worst-case scenario' by making the exacerbation rate for ICS + LTRA as high as the 95% confidence interval's upper limit did not make ICS + LABA a cost-effective option to start patients on. Using the cheapest branded medication for all treatment options did not close the cost difference between treatments by a higher enough amount to change the cost-effectiveness rankings. It is worth noting that the data on prescriptions shows that ICS + LABA dual inhalers are prescribed frequently across multiple brands, whereas most other treatment options are predominantly prescribed by a single brand. Therefore it is unlikely that the cheapest brand of ICS + LABA inhalers would be predominantly provided unless there were significant changes in prescribing patterns. Many of the model's assumptions biased against the use of ICS + LTRA so the relaxation of these assumptions strengthened the model's conclusion.

Finally, the sensitivity analyses explored the main model assumption concerning treatment switching for those starting on low dose and moderate dose ICS as no data were available on this. Completely removing treatment switching for these options or increasing the rate at which it occurred did not change the conclusions concerning the cost effectiveness of ICS + LTRA. However it is worth noting that increasing treatment switching for moderate dose ICS made it a more costly option than starting individuals on ICS + LABA straight away.

Limitations

The main limitation of the model was that direct evidence only existed against ICS + LABA. There was no direct evidence between low dose ICS, moderate dose ICS and ICS + LTRA. The committee noted that for low dose ICS the clinical evidence was so conclusive that this treatment option was worse than ICS + LABA that it would be highly unlikely for a direct comparison between ICS + LTRA and low dose ICS to alter the model's conclusions. For moderate dose ICS the clinical evidence was less clear

cut. However, the committee noted that moderate dose ICS costs more than ICS + LTRA. This cost is exacerbated when one considers that stepping up medication would likely involve staying on the same dose but adding an additional preventer. The committee felt it would be unlikely for a clinician to step down the medication dose and add an additional preventer. This means that it is highly likely that moderate dose ICS costs more than ICS + LTRA. Therefore, for moderate dose to be considered cost effective it would need to produce better clinical outcomes than ICS + LTRA. The committee felt this was unlikely given the clinical evidence presented but also that such a study is not likely to ever be conducted.

Many of the model assumptions biased against the use of ICS + LTRA. The committee noted that when the pragmatic trial by Price et al. was conducted, LTRAs were not a commonly used treatment. Therefore clinicians would be more likely to switch patients over to LABAs, given they are the predominantly used treatment. This means that the amount of treatment switching that occurs for ICS + LTRA in the model is likely an over-estimate and that the amount of clinically indicated treatment switching would likely be lower. Secondly the disutility from exacerbating is based on a single study. The committee noted that although exacerbating has a significant impact on quality of life the disutility values determined by the study seemed very high. It was felt that quality of life may fall to this level however would perhaps not remain this low for the full duration used in the model. Finally, the non-exacerbation-related healthcare costs remained higher for ICS + LTRA throughout the model. The committee felt that over time these costs could become much closer once people who did not respond to LTRAs had switched to LABAs.

7.1.1.4 Conclusion

An original economic evaluation found that the most cost-effective treatment option for individuals who remain uncontrolled on low dose ICS alone was to trial ICS + LTRA. This option dominated starting on low dose and moderate dose ICS, and the ICER for starting on ICS + LABA was £56,977 per QALY, above the £20,000 per QALY threshold.

Evidence statements

7.1.1.5 Clinical

People over the age of 16

ICS high dose versus ICS low dose

- Clinical benefit in terms of severe exacerbations (1 study, 106 participants, Very Low quality evidence)
- No clinical difference in terms of PEF (L/min) (1 study, 93 participants, Very Low quality evidence)
- No clinical difference in terms of infections (all respiratory) (1 study, 106 participants, Very Low quality evidence)

ICS low dose + LABA versus ICS low dose

- Clinical benefit in terms of severe exacerbations (1 study, 1272 participants, Low quality evidence)
- Clinical benefit in terms of hospitalisations (1 study, 1233 participants, Very Low quality evidence)
- No clinical difference in terms of reliever medication use (reliever free days) (1 study, 616 participants, High quality evidence)

- Clinical benefit in terms of reliever medication use (puffs/day) (1 study, 680 participants, Low quality evidence)
- Clinical benefit in terms of PEF (L/min) (2 studies, 1296 participants, Moderate quality evidence)
- Clinical benefit in terms of FEV_1 (L) (2 studies, 1296 participants, Low quality evidence)
- No clinical difference in terms of infections (all respiratory) (1 study, 616 participants, Low quality evidence)

ICS low dose + LTRA versus ICS low dose

- No clinical difference in terms of reliever medication use (puffs/day, % change from baseline) (1 study, 393 participants, High quality evidence)
- No clinical difference in terms of FEV_1 (L) (1 study, 393 participants, High quality evidence)
- No clinical difference in terms of PEF (L/min) (1 study, 393 participants, High quality evidence)
- No clinical difference in terms of infections (all respiratory) (1 study, 393 participants, Moderate quality evidence)

ICS low dose + theophylline versus ICS low dose

- Clinical benefit in terms of severe exacerbations (1 study, 103 participants, Low quality evidence)
- No clinical difference in terms of PEF (L/min) (1 study, 83 participants, Very Low quality evidence)
- Clinical benefit in terms of infections (all respiratory) (1 study, 103 participants, Very Low quality evidence)

ICS low dose + LAMA versus ICS low dose

- No clinical difference in terms of FEV_1 (%) (1 study, 306 participants, Moderate quality evidence)
- Clinical benefit in terms of PEF (L/min) (1 study, 304 participants, Moderate quality evidence)
- No clinical difference in terms of asthma control (ACQ-7) (1 study, 306 participants, High quality evidence)

ICS low dose + LABA versus ICS moderate dose

- Clinical benefit in terms of severe exacerbations (1 study, 446 participants, Very Low quality evidence)
- No clinical difference in terms of hospitalisations (1 study, 446 participants, Very Low quality evidence)
- Clinical benefit in terms of PEF (L/min) (1 study, 134 participants, Very Low quality evidence)

LTRA alone versus ICS high dose

- No clinical difference in terms of reliever medication use (1 study, 50 participants, Low quality evidence)
- Clinical harm in terms of FEV_1 (%predicted) (1 study, 50 participants, Very Low quality evidence)

ICS low dose + LABA versus ICS high dose

- Clinical benefit in terms of FEV_1 (%predicted) (1 study, 60 participants, Very Low quality evidence)

LTRA alone versus theophylline alone

- No clinical difference in terms of reliever medication use (puffs/day) (1 study, 49 participants, Low quality evidence)
- No clinical difference in terms of FEV_1 (%predicted) (1 study, 49 participants, Very Low quality evidence)

ICS high dose versus ICS low dose + theophylline

- Clinical harm in terms of severe exacerbations (1 study, 101 participants, Very Low quality evidence)
- No clinical difference in terms of PEF (L/min) (1 study, 86 participants, Very Low quality evidence)
- No clinical difference in terms of infections (all respiratory) (1 study, 101 participants, Very Low quality evidence)

ICS high dose versus theophylline alone

- No clinical difference in terms of reliever medication use (puffs/day) (1 study, 50 participants, Low quality evidence)
- No clinical difference in terms of FEV_1 (%predicted) (1 study, 49 participants, Very Low quality evidence)

ICS low dose + LTRA versus ICS low dose + LABA

- No clinical difference in terms of severe exacerbations (3 studies, 3294 participants, Low quality evidence)
- No clinical difference in terms of quality of life (AQLQ/mini AQLQ) (3 studies, 3260 participants, Moderate quality evidence)
- No clinical difference in terms of quality of life (EQ-5D) (1 study, 330 participants, Very Low quality evidence)
- No clinical difference in terms of asthma control (ACQ) (1 study, 296 participants, Low quality evidence)
- No clinical difference in terms of hospitalisations (3 studies, 3287 participants, Low quality evidence)
- No clinical difference in terms of reliever medication use (puffs/day) (3 studies, 2099 participants, Moderate quality evidence)
- No clinical difference in terms of reliever medication use (puffs/night) (1 study, 162 participants, Very Low quality evidence)
- No clinical difference in terms of reliever medication use (% reliever free nights) (1 study, 66 participants, Moderate quality evidence)
- No clinical difference in terms of reliever medication use (reliever free days during study period) (1 study, 725 participants, Very Low quality evidence)
- No clinical difference in terms of FEV_1 (L) (4 studies, 2728 participants, Moderate quality evidence)
- Clinical harm in terms of FEV_1 (%predicted) (1 study, 1473 participants, High quality evidence)

- No clinical difference in terms of PEF (L/min) (5 studies, 4316 participants, Moderate quality evidence)
- No clinical difference in terms of infections (all respiratory) (2 studies, 1157 participants, Very Low quality evidence)

Young people and children between the ages of 5 and 16

ICS moderate dose versus ICS low dose

- No clinical difference in terms of reliever medication use (puffs/day) (1 study, 197 participants, High quality evidence)
- No clinical difference in terms of FEV_1 (%predicted) (1 study, 197 participants, High quality evidence)
- No clinical difference in terms of PEF (L/min) (1 study, 197 participants, Low quality evidence)
- No clinical difference in terms of infections (all respiratory) (1 study, 197 participants, Low quality evidence)

ICS low dose + LABA versus ICS low dose

- Clinical harm in terms of severe exacerbations (1 study, 26 participants, Very Low quality evidence)
- Clinical harm in terms of quality of life (pAQLQ) (1 study, 25 participants, Very Low quality evidence)
- No clinical difference in terms of hospitalisations (1 study, 26 participants, Very Low quality evidence)
- Clinical benefit in terms of FEV_1 (%predicted) (1 study, 21 participants, Very Low quality evidence)
- No clinical difference in terms of infections (all respiratory) (2 studies, 245 participants, Very Low quality evidence)

ICS low dose + LTRA versus ICS low dose

- No clinical difference in terms of severe exacerbations (1 study, 23 participants, Very Low quality evidence)
- No clinical difference in terms of quality of life (pAQLQ) (1 study, 22 participants, Very Low quality evidence)
- No clinical difference in terms of hospitalisations (1 study, 23 participants, Low quality evidence)
- Clinical benefit in terms of FEV_1 (%predicted) (1 study, 23 participants, Very Low quality evidence)
- No clinical difference in terms of infections (all respiratory) (1 study, 40 participants, Very Low quality evidence)

ICS low dose + LTRA versus ICS low dose + LABA

- Clinical benefit in terms of severe exacerbations (1 study, 27 participants, Very Low quality evidence)
- Clinical benefit in terms of quality of life (pAQLQ) (1 study, 27 participants, Very Low quality evidence)

- Clinical benefit in terms of hospitalisations (1 study, 27 participants, Very Low quality evidence)
- No clinical difference in terms of FEV_1 (%predicted) (1 study, 28 participants, Very Low quality evidence)
- No clinical difference in terms of infections (all respiratory) (1 study, 44 participants, Very Low quality evidence)

ICS low dose + LABA versus ICS moderate dose

- Clinical harm in terms of severe exacerbations (1 study, 151 participants, Very Low quality evidence)
- No clinical difference in terms of FEV_1 (%predicted) (1 study, 158 participants, Moderate quality evidence)
- No clinical difference in terms of PEF (L/min) (1 study, 265 participants, Moderate quality evidence)
- No clinical difference in terms of adherence (1 study, 303 participants, Moderate quality evidence)

7.1.1.6 Economic

- An original cost-utility analysis found that low dose ICS + LABA was not cost effective compared to low dose ICS + LTRA (ICER: £56,977 per QALY). Low dose ICS + LTRA was the most cost-effective option, dominating moderate dose ICS and low dose ICS alone for treating individuals with asthma more than 16 years of age. This analysis was assessed as directly applicable with minor limitations.
- One cost–utility analysis found that low dose ICS + LTRA was cost effective relative to ICS + LABA for treating individuals with asthma over 16 years of age (ICER: £11,919 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.
- One cost-effectiveness analysis found that for individuals with asthma over 16 years of age low dose ICS + LABA was more costly and more effective than low dose ICS alone (£196.50 per severe exacerbation avoided). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that low dose ICS + LTRA was cost effective compared to low dose ICS alone (ICER: £6,827 per QALY gained) and low dose ICS + LABA (dominant: less costly and more effective) for treating individuals with asthma less than 16 years of age. This analysis was assessed as directly applicable with potentially serious limitations.

7.1.1.7 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80

Research recommendation	**2. Is maintenance therapy more effective with a paediatric low dose of ICS plus a leukotriene receptor antagonist (LTRA) or with a paediatric low dose of ICS plus a long-acting beta$_2$ agonist (LABA) in the treatment of asthma in children and young people (under 16) who have uncontrolled asthma on a paediatric low dose of ICS alone?**
Relative values of different outcomes	The committee considered the following outcomes as critical for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee considered the following outcomes as important: asthma control (as assessed by a validated questionnaire), hospital admission, SABA use, lung function (FEV_1 or morning PEF) and adverse events.
Quality of the clinical evidence	The quality of the evidence ranged from High to Very Low, but the majority was either Low or Very Low quality. In most cases this was due to either risk of bias or imprecision, or a combination of the two. The majority of the evidence compared possible additional preventers (or higher doses of ICS) with low dose ICS/placebo. There was limited evidence directly comparing additional preventers. There was little evidence in the 5–16 population. Much of the evidence from this population was derived from one study with a low number of participants (around

[7] At the time of publication (November 2017), not all LTRAs have a UK marketing authorisation for use in children and young people aged under 18 for this indication.
[8] At the time of publication (November 2017), not all LABAs have a UK marketing authorisation for use in children and young people aged under 18 for this indication.
[9] At the time of publication (November 2017), not all LTRAs have a UK marketing authorisation for use in children and young people aged under 18 for this indication.

	50 with fewer available for certain outcomes). There was no evidence in the under 5 age group.
Trade-off between clinical benefits and harms	Over 16 age group There was evidence that ICS high dose, ICS + LABA and ICS + theophylline had a clinical benefit over continuing on ICS low dose for selected outcomes, whereas there was no evidence of clinical difference between ICS + LTRA and continuing on low dose ICS for the outcomes reported (which did not include severe exacerbations). Based on our pre-determined thresholds, the evidence showed no clinical difference between ICS + LTRA versus ICS + LABA for severe exacerbations, reliever medication use, lung function or infections. The committee discussed ICS + LTRA and ICS + LABA as the additional preventers most commonly used in current clinical practice. The committee noted the direct comparison of the two additional preventers suggested the two had roughly equivalent effects. ICS + LABA appeared to be more effective than ICS + LTRA for the critical outcome of severe exacerbations, although this did not breach the pre-determined minimally important difference relative risk ratio of 1.1. However the committee also noted that ICS + LABA appeared to have greater benefit compared to ICS low dose than ICS + LTRA. Purely based on the clinical evidence, the committee considered the addition of LABA to be marginally more effective than the addition of LTRA. Based on consensus and their clinical experience the committee noted that people often either benefit considerably from LTRAs or do not respond at all. The committee emphasised that if people do not appear to be gaining any benefit from LTRAs, they should be stopped. 5–16 age group Based on our pre-determined thresholds, the evidence showed no clinical difference between ICS moderate dose and ICS low dose for reliever medication use and lung function. There was a benefit of ICS moderate dose compared to ICS low dose for infections, but this was Low quality and the committee noted the biological implausibility of this effect. There was evidence of clinical benefit of ICS moderate dose compared to ICS + LABA for severe exacerbations but no clinical difference for lung function. The other comparisons in this age group came from a single study with 40 participants. Overall the evidence from that study suggested that ICS + LTRA and ICS low dose had a clinical benefit over ICS + LABA, particularly for severe exacerbations, quality of life and hospitalisations. However the committee noted the very low quality of the evidence and the small sample size. Due to the concerns about overmedication in this age group, the committee recommended that this age group stop their LTRA prior to starting a LABA. Under 5 age group

	There was no evidence available in the under 5 age group. The committee discussed the benefits and harms of additional treatment for this age group based on their clinical experience. Due to the particular concerns around overmedication and the fact that combination ICS/LABA is not licensed in this age group, the committee recommended that this age group receive a specialist opinion prior to progressing beyond an LTRA. The committee were also concerned that symptoms resistant to low dose ICS and an LTRA in children of this age were unlikely to be due to asthma and therefore decided it would be appropriate for the child to stop taking an LTRA if it did not control their symptoms. Any further medication would be provided by the clinician with an expertise in asthma. Review The committee chose to recommend that after starting or adjusting medicines for asthma, healthcare professionals should review the response to treatment in 4 to 8 weeks. This recommendation was based on the committee's clinical experience and consensus. The committee agreed that for every patient the most appropriate point to review treatment will be context specific but that in general if someone has asthma that is so poorly controlled it merits a change in treatment, it would be appropriate to review how the asthma has responded within 1 to 2 months. The committee acknowledge that for some people review would be useful even sooner or even later but felt that 4 to 8 weeks was an appropriate starting point. The committee noted that this review applies to all new or changed medicines but also specifically included it within the wording of the recommendations around the use of LTRAs as they were aware that the recommendations in this guideline represent a change in current practice.
Trade-off between net clinical effects and costs	Three relevant economic studies were identified for this review. Two studies were in an adult population and one study was in a population of 5–16 year olds. One study by Jönsson et al., comparing low dose ICS to low dose ICS + LABA in adults, found that low dose ICS + LABA was more expensive, at a mean cost per person of £112, but reduced the mean number of exacerbations and symptom free days compared to ICS alone. This equates to a cost of £196.50 per severe exacerbation avoided and would therefore require an exacerbation to have a QALY detriment of at least 0.005. The committee felt that this would be true and therefore low dose ICS + LABA would be under the £20,000 threshold and a cost-effective second-line preventer compared to low dose ICS alone. One study by Price et al., comparing ICS + LABA to ICS + LTRA in adults, found that low dose ICS + LTRA was more expensive, at a mean cost per person of £113. However, ICS + LTRA obtained a greater mean QALY per person increase when including imputed data and adjusting for baseline values compared to low dose ICS + LABA by 0.009 QALYs. The ICER showed that low dose ICS + LTRA cost £11,919 per QALY gained compared to low dose ICS + LABA, with probabilistic analysis showing a 48.5% probability of being under the £20,000 threshold. The committee acknowledged the cost-effectiveness evidence but felt that the pragmatic nature of the clinical evidence on which the study was based may limit its conclusions. One study by Lenney et al., comparing low dose ICS alone, low dose ICS + LABA and low dose ICS + LTRA in 5–16 year olds, found low dose ICS + LABA to be the most expensive with a mean total cost per person of £458.80 over two years. Low dose ICS + LTRA was the second most expensive option at £447.99 and low dose ICS alone

	was the least expensive at £144.75. The study also found low dose ICS + LTRA to obtain the largest mean QALY increase per person at 0.13 from baseline. Low dose ICS + LABA had the second largest QALY increase at 0.12 and ICS alone had the smallest QALY increase at 0.09. Low dose ICS + LABA and low dose ICS + LTRA had an ICER under the £20,000 threshold when compared to ICS alone. However, low dose ICS + LTRA dominated low dose ICS + LABA, being both cheaper and more effective. The committee noted that, based on this evidence, low dose ICS + LTRA is likely be a cost-effective second-line preventer in 5–16 year olds. However, they also acknowledged the limitations of the study and felt that further clinical and cost-effectiveness evidence would be needed to make a stronger recommendation. Given the uncertainty in the economic literature an economic model was built to fully assess the cost effectiveness of alternative options at this point in the pathway. The committee noted that the evidence was not sufficient in children to make a meaningful analysis as it was either very weak or had already been used to produce health economic evidence. The full model was therefore focused on adults and the full write-up can be found in Appendix N. The model used evidence from the clinical review to compare low dose ICS + LABA to low dose ICS, moderate dose ICS and low dose ICS + LTRA. The committee noted that the quality of life impact of exacerbating may not have been captured in the economic literature assessed for the guideline as only quality of life questionnaires fed into the quality-adjusted life-year estimations. If an individual in the trial completed the questionnaire during a period when they were not experiencing an exacerbation then the short term disutility of exacerbating would not be captured. Therefore disutility associated with exacerbating was an important inclusion in the economic model. Another important aspect of the model was to include treatment switching. In reality it is unlikely that an individual will remain on the same medication for the rest of their life. The committee felt that if an individual did not respond to a medication then they would have their treatment changed. One study by Price et al., included in the clinical review, was a pragmatically run RCT that allowed treatment switching to occur at the discretion of the physician. The impact of this was therefore explored in the model. The model results showed that both moderate dose and low dose ICS were dominated options. This means they produced higher costs and lower health outcomes when compared to low dose ICS + LTRA. This supports the prevailing practice that adding in an additional preventer is better than stepping up medication dose at this step. The model showed that although low dose ICS+LABA produced the highest health outcomes, they were not cost effective at a £20,000 per QALY threshold with an ICER of £56,977 per QALY when compared to low dose ICS + LTRA. The model was built on a number of assumptions and all of these were tested in various sensitivity analyses. These included: • using the cheapest brand of medication for each comparator • increasing the health impact from exacerbating by increasing the length of time they last and the impact they have on quality of life • running the model for only 10 years • varying the rate at which individuals who start on ICS+LTRA switch medications • varying the level of adherence and clinical efficacy of ICS+LABA • varying hospitalisation rates for those taking low dose ICS alone • discounting at a lower rate of 1.5% for both costs and QALYs • varying the exacerbation rate ratio for ICS+LTRA vs ICS + LABA to the most extreme values identified in the literature

	• increasing the number of GP appointments for those starting on ICS+LTRA • doubling the disutility of starting on ICS+LTRA. The conclusions from all of these sensitivity analyses agreed with the results from the base case that ICS + LTRA is the most cost effective treatment option for individuals with asthma at this point in the treatment pathway. These sensitivity analyses used extreme values in many cases, such as significantly increasing the exacerbation rate of individuals taking ICS+LTRA whilst keeping all other parameters equal. Given the results from the model and the economic literature, the committee concluded that for adults low dose ICS + LTRA was the most cost-effective option to start on for individuals who have failed on low dose ICS alone. It was noted that given the size of the asthma population the movement to LTRAs at this point in the pathway could save tens of millions each year. The clinical efficacy of low dose ICS + LABA was not sufficient to justify such a large spend. There were several comparators the model did not include such as high dose ICS, theophyllines and cromolyns. For high dose ICS there was no strong evidence to support its use over any of the other comparators. The committee noted that increasing the ICS dose to such a high level this early on in the pharmacological pathway would complicate the future pathway for the individual with asthma as if it did not work then there would be complexity decreasing the dose before adding in another preventer, which would likely lead to much higher future costs. Likewise it was considered a very expensive option and would need clear evidence of effect to warrant its use. The committee noted that both theophyllines and cromolyns were very rarely prescribed treatments and would need a clear evidence of effect to replace prevailing practices. If the individual fails on low dose ICS + LTRA the committee agreed that being placed on a LABA, either replacing or alongside the LTRA, would be the next best option. Although there was no evidence for this population the committee acknowledged that increasing the ICS dose to moderate could lead to higher costs in the long run as the individual would likely not have their medication stepped down should they need further therapy to control their asthma. Likewise it was felt ICS + LABA was a more effective treatment than moderate dose ICS alone. In the economic model low dose ICS + LABA was the second most cost-effective option, although this evidence was gathered from a different population. All things considered the committee felt that should the LTRA fail, adding a LABA or replacing the LTRA with a LABA would be the most clinically and cost-effective option at this point. Given the differences in treatment effects the committee felt the conclusions of the model could not be easily extrapolated to children. Therefore for children a weaker recommendation was made concerning the use of LTRAs based on the clinical and cost-effectiveness studies gathered for the review.
Other considerations	The committee noted that recommending the use of LTRAs prior to the use of LABAs reflected a change in clinical practice. The committee considered that the body of clinical and cost-effectiveness evidence justified this change. The committee were keen to emphasise that these recommendations were for people whose asthma was uncontrolled on ICS low dose alone. The committee did not intend for the recommendations to pertain to people whose asthma is currently controlled on ICS + LABA and that there should not be pressure on these people to switch their LABA to an LTRA. The committee noted that in one of the studies[137] comparing ICS low dose + LTRA to

	ICS low dose + LABA, adherence to both the ICS and non-ICS component of the intervention arms was higher in the LTRA arm. The committee considered that some element of the difference between intervention arms could be attributed to the adherence differences, although there was no evidence of differences in adherence in the other studies contributing to this comparison. The committee noted that the increased adherence in the ICS + LTRA arm could be due to LTRA being available as a tablet whereas LABA was available in a separate inhaler. People with asthma may benefit from the option of choosing between additional oral and additional inhaled therapy. The committee noted that increasing the use of LTRA could have a number of possible effects on adherence. Some people may use their oral therapy and adhere less to their ICS which would likely lead to worse outcomes overall. However there may be other people with asthma who are already non-adherent to their inhaled treatment who may adhere better to oral treatment; for this group providing an oral option may improve outcomes overall. Issues relating to adherence with LTRAs should be discussed with the person with asthma when reviewing the response of their treatment to a change in maintenance therapy. The committee was unable to make recommendations about inhaler devices as these were excluded from the scope of the guideline. However, the committee noted that whenever LABAs are used, best practice would be to provide them in a combined inhaler with ICS where possible. Use of combined inhalers prevents safety issues associated with people taking their LABA inhaler but not their ICS. The committee noted that providing people with an ICS and an LTRA as opposed to a combined ICS and LABA inhaler would result in an additional prescription charge for people with asthma. An increase in prescription costs could affect people's adherence. The committee felt that this could also be discussed when reviewing a person's response to the change in their maintenance treatment. However the committee also noted that prescription charges are effectively capped at 12 items per year and there are a number of exemptions, including for those requiring some form of income support. As a consequence of these counterbalances, the committee did not feel that the change to prescription charges justified changing their recommendations. The committee noted that studies often included a population with a high degree of reversibility in response to bronchodilators, and that this may not necessarily accurately represent the majority of people with asthma in the UK.

7.1.2 Review question: What is the clinical and cost effectiveness of using ICS + LABA as preventer and reliever therapy compared to using ICS + LABA as preventer and a SABA as reliever therapy?

For full details see review protocol in Appendix C.

Table 67: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma who are using ICS + LABA as preventer therapy or who are deemed to require ICS + LABA as preventer therapy.

	Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years
Intervention	ICS + LABA as daily preventer and reliever therapy
Comparison	ICS + LABA as daily preventer and reliever therapy versus ICS + LABA as daily preventer with SABA as reliever therapy
Outcomes	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Total steroid dose • Reliever medication use • Lung function (change in FEV_1 or morning PEF) • Adverse events ○ linear growth ○ all respiratory infections ○ serious respiratory infections ○ adrenal insufficiency
Study design	RCT Systematic review of RCTs

7.1.2.1 Clinical evidence

A search was conducted for randomised trials comparing ICS + LABA treatment regimens in which the reliever is ICS + LABA (maintenance and reliever therapy, MART) with ICS + LABA treatment regimens in which the reliever is a SABA. The review population was restricted to those already using ICS + LABA or deemed to require ICS + LABA as preventer therapy. Trials were only included in which the daily preventer dose of ICS + LABA was the same in both arms as the committee wished to compare the effects of the different reliever therapies and not differing preventer doses.

Eight studies were included in the review;[3,12,118,126,131,142,163,184] these are summarised in Table 68 below.

Seven studies were in the adult (aged 16 or older) stratum, one study was in the aged 5–16 stratum. Two studies included a mix of those controlled and uncontrolled on their previous preventers, six studies included only those uncontrolled on their previous preventers. In four studies the majority of participants were using ICS moderate dose + LABA prior to the randomisation, in two studies they were using ICS moderate dose alone, in one study they were using ICS high dose alone and in one study they were using ICS high dose + LABA.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 69 and Table 70). See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Table 68: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Atienza 2009[3]vo	MART (ICS low dose + LABA), n=1049 ICS low dose + LABA + SABA when required, n=1042	Stratum: >16 years Age – mean 46, SD 14.5 Uncontrolled on ICS high dose + LABA	• Severe exacerbations • Mortality • Asthma control (ACQ) • Hospitalisations • Reliever medication use (puffs/day) • FEV_1 (L) • PEF (L/min) • Infections (all respiratory) Reported at 1 year	
Bisgaard 2006 [12]	MART (ICS low dose + LABA), n=118 ICS low dose + LABA, n=117	Stratum: 5 to <16 years Age – mean (range): 8 (4–11) years Uncontrolled on ICS moderate dose	• Severe exacerbations (requiring OCS) • Reliever medication use • FEV_1 (L) • Morning PEF (L/min) Reported at 1 year	Sub-analysis of paediatric population of O'Byrne 2005, ~1/9th of population are double counted
O'Byrne 2005 [118]	MART (ICS low dose + LABA), n=925 ICS low dose + LABA, n=909	Stratum: >16 years Age – mean 36, range 4-79 Uncontrolled on ICS moderate dose	• Severe exacerbations • Reliever medication use • FEV_1 (L) • PEF (L/min) • Infections (all respiratory) Reported at 1 year	
Papi 2013[126]	MART (ICS low dose + LABA), n=857 ICS low dose + LABA + SABA when	Stratum: >16 years Age – 48 (range 18 to 83)	• Severe exacerbations • Asthma control (ACQ) • Hospitalisations	

Study	Intervention and comparison	Population	Outcomes	Comments
	required, n=857	Uncontrolled on ICS moderate dose + LABA	• Reliever medication use (puffs/day) • FEV_1 (L) • PEF (L/minute) Reported at 48 weeks	
Patel 2013[128]	MART (ICS moderate dose + LABA), n =151 ICS moderate dose + LABA + SABA when required, n=152	Stratum: >16 years Age – range of means: 41–42 years Heterogeneous control status on ICS moderate dose + LABA	• Severe exacerbations • Asthma control (ACQ) • Hospitalisations • Total steroid dose (mg/predicted equiv/year) • FEV_1 (%predicted) • FEV_1 (L) Reported at 6 months	
Rabe 2006[142]	MART (ICS low dose + LABA), n =1113 ICS low dose + LABA + SABA when required, n=1141	Stratum: >16 years Age – range of means: 42-43 years Uncontrolled on ICS moderate dose + LABA	• Severe exacerbations • Asthma control • Reliever medication use • FEV_1 (L) • PEF (L/minute) • Infections (all respiratory) Reported at 1 year	
Stallberg 2008[163]	MART (ICS low/moderate dose + LABA), n=887 ICS low/moderate dose + LABA, n=456	Stratum: >16 years Age – mean 44 Heterogeneous control status on ICS moderate dose + LABA	• Severe exacerbations Reported at 1 year	
Vogelmeier 2005 [184]	MART (ICS moderate dose + LABA), n=1067	Stratum: >16 years Age – mean 45	• Severe exacerbations (requiring OCS)	Participants (in conjunction with their physicians during

Study	Intervention and comparison	Population	Outcomes	Comments
	ICS moderate dose + LABA, n=1076	(range 12–84) Uncontrolled on ICS high dose	• Quality of life (AQLQ, 1–7, higher is better outcome) • Control (ACQ, 0–6, higher is worse outcome) • Reliever medication use (puffs/day, average across treatment period) • FEV_1 (L) Reported at 1 year	scheduled or unscheduled visits) were able to titrate their maintenance dose of ICS up and down (ICS + LABA group) or just down (MART group). Mean overall dose by end of study was in ICS high dose range in both groups. Study was open label.

Table 69: Clinical evidence summary: MART versus ICS + LABA as maintenance and SABA as reliever, people over the age of 16

				Anticipated absolute effects	
Outcomes	**No of Participants (studies) Follow up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Risk with ICS + LABA as maintenance and SABA as reliever, >16**	**Risk difference with MART (95% CI)**
Severe exacerbations	11653 (7 studies) 6-12 months	MODERATE[a] due to indirectness	RR 0.66 (0.6 to 0.72)	180 per 1000	61 fewer per 1000 (from 50 fewer to 72 fewer)
Mortality	2091 (1 study) 12 months	LOW[b] due to imprecision	RR 0.99 (0.06 to 15.86)	1 per 1000	0 fewer per 1000 (from 1 fewer to 14 more)
Quality of life (AQLQ, 1–7, higher is better outcome)	2143 (1 study) 12 months	MODERATE[c] due to risk of bias	-	-[e]	The mean quality of life (AQLQ) in the intervention groups was 0.03 higher (0.07 lower to 0.13 higher)
Control (ACQ, 0–6, higher is worse outcome)	8470 (5 studies) 6-12 months	HIGH	-	-[e]	The mean control (ACQ) in the intervention groups was 0.11 lower (0.14 to 0.08 lower)
Hospitalisations	4095 (3 studies) 6-12 months	HIGH	RR 0.34 (0.2 to 0.59)	25 per 1000	17 fewer per 1000 (from 10 fewer to 20 fewer)
Reliever medication use (puffs/day)	9983 (5 studies) 11-12 months	HIGH	-	-[e]	The mean reliever medication use (puffs/day) in the intervention groups was 0.15 lower (0.19 to 0.11 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA as maintenance and SABA as reliever, >16	Risk difference with MART (95% CI)
FEV_1 (%predicted)	303 (1 study) 6 months	LOW[a,c] due to risk of bias, indirectness	-	-[e]	The mean FEV_1 (%predicted) in the intervention groups was 2.5 higher (2 lower to 7 higher)
FEV_1 (L)	10286 (6 studies) 6–12 months	HIGH	-	-[e]	The mean FEV_1 (L) in the intervention groups was 0.05 higher (0.03 to 0.06 higher)
PEF (L/minute)	7840 (4 studies) 11-12 months	HIGH	-	-[e]	The mean PEF (L/minute) in the intervention groups was 6.84 higher (4.71 to 8.98 higher)
Infection (all respiratory)	6164 (3 studies) 12 months	LOW[c,d] due to risk of bias, inconsistency	RR 1.05 (0.89 to 1.24)	73 per 1000	4 more per 1000 (from 8 fewer to 18 more)
Total steroid dose (prednisolone equivalent, mg/year)	303 (1 study) 6 months	LOW[a,c] due to risk of bias, indirectness	-	-[e]	The mean total steroid dose (prednisolone equivalent, mg/year) in the intervention groups was 21.6 higher (199.38 lower to 242.58 higher)

a Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA as maintenance and SABA as reliever, >16	Risk difference with MART (95% CI)
d Downgraded by 1 or 2 increments because the point estimate and/or the confidence intervals varied widely across studies, unexplained by subgroup analysis					
e Adjusted baseline values for control group not available					

Table 70: Clinical evidence summary: MART versus ICS + LABA as maintenance and SABA as reliever, young people and children aged 5–16

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA as maintenance and SABA as reliever, 5 to 16	Risk difference with MART (95% CI)
Severe exacerbations	235 (1 study) 12 months	HIGH	RR 0.28 (0.14 to 0.53)	308 per 1000	222 fewer per 1000 (from 145 fewer to 265 fewer)
Reliever medication use (puffs/day)	235 (1 study) 12 months	HIGH	-	The mean reliever medication use (puffs/day) in the control groups was 0.76	The mean reliever medication use (puffs/day) in the intervention groups was 0.18 lower (0.34 to 0.02 lower)
FEV_1 (L)	235 (1 study) 12 months	MODERATE[a] due to imprecision	-	The mean FEV_1(L) in the control groups was 1.70	The mean FEV_1 (L) in the intervention groups was 0.16 higher (0.04 lower to 0.36 higher)
PEF (L/min)	235 (1 study) 12 months	LOW[a,b] due to risk of bias, imprecision	-	The mean PEF (L/min) in the control groups was 242	The mean PEF (L/min) in the intervention groups was 13 higher (10.52 lower to 36.52 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS + LABA as maintenance and SABA as reliever, 5 to 16	Risk difference with MART (95% CI)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

7.1.2.2 Economic evidence

Published literature

Three health economic studies were identified with the relevant comparison and have been included in this review.[76] [163] [188] These are summarised in the health economic evidence profile below (Table 71) and the health economic evidence tables in Appendix I.

Six economic studies relating to this review question were identified but were excluded due to limited applicability.[22] [58] [97] [105] [138] [168] These are listed in Appendix M, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix F.

Unit costs

Full details on medication costs can be found in Appendix O.

Table 71: Economic evidence profile: MART versus ICS + LABA as maintenance and SABA as reliever in adults

Study	Applicability	Limitations	Other comments	Incremental cost (1-2)	Incremental effects (1-2)	Cost effectiveness	Uncertainty
Stallberg 2008 [163] Sweden	Partially applicable [(a)]	Potentially serious limitations[(b)]	CEA within-trial analysis (RCT) Population: People with persistent asthma Two comparators: 1) MART (ICS low/moderate dose + LABA), n=887 2) ICS low/moderate dose + LABA, n=456 Time horizon: 1 year	**Total costs (mean per patient):** - £99 (excluding societal costs) - £28 (including societal costs)	**Severe exacerbations:** -19% reduction in exacerbations	MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy.	Increasing the cost of MART therapy by 18% resulted in costs being equal. The cost savings were robust to changes in costs not related to the cost of medication.
Johansson 2006	Partially applicable [(c)]	Potentially serious limitations[(d)]	CEA within-trial analysis (RCT) Population: People with persistent asthma Two comparators: 1) MART (ICS moderate dose + LABA), n=1067 2) ICS moderate dose + LABA, n=1076 Time horizon: 1 year	**Total costs (mean per patient):** - £34 (excluding societal costs) - £55 (including societal costs)	**Severe exacerbations:** -0.07 exacerbations per patient per year	MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy.	Bootstrapping was conducted but results were only presented on a cost-effectiveness plane. On the plane MART reduces exacerbations at a lower cost >95% of the time.

Study	Applicability	Limitations	Other comments	Incremental cost (1-2)	Incremental effects (1-2)	Cost effectiveness	Uncertainty
Wickstrom 2009	Partially applicable [c]	Potentially serious limitations[d]	Systematic review that conducts 5 separate economic evaluations, based on 5 separate RCTs. Only 4 of the results are included below as one study was based on an inappropriate comparison. Kuna 2007 1) MART (ICS [moderate dose] + LABA), n=1144 2) ICS (high dose) + LABA, n=1145 Bousquet 2007 1) MART (ICS [moderate dose] + LABA), n=1107 2) ICS (moderate dose) + LABA, n=1105 O'Byrne 2005 1) MART (ICS low dose + LABA), n=925 2) ICS low dose + LABA, n=909 Rabe 2006 1) MART (ICS low dose + LABA), n =1113 2) ICS low dose + LABA + SABA when required, n=1141	**Total costs (mean per patient):** Kuna 2007 - £166 Bousquet 2007 £50 O'Byrne 2005 - £17 Rabe 2006 £55	**Severe exacerbations per patient per year:** Kuna 2007 - 0.08 Bousquet 2007 - 0.06 O'Byrne 2005 - 0.21 Rabe 2006 - 0.18	Kuna 2007 MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy. Bousquet 2007 £783 per exacerbation avoided O'Byrne 2005 MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy. Rabe 2006 MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy.	No uncertainty analysis was conducted.

Abbreviations: CEA: cost-effectiveness analysis; ICS: inhaled corticosteroids; LABA; long-acting beta-agonist; MART: maintenance and reliever therapy

(a) Swedish healthcare system may not be reflective of the UK NHS.
(b) EQ-5D not included as an outcome, though reported outcomes would suggest it is at least not lower in the MART group. Time horizon of only 1 year may not be capturing the full effect.
(c) Resource use was pooled across 16 countries rather than just the UK; although UK unit costs were applied this makes the results slightly less applicable.
(d) EQ-5D not included as an outcome, though reported outcomes would suggest it is at least not lower in the MART group. Time horizon of only 1 year may not be capturing the full effect.
(e) Danish unit costs were applied to each RCT.
(f) EQ-5D not included as an outcome, though reported outcomes would suggest it is at least not lower in the MART group. Time horizon of only 1 year may not be capturing the full effect.

7.1.2.3 Evidence statements

Clinical – adult stratum

- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in a clinical benefit for severe exacerbations (7 studies, 11653 participants, Moderate quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for mortality (1 study, 2091 participants, Low quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for quality of life (1 study, 2143 participants, Moderate quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for asthma control (5 studies, 8470 participants, High quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in a clinical benefit for hospitalisations (3 studies, 4095 participants, High quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for reliever medication use (5 studies, 9983 participants, High quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for FEV_1 (%predicted, 1 study, 303 participants, Low quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for FEV_1 ([L], 6 studies, 10286 participants, High quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for PEF (4 studies, 7840 participants, High quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for infection (all respiratory, 3 studies, 6164 participants, Low quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for total steroid dose (1 study, 303 participants, Low quality evidence)

Clinical – 5 to 16 stratum

- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in a clinical benefit for severe exacerbations (1 study, 235 participants, high quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for reliever medication use (1 study, 235 participants, high quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for FEV_1 ([L], 1 study, 235 participants, moderate quality evidence)
- MART vs ICS + LABA as maintenance and SABA as reliever ICS + LABA treatment resulted in no clinical difference for PEF (1 study, 235 participants, low quality evidence)

Economic

- Five separate economic analyses (3 from one study) found that MART was dominant compared to ICS + LABA as maintenance and SABA as reliever, reducing costs and number of exacerbations.

- One cost-effectiveness analysis found that the ICER of MART versus ICS + LABA as maintenance and SABA as reliever was £783 per exacerbation avoided.

7.1.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80
Relative values of different outcomes	The committee considered the following outcomes as critical for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee considered the following outcomes as important: total steroid dose, asthma control (as assessed by a validated questionnaire), hospital admission, reliever medication use, lung function (FEV_1 or morning PEF) and adverse events.
Quality of the clinical evidence	The quality of the evidence ranged from High to Very Low quality. The majority of the evidence was either Moderate or High quality. There was limited evidence regarding the total steroid dose, with only one study, one of the smaller studies, reporting this particular outcome. The committee noted that 2 of the studies[163 ,185] compared MART versus ICS + LABA as maintenance and SABA as reliever where the doses were in the same category

[10] At the time of publication (November 2017), MART regimens did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[11] At the time of publication (November 2017), MART regimens did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	(i.e. low dose ICS + LABA) but there were differences in precise dosing or within class drug choice. The conclusions of these studies were similar to the overall body of evidence.
Trade-off between clinical benefits and harms	There was a clinically important benefit of MART versus ICS + LABA as maintenance and SABA as reliever in both adults and children in terms of severe exacerbations, and in adults there was an additional clinically important benefit in terms of hospitalisations. There was no clinically important difference of MART versus ICS + LABA as maintenance and SABA as reliever in terms of mortality, quality of life, asthma control, reliever medication use, lung function, infection or total steroid dose. The committee noted that the evidence in children and young people aged 5–16 was sufficient to recommend the use of MART in this age group, despite the lack of licensing. However the lack of any evidence in children under the age of 5 meant the committee did not extrapolate any further, particularly given the requirement for higher quality evidence to allow recommendations outside licensed indications. The committee considered that on balance MART appears to have a significant benefit over ICS + LABA as maintenance and SABA as reliever therapy in the population analysed within this review. While MART may be expected to increase steroid exposure through additional use of ICS as reliever medication, this is likely to be at least partially offset by the reduction in exacerbations requiring OCS. While the evidence on total steroid dose identified here was limited, it was consistent with this suggestion as no clinically important difference in total steroid dose was seen. The population assessed in this review was a mixed group. No trials were identified that assessed MART exclusively in a population previously uncontrolled on ICS low dose alone. In general the population was uncontrolled on their previous preventers and these preventers were typically ICS moderate dose + LABA but some studies included predominantly those with moderate dose ICS without LABA and higher doses of ICS, with or without LABA. The committee considered potential recommendations for people whose asthma was uncontrolled on MART with a low maintenance dose of ICS. While the majority of studies prescribed MART with a low maintenance dose of ICS (i.e. the daily ICS dose without including any reliever doses), two studies prescribed MART with a moderate daily maintenance dose of ICS. These two studies showed benefits consistent with the overall effect of MART vs ICS + LABA as maintenance and SABA as reliever. However there was no evidence specific to a population of people whose asthma was uncontrolled on MART with a low maintenance dose of ICS. In addition, the experience of the committee is that some people are unsuited to a MART dosing strategy; for example, they may get less satisfactory symptom relief from ICS/LABA as a reliever than they do from a SABA. The committee therefore chose to recommend that for people whose asthma was uncontrolled on MART with a low daily dose of ICS, the next option would be to increase ICS dose either as part of MART or as part of a fixed dose regimen. The GC emphasised that if people are using MART with a moderate maintenance ICS dose, the reliever should still be at a low dose. For example if a person was using an inhaler with budesonide and formoterol at 200/6ug, their maintenance dose could be 2 puffs twice a day (a moderate ICS daily dose of 800ug) but each individual reliever puff would be at a low dose (200ug of ICS).
Trade-off between net clinical effects	Three health economic studies were identified that evaluated the cost effectiveness of MART therapy.

and costs	Two of these studies were within trial analyses that measured the resource use to the health service alongside the randomised controlled trial. A study by Johansson 2006 was based on the clinical evidence presented in Vogelmeier 2005. A study by Stalberg presented the economic evidence alongside the clinical evidence in the same paper. In both of these analyses the MART therapy was dominant, meaning it reduced costs and improved health outcomes. One reason for this conclusion was that MART therapy appeared to reduce exacerbations and hospitalisations. However the main cost saving came from reducing the fixed dose the person with asthma would be on. Therefore even though the individual was taking their combined inhaler for reliever therapy (rather than a short-acting beta agonist) they were taking less medication overall as they were titrated down to a lower fixed dose used for maintenance therapy. One study conducted an economic evaluation alongside 5 separate randomised controlled trials using a Danish healthcare perspective. Of the 5 RCTs, 4 were deemed applicable for this review. The analyses conducted alongside 3 of these RCTs concluded that MART therapy was cost-saving whereas one found that the ICER of going from ICS + LABA as maintenance and SABA as reliever to MART therapy was £783 per severe exacerbation avoided. A non-hospitalised severe exacerbation costs approximately £75, if it is assumed it leads to 2 unscheduled GP visits and a course of oral steroids. A study by Lloyd shows that the disutility from a severe exacerbation is 0.33. If it is assumed this disutility lasts for 2 weeks then this results in a loss of 0.0126 QALYs. Given this information, at a £20,000 per QALY threshold it could be estimated that the threshold of cost effectiveness for avoiding a non-hospitalised exacerbation is £328 per exacerbation avoided. This assumes a severe exacerbation has no lasting impact on quality of life. Therefore from exacerbations alone this one analysis would suggest MART therapy is not cost effective. However, exacerbations is only one clinical outcome that feeds into the QALY and this evaluation does not take into account quality of life. The review also shows that MART therapy significantly reduces hospitalisations, which will have an additional cost and potentially mortality impact. Alongside the economic evidence presented the committee considered the additional costs of reliever medication using MART therapy. A SABA costs approximately £0.02 per puff whereas a puff of a combined inhaler costs approximately £0.24 - £0.32, depending on which brand is used. Therefore if an individual was using reliever medication three times a week this would cost, approximately, an additional £35 - £46 per year in reliever medication. If they were taking one puff of reliever medication a day this would cost an additional £82 - £108. The committee noted that the clinical evidence showed that MART significantly reduced exacerbations and hospitalisations, both of which would have a resource impact for the health service. It was also noted that if an individual was frequently using their reliever medication (more than 3 times a week) then this should be a prompt to change or titrate the individual's medication, meaning high reliever medication use should not be happening as this would indicate the medication is not working and is therefore not a cost effective use of resources. Finally as shown in the economic studies assessed, although there may be additional costs incurred for reliever therapy these may be counter-balanced by cost savings by taking less medication for maintenance therapy. Two economic studies showed that the individual was taking less medication overall on MART therapy when compared to ICS + LABA as maintenance and SABA as reliever. Therefore the committee felt that although the additional costs of reliever medication could be significant, these would be counter-balanced by other cost savings. Once the additional health gains of lower exacerbations and hospitalisations are taken into account it is highly likely that MART

	therapy would be cost effective at a £20,000 per QALY threshold. Overall there is strong evidence to indicate that MART is a cost effective and perhaps cost-saving therapy. The clinical evidence showed that MART reduced exacerbations and hospitalisations which will have considerable health benefits to individuals with asthma. Although one study showed the reduction in non-hospitalised exacerbations alone may not be considered cost effective, it is not using the complete wealth of evidence available for MART therapy, such as the reduced hospitalisations. Given the clear clinical benefit and economic evidence the committee decided that MART therapy would be a cost effective option for individuals who failed on a ICS + LABA as maintenance and SABA as reliever regimen. In children aged 5–16 one study showed MART therapy also having an impact on severe exacerbations. However given the lack of any cost-effectiveness evidence and the rarity of their use amongst children the committee felt a weaker recommendation was appropriate.
Other considerations	The committee noted that some inhaler devices that are used for MART are difficult to use for children and therefore not appropriate for them. Healthcare professionals should take this into account when prescribing MART. The committee noted that MART regimens are not currently licensed for use in children. The committee considered that the body of evidence here was sufficient to justify their use. The GC discussed the role of SABA prescriptions alongside MART. The committee was aware that with some formulations of MART there is a recommendation to prescribe a SABA inhaler for use in acute situations when the maximum licensed dose of MART has been reached. The management of acute asthma is outside the scope of this guideline. The committee noted that people should be discouraged from regularly using a SABA as a reliever alongside MART as this would be an indicator of loss of control and the MART regimen should suffice. However the committee did not feel they could make generally applicable recommendations about whether or not a SABA should be provided alongside MART at all. The benefits of prescribing a SABA would include allowing additional puffs of beta agonist during exacerbations, whilst the harms would include potentially encouraging people to continue using their MART beyond the point at which the committee would want the person with asthma to contact a healthcare professional.

7.1.3 Review question: What is the most clinically and cost-effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking optimal preventer therapy beyond ICS low dose when this fails to provide adequate control?

For full details see review protocol in Appendix C.

Table 72: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma who are uncontrolled on optimal preventer therapy beyond ICS low dose. Population strata: • Age:

	○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years • Prior treatment: ○ ICS moderate dose ○ ICS high dose ○ ICS + LABA ○ ICS + LTRA
Interventions	Addition of one of the following interventions to optimal second line preventer therapy: • Placebo– that is, staying on optimal preventer therapy • Increase ICS dose • LABA + SABA when required • LABA + ICS when required + LABA (in other words MART therapy) • LAMA (tiotropium) • LTRA • Theophylline or aminophylline • Cromolyns (sodium cromoglicate, nedocromil) • Oral steroids
Comparison	Third-line preventer versus continuing on second-line preventer Any listed intervention versus any other
Outcomes	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever medication use • Lung function (change in FEV_1 or morning PEF) • Adverse events ○ linear growth ○ all respiratory infections ○ serious respiratory infections ○ adrenal insufficiency
Study design	RCT Systematic review of RCTs

7.1.3.1 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of preventer drugs as third line treatment for patients with asthma who are uncontrolled on second line preventer treatment alone. For this review second line preventers were considered to include ICS moderate

dose, ICS high dose, ICS + LABA or ICS + LTRA. These populations were kept in separate strata as the committee opinion was that the previous treatments could influence subsequent efficacy.

The review population was people who had been using second line preventers for at least one month. Studies recruiting a mix of people with asthma on different stages of treatment were only included if at least 75% of people included in the study were on second line preventers at inclusion. Studies were analysed within the strata that best fit their population's previous pharmacotherapy.

Studies were included that recruited people with asthma who were uncontrolled in line with BTS/SIGN guidelines (using SABA three times a week or more; symptomatic three times a week or more; or waking one night a week). Studies recruiting a mix of people with asthma including both people who were controlled and uncontrolled were only included if at least 75% of people included in the study were uncontrolled.

Forty one studies were included in the review[4,7,11,12,17,19,32,36,40,45,47,50,63,73-75,79,82-84,91,106,107,118,119,121,131,134,139,142,145,150,159,160,181,182,184,187,192,194,200]; these are summarised in Table 73 below.

Seven studies included a population predominantly uncontrolled on ICS + LABA; 27 studies included a population predominantly uncontrolled on ICS moderate dose; 7 studies included a population predominantly uncontrolled on ICS high dose. No studies included a population predominantly uncontrolled on ICS + LTRA.

Thirty eight studies included participants over the age of 16 and three studies included participants between the ages of 5 and 16.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 74,

Table 75,

Table **76**, Table 77, Table 78, Table 79, Table 80,

Table **81**, Table 82,

Table **83**, Table 84, Table 85, Table 86, Table 87, Table 88, Table 89, Table 90, Table 91, Table 92, Table 93, Table 94, Table 95, Table 96, Table 97,Table 98, Table 99, Table 100, Table 101, Table 102,Table 103, Table 104, Table 105 and Table 106). See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Table 73: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
ICS + LABA				
Bousquet 2007[17]	MART (ICS (moderate dose) + LABA), n=1144 ICS (high dose) + LABA, n=1145	Stratum: >16 years Age – range of means: 39–40 years At baseline, majority of participants were	• Severe exacerbations (requiring OCS) • Asthma control • Reliever medication use • Morning PEF	In the ICS + LABA as maintenance and SABA as reliever arm, both the ICS and LABA dose are higher than the regular doses used in the MART arm.

Study	Intervention and comparison	Population	Outcomes	Comments
		using ICS moderate dose + LABA. Participants had used either moderate dose ICS + LABA (55%) or high dose ICS alone (45%) for at least 3 months preceding trial. Participants used their SABA when required on at least 5 of the 7 days preceding screening.	Reported at 6 months	
Ohta 2015[121]	ICS (moderate dose) + LABA + LAMA, n=114 ICS (moderate dose) + LABA + placebo, n=57	Stratum: >16 years Age – range of means: 43–48 years At baseline, majority of participants were using ICS moderate dose + LABA. Participants had used moderate dose ICS with (57%) or without (43%) LABA for at least 1 month preceding trial. Participants had an ACQ-7 of at least 1.5 at screening and randomisation.	• FEV_1 • Morning PEF • Infections Reported at 1 year	
Pavord 2009[131]	MART (ICS low dose + LABA), n=64 ICS (high dose) + LABA, n=63	Stratum: >16 years Age – mean 40, range 19–65 At baseline majority of participants were using ICS moderate	• Reliever medication use (puffs/day) Reported at 1 year	

Study	Intervention and comparison	Population	Outcomes	Comments
		dose + LABA. Participants had either used ICS high dose alone or ICS moderate dose with LABA (81%). Participants used their SABA/had asthma symptoms on 4 or more of last 7 days of run-in.		
Peters 2008[134]	ICS (high dose) + LABA, n=443 ICS (high dose) alone, n=133 ICS (moderate dose) + LABA, n=132	Stratum: >16 years Age – range of means: 39–41 years At baseline, majority of participants were using ICS moderate dose + LABA. Participants had used low to moderate ICS with a LABA (53%) or moderate to high ICS without a LABA (47%) for at least 1 month preceding trial. Participants had at least 2 asthma awakenings or at least 3 days of rescue medication use in week before screening.	• Severe exacerbations • Hospitalisations • Reliever medication use (puffs/day) • FEV_1 (L) • PEF (L/minute) • Infections (all respiratory) Reported at 1 year	
Rabe 2006[142]	MART (ICS low dose + LABA), n =1113 ICS low dose + LABA + SABA when required, n=1141	Stratum: >16 years Age – range of means: 42–43 years At baseline majority of participants were	• Severe exacerbations • Asthma control • Reliever medication use • FEV_1 (L) • PEF (L/minute) • Infections (all	

Study	Intervention and comparison	Population	Outcomes	Comments
		using ICS low dose + LABA. Participants had used ICS (mean dose moderate) with (59%) or without (41%) LABA prior to 2 week run-in on ICS low dose + LABA. Participants used reliever medication on at least 5 of the last 7 days of run-in.	respiratory) Reported at 1 year	
Kerstjens 2012 [84]	ICS high dose + LABA + LAMA, n=456 ICS high dose + LABA + placebo, n=456	Stratum: >16 years Age – mean 53 (12) At baseline all participants were using high dose ICS and a LABA. Participants had an ACQ >1.5 at screening despite above treatment.	• Severe exacerbations (requiring OCS) • Quality of life (AQLQ) • Control (ACQ) • Reliever medication use (puffs/day) • FEV_1 (L) • PEF (L/minute) • Infections (all respiratory) • Infections (serious respiratory) Reported at 24 or 48 weeks	Publication reports results from two individual trials: some outcomes are pre-pooled, others are reported separately
Wechsler 2015[187]	ICS (low dose) + LAMA, n=532 ICS (low dose) + LABA, n=538	Stratum: >16 years Age – mean: 45 years At baseline, majority of participants were using ICS low dose + LABA. Participants had	• Severe exacerbations (requiring OCS) • Quality of life (AQLQ) • Control (ACQ) • Reliever medication use (puffs/day) • FEV_1 (L)	

Study	Intervention and comparison	Population	Outcomes	Comments
		used either low dose ICS + LABA (70%) or ICS alone (30%) for at least 3 months preceding trial.	Reported at 18 months	
ICS (moderate dose)				
O'Byrne 2005 [118]	MART (ICS low dose + LABA), n=925 ICS low dose + LABA, n=909 ICS (moderate dose), n=926	Stratum: >16 years Age – mean (range): 36 (4–79) years At baseline, majority of participants were uncontrolled on ICS moderate dose, 27–29% were also on LABA. 12 or more inhalations of as-needed medication during last 10 days of run-in period.	• Severe exacerbations • Reliever medication use (puffs/daytime) • Reliever medication use (puffs/night-time) • FEV_1 (L) • Morning PEF (L/minute) Reported at 12 months	Contains paediatric population also included in Bisgaard 2006 [12]. ~1/9th population will be double counted.
O'Byrne 2014 [119]	ICS low dose + LABA, n=197 ICS high dose, n=195	Stratum: >16 years Age – mean (SD): 45.2 (14.51) At baseline, use of ICS with or without LABA (FP/Salmeterol 250/50 ug twice daily or equivalent) for at least 4 weeks. Asthma symptoms and/or daily SABA use on >3 or last 7 days of run-in period.	• Quality of life (AQLQ) • ACT • FEV_1 (L) • Morning PEF Reported at 24 months	Four week run-in period during which patients entering ICS + LABA arm were switched to the same ICS at the same dose contained in the ICS + LABA combination. Those in the ICS alone arm continued ICS only therapy.
Barnes	ICS moderate dose +	Stratum: >16 years	• Quality of life	

Study	Intervention and comparison	Population	Outcomes	Comments
2007[7]	LTRA, n=37 ICS high dose, n=38	Age – range of means: 41–45 years At baseline, participants were on 600–1200 ug/day budesonide. Remained symptomatic during final two weeks of 4 week run-in during which 800 ug budesonide was given.	(AQLQ) • Morning PEF Reported at 12 weeks	
Bisgaard 2006 [12]	MART (ICS low dose + LABA), n=118 ICS low dose + LABA, n=117 ICS moderate dose, n=106	Stratum: 5 – <16 years Age – mean (range): 8 (4–11) years At baseline, treated with 200–500 ug/day of ICS. 12 or more inhalations of as-needed medication during last 10 days of run-in period.	• Severe exacerbations (requiring OCS) • Reliever medication use • FEV_1 (L) • Morning PEF • Growth Reported at 12 months	Any brand ICS at baseline; differing potencies.
Chervinsky 2008 [32]	ICS moderate dose + LABA, n=117 ICS moderate dose, n=102	Stratum: >16 years Age – mean (SD): 42.45 (13.77) years At baseline, participants used medium to high doses of ICS alone or in combination with other maintenance medication. Symptomatic on 3 or more of 7 consecutive days during run-in	• Quality of life (AQLQ) • Reliever medication use Reported at 12 weeks	Participants received low dose ICS (Budesonide 160 ug, twice daily) during 14 day run-in period. Mean dose at study entry: • ICS + LABA: 571.9 ug • ICS (moderate dose): 594.7 ug Unable to pool data for ICS+LABA combination inhaler and ICS+LABA as separate inhalers due to format of data

Study	Intervention and comparison	Population	Outcomes	Comments
		period.		presented.
Corren 2013 [36]	ICS moderate dose + LABA, n=110 ICS moderate dose, n=113	Stratum: >16 years Age – range of means: 41.9–44.8 years At baseline, patients had been taking ICS for at least 4 weeks at a dose of no more than 500 ug/day or equivalent. Use of rescue medication 2 or more times a day on 3 days during any 7 consecutive days during 14 day run-in.	• Reliever medication use • FEV_1 (L) • Morning PEF • Infection (all respiratory) Reported at 12 weeks	
Evans 1997 [45]	ICS moderate dose + Theophylline, n=33 ICS high dose, n=33	Stratum: >16 years Age – range of means: 38.1–39.5 years At baseline, patients continued to experience cough, wheeze or breathlessness despite treatment of budesonide 800-1000 ug (or equivalent. Scored 4 on a 4-point symptom scale or more than a 10% variation in day-to-day PEF during final week of run-in period.	• FEV_1 (L) • Morning PEF Reported at 12 weeks	Mean baseline inhaled budesonide doses: • ICS (high dose) arm: 702 ug • ICS + Theophylline arm: 671 ug
Fish 2001 [47]	ICS moderate dose + LTRA, n=472	Stratum: >16 years	• Reliever medication use	

Study	Intervention and comparison	Population	Outcomes	Comments
	ICS moderate dose + LABA, n=476	Age – mean (range): 40 (15–83) years At baseline, symptomatic despite receiving ICS (moderate dose) for at least 6 weeks. In 7 days preceding randomisation, at least one of: use of an average of >3 puffs per day of salbutamol, symptoms score of >1 on >2 days, and >2 nights when the patient awakened due to symptoms.	• Morning PEF Reported at 12 weeks	
Hamelmann 2016 [63]	ICS moderate dose + LAMA, n=134 ICS moderate dose, n=138	Stratum: 5 to 16 years Age – mean (SD): 14.3 (1.7) years At baseline, majority of participants were using ICS moderate dose alone. At 3 months before screening, a minority of participants used concomitant LABA (29%) or LTRA (13%).	• Severe exacerbations (requiring OCS) • Quality of life (AQLQ) • Reliever medication use • FEV_1 (L) Reported at 12 weeks	Patients were required to stop LABA at least 72 hours before screening, but were permitted to continue LTRAs throughout the study: ICS + LAMA (11%), ICS (10%).
Juniper 2002 [79]	ICS moderate dose + LABA, n=55 ICS high dose, n=58	Stratum: >16 years Age – mean (SD): 50.5 (15) years At baseline, participants had	• Quality of life (AQLQ) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		received ~BDP 800–1200 ug or equivalent for at least 4 weeks. Total symptom score of >2 on >4 of the previous 7 evaluable days, use of SABA on >2 occasions per 24 hours on 4 of previous 7 evaluable days.		
Kerstjens 2015 [83]	ICS moderate dose + LAMA, n=519 ICS moderate dose + LABA, n=541 ICS moderate dose, n=523	Stratum: >16 years Age – mean (SD): 43.5 (12.85) years At baseline, all participants on stable medium dose ICS 400–800 ug budesonide or equivalent. At randomisation, participants were symptomatic (ACQ mean score >1.5)	• AQLQ • ACQ-7 • FEV_1 (L) • Morning PEF • Infections (all respiratory) Reported at 6 months	
Mitchell 2003 [106]	ICS moderate dose + LABA, n=102 ICS high dose, n=101	Stratum: >16 years Age – mean (SD): 43.88 (15.15) years At baseline, participants received treatment with ICS at a constant daily dose of 1000 ug BDP or 800 ug budesonide for at least one month before screening. On any two days during final 7 days	• Reliever medication use • Morning PEF Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		of run-in period experiencing two of: waking at night due to asthma, asthma interfering with activities in the day, 4+ puffs of salbutamol a day, PEF diurnal variation of 15%.		
Price 2003 [139]	ICS moderate dose + LTRA, n=448 ICS high dose + placebo, n=441	Stratum: >16 years Age – mean 43, SD 14 At baseline all participants were using moderate dose ICS. Participants required at least an average of 1 puff/day of SABA during last 2 weeks of run-in period on moderate dose ICS.	• Quality of life (AQLQ) • Reliever medication use (puffs/day) • PEF (L/min) Reported at 12 weeks	
Scicchitano 2004 [159]	MART (ICS [low dose] + LABA), n=947 ICS (moderate dose), n=943	Stratum: >16 years Age – mean (range): 43 (11–80) years At baseline, all participants used ICS at dose 400–1600 ug/day for at least 3 months. Symptomatic and had moderate to severe asthma during 14 day run-in period.	• Severe exacerbations (requiring OCS) • Reliever medication use • Morning PEF Reported at 1 year	
Van Noord 1999 [181]	ICS moderate dose + LABA, n=139 ICS high dose, n=135	Stratum: >16 years Age – mean 47, SD 15	• PEF (L/min) Reported at 12 weeks	Trial includes some participants whose baseline ICS dose was low and who were

Study	Intervention and comparison	Population	Outcomes	Comments
		At baseline participants were using low to moderate dose ICS. Participants had symptoms/SABA use on at least 4 days of the last 2 weeks of the run-in period.		randomised to step up to moderate dose or add in LABA. Breakdown not provided.
Vaquerizo 2003 [182]	ICS moderate + LTRA, n=326 ICS moderate + placebo, n=313	Stratum: >16 years Age – mean 43, SD 16 At baseline participants were using ICS (moderate to high, ~68% moderate). Participants used at least a mean of 1 puff/day of SABA during run-in period on regular ICS.	• Quality of life (AQLQ) • Reliever medication use (% of days) • FEV_1 (% change) • PEF (L/min) Reported at 16 weeks	
Woolcock 1996 [192]	ICS (moderate dose) + LABA, n=487 ICS (high dose), n=251	Stratum: >16 years Age – mean (range): 44 (17–79) years At baseline, participants receiving 400–500 ug twice daily BDP or equivalent. During run-in period; FEV_1 or PEF >50% predicted, 15% reversibility in FEV_1 with salbutamol,	• FEV_1 (% of predicted) • Morning PEF (% of predicted) Reported at 6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		daytime plus night-time symptom score >2, diurnal variation of PEF >15%, rescue use >3 times /24 hours on 4 of 7 days prior to randomisation.		
Yurdakul 2002 [194]	ICS moderate + LABA, n=25 ICS moderate + LTRA, n=19 ICS moderate + theophylline, n=20	Stratum: >16 years Age – mean 38 (SD 6) At baseline participants were using ICS (moderate to high, majority moderate). Participants had mean baseline SABA puffs per day 3.4–3.8.	• Reliever medication use (puffs/day) • FEV_1 (% predicted) Reported at 12 weeks	
Molimard 2001 [107]	ICS moderate dose + LABA, n=130 ICS moderate dose, n=129	Stratum: >16 years Age – mean 39, SD 15 At baseline all participants were using low to moderate dose ICS. Participants were using on average 1.1 puffs/day SABA at baseline.	• Quality of life (SGRQ, 0–100, higher is worse outcome) • Reliever medication use (puffs/day) • PEF (L/minute) Reported at 12 weeks	Open-label study
Kemp 1998 [82]	ICS moderate dose + LABA, n=252 ICS moderate dose + placebo, n=254	Stratum: >16 years Age – mean 42, SD 16 At baseline all participants were using low to	• Quality of life (AQLQ, 1–7, higher is better outcome) • Reliever medication use (puffs/day) • PEF (L/minute)	

Study	Intervention and comparison	Population	Outcomes	Comments
		moderate dose ICS. Participants used SABA on a daily basis.	• FEV_1 (L) Reported at 12 weeks	
FitzGerald 1998 [50]	ICS (moderate dose) + LABA, n=89 ICS (moderate dose), n=91	Stratum: >16 years Age – mean (SD): 36 (13) years At baseline, participants using ICS constant dose of 400–1200 ug/day and SABA for at least one month. Reversibility of broncho-constriction – FEV_1 15% increase following SABA, rescue use on at least 5 of the last 7 run-in days.	• Reliever medication use (daytime) • Reliever medication use (night-time) • FEV_1 • Morning PEF Reported at 6 months	
D'Urzo 2000 [40]	ICS (moderate dose) + LABA, n=455 ICS (moderate dose), n=455	Stratum: >16 years Age – mean (SD): 46.2 (16.3) Receiving optimum doses of anti-inflammatory treatment while still requiring SABA. Demonstration of airflow obstruction reversibility (with no time restriction).	• Morning PEF Reported at 6 months	
Ind 2003 [73]	ICS (moderate dose) + LABA, n=171 ICS (high dose), n=165 ICS (moderate dose),	Stratum: >16 years Age – mean (SD): 44.8 (15.2) At baseline, participants were	• Severe exacerbations • Morning PEF Reported at 6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=160	symptomatic on BDP 500–800 ug twice daily (or equivalent). Demonstrated a period variation in PEF of 15% over last 10 days of run-in.		
Shapiro 2000 [160]	ICS (moderate dose) + LABA, n=84 ICS (moderate dose), n=84	Stratum: >16 years Age – mean (range): 39 (12–69) Received ICS continuously for at least 12 weeks. >15% increase in FEV_1 following 180 ug inhaled salbutamol. Stable asthma confirmed by diary cards at end of run-in period.	• Reliever medication use • FEV_1 • Morning PEF Reported at 12 weeks	
Kuna 2007 [91]	MART (ICS [moderate dose] + LABA), n=1107 ICS (moderate dose) + LABA, n=1105	Stratum: >16 years Age – mean (SD): 38 (17) At baseline, participants using ≥500 ug/day budesonide or fluticasone, or ≥1000 ug of another ICS. Use of reliever medication on ≥5 of the last 7 days of 2-week run-in period.	• Severe exacerbation • Reliever medication use • FEV_1 • Morning PEF Reported at 6 months	
Bergmann 2004 [11]	ICS low + LABA, n=170	Stratum: >16 years Age – mean (SD):	• Reliever medication use • FEV_1	

Study	Intervention and comparison	Population	Outcomes	Comments
	ICS moderate, n=177	49.34 (14.05) At baseline, treated with ICS (BDP or budesonide 800–1000 ug/day, or fluticasone 800 ug/day) Use of rescue medication on ≥7 of the 14-day run-in period, or total symptom score of ≥10.	• Morning PEF Reported at 12 weeks	
Jenkins 2000 [75]	ICS moderate + LABA, n=180 ICS high, n =173	Stratum: >16 years Age – mean (range): 46.5 (14–80) At baseline, participants receiving budesonide or BDP 800–1200 ug/day or fluticasone 400–600 ug/day. Used salbutamol >2 times a day or zero daytime plus night-time symptom score of >1 on >3 of last 7 days during run-in period.	• Severe exacerbations • Reliever medication use • FEV_1 • Morning PEF	
ICS high dose				
Reid 2008[145]	ICS high dose + LTRA, n=16 ICS high dose + placebo, n=8	Stratum: >16 years Age – range of means 37–45 At baseline all participants were using high dose ICS. Participants had a symptom score of	• Reliever medication use (puffs/day) • FEV_1 (L) • PEF (L/minute) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		at least 10 on last 7 days of screening period (0=no symptoms; 1=mild symptoms; up to 3=severe symptoms).		
Aubier 1999[4]	ICS high dose + LABA, n=338 ICS high dose + placebo, n=165	Stratum: >16 years Age – mean 48, range 12–79 At baseline all participants were using high dose ICS. Participants were symptomatic on at least 4 of the last 7 days of the run-in on their usual ICS.	• PEF (L/minute) Reported at 12 weeks	ICS + LABA composed of two arms (combination inhaler versus separate inhalers) that are pooled in this analysis
Jenkins 2006[74]	ICS high dose + LABA, n=341 ICS high dose + placebo, n=115	Stratum: >16 years Age – mean 46, range 12–79 At baseline the majority of participants were using high dose ICS alone. All participants were using ICS prior to the study (mean dose high) and only 49% were using LABA. Participants had symptoms on at least 4 of the last 7 days of the run-in on their regular preventer.	• Reliever medication (puffs/day) • PEF (L/minute) • Infection (all respiratory) Reported at 12 weeks	ICS + LABA composed of two arms (combination inhaler versus separate inhalers) that are pooled in this analysis where possible; if not possible, combination inhaler results have been analysed preferentially.
Ringdal 2002[150]	ICS high dose + LABA, n=216	Stratum: >16 years	• PEF (L/minute) • Infection (all	

Study	Intervention and comparison	Population	Outcomes	Comments
	ICS moderate dose + LABA, n=212	Age – mean 47 (SD 14) At baseline all participants were using high dose ICS alone. Participants had symptoms or SABA use on at least 4 of the last 7 days of the run-in on their regular preventer.	respiratory) • Infection (serious respiratory) Reported at 12 weeks	
Zimmerman 2004[200]	ICS high dose + LABA, n=95 ICS high dose + placebo, n=101	Stratum: 5–16 years Age – mean 9, range 6–11 At baseline all participants were using ICS, mean dose high. Participants had asthma symptoms "sufficient to suggest additional therapy might be needed"; in last 10 days of run-in had one of: 4 or more uses of rescue medication, symptoms on 4 or more days, 1 or more night awakening.	• PEF (L/minute) • FEV_1 (L) • Infection (all respiratory) Reported at 12 weeks	Trial includes two ICS + LABA arms, with formoterol 4.5 ug and 9 ug twice daily. Formoterol 9 ug twice daily preferentially extracted as results not able to be pooled and 9 ug twice daily closest to BNF recommended dose (12 ug twice daily).
Boyd 1995[19]	ICS high dose + LABA, n=55 ICS high dose + placebo, n=64	Stratum: >16 years Age – mean 47 (18–79) At baseline all participants were using high dose ICS.	• Reliever medication use (puffs/day) • FEV_1 (L) • PEF (L/minute) Reported at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		Participants had night-time symptoms/day-time symptoms or at least 8 SABA puffs on at least 3 of last 7 days of run-in.		
Vogelmeier 2005 [184]	MART (ICS moderate dose + LABA), n=1067 ICS moderate dose + LABA, n=1076	Stratum: >16 years Age – mean 45 (range 12–84) At baseline all participants were using moderate to high dose ICS, mean dose high, majority (62%) without LABA. Participants had reliever medication use on at least 4 of the last 7 days of run-in period.	• Severe exacerbations (requiring OCS) • Quality of life (AQLQ, 1–7, higher is better outcome) • Control (ACQ, 0–6, higher is worse outcome) • Reliever medication use (puffs/day, average across treatment period) • FEV_1 (L) Reported at 1 year	Participants (in conjunction with their physicians during scheduled or unscheduled visits) were able to titrate their maintenance dose of ICS up and down (ICS + LABA group) or just down (MART group). Mean overall dose by end of study was in ICS high dose range in both groups. Study was open label.

Population uncontrolled on ICS + LABA at baseline

Table 74: Clinical evidence summary: MART (ICS moderate + LABA) compared to ICS high + LABA + SABA when required, people over the age of 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high + LABA + SABA when required	Risk difference with MART (ICS moderate + LABA) (95% CI)
Severe exacerbations	2304 (1 study) 6 months	LOW[a,b] due to indirectness, imprecision	RR 0.83 (0.65 to 1.06)	113 per 1000	19 fewer per 1000 (from 39 fewer to 7 more)
Asthma control (ACQ, 0-6, higher is worse outcome)	2289 (1 study) 6 months	HIGH	-	-	The mean asthma control (ACQ, 0–6, higher is worse outcome) in the intervention groups was 0.02 lower (0.07 lower to 0.03 higher)
Rescue medication use (puffs/day)	2289 (1 study) 6 months	HIGH	-	-	The mean rescue medication use (puffs/day) in the intervention groups was 0.04 lower (0.12 lower to 0.04 higher)
PEF (L/min)	2289 (1 study) 6 months	HIGH	-	-	The mean PEF (L/min) in the intervention groups was 0.8 lower (4.4 lower to 2.8 higher)

a Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 75: Clinical evidence summary: MART (ICS low + LABA) compared to ICS low + LABA + SABA when required, people over the age of 16

Outcomes	Number of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with ICS low + LABA + SABA when required	Risk difference with MART (ICS low + LABA) (95% CI)
Severe exacerbations (requiring OCS)	2245 (1 study) 1 years	HIGH	RR 0.6 (0.5 to 0.72)	215 per 1000	86 fewer per 1000 (from 60 fewer to 108 fewer)
Asthma control (ACQ-5, 0–6, higher is worse outcome)	2244 (1 study) 1 years	HIGH	-	-	The mean asthma control (ACQ-5, 0–6, higher is worse outcome) in the intervention groups was 0.15 lower (0.21 to 0.09 lower)
Reliever medication use (puffs/day)	2244 (1 study) 1 years	HIGH	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.2 lower (0.28 to 0.12 lower)
FEV_1 (L)	2245 (1 study) 1 years	HIGH	-	-	The mean FEV_1 (L) in the intervention groups was 0.08 higher (0.05 to 0.11 higher)
PEF (L/min)	2245 (1 study) 1 years	HIGH	-	-	The mean PEF (L/min) in the intervention groups was 7.5 higher (4.2 to 10.8 higher)
Infections (all respiratory)	2245 (1 study) 1 years	MODERATE[a] due to imprecision	RR 2.26 (1.08 to 4.75)	9 per 1000	11 more per 1000 (from 1 more to 33 more)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 76: Clinical evidence summary: MART (ICS low + LABA) compared to ICS high + LABA + SABA when required, people over the age of 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with ICS moderate	Risk difference with ICS high (95% CI)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS high (95% CI)
Reliever medication use	127 (1 study) 12 months	HIGH	-	The mean change in reliever medication (puffs/day) in the control groups was -0.5 puffs/day	The mean change in reliever medication (puffs/day) in the intervention groups was 0.04 higher (0.47 lower to 0.55 higher)

Table 77: ICS moderate/high + LABA + LAMA compared to ICS moderate/high + LABA, people over the age of 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate/high + LABA	Risk difference with ICS moderate/high + LABA + LAMA (95% CI)
Severe exacerbations (requiring OCS)	907 (1 study) 48 weeks	LOW[a,b] due to risk of bias, imprecision	RR 0.82 (0.67 to 1)	328 per 1000	59 fewer per 1000 (from 108 fewer to 0 more)
Quality of life (AQLQ, 1–7, higher is better outcome)	912 (2 studies) 24 weeks	MODERATE[a] due to risk of bias	-	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was 0.11 higher (0 to 0.21 higher)
Control (ACQ, 0–6, higher is worse outcome)	912 (2 studies) 24 weeks	MODERATE[a] due to risk of bias	-	-	The mean control (ACQ, 0–6, higher is worse outcome) in the intervention groups was 0.17 lower (0.25 to 0.09 lower)
Reliever medication use (puffs/day)	912 (2 studies) 24 weeks	MODERATE[a] due to risk of bias	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.17 lower (0.42 lower to 0.09 higher)
FEV_1 (L)	990 (3 studies) 24–52	HIGH	-	-	The mean FEV_1 (L) in the intervention groups was 0.08 higher (0.04 to 0.12 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate/high + LABA	Risk difference with ICS moderate/high + LABA + LAMA (95% CI)
	weeks				
PEF (L/min)	918 (3 studies) 24–52 weeks	MODERATE[b] due to imprecision	-	-	The mean PEF (L/min) in the intervention groups was 18.2 higher (12.08 to 24.32 higher)
Infections (all respiratory)	1083 (2 studies) 24–48 weeks	LOW[a,b] due to risk of bias, imprecision	RR 1.4 (1.11 to 1.76)	97 per 1000	39 more per 1000 (from 11 more to 74 more)
Infections (serious respiratory)	912 (1 study) 48 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.71 (0.68 to 4.31)	15 per 1000	11 more per 1000 (from 5 fewer to 51 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 78: Clinical evidence summary: ICS high + LABA compared to ICS moderate + LABA, people over the age of 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with ICS high + LABA (95% CI)
Severe exacerbations (requiring OCS)	575 (1 study) 1 years	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.85 (0.52 to 1.38)	144 per 1000	22 fewer per 1000 (from 69 fewer to 55 more)
Hospitalisations	575 (1 study) 1 years	VERY LOW[a,c] due to risk of bias, imprecision	OR 0.22 (0.02 to 2.22)	15 per 1000	12 fewer per 1000 (from 15 fewer to 18 more)
Reliever medication use (puffs/day)	568	MODERATE[a]	-	-	The mean reliever medication use (puffs/day) in

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with ICS high + LABA (95% CI)
	(1 study) 1 years	due to risk of bias			the intervention groups was 0.16 lower (0.37 lower to 0.05 higher)
FEV_1 (L)	565 (1 study) 1 years	MODERATE[a] due to risk of bias	-	-	The mean FEV_1 (L) in the intervention groups was 0.02 higher (0.02 lower to 0.06 higher)
PEF (L/min)	571 (1 study) 1 years	MODERATE[a] due to risk of bias	-	-	The mean PEF (L/min) in the intervention groups was 6.67 higher (0.99 lower to 14.33 higher)
Infections (all respiratory)	565 (1 study) 1 years	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.99 (0.89 to 1.1)	765 per 1000	8 fewer per 1000 (from 84 fewer to 77 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 79: Clinical evidence summary: ICS high + LABA compared to ICS high, people over the age of 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS high + LABA (95% CI)
Severe exacerbations (requiring OCS)	576 (1 study) 1 years	LOW[a,b] due to risk of bias, indirectness	RR 0.56 (0.37 to 0.84)	218 per 1000	96 fewer per 1000 (from 35 fewer to 137 fewer)
Hospitalisations	576 (1 study)	VERY LOW[a,c] due to risk of bias,	OR 3.68 (0.14 to	0 per 1000	-

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS high + LABA (95% CI)
	1 years	imprecision	98.9)		
Reliever medication use (puffs/day)	568 (1 study) 1 years	LOW[a,c] due to risk of bias, imprecision	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.87 lower (1.08 to 0.66 lower)
FEV_1 (L)	568 (1 study) 1 years	MODERATE[a] due to risk of bias	-	-	The mean FEV_1 (L) in the intervention groups was 0.11 higher (0.06 to 0.16 higher)
PEF (L/min)	573 (1 study) 1 years	MODERATE[a] due to risk of bias	-	-	The mean PEF (L/min) in the intervention groups was 34.7 higher (27.1 to 42.3 higher)
Infections (all respiratory)	576 (1 study) 1 years	MODERATE[a] due to risk of bias	RR 0.93 (0.84 to 1.04)	789 per 1000	55 fewer per 1000 (from 126 fewer to 32 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 80: Clinical evidence summary: ICS high compared to ICS moderate + LABA, people over the age of 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with ICS high (95% CI)
Severe exacerbations (requiring OCS)	265 (1 study) 1 years	LOW[a,b] due to risk of bias, indirectness	RR 1.51 (0.9 to 2.56)	144 per 1000	73 more per 1000 (from 14 fewer to 225 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with ICS high (95% CI)
Hospitalisations	265 (1 study) 1 years	LOW[a,c] due to risk of bias, imprecision	OR 0.13 (0.01 to 2.14)	15 per 1000	13 fewer per 1000 (from 15 fewer to 17 more)
Reliever medication use (puffs/day)	260 (1 study) 1 years	LOW[a,c] due to risk of bias, imprecision	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.72 higher (0.45 to 0.99 higher)
FEV_1 (L)	261 (1 study) 1 years	MODERATE[a] due to risk of bias	-	-	The mean FEV_1 (L) in the intervention groups was 0.09 lower (0.15 to 0.03 lower)
PEF (L/min)	262 (1 study) 1 years	LOW[a,c] due to risk of bias, imprecision	-	-	The mean PEF (L/min) in the intervention groups was 28.04 lower (37.51 to 18.57 lower)
Infections (all respiratory)	265 (1 study) 1 years	MODERATE[a] due to risk of bias	RR 1.03 (0.91 to 1.17)	765 per 1000	23 more per 1000 (from 69 fewer to 130 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 81: Clinical evidence summary: ICS low + LAMA compared to ICS low + LABA, people over the age of 16

Outcomes	Number of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with ICS low + LABA	Risk difference with ICS low + LAMA (95% CI)
Number of participants experiencing at least one severe exacerbation (requiring OCS)	1070 (1 study) 18 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.92 (0.73 to 1.16)	227 per 1000	18 fewer per 1000 (from 61 fewer to 36 more)
Quality of life (AQLQ, 1–7, higher is better outcome)	720 (1 study) 18 months	VERY LOW[a,b] due to risk of bias, indirectness	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the control groups was 0.93	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was 0.07 higher (0.21 lower to 0.35 higher)
Asthma control (ACQ, 0–6, higher is worse outcome)	720 (1 study) 18 months	VERY LOW[a,b] due to risk of bias, indirectness	-	The mean asthma control (ACQ, 0–6, higher is worse outcome) in the control groups was -0.68	The mean asthma control (ACQ, 0–6, higher is worse outcome) in the intervention groups was 0.04 lower (0.27 lower to 0.19 higher)
FEV_1 (L)	720 (1 study) 18 months	VERY LOW[a,b] due to risk of bias, indirectness	-	The mean FEV_1 (L) in the control groups was -0.053	The mean FEV_1 (L) in the intervention groups was 0.03 lower (0.09 lower to 0.04 higher)
Rescue medication use (puffs/day)	720 (1 study) 18 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean rescue medication use (puffs/day) in the control groups was -1.05 puffs/day	The mean rescue medication use (puffs/day) in the intervention groups was 0.05 lower (0.84 lower to 0.74 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS low + LABA	Risk difference with ICS low + LAMA (95% CI)
population c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Population uncontrolled on ICS moderate dose at baseline

Table 82: Clinical evidence summary: ICS high compared to ICS moderate in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS high (95% CI)
Severe exacerbations	325 (1 study) 6 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.88 (0.65 to 1.21)	350 per 1000	42 fewer per 1000 (from 123 fewer to 74 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 83: Clinical evidence summary: ICS low + LABA compared to ICS moderate in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS low + LABA (95% CI)
Severe exacerbations	1835 (1 study) 1 years	LOW[a,b] due to indirectness,	RR 1.11 (0.92 to 1.33)	190 per 1000	21 more per 1000 (from 15 fewer to 63 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS low + LABA (95% CI)
		imprecision			
Reliever medication (puffs/day)	347 (1 study) 12 weeks	MODERATE[b] due to imprecision	-	The mean change in reliever medication (puffs/day) in the control groups was -1 puffs/day	The mean reliever medication (puffs/day) in the intervention groups was 0.6 lower (1.03 to 0.17 lower)
Reliever medication use (puffs/daytime)	1835 (1 study) 1 years	HIGH	-	-	The mean reliever medication use (puffs/daytime) in the intervention groups was 0.19 lower (0.3 to 0.08 lower)
Reliever medication use (puffs/night-time)	1835 (1 study) 12 weeks	HIGH	-	-	The mean reliever medication use (puffs/night-time) in the intervention groups was 0.06 lower (0.1 to 0.02 lower)
FEV_1 (L)	1835 (1 study) 1 years	HIGH	-	-	The mean FEV_1 (L) in the intervention groups was 0.02 higher (0 to 0.04 higher)
FEV_1 (%predicted)	347 (1 study) 12 weeks	HIGH	-	The mean FEV_1 (%predicted) in the control groups was 83 %	The mean FEV_1 (%predicted) in the intervention groups was 3 higher (2.17 lower to 8.17 higher)
PEF (L/min)	2182 (2 studies) 12-52 weeks	HIGH	-	-	The mean PEF (L/min) in the intervention groups was 7.65 higher (3.65 to 11.65 higher)

a Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS low + LABA (95% CI)
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 84: Clinical evidence summary: ICS moderate + LABA compared to ICS moderate in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS moderate + LABA (95% CI)
Severe exacerbations	1395 (2 studies) 6 months	LOW[a,b] due to risk of bias, indirectness	RR 0.66 (0.50 to 0.87)	145 per 1000	49 fewer per 1000 (from 19 fewer to 72 fewer)
Quality of life (pooled AQLQ, SGRQ)	2048 (4 studies) 12–24 weeks	MODERATE[a] due to risk of bias	-	-	The mean quality of life (pooled AQLQ, SGRQ) in the intervention groups was 0.26 standard deviations higher (0.17 to 0.35 higher)
Asthma control (ACQ, 0–6, high is poor outcome)	1064 (1 study) 24 weeks	HIGH	-	-	The mean asthma control (ACQ, 0–6, high is poor outcome) in the intervention groups was 0.2 lower (0.28 to 0.12 lower)
Reliever medication (puffs/day)	1363 (5 studies) 12–24 weeks	MODERATE[a] due to risk of bias	-	-	The mean reliever medication (puffs/day) in the intervention groups was 1.03 lower (1.21 to 0.85 lower)
Reliever medication use (puffs/daytime)	180 (1 study) 6 months	LOW[a,c] due to risk of bias, imprecision	-	-	The mean reliever medication use (puffs/daytime) in the intervention groups was 0.54 lower (1.07 to 0.01 lower)
Reliever medication use (puffs/night-time)	180 (1 study)	LOW[a,c] due to risk of bias,	-	-	The mean reliever medication use (puffs/night-time) in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS moderate + LABA (95% CI)
	6 months	imprecision			0.41 lower (0.82 lower to 0 higher)
PEF (L/min)	3630 (8 studies) 12–24 weeks	LOW[a,c] due to risk of bias, imprecision	-	-	The mean PEF (L/min) in the intervention groups was 21.72 higher (18.03 to 25.42 higher)
FEV_1 (L)	2130 (5 studies) 12–24 weeks	MODERATE[a] due to risk of bias	-	-	The mean FEV_1 (L) in the intervention groups was 0.19 higher (0.16 to 0.23 higher)
Infection (all respiratory)	1287 (2 studies) 12–24 weeks	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.95 (0.64 to 1.42)	71 per 1000	4 fewer per 1000 (from 25 fewer to 30 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 85: Clinical evidence summary: MART (ICS low + LABA) compared to ICS moderate in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with MART (ICS low + LABA) (95% CI)
Severe exacerbations	3741 (2 studies) 1 years	LOW[a,b] due to risk of bias, indirectness	RR 0.62 (0.54 to 0.72)	233 per 1000	88 fewer per 1000 (from 65 fewer to 107 fewer)
Reliever medication use (puffs/daytime)	1851 (1 study)	HIGH	-	-	The mean reliever medication use (puffs/daytime) in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with MART (ICS low + LABA) (95% CI)
	1 years				0.3 lower (0.48 to 0.12 lower)
Reliever medication use (puffs/night-time)	1851 (1 study) 1 years	HIGH	-	-	The mean reliever medication use (puffs/night-time) in the intervention groups was 0.15 lower (0.24 to 0.06 lower)
Reliever medication use (rescue-free days %)	1890 (1 study) 1 years	MODERATE[a] due to risk of bias	-	-	The mean reliever medication use (rescue-free days %) in the intervention groups was 11 higher (8.2 to 13.8 higher)
FEV_1 (L)	1851 (1 study) 1 years	HIGH	-	-	The mean FEV_1 (L) in the intervention groups was 0.1 higher (0.04 to 0.16 higher)
PEF (L/min)	3741 (2 studies) 1 years	LOW[a,c] due to risk of bias, imprecision	-	-	The mean PEF (L/min) in the intervention groups was 19.71 higher (16.18 to 23.24 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 86: Clinical evidence summary: ICS moderate + LTRA compared to ICS moderate in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with ICS moderate	Risk difference with ICS moderate + LTRA (95% CI)
Quality of life (AQLQ, 1-7, higher	625	HIGH	-	The mean quality of life (AQLQ, 1–7,	The mean quality of life (AQLQ, 1–7, higher

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS moderate + LTRA (95% CI)
is better outcome)	(1 study) 16 weeks			higher is better outcome) in the control groups was 0.52	is better outcome) in the intervention groups was 0.08 higher (0.06 lower to 0.22 higher)
Reliever medication use (% change from baseline)	3446 (1 study) 16 weeks	HIGH	-	The mean reliever medication use (% change from baseline) in the control groups was -4.92 %	The mean reliever medication use (% change from baseline) in the intervention groups was 12.34 lower (33.21 lower to 8.53 higher)
FEV_1 ([L], % change from baseline)	625 (1 study) 16 weeks	HIGH	-	The mean FEV_1 ([L], % change from baseline) in the control groups was 2.49%	The mean FEV_1 ([L], % change from baseline) in the intervention groups was 0.14 higher (4.36 lower to 4.64 higher)
PEF (L/min)	625 (1 study) 16 weeks	HIGH	-	The mean PEF (L/min) in the control groups was 11.3 L/min	The mean PEF (L/min) in the intervention groups was 5.56 higher (3.95 lower to 15.07 higher)

Table 87: Clinical evidence summary: ICS moderate + LAMA compared to ICS moderate in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS moderate + LAMA (95% CI)
Severe exacerbations (requiring OCS)	1042 (1 study) 6 months	LOW[b] due to imprecision	RR 0.73 (0.47 to 1.13)	82 per 1000	21 fewer per 1000 (from 44 fewer to 11 fewer)
Quality of life (AQLQ, 1–7, higher is better outcome)	1064 (1 study)	HIGH	-	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS moderate + LAMA (95% CI)
	6 months				0.04 higher (0.05 lower to 0.14 higher)
Asthma control (ACQ, 0–6, high is poor outcome)	1064 (1 study) 6 months	HIGH	-	-	The mean asthma control (ACQ, 0–6, high is poor outcome) in the intervention groups was 0.12 lower (0.2 to 0.04 lower)
FEV_1 (L)	1064 (1 study) 6 months	HIGH	-	-	The mean FEV_1 (L) in the intervention groups was 0.19 higher (0.15 to 0.22 higher)
PEF (L/min)	1064 (1 study) 6 months	MODERATE[a] due to imprecision	-	-	The mean PEF (L/min) in the intervention groups was 24.3 higher (17.9 to 30.7 higher)
Infection (all respiratory)	1040 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	RR 0.47 (0.28 to 0.8)	78 per 1000	42 fewer per 1000 (from 16 fewer to 56 fewer)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 88: Clinical evidence summary: ICS low + LABA compared to ICS high in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS low + LABA (95% CI)
Quality of life (AQLQ, 1–7, higher is better outcome)	391 (1 study) 6 months	MODERATE[a] due to risk of bias	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the control groups was 0.9	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was 0.03 higher (0.15 lower to 0.21 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS low + LABA (95% CI)
Asthma control (ACT, 5–25, high is good outcome)	391 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	-	The mean asthma control (ACT, 5–25, high is good outcome) in the control groups was 4.7	The mean asthma control (ACT, 5–25, high is good outcome) in the intervention groups was 0.8 higher (0.01 to 1.59 higher)
FEV_1 (L)	377 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	-	The mean FEV_1 (L) in the control groups was 0.183 L	The mean FEV_1 (L) in the intervention groups was 0.21 higher (0.13 to 0.29 higher)
PEF (L/min)	391 (1 study) 6 months	MODERATE[a] due to risk of bias	-	The mean PEF (L/min) in the control groups was 18.8 L/min	The mean PEF (L/min) in the intervention groups was 33 higher (24.84 to 41.16 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 89: Clinical evidence summary: ICS moderate + LABA compared to ICS high in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS moderate + LABA (95% CI)
Severe exacerbations	689 (2 studies) 6 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.87 (0.63 to 1.22)	157 per 1000	20 fewer per 1000 (from 58 fewer to 34 more)
Quality of life (AQLQ, 1–7, higher is better outcome)	113 (1 study) 12 weeks	MODERATE[c] due to imprecision	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the control groups was	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS moderate + LABA (95% CI)
				0.44	0.45 higher (0.16 to 0.74 higher)
Reliever medication use (puffs/day)	178 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-	The mean reliever medication use (puffs/day) in the control groups was 2.43 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 1.5 lower (2.08 to 0.92 lower)
Reliever medication use (rescue-free days %)	353 (1 study) 6 months	LOW[a,c] due to risk of bias, imprecision	-	-	The mean reliever medication use (rescue-free days %) in the intervention groups was 32 higher (13.11 to 50.89 higher)
FEV_1 (%predicted)	738 (1 study) 6 months	HIGH	-	The mean FEV_1 (%predicted) in the control groups was 3%	The mean FEV_1 (%predicted) in the intervention groups was 5 higher (4.45 to 5.55 higher)
FEV_1 (L)	353 (1 study) 6 months	MODERATE[a] due to risk of bias	-	-	The mean FEV_1 (L) in the intervention groups was 0.09 higher (0 to 0.18 higher)
PEF (L/min)	1126 (4 studies) 12-24 weeks	MODERATE[a] due to risk of bias	-	-	The mean PEF (L/min) in the intervention groups was 21.74 higher (16.07 to 27.4 higher)
PEF (% predicted)	738 (1 study) 6 months	HIGH	-	The mean PEF (% predicted) in the control groups was 85%	The mean PEF (% predicted) in the intervention groups was 7 higher (5.51 to 8.49 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. No explanation was provided

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS moderate + LABA (95% CI)

b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 90: Clinical evidence summary: ICS moderate + LTRA compared to ICS high in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects: Risk with ICS high	Anticipated absolute effects: Risk difference with ICS moderate + LTRA (95% CI)
Quality of life (AQLQ, 1–7, higher is better outcome)	964 (2 studies) 12 weeks	MODERATE[a] due to risk of bias	-	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was 0.08 higher (0.05 lower to 0.21 higher)
Reliever medication use (puffs/day)	889 (1 study) 12 weeks	HIGH	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.03 lower (0.11 lower to 0.05 higher)
PEF (L/min)	964 (2 studies) 12 weeks	MODERATE[a] due to risk of bias	-	-	The mean PEF (L/min) in the intervention groups was 3.21 higher (4.7 lower to 11.12 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 91: Clinical evidence summary: ICS moderate + theophylline compared to ICS high in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects: Risk with ICS high	Anticipated absolute effects: Risk difference with ICS moderate + theophylline (95% CI)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS high	Risk difference with ICS moderate + theophylline (95% CI)
FEV_1 (L)	62 (1 study) 12 weeks	LOW[a] due to imprecision	-	The mean FEV_1 (L) in the control groups was 2.61 L	The mean FEV_1 (L) in the intervention groups was 0.08 higher (0.35 lower to 0.51 higher)
PEF (L/min)	62 (1 study) 12 weeks	LOW[a] due to imprecision	-	The mean PEF (L/min) in the control groups was 405 L/min	The mean PEF (L/min) in the intervention groups was 6 higher (43.97 lower to 55.97 higher)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 92: Clinical evidence summary: MART (ICS low + LABA) compared to ICS high in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS low + LABA	Risk difference with MART (ICS low + LABA) (95% CI)
Severe exacerbations	1834 (1 study) 1 years	MODERATE[a] due to indirectness	RR 0.52 (0.42 to 0.66)	210 per 1000	101 fewer per 1000 (from 71 fewer to 122 fewer)
Reliever medication use (puffs/daytime)	1834 (1 study) 1 years	HIGH	-	-	The mean reliever medication use (puffs/daytime) in the intervention groups was 0.11 lower (0.17 to 0.05 lower)
Reliever medication use (puffs/night-time)	1834 (1 study) 1 years	HIGH	-	-	The mean reliever medication use (puffs/night-time) in the intervention groups was 0.09 lower (0.14 to 0.04 lower)
FEV_1 (L)	1834 (1 study) 1 years	HIGH	-	-	The mean FEV_1 (L) in the intervention groups was 0.08 higher (0.03 to 0.13 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS low + LABA	Risk difference with MART (ICS low + LABA) (95% CI)
PEF (L/min)	1834 (1 study) 1 years	HIGH	-	-	The mean PEF (L/min) in the intervention groups was 9 higher (3.65 to 14.35 higher)
1 Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes					

Table 93: Clinical evidence summary: ICS moderate + LTRA compared to ICS moderate + LABA in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with ICS moderate + LTRA (95% CI)
Reliever medication use (puffs/day)	944 (2 studies) 12 weeks	LOW[a,c] due to risk of bias, inconsistency	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.2 higher (0.14 to 0.25 higher)
FEV_1 (%predicted)	44 (1 study) 12 weeks	HIGH	-	The mean FEV_1 (%predicted) in the control groups was 89.5%	The mean FEV_1 (%predicted) in the intervention groups was 2.2 lower (5.6 lower to 1.2 higher)
PEF (L/min)	948 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean PEF (L/min) in the control groups was 30 L/min	The mean PEF (L/min) in the intervention groups was 8.3 lower (22.16 lower to 5.56 higher)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c Downgraded by 1 or 2 increments because the point estimate and/or the confidence intervals varied widely across studies, unexplained by subgroup analysis					

Table 94: Clinical evidence summary: ICS moderate + LAMA compared to ICS moderate + LABA in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with ICS moderate + LAMA (95% CI)
Severe exacerbations	1060 (1 study) 6 months	LOW[b] due to imprecision	RR 1.47 (0.86 to 2.50)	41 per 1000	19 more per 1000 (from 6 fewer to 61 more)
Infection (all respiratory)	1058 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	RR 0.48 (0.29 to 0.82)	76 per 1000	39 fewer per 1000 (from 14 fewer to 54 fewer)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 95: Clinical evidence summary: MART (ICS moderate + LABA) compared to ICS moderate + LABA in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with MART (ICS moderate + LABA) (95% CI)
Severe exacerbations	2212 (1 study) 6 months	MODERATE[a] due to imprecision	RR 0.74 (0.58 to 0.96)	114 per 1000	30 fewer per 1000 (from 5 fewer to 48 fewer)
Reliever medication use (puffs/day)	2211 (1 study) 6 months	HIGH	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.03 lower (0.12 lower to 0.06 higher)
PEF (L/min)	2211 (1 study) 6 months	HIGH	-	-	The mean PEF (L/min) in the intervention groups was 0.7 lower (4.5 lower to 3.1 higher)
FEV_1 (L)	2211 (1 study)	HIGH	-	-	The mean FEV_1 (L) in the intervention groups was 0.01 higher

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with MART (ICS moderate + LABA) (95% CI)
	6 months				(0.03 lower to 0.04 higher)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 96: Clinical evidence summary: ICS moderate + LABA compared to ICS moderate + theophylline in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + theophylline	Risk difference with ICS moderate + LABA (95% CI)
Reliever medication use (puffs/day)	45 (1 study) 12 weeks	HIGH	-	The mean reliever medication use (puffs/day) in the control groups was 0.2 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0 higher (0.06 lower to 0.06 higher)
FEV_1 (%predicted)	45 (1 study) 12 weeks	MODERATE[a] due to imprecision	-	The mean FEV_1 (%predicted) in the control groups was 86.6%	The mean FEV_1 (%predicted) in the intervention groups was 2.9 higher (0.48 lower to 6.28 higher)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 97: Clinical evidence summary: ICS moderate + LTRA compared to ICS moderate + theophylline in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + theophylline	Risk difference with ICS moderate + LTRA (95% CI)
Reliever medication use (puffs/day)	39 (1 study) 12 weeks	HIGH	-	The mean reliever medication use (puffs/day) in the control groups was 0.2 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.1 higher (0.04 to 0.16 higher)
FEV_1 (%predicted)	39	MODERATE[a]	-	The mean FEV_1 (%predicted) in the	The mean FEV_1 (%predicted) in the

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + theophylline	Risk difference with ICS moderate + LTRA (95% CI)
	(1 study) 12 weeks	due to imprecision		control groups was 86.6%	intervention groups was 0.7 higher (2.91 lower to 4.31 higher)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 98: Clinical evidence summary: ICS low + LABA compared to ICS moderate in people aged 5–16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS low + LABA (95% CI)
Severe exacerbations	223 (1 study) 1 years	LOW[a,b] due to indirectness, imprecision	RR 1.55 (0.97 to 2.48)	198 per 1000	109 more per 1000 (from 6 fewer to 293 more)
Reliever medication use (puffs/day)	223 (1 study) 1 years	LOW[b] due to imprecision	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.02 higher (1.08 lower to 1.12 higher)
FEV_1 (L)	223 (1 study) 1 years	LOW[b] due to imprecision	-	-	The mean FEV_1 (L) in the intervention groups was 0.6 lower (2.09 lower to 0.89 higher)
PEF (L/min)	223 (1 study) 1 years	HIGH	-	-	The mean PEF (L/min) in the intervention groups was 4 higher (0.04 lower to 8.04 higher)
Growth (cm)	223 (1 study) 1 years	MODERATE[b] due to imprecision	-	-	The mean growth (cm) in the intervention groups was 0.9 higher (0.2 to 1.6 higher)

a Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with ICS low + LABA (95% CI)

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 99: Clinical evidence summary: MART (ICS low + LABA) compared to ICS moderate in people aged 5–16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with MART (ICS low + LABA) (95% CI)
Severe exacerbations	224 (1 study) 1 years	MODERATE[a] due to indirectness	RR 0.43 (0.21 to 0.87)	198 per 1000	113 fewer per 1000 (from 26 fewer to 157 fewer)
Reliever medication use (puffs/day)	224 (1 study) 1 years	HIGH	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.16 lower (0.35 lower to 0.03 higher)
FEV_1 (L)	224 (1 study) 1 years	MODERATE[b] due to imprecision	-	-	The mean FEV_1 (L) in the intervention groups was 0.1 higher (0.14 lower to 0.34 higher)
PEF (L/min)	224 (1 study) 1 years	MODERATE[b] due to imprecision	-	-	The mean PEF (L/min) in the intervention groups was 17 higher (6.4 to 27.6 higher)
Growth (cm)	224 (1 study) 1 years	MODERATE[b] due to imprecision	-	-	The mean growth (cm) in the intervention groups was 1 higher (0.3 to 1.7 higher)

a Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 100: Clinical evidence summary: MART (ICS low + LABA) compared to ICS low + LABA in people aged 5–16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS low + LABA	Risk difference with MART (ICS low + LABA) (95% CI)
Severe exacerbations	235 (1 study) 1 years	MODERATE[a] due to indirectness	RR 0.28 (0.14 to 0.53)	308 per 1000	222 fewer per 1000 (from 145 fewer to 265 fewer)
Reliever medication use (puffs/day)	235 (1 study) 1 years	LOW[b] due to imprecision	-	-	The mean reliever medication use (puffs/day) in the intervention groups was 0.18 lower (1.24 lower to 0.88 higher)
FEV_1 (L)	235 (1 study) 1 years	MODERATE[b] due to imprecision	-	-	The mean FEV_1 (L) in the intervention groups was 0.16 higher (0.03 lower to 0.35 higher)
PEF (L/min)	235 (1 study) 1 years	MODERATE[b] due to imprecision	-	-	The mean PEF (L/min) in the intervention groups was 13 higher (7.72 lower to 33.72 higher)

a Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 101: Clinical evidence summary: ICS moderate + LAMA compared to ICS moderate in people aged 5–16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with 5–16, ICS moderate + LAMA (95% CI)
Severe exacerbations	272 (1 study) 48 weeks	MODERATE[a] due to imprecision	RR 0.23 (0.05 to 1.04)	65 per 1000	50 fewer per 1000 (from 62 fewer to 3 more)
Quality of life (AQLQ, 1–7, higher is better outcome) - New Subgroup	261 (1 study) 48 weeks	HIGH	-	Result given as mean difference	The mean quality of life (AQLQ, 1–7, higher is better outcome) - new subgroup in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate	Risk difference with 5–16, ICS moderate + LAMA (95% CI)
					0.03 higher (0.14 lower to 0.2 higher)
Reliever medication (puffs/day)	249 (1 study) 48 weeks	HIGH	-	The mean reliever medication (puffs/day) in the control groups was -0.372 puffs/day	The mean reliever medication (puffs/day) in the intervention groups was 0.28 lower (0.55 lower to 0 higher)
FEV_1 (L)	261 (1 study) 24 weeks	MODERATE[a] due to imprecision	-	The mean FEV_1 (L) in the control groups was 2.83	The mean FEV_1 (L) in the intervention groups was 1.17 higher (0.05 to 2.29 higher)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Population uncontrolled on ICS high dose at baseline

Table 102: Clinical evidence summary: ICS high dose + LABA compared to ICS high dose in adults over 16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Add LABA (95% CI)
Reliever medication use (puffs/day)	456 (2 studies) 12 months	MODERATE[a] due to imprecision	-		The mean reliever medication use (puffs/day) in the intervention groups was 0.74 lower (1.1 to 0.38 lower)
FEV_1 (L)	96 (1 study) 12 weeks	HIGH	-		The mean FEV_1 (L) in the intervention groups was 0.03 higher (0.13 lower to 0.19 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Add LABA (95% CI)
PEF (L/min)	944 (3 studies) 12 weeks	MODERATE[a] due to imprecision	-		The mean PEF (L/min) in the intervention groups was 24.12 higher (18.65 to 29.59 higher)
Infection (all respiratory)	456 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.52 (0.64 to 3.58)	52 per 1000	27 more per 1000 (from 19 fewer to 135 more)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 103: Clinical evidence summary: ICS high dose + LTRA compared to ICS high dose in adults

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Add LTRA (95% CI)
Reliever medication use (puffs/day)	21 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean reliever medication use (puffs/day) in the control groups was -0.3 puffs/day	The mean reliever medication use (puffs/day) in the intervention groups was 0.8 lower (1.53 to 0.07 lower)
FEV_1 (L)	21 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean FEV_1 (L) in the control groups was -0.024 L	The mean FEV_1 (L) in the intervention groups was 0.17 higher (0.08 to 0.25 higher)
PEF (L/min)	21 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	-	The mean PEF (L/min) in the control groups was 17.5 L/min	The mean PEF (L/min) in the intervention groups was 14.8 lower (26.62 to 2.98 lower)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Add LTRA (95% CI)
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 104: Clinical evidence summary: ICS high dose + LABA compared to ICS moderate dose + LABA in adults

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Add LABA, reduce ICS to moderate	Risk difference with Add LABA (95% CI)
PEF (L/min)	324 (1 study) 12 weeks	HIGH	-		The mean PEF (L/min) in the intervention groups was 3.2 higher (8.6 lower to 15 higher)
Infection (all respiratory)	428 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision	RR 0.68 (0.38 to 1.2)	123 per 1000	39 fewer per 1000 (from 76 fewer to 25 more)
Infection (serious respiratory)	428 (1 study) 12 weeks	LOW[b] due to imprecision	OR 7.25 (0.14 to 365.61)	0 per 1000	-
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 105: Clinical evidence summary: MART (ICS moderate + LABA) compared to ICS moderate + LABA in adults

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with MART (ICS moderate) (95% CI)
Severe exacerbations (requiring OCS)	2143	LOW[a,b]	RR 0.8	155 per	31 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ICS moderate + LABA	Risk difference with MART (ICS moderate) (95% CI)
	(1 study) 1 years	due to risk of bias, imprecision	(0.64 to 0.99)	1000	(from 2 fewer to 56 fewer)
Quality of life (AQLQ, 1–7, higher is better outcome)	2143 (1 study) 1 years	MODERATE[a] due to risk of bias	-		The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was 0.03 higher (0.07 lower to 0.13 higher)
Control (ACQ, 0–6, higher is worse outcome)	2143 (1 study) 1 years	MODERATE[a] due to risk of bias	-		The mean control (ACQ, 0–6, higher is worse outcome) in the intervention groups was 0.08 lower (0.16 lower to 0 higher)
Reliever medication use (puffs/day, average over whole treatment)	2143 (1 study) 1 years	MODERATE[a] due to risk of bias	-		The mean reliever medication use (puffs/day, average over whole treatment) in the intervention groups was 0.35 lower (0.55 to 0.15 lower)
FEV_1 (L)	2143 (1 study) 1 years	MODERATE[a] due to risk of bias	-		The mean FEV_1 (L) in the intervention groups was 0.03 higher (0.01 lower to 0.07 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 106: Clinical evidence summary: ICS high dose + LABA compared to ICS high dose in people aged 5–16

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Add LABA (95% CI)
FEV_1 (% predicted)	185 (1 study)	MODERATE[a] due to risk of bias	-		The mean FEV_1 (% predicted) in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Add LABA (95% CI)
	12 weeks				3.63 higher (0.72 to 6.54 higher)
PEF (L/min)	191 (1 study) 12 weeks	MODERATE[a] due to risk of bias	-		The mean PEF (L/min) in the intervention groups was 10.8 higher (3.4 to 18.2 higher)
Infection (all respiratory)	196 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.92 (0.62 to 1.35)	356 per 1000	29 fewer per 1000 (from 135 fewer to 125 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

7.1.3.2 Economic evidence

Published literature

Three health economic studies were identified with the relevant comparison and have been included in this review.[76 ,188]These are summarised in the health economic evidence profile below (Table 107) and the health economic evidence tables in Appendix I.

See also the health economic study selection flow chart in Appendix F.

Unit costs

Full details on medication costs can be found in Appendix O.

Table 107: Economic evidence profile: MART versus ICS + LABA as maintenance and SABA as reliever in adults

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Johansson 2006[76]	Partially applicable [(a)]	Potentially serious limitations[(b)]	CEA within-trial analysis (RCT) Population: People with persistent asthma Two comparators: 1) MART (ICS moderate dose + LABA), n=1067 2) ICS moderate dose + LABA, n=1076 Time horizon: 1 year	**Total costs (mean per patient):** −£34 (excluding societal costs) −£55 (including societal costs)	**Severe exacerbations:** −0.07 exacerbations per patient per year	MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy.	Bootstrapping was conducted but results were only presented on a cost-effectiveness plane. On the plane MART reduces exacerbations at a lower cost >95% of the time.
Wickstrom 2009[188]	Partially applicable [(c)]	Potentially serious limitations[(d)]	Systematic review that conducts 5 separate economic evaluations, based on 5 separate RCTs. Only 4 of the results are included below as one study was based on an inappropriate comparison. Kuna 2007 1) MART (ICS (moderate dose) + LABA), n=1144 2) ICS (high dose) + LABA, n=1145 Bousquet 2007 1) MART (ICS (moderate dose) + LABA), n=1107 2) ICS (moderate dose) + LABA, n=1105	**Total costs (mean per patient):** Kuna 2007 −£166 Bousquet 2007 £50 O'Byrne 2005 −£17 Rabe 2006 £55	**Severe exacerbations per patient per year:** Kuna 2007 −0.08 Bousquet 2007 -0.06 O'Byrne 2005 −0.21 Rabe 2006 −0.18	Kuna 2007 MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy. Bousquet 2007 £783 per exacerbation avoided O'Byrne 2005 MART therapy dominated ICS	No uncertainty analysis was conducted

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			O'Byrne 2005 1) MART (ICS low dose + LABA), n=925 2) ICS low dose + LABA, n=909 Rabe 2006 1) MART (ICS low dose + LABA), n =1113 2) ICS low dose + LABA + SABA when required, n=1141			+ LABA as maintenance and SABA as reliever therapy. Rabe 2006 MART therapy dominated ICS + LABA as maintenance and SABA as reliever therapy.	

Abbreviations: CEA: cost-effectiveness analysis; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; MART: maintenance and reliever therapy

(a) Resource use was pooled across 16 countries rather than just the UK; although UK unit costs were applied this makes the results slightly less applicable.

(b) EQ-5D not included as an outcome, though reported outcomes would suggest it is at least not lower in the MART group. Time horizon only 1 year may not capturing full effect.

(c) Danish unit costs were applied to each RCT.

(d) EQ-5D not included as an outcome, though reported outcomes would suggest it is at least not lower in the MART group. Time horizon only 1 year may not capturing full effect.

Table 108: Economic evidence profile: moderate dose ICS + LABA versus moderate dose ICS + tiotropium

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Willson 2014[190,191]	Directly applicable	Potentially serious limitations[(a)]	CUA Markov model Population: People with uncontrolled asthma despite treatment with moderate dose ICS and LABA Two comparators: 1) Moderate dose ICS + LABA	**Total costs (mean per patient):** £5,238 (excluding societal costs however using more expensive	0.19 QALYs	£28,838 per QALYs gained when the older, higher cost of respimat is used (£33.50) £16,288 per QALY gained	Probabilistic sensitivity analysis found the probability of tiotropium being cost effective at a £20,000 per QALY threshold to be: 32% when the older, higher cost of respimat is used (£33.50)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			2) Moderate dose ICS + LABA + tiotropium (respimat) Time horizon: Lifetime	£33.50 list price for respimat)		when the current, lower cost of respimat is used (£23.00)	52.9% when the current, lower cost of respimat is used (£23.00) The model ran various sensitivity analyses and found the results to be most sensitive to changes in the cost of uncontrolled and partly controlled asthma.

Abbreviations: CUA: cost-utility analysis; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist

(a) Although EQ-5D was gathered in the clinical study the model was based on, the model did not use this data and instead attempted to re-calculate quality of life based on asthma control. The cost of a branded version of montelukast was used as opposed to the generic cost. Since publication the cost of respimat has fallen from £33.50 to £23.00 and the impact this has had on the model's results have been noted, this result has not been published however.

7.1.3.3 Evidence statements

7.1.3.3.1 Clinical

Uncontrolled on ICS + LABA, people over 16

MART (ICS moderate + LABA) compared to ICS high + LABA + SABA when required

- Clinically important benefit for severe exacerbations (1 study, 2304 participants, Low quality evidence)
- No clinically important difference for asthma control (1 study, 2289 participants, High quality evidence)
- No clinically important difference for reliever medication use (1 study, 2289 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 2289 participants, High quality evidence)

MART (ICS low + LABA) compared to ICS low + LABA + SABA when required

- Clinically important benefit for severe exacerbations (1 study, 2245 participants, High quality evidence)
- No clinically important difference for asthma control (1 study, 2244 participants, High quality evidence)
- No clinically important difference for reliever medication use (1 study, 2244 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 2245 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 2245 participants, High quality evidence)
- No clinically important difference for infections (all respiratory) (1 study, 2245 participants, Moderate quality evidence)

ICS moderate/high + LABA + LAMA compared to ICS moderate/high + LABA

- Clinically important benefit for severe exacerbations (1 study, 907 participants, Low quality evidence)
- No clinically important difference for quality of life (AQLQ) (2 studies, 912 participants, Moderate quality evidence)
- No clinically important difference for asthma control (ACQ) (2 studies, 912 participants, Moderate quality evidence)
- No clinically important difference for lung function (FEV_1, L) (3 studies, 990 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (3 studies, 918 participants, Moderate quality evidence)
- Clinically important harm for infections (all respiratory) (2 studies, 1082 participants, Low quality evidence)

- Clinically important harm for infections (serious respiratory) (1 study, 912 participants, Very Low quality evidence)

ICS high + LABA compared to ICS moderate + LABA

- Clinically important benefit for severe exacerbations (1 study, 575 participants, Very Low quality evidence)
- Clinically important benefit for hospitalisations (1 study, 575 participants, Very Low quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 568 participants, Moderate quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 565 participants, Moderate quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 571 participants, Moderate quality evidence)
- No clinically important difference for infections (all respiratory) (1 study, 565 participants, Very Low quality evidence)

ICS high + LABA compared to ICS high

- Clinically important benefit for severe exacerbations (1 study, 576 participants, Low quality evidence)
- Clinically important harm for hospitalisations (1 study, 576 participants, Very Low quality evidence)
- Clinically important benefit for reliever medication use (puffs/day) (1 study, 568 participants, Moderate quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 568 participants, Moderate quality evidence)
- Clinically important benefit for lung function (PEF, L/min) (1 study, 573 participants, Moderate quality evidence)
- No clinically important difference for infections (all respiratory) (1 study, 576 participants, Moderate quality evidence)

ICS high compared to ICS moderate + LABA

- Clinically important harm for severe exacerbations (1 study, 265 participants, Low quality evidence)
- Clinically important benefit for hospitalisations (1 study, 265 participants, Low quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 260 participants, Low quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 261 participants, Moderate quality evidence)
- Clinically important harm for lung function (PEF, L/min) (1 study, 262 participants, Low quality evidence)
- No clinically important difference for infections (all respiratory) (1 study, 265 participants, Moderate quality evidence)

ICS high compared to ICS moderate + LABA

- No clinically important difference for severe exacerbations (1 study, 1070 participants, Very Low quality evidence)
- No clinically important difference for quality of life (AQLQ) (1 study, 720 participants, Very Low quality evidence)
- No clinically important difference for asthma control (ACQ) (1 study, 720 participants, Very Low quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 720 participants, Very Low quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 720 participants, Very Low quality evidence)

Uncontrolled on ICS moderate dose, people over 16

ICS high compared to ICS moderate

- Clinically important benefit for severe exacerbations (1 study, 325 participants, Very Low quality evidence)

ICS low + LABA compared to ICS moderate

- Clinically important harm for severe exacerbations (1 study, 1385 participants, Low quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 347 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (puffs/daytime) (1 study, 1835 participants, High quality evidence)
- No clinically important difference for reliever medication use (puffs/night-time) (1 study, 1835 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 1385 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, % predicted) (1 study, 347 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (2 studies, 2182 participants, High quality evidence)

ICS moderate + LABA compared to ICS moderate

- Clinically important benefit for severe exacerbations (2 studies, 1395 participants, Low quality evidence)
- No clinically important difference for quality of life (pooled AQLQ, SGRQ) (4 studies, 2048 participants, Moderate quality evidence)
- No clinically important difference for asthma control (ACQ) (1 study, 1064 participants, High quality evidence)
- Clinically important benefit for reliever medication use (puffs/day) (5 studies, 1363 participants, Moderate quality evidence)
- Clinically important benefit for reliever medication use (puffs/daytime) (1 study, 180 participants, High quality evidence)

- Clinically important benefit for reliever medication use (puffs/night-time) (1 study, 180 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (8 studies, 3630 participants, Low quality evidence)
- No clinically important difference for lung function (FEV_1, L) (5 studies, 2130 participants, Moderate quality evidence)
- No clinically important difference for infections (all respiratory) (2 studies, 1287 participants, Very Low quality evidence)

MART (ICS low + LABA) compared to ICS moderate

- Clinically important benefit for severe exacerbations (2 studies, 3741 participants, Low quality evidence)
- No clinically important difference for reliever medication use (puffs/daytime) (1 study, 1851 participants, High quality evidence)
- No clinically important difference for reliever medication use (puffs/night-time) (1 study, 1851 participants, High quality evidence)
- No clinically important difference for reliever medication use (rescue-free days, %) (1 study, 1890 participants, Moderate quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 1851 participants, High quality evidence)
- Clinically important benefit for lung function (PEF, L/min) (2 studies, 3741 participants, Low quality evidence)

ICS moderate + LTRA compared to ICS moderate

- No clinically important difference for quality of life (AQLQ) (1 study, 625 participants, High quality evidence)
- No clinically important difference for reliever medication use (change from baseline, %) (1 study, 3446 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L change from baseline, %) (1 study, 625 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 625 participants, High quality evidence)

ICS moderate + LAMA compared to ICS moderate

- Clinically important benefit for severe exacerbations (1 study, 1042 participants, Low quality evidence)
- No clinically important difference for quality of life (AQLQ) (1 study, 1064 participants, High quality evidence)
- No clinically important difference for asthma control (ACQ) (1 study, 1064 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 1064 participants, High quality evidence)
- Clinically important benefit for lung function (PEF, L/min) (1 study, 1064 participants, Moderate quality evidence)

- Clinically important benefit for infections (all respiratory) (1 study, 1040 participants, Low quality evidence)

ICS low + LABA compared to ICS high

- No clinically important difference for severe exacerbations (1 study, 391 participants, Moderate quality evidence)
- Clinically important benefit for asthma control (ACT) (1 study, 391 participants, Low quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 377 participants, Low quality evidence)
- Clinically important benefit for lung function (PEF, L/min) (1 study, 391 participants, Moderate quality evidence)

ICS moderate + LABA compared to ICS high

- Clinically important benefit for severe exacerbations (2 studies, 689 participants, Very Low quality evidence)
- No clinically important difference for quality of life (AQLQ) (1 study, 113 participants, Moderate quality evidence)
- Clinically important benefit for reliever medication use (puffs/day) (1 study, 178 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (rescue-free days, %) (1 study, 353 participants, Low quality evidence)
- Clinically important benefit for lung function (FEV_1, % predicted) (1 study, 738 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 353 participants, Moderate quality evidence)
- Clinically important benefit for lung function (PEF, L/min) (4 studies, 1126 participants, Moderate quality evidence)
- Clinically important benefit for lung function (PEF, % predicted) (1 study, 738 participants, High quality evidence)

ICS moderate + LTRA compared to ICS high

- No clinically important difference for quality of life (AQLQ) (2 studies, 964 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 889 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (2 studies, 964 participants, Moderate quality evidence)

ICS moderate + theophylline compared to ICS high

- No clinically important difference for lung function (FEV_1, L) (1 study, 62 participants, Low quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 62 participants, Low quality evidence)

MART (ICS low + LABA) compared to ICS high

- Clinically important benefit for severe exacerbations (1 study, 1834 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (puffs/daytime) (1 study, 1834 participants, High quality evidence)
- No clinically important difference for reliever medication use (puffs/night-time) (1 study, 1834 participants, high quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 1834 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 1834 participants, High quality evidence)

ICS moderate + LTRA compared to ICS moderate + LABA

- No clinically important difference for reliever medication use (puffs/day) (2 studies, 944 participants, Low quality evidence)
- No clinically important difference for lung function (FEV_1, % of predicted) (1 study, 44 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 948 participants, Low quality evidence)

ICS moderate + LAMA compared to ICS moderate + LABA

- Clinically important harm for severe exacerbations (1 study, 1060 participants, Low quality evidence)
- Clinically important benefit for infections (all respiratory) (1 study, 1058 participants, Low quality evidence)

MART (ICS moderate + LABA) compared to ICS moderate + LABA

- Clinically important benefit for severe exacerbations (1 study, 2212 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 2211 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 2211 participants, High quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 2211 participants, High quality evidence)

ICS moderate + LABA compared to ICS moderate + theophylline

- No clinically important difference for reliever medication use (puffs/day) (1 study, 45 participants, High quality evidence)
- Clinically important benefit for lung function (FEV_1, % of predicted) (1 study, 45 participants, Moderate quality evidence)

ICS moderate + LTRA compared to ICS moderate + theophylline

- No clinically important difference for reliever medication use (puffs/day) (1 study, 39 participants, High quality evidence)
- Clinically important benefit for lung function (FEV_1, % of predicted) (1 study, 39 participants, Moderate quality evidence)

Uncontrolled on ICS moderate dose, people aged 5–16

ICS low + LABA compared to ICS moderate

- Clinically important harm for severe exacerbations (1 study, 223 participants, Low quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 223 participants, Low quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 223 participants, Low quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 223 participants, High quality evidence)
- No clinically important difference for growth (cm) (1 study, 223 participants, Moderate quality evidence)

MART (ICS low + LABA) compared to ICS moderate

- Clinically important benefit for severe exacerbations (1 study, 224 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 224 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 224 participants, Moderate quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 224 participants, Moderate quality evidence)
- No clinically important difference for growth (cm) (1 study, 224 participants, Moderate quality evidence)

MART (ICS low + LABA) compared to ICS low + LABA

- Clinically important benefit for severe exacerbations (1 study, 235 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 235 participants, Low quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 235 participants, Moderate quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 235 participants, Moderate quality evidence)

ICS moderate + LAMA compared to ICS moderate

- Clinically important benefit for severe exacerbations (1 study, 272 participants, Moderate quality evidence)
- No clinically important difference for quality of life (AQLQ) (1 study, 261 participants, High quality evidence)
- No clinically important difference for reliever medication use (puffs/day) (1 study, 249 participants, High quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 261 participants, Moderate quality evidence)

Uncontrolled on ICS high dose, people over 16

ICS high dose + LABA compared to ICS high dose

- No clinically important difference for reliever medication use (puffs/day) (2 studies, 456 participants, Moderate quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 96 participants, High quality evidence)
- Clinically important benefit for lung function (PEF, L/min) (3 studies, 944 participants, Moderate quality evidence)
- Clinically important harm for infections (all respiratory) (1 study, 456 participants, Very Low quality evidence)

ICS high dose + LTRA compared to ICS high dose

- No clinically important difference for reliever medication use (puffs/day) (1 study, 21 participants, Low quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 21 participants, Low quality evidence)
- No clinically important difference for lung function (PEF, L/min) (1 study, 21 participants, Moderate quality evidence)

ICS high dose + LABA compared to ICS moderate dose + LABA

- No clinically important difference for lung function (PEF, L/min) (1 study, 324 participants, High quality evidence)
- Clinically important benefit for infections (all respiratory) (1 study, 428 participants, Low quality evidence)
- Clinically important harm for infections (serious respiratory) (1 study, 428 participants, Low quality evidence)

MART (ICS moderate + LABA) compared to ICS moderate + LABA

- Clinically important benefit for severe exacerbations (1 study, 2143 participants, Low quality evidence)
- No clinically important difference for quality of life (AQLQ) (1 study, 2143 participants, Moderate quality evidence)
- No clinically important difference for asthma control (ACQ) (1 study, 2143 participants, Moderate quality evidence)
- No clinically important difference for reliever medication use (puffs/day, average over whole treatment) (1 study, 2143 participants, Moderate quality evidence)
- No clinically important difference for lung function (FEV_1, L) (1 study, 2143 participants, Moderate quality evidence)

Uncontrolled on ICS high dose, people aged 5–16

ICS high dose + LABA compared to ICS high dose

- No clinically important difference for lung function (FEV_1, % of predicted) (1 study, 185 participants, Moderate quality evidence)

- No clinically important difference for lung function (PEF, L/min) (1 study, 191 participants, Moderate quality evidence)
- No clinically important difference for infections (all respiratory) (1 study, 196 participants, Very Low quality evidence)

7.1.3.3.2 Economic

- Four separate economic analyses (3 conducted in one study) found that MART was dominant compared to ICS + LABA as maintenance and SABA as reliever, reducing costs and number of exacerbations.
- One cost-effectiveness analysis found that the ICER of MART versus ICS + LABA as maintenance and SABA as reliever was £783 per exacerbation avoided.
- One cost–utility analysis found that moderate dose ICS + LABA + LAMA was cost effective, at a £20,000 per QALY threshold, relative to moderate dose ICS + LABA alone (ICER: £16,288 per QALY). This analysis was assessed as directly applicable with potentially serious limitations.

7.1.3.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80

[12] At the time of publication (November 2017), MART regimens did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Research recommendation	3. What is the clinical and cost effectiveness of offering additional maintenance therapy to adults, young people and children with asthma that is uncontrolled on a moderate dose of ICS plus LABA with or without LTRA?
Relative values of different outcomes	The committee considered the following outcomes as critical for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee considered the following outcomes as important: asthma control (as assessed by a validated questionnaire), hospital admission, reliever medication use, lung function (FEV_1 or morning PEF) and adverse events. No evidence was identified for mortality.
Quality of the clinical evidence	The quality of the evidence for this review ranged from Very Low to High quality. The majority of the evidence was either Low or Moderate quality. Most of the studies compared adding a new agent or increasing ICS dose against continuing on previous treatment with or without a placebo. The majority of the evidence was in people uncontrolled on ICS moderate dose. None of the evidence addressed the addition of treatment in people uncontrolled on ICS and LTRA. Studies were found in which the baseline population were on treatment not recommended by the committee in this guideline. This included studies in people who were using a high or moderate dose ICS (without first adding in a LABA or LTRA). The committee included this population as it represents a group who are uncontrolled despite preventer treatment beyond the first line of low dose ICS, and because there will be patients currently on this treatment.
Trade-off between clinical benefits and harms	**Uncontrolled on ICS (any dose) + LABA, adults** Possible interventions identified in the evidence at this stage included converting the ICS + LABA treatment into MART therapy, increasing ICS dose or adding a LAMA. All three of these interventions had a clinically important benefit in terms of severe exacerbations compared to continuing on the previous dose of ICS with LABA. There was no direct comparison of the addition of LAMA to either conversion to MART or increase in ICS dose. However there was some suggestion of a clinically important harm of the addition of LAMA compared to continuing on previous dose of ICS with LABA in terms of infections. The committee felt that while all three of the interventions may be appropriate, conversion to MART or increase of ICS dose in a fixed regimen would be preferable due to the potential harms of adding an additional agent. The direct comparison between conversion to MART and the increase of ICS dose showed a clinically important benefit of MART. The committee noted that there was a clinically important harm for some critical outcomes (severe exacerbations) of removing the LABA even when the ICS dose was increased.

Uncontrolled on ICS moderate dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART, increasing ICS dose, addition of an LTRA, addition of a LAMA and addition of a theophylline. Any one of the additional preventers could be accompanied by an increase or decrease in steroid dose simultaneously.

Consistent with the review of interventions for those uncontrolled on ICS low dose, the addition of a LABA appeared to have the greatest benefit for critical outcomes like severe exacerbations. Again consistent with the previous review there was little difference between addition of a LABA and addition of an LTRA when compared directly, although the addition of an LTRA had less benefit than addition of a LABA when compared to continuing on ICS moderate dose. Consistent with the evidence in the population uncontrolled on ICS + LABA, the use of MART appeared to have clinically important benefits over ICS + LABA + SABA when required.

Uncontrolled on ICS high dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART and addition of an LTRA. Any one of the additional preventers could be accompanied by a change in steroid dose.

There was evidence of a clinically important benefit of addition of LABA compared to continuation on ICS high dose in terms of reliever medication use. The direct comparison between addition of LABA and conversion to MART as opposed to just addition of LABA showed a clinically important benefit for MART in terms of severe exacerbations.

Paediatric evidence

There was no evidence in the 5–16 age group for those uncontrolled on ICS + LABA. In the population uncontrolled on ICS moderate dose aged 5–16, there was evidence of a clinically important benefit in terms of severe exacerbations of MART over both ICS + LABA + SABA when required and continuing on ICS moderate dose. In the population uncontrolled on ICS high dose aged 5–16, there was a comparison of addition of LABA versus continuation on ICS high dose that showed no clinically important differences for FEV_1, PEF or infection.

In summary in the paediatric strata there was considerably less evidence than in the adult stratum, however the use of ICS + LABA in MART appeared to have the most clinical benefit.

	There was no evidence in the under 5 age group. The committee did not feel that consensus recommendations on the approach in this age group were appropriate. The committee chose to end their recommendations in this age group with the previous recommendation to seek specialist opinion at the point of stopping LTRA.
Trade-off between net clinical effects and costs	The economic review identified 3 studies that looked at treatment options for this population. Two of these studies were included in the MART versus ICS + LABA as maintenance and SABA as reliever review. The overall conclusion from these studies is that MART therapy is cost effective in this population; a full detailed review of these studies can be found in the Recommendations and link to evidence section for the review question 'What is the clinical and cost effectiveness of using ICS + LABA as preventer and a reliever therapy compared to using ICS + LABA as preventer and a SABA as reliever therapy?' (section 7.1.2.4). One additional study was found comparing placebo treatment to LAMA. The study found that the ICER of adding LAMA was £28,383 per QALY. However since publication the price of the drug has decreased subsequently decreased from £33.50 to £23. According to the authors this reduces the ICER from £28,383 to £16,288. The committee noted that this was likely a conservative estimate of the cost effectiveness meaning that the true ICER would likely be much higher. The clinical evidence showed a slight reduction in exacerbations but no significant or clinically important improvement in quality of life, meaning a 0.19 QALY increase seemed very high. Methodological limitations of the study, such as over-estimating the cost of being uncontrolled by using the branded version of leukotriene receptor agonist also limited the weight of the paper. However the committee noted that placebo was probably not the most relevant comparator as it was unlikely the individual at this stage would have no additional treatment added in. The committee felt that oral steroids may be a more appropriate comparator. Overall the committee felt there was not enough evidence to make a strong recommendation and further research should be conducted to analyse the clinical and cost effectiveness of other therapies at this treatment stage.
Other considerations	Taking into account the evidence in this review and the MART review, their experience and current clinical practice, the committee felt it was appropriate to recommend MART and increasing ICS dose to moderate after having tried LTRAs and LABAs added to low dose ICS. The committee noted that the addition of LAMA in current clinical practice occurs when people with asthma have already tried escalation of ICS dose, LTRA, LABA and (sometimes) theophylline. At this stage the choice of additional medication other than LAMA is limited, and includes expensive agents such as omalizumab, mepolizumab or potentially toxic agents such as regular oral corticosteroids or methotrexate which were outside the scope of this review. The committee felt that there was insufficient clinical and cost-effectiveness evidence to support strongly recommending LAMAs, theophyllines or high dose ICS or to recommend they are routinely prescribed by those without specialist skills or training in asthma. However

the committee were aware that there are some people whose asthma remains uncontrolled at this stage and therefore they chose to weakly recommend trials of any of those three strategies in adults with asthma. A similar approach was recommend in children aged 5–16, without the inclusion of LAMAs which are not licensed in this age group. The committee noted that in general these approaches would require the input of someone with specialist skills or training in asthma, though this may not always require referral to secondary care depending on the resources at local primary care levels.

8 Intermittent versus daily ICS with seasonal or trigger-specific symptoms

8.1 Introduction

Many patients with asthma only become symptomatic when exposed to specific allergens that cause the release of inflammatory mediators in the airway. The commonest trigger is probably viral infections, which tend to occur all year round but with a peak in the winter months. Other triggers include specific pollens which may also cause an exacerbation of seasonal allergic rhinitis, exposure to animals or mould spores. Patients whose triggers occur during discrete time periods may be symptom free and well controlled during the majority of the year but then have clusters of asthma attacks or episodes of poor control.

Current preventive treatment for these patients is inhaled corticosteroids taken regularly all year but many patients limit or stop their treatment when their symptoms are controlled. The review therefore looked for evidence of clinical and cost effectiveness of the regular use of preventive treatment only during periods associated with specific triggers with the remainder of the time limited to treatment solely with reliever medication.

8.1.1 Review question: In children, young people and adults with asthma on ICS preventer therapy or requiring ICS, is intermittent ICS more clinically and cost effective than regular ICS?

For full details see review protocol in Appendix C.

Table 109: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma who are on ICS only (alongside reliever SABA when required therapy) or require ICS therapy according to the study (i.e. uncontrolled on SABA when required alone). Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years
Intervention(s)	• Regular (daily, all year round) 'low dose' ICS • Intermittent ICS (any dose)
Comparison	Intermittent ICS versus regular ICS
Outcomes	**Critical outcomes:** • Severe asthma exacerbations

	• Mortality
	• Quality of life
	Important outcomes:
	• Asthma control assessed by a validated questionnaire
	• Hospital admissions
	• Reliever/rescue medication use
	• Lung function (change in FEV_1 or morning PEF)
	• Adverse events
	  ○ linear growth
	  ○ infection
	  ○ adrenal insufficiency

Study design	RCT Systematic review of RCTs

8.1.1.1 Clinical evidence

Six studies were included in the review;[16 ,100 ,125 ,127 ,178 ,198] these are summarised in Table 110 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 111, Table 112 and Table 113). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

The included studies compared intermittent ICS with regular ICS. The 'regular' arms of each study varied as some involved only taking ICS regularly whereas others involved regular ICS with an additional intermittent increase in ICS. These studies were pooled as both were relevant comparators and even in a study with a regular arm that does not specify an intermittent increase, it is possible that people may informally increase their ICS dose at time of exacerbations anyway.

As a consequence of this decision, in the analysis of one study[100], two 'regular' arms were combined as they were distinguished purely on the basis of one receiving additional intermittent ICS.

All the studies identified for inclusion in the review comprised an intermittent arm that received ICS only during times of exacerbation or symptoms. No studies were identified that comprised an intermittent arm receiving ICS during a particular time of year, such as during hayfever season.

Table 110: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Boushey 2005[16]	(n=76) Intermittent ICS. BD placebo via Turbuhaler. Budesonide (800 micrograms twice daily) for 10 days OR oral prednisone (0.5 mg/kg per day) for 5 days if their	USA Adults Inclusion criteria - Physician diagnosed	• Severe asthma exacerbations – number of 10-day oral corticosteroid rescue courses • Quality of life	Regular arm included additional intermittent ICS when symptomatic.

Study	Intervention and comparison	Population	Outcomes	Comments
	asthma symptoms worsened. Duration 52 weeks. (n=73) Regular ICS. Budesonide (twice daily inhalation of 200 micrograms of budesonide via Turbuhaler). Budesonide (800 micrograms twice daily) for 10 days OR oral prednisone (0.5 mg/kg per day) for 5 days if their asthma symptoms worsened. Duration 52 weeks.	asthma, age 18–65, FEV_1 >70% predicted (mild), BDR at least 12% and 200 ml after salbutamol inhalation or a fall in FEV_1 of at least 20% following inhalation of 16 mg methacholine. Met further criteria during 4 week run-in (while not on preventer): self-treatment with SABA more than 2 days per week, night awakenings with asthma more than 2 days per month, variability in PEF of 20–30%. Exclusion criteria: smoking, respiratory infection/steroid use in previous 6 weeks, hospitalisation or two or more visits to emergency department for asthma in previous year, lack of compliance (failure to complete at least 70% of their diary in the 4 week run-in), met the criteria for moderate asthma (that is, daily self-treatment with SABA, night-time awakenings once a week or more than 30% PEF variability).	• Asthma control • Hospitalisation • Lung function	Mild, uncontrolled asthma.
Papi 2007[125]	(n=124) Intermittent ICS	Multi-national,	• Rescue	Regular arm

Study	Intervention and comparison	Population	Outcomes	Comments
	BD placebo + 250 ug of beclometasone & 100 ug of salbutamol in a single inhaler as needed. Patients were instructed to use them at any time they were needed for relief of symptoms. Duration 6 months. (n=110) Regular ICS Twice daily 250 ug beclometasone. As needed 100 ug of salbutamol. Duration 6 months.	European Adults Inclusion criteria: Age 18–65, history of mild persistent asthma for at least 6 months according to National Asthma Education and Prevention Program guidelines. FEV_1 ≥75% predicted with either BDR or a positive methacholine challenge test. Asthma controlled as defined by the absence of the following during the 4 week run-in (250 ug twice daily of inhaled beclometasone dipropionate and SABA when required): diurnal variation in the peak expiratory flow rate >20% on two consecutive days, use of four or more puffs of SABA on two consecutive days, use of OCS. Exclusion criteria: Current or ex-smoking habits (>10 packs/year), COPD, history of near fatal asthma, admission to emergency room because of asthma, 3 or more courses of	medication use • Lung function	did not take intermittent ICS in addition to regular ICS Mild, controlled asthma

Study	Intervention and comparison	Population	Outcomes	Comments
		oral corticosteroids or hospitalisation for asthma during the previous year, regular treatment for >6 months with >500 ug/day of beclometasone or equivalent.		
Papi 2009[127]	(n=110) Intermittent ICS Nebulised placebo vial (one vial twice a day), plus fixed combination of nebulised 800 ug Beclomethasone + 1800 ug Salbutamol/vial (one vial when required). Duration 12 weeks. (n=110) Regular ICS Nebulised 400 ug/vial beclometasone (one vial bid/twice a day), plus Salbutamol 2500 ug/vial (one vial when required). Duration 12 weeks.	Multinational, European Children (<5) Inclusion criteria: Aged 1–4 years, frequent wheeze (documented history of at least three episodes of wheezing requiring medical attention in the previous 6 months), had wheeze and/or cough, and/or shortness of breath, and/or required relief medication on at least 7 days of the 2-week run-in (nebulised salbutamol 2500 ug when required). Exclusion criteria: History of severe exacerbations requiring systemic glucocorticoid, a chest infection or hospitalisation for asthma or treatment with inhaled glucocorticoids or methylxanthine during the previous 4	• Rescue medication use (day/night)	Regular arm did not take intermittent ICS in addition to regular ICS. Uncontrolled asthma.

Study	Intervention and comparison	Population	Outcomes	Comments
		weeks or with oral glucocorticoid in the previous 8 weeks.		
The Helsinki early intervention childhood asthma study trial: Turpeinen 2008[178]	(n=58) Intermittent ICS Months 6–18: Placebo, twice a day, inhaled. During exacerbations: placebo replaced with 400 ug budesonide twice daily for two weeks. Duration 12 months. Terbutaline when required 0.25 mg. (n=59) Regular ICS Months 6–18:100 ug budesonide twice daily, inhaled. During exacerbations: 100 ug budesonide replaced with 400 ug budesonide twice daily for two weeks. Duration 12 months. Terbutaline when required 0.25 mg.	Finland Children (5–16), mean age 6.9 years Inclusion criteria: Symptoms such as wheezing, prolonged cough or shortness of breath for at least 1 month AND reversibility of either PEF or FEV_1 (at least a 20% diurnal variation in PEF, or at least a 15% increase in PEF at least three times within 2 weeks of home recording, or at least a 15% increase in FEV_1 15 minutes after inhalation of SABA). 5–10 years old. Exclusion criteria: Acute asthma, FEV_1 <50%, treatment in the previous 2 months with ICS/chromones/LTRAs/LABAs, total cumulative doses of previous ICS >36 mg inhaled/>12 mg nasal/>200 mg oral prednisolone.	• Linear growth	Regular arm took intermittent ICS in addition to regular ICS.
TREXA trial: Martinez 2011[100]	(n=71) Intermittent ICS Daily placebo. 180 ug salbutamol and 8 0ug	USA Children (5–16), mean age 10.9 years	• Severe asthma exacerbations – number of courses of oral	One regular arm took additional intermittent

Study	Intervention and comparison	Population	Outcomes	Comments
	beclometasone combined as rescue medication, referred to as "rescue" group in paper. Duration 44 weeks. (n=71) Regular ICS 1 40 ug beclometasone twice daily with 180 ug salbutamol and 80 ug beclometasone combined as rescue medication, referred to as "combined" group in paper. Duration 44 weeks. (n=72) Regular ICS 2 40 ug beclometasone twice daily with 180 ug salbutamol and placebo combined as rescue medication, referred to as "daily" group in paper. Duration 44 weeks.	Inclusion criteria – Aged 6–18 years. If on controller treatment, qualified for interruption or discontinuation of controller treatment because their illness was well controlled (as defined in US National Asthma Education and Prevention Program asthma care guidelines). Either naïve to controller treatment and had a history of 1–2 exacerbations in the previous year OR they were treated for the previous 8 weeks with a monotherapy other than inhaled corticosteroids OR their illness was controlled for the previous 8 weeks on low-dose corticosteroids as monotherapy (≤160 µg daily with a beclometasone equivalent). Disease remained well controlled and they did not have any exacerbations during the run-in period (2 weeks with daily beclometasone and SABA when required). Exclusion criteria:	corticosteroids in response to symptoms • Adverse events	ICS, one regular arm did not. These two arms were combined for analysis. Asthma mild, persistent (uncontrolled without preventer therapy). This trial included both patients starting on ICS and randomised to either daily or intermittent treatment and patients who were previously on daily ICS who were randomised to either continue on daily ICS or switch to intermittent ICS.

Study	Intervention and comparison	Population	Outcomes	Comments
		FEV_1 <60% predicted, admitted to hospital for asthma in previous year, exacerbation in last 3 months or more than 2 in the last year, ever had a "life-threatening" asthma exacerbation (requiring intubation/ mechanical ventilation or that resulted in a hypoxic seizure).		
Zeiger 2011[198]	(n=139) Intermittent ICS At "onset of symptoms or signs of respiratory tract illness" that (parents) identified as their child's usual starting point before the development of wheezing, 7 days of 1.0 mg budesonide BD, nebulised. Duration 1 year. Open-label rescue salbutamol was administered per protocol during a respiratory tract illness (4 times daily) and as needed. (n=139) Regular ICS 0.5 mg once nightly nebulised budesonide (Pulmicort respules). Dose maintained during periods of respiratory tract illness with placebo once in the morning for comparison with BD intermittent group. Duration 1 year. Open label rescue salbutamol administered per protocol during respiratory	USA Children (0–5), mean not reported Inclusion criteria: All of: at least 4 episodes of wheezing in previous year, positive values on modified API, at least one exacerbation requiring systemic steroids/emergency care/hospitalisation, during the 2 week run-in (on BD placebo + salbutamol when required) they had fewer than 3 days per week of salbutamol use and fewer than 2 nights with awakening. Age between 12 and 53 months. Exclusion criteria: Received more than	• Severe asthma exacerbations – number of course of an oral glucocorticoid started for acute wheezing after consultation with a physician • Mortality • Hospitalisation • Rescue medication use • Linear growth	Regular arm did not take intermittent ICS in addition to regular ICS. Asthma mild, controlled.

Study	Intervention and comparison	Population	Outcomes	Comments
	tract illness.	6 courses of oral steroids or hospitalised more than two times for wheezing during the previous year.		

Table 111: Clinical evidence summary: Intermittent versus regular ICS in people over 16

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular ICS (>16)	Risk difference with Intermittent ICS (95% CI)
Severe asthma exacerbations Requirement for OCS, either self-administered or from ED	137 (1 study) 1 years	LOW[a] due to imprecision	RR 0.77 (0.32 to 1.82)	149 per 1000	34 fewer per 1000 (from 101 fewer to 122 more)
AQLQ	137 (1 study) 1 years	HIGH	-	The mean AQLQ (change score) in the control group was 0.5	The mean AQLQ (change score) in the intervention groups was 0.2 lower (0.48 lower to 0.08 higher)
ACQ	143 (1 study) 1 years	HIGH	-	The mean ACQ (change score) in the control group was -0.4	The mean ACQ (change score) in the intervention groups was 0.1 higher (0.12 lower to 0.32 higher)
Exacerbations requiring hospitalisation	149 (1 study) 1 years	HIGH	Unable to calculate	Zero events occurred in either arm	
Rescue medication use (puffs/day)	234 (1 study) 6 months	HIGH	-	The mean rescue medication use (puffs/day) in the control group was 0.44	The mean rescue medication use (puffs/day) in the intervention groups was 0.06 higher (0.13 lower to 0.25 higher)
Lung function (morning PEF, %)	136 (1 study)	HIGH	-	The mean lung function	The mean lung function (morning PEF, change score, %) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular ICS (>16)	Risk difference with Intermittent ICS (95% CI)
	1 years			(morning PEF, change score, %) in the control groups was 8.3	1.2 lower (6.61 lower to 4.21 higher)
Lung function (morning PEF, l/min)	234 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	-	The mean lung function (morning PEF, final value, L/min) in the intervention groups was 433.08	The mean lung function (morning PEF, final value, L/min) in the intervention groups was 9.67 higher (18.8 lower to 38.14 higher)
Lung function (FEV_1, %)	137 (1 study) 1 years	MODERATE[a] due to imprecision	-	The mean lung function (FEV_1, change score, %) in the control groups was 4.0	The mean lung function (FEV_1, change score, %) in the intervention groups was 3.3 lower (6.49 to 0.11 lower)
Lung function (FEV_1, %predicted)	234 (1 study) 6 months	HIGH	-	The mean lung function (FEV_1, final value, %predicted) in the control group was	The mean lung function (FEV_1, final value, %predicted) in the intervention groups was 1.91 higher (1.29 lower to 5.11 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular ICS (>16)	Risk difference with Intermittent ICS (95% CI)
				90.32	

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 112: Clinical evidence summary: Intermittent versus regular ICS in children 5–16

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular ICS (5–16)	Risk difference with Intermittent ICS (95% CI)
Severe asthma exacerbations - number of courses of oral corticosteroids	184 (1 study) 44 weeks	VERY LOW[a,b] due to indirectness, imprecision	RR 1.29 (0.88 to 1.9)	333 per 1000	97 more per 1000 (from 40 fewer to 300 more)
Linear growth (cm)	184 (1 study) 44 weeks	LOW[a,b] due to indirectness, imprecision	-	The mean linear growth (cm) in the control group was approximately 3.5	The mean linear growth (cm) in the intervention groups was 0.8 higher (0.05 to 1.55 higher)
Linear growth (velocity, cm)	98 (1 study) 12 months	VERY LOW[b,c] due to risk of bias, imprecision	-	The mean linear growth (velocity, cm) in the control group was 5.6	The mean linear growth (velocity, cm) in the intervention groups was 0.6 higher (0.13 to 1.07 higher)

a Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular ICS (5–16)	Risk difference with Intermittent ICS (95% CI)
population b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

Table 113: Clinical evidence summary: Intermittent versus regular ICS in children under 5

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular ICS	Risk difference with Intermittent ICS (95% CI)
Severe asthma exacerbations (time to event) - number of course of an oral glucocorticoid started for acute wheezing after consultation with a physician	278 (1 study) 1 years	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	HR 1.03 (0.82 to 1.29)	No event rate data provided	-
Mortality	278 (1 study) 1 years	MODERATE[b] due to indirectness	Unable to calculate	Zero events occurred in either arm	
Exacerbations requiring hospitalisation	278 (1 study) 1 years	VERY LOW[b,c] due to indirectness, imprecision	RR 1.25 (0.34 to 4.56)	29 per 1000	7 more per 1000 (from 19 fewer to 102 more)
Rescue medication use (daytime, puffs/day)	220 (1 study) 12 weeks	MODERATE[b] due to indirectness	-	The mean rescue medication use (daytime, puffs/day) in the control group was	The mean rescue medication use (daytime, puffs/day) in the intervention groups was 0 higher (0.08 lower to 0.08 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular ICS	Risk difference with Intermittent ICS (95% CI)
				0.09	
Rescue medication use (night, puffs/day)	220 (1 study) 12 weeks	MODERATE[b] due to indirectness	-	The mean rescue medication use (night, puffs/day) in the control group was 0.04	The mean rescue medication use (night, puffs/day) in the intervention groups was 0 higher (0.04 lower to 0.04 higher)
Rescue medication use (% of days with SABA use)	278 (1 study) 1 years	LOW[a,b] due to risk of bias, indirectness	-	The mean rescue medication use (% of days with SABA use) in the control group was 5	The mean rescue medication use (% of days with SABA use) in the intervention groups was 0.4 higher (1 lower to 1.8 higher)
Linear growth (cm)	278 (1 study) 1 years	LOW[a,b] due to risk of bias, indirectness	-	The mean linear growth (cm) in the control groups was 7.76	The mean linear growth (cm) in the intervention groups was 0.26 higher (0.17 lower to 0.69 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

8.1.1.2 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

8.1.1.3 Economic considerations

This section uses the evidence gathered in the clinical review to calculate potential cost differences between intermittent and daily ICS use.

8.1.1.3.1 Under 5s

The following section will evaluate the cost effectiveness of daily versus intermittent use of ICS in under 5s by attaching cost and health outcomes to the clinical outcomes presented in the paper by Papi.

Cost effectiveness of intermittent versus daily use of ICS using data from Papi 2009

In this study 400 µg of beclometasone was administered twice a day for the 'daily' intervention. Then 2500 µg of salbutamol was taken when required.

In the 'intermittent' intervention only 2500 µg of salbutamol and 400 µg of beclometasone was taken when required.

As the study does not define an exacerbation as the use of oral corticosteroids the costs associated with this outcome are not calculated.

The annual drug costs of these interventions are presented in Table 114 and Table 115 below.

Table 114: Annual unit costs of 'daily' drug use

Drug	Preparation	Dose per unit	Number of units per pack	Cost per pack	Cost per unit	Annual number of units used	Annual cost
Beclometasone	Metered dose inhaler	200 µg	200	£16.17	£0.08	2,672[(a)]	£215.95
Salbutamol	Dry powder inhaler	200 µg	100	£4.85	£0.05	686[(b)]	£33.27
						Total	£249.22

Source: NHS Drug Tariff

a) The study reports 66.8 mg of use on average per patient over the study. At 100 µg per use this equates to 668 uses over three months. This value was then multiplied by 4 to obtain the annual use.

b) The study reports 34.3 mg of use on average per patient over the study. At 200 µg per use this equates to 171 uses over three months. This value was then multiplied by 4 to obtain the annual use.

Table 115: Annual unit costs of 'intermittent' drug use

Drug	Preparation	Dose per unit	Number of units per pack	Cost per pack	Cost per unit	Annual number of units used	Annual cost
Beclometasone	Metered dose inhaler	200 µg	200	£16.17	£0.08	604[(a)]	£48.83
Salbutamol	Dry powder inhaler	200 µg	100	£4.85	£0.05	604[(b)]	£29.20
						Total	£78.03

Source: NHS Drug Tariff

a) The study reports 15.1 mg of use on average per patient over the study. At 100 µg per use this equates to 151 uses over three months. This value was then multiplied by 4 to obtain the annual use.

b) The study reports 30.1 mg of use on average per patient over the study. At 200 µg per use this equates to 151 uses over three months. This value was then multiplied by 4 to obtain the annual use.

The study gives no additional information that could be used to generate costs for healthcare utilisation.

Using information from Table 114 and Table 115 the total annual cost of each intervention can be calculated along with the cost difference.

Table 116: Total annual costs of each intervention

Intervention	Drug cost	Healthcare utilisation cost	Annual cost
'Daily'	£249.22	NR	£249.22
'Intermittent'	£78.03	NR	£78.03
		Difference:	£171.19

Now the difference in costs between the two interventions has been established we need to evaluate the difference in health outcomes so that the cost effectiveness can be established.

No clinical outcomes were statistically significant, therefore it could be interpreted that there was no difference in health between the two groups.

Conclusions from the Papi study

Intermittent use of ICS leads to lower costs (£171.19) to the NHS. The study did not identify any statistical differences in health outcomes. Therefore, it could be interpreted that intermittent ICS is cost effective at the £20,000 per QALY threshold, however unscheduled healthcare utilisation was not measured.

8.1.1.3.2 5–16 years

The following section will evaluate the cost effectiveness of daily versus intermittent use of ICS in 5–16 year olds by attaching cost and health outcomes to the clinical outcomes presented in the paper by Turpeinen.

Cost effectiveness of intermittent versus daily use of ICS using data from Turpeinen 2008

In this study 100 µg budesonide was administered twice daily for the 'daily' intervention. During exacerbations the 100 µg budesonide was replaced with 400 µg budesonide twice daily for two weeks.

A placebo device was used in the 'intermittent' intervention, with only 400 µg budesonide twice daily for two weeks prescribed for exacerbations.

The annual drug cost of these interventions is displayed in Table 117 and Table 118 below.

Table 117: Annual unit costs of 'daily' drug use

Drug	Preparation	Dose per unit	Number of units per pack	Cost per pack	Cost per unit	Annual number of units used	Annual cost
Budesonide	Metered-dose inhaler	100 µg	200	£7.42	£0.04	730[a]	£27.08
Budesonide	Dry powder inhaler	400 µg	50	£13.86	£0.28	27.16[b]	£7.60
						Total	£34.68

Source: NHS Drug Tariff

a) *Based on one 100 µg puff twice daily*

b) *Based on one 400 µg puff twice daily for 2 weeks per study-defined exacerbation and an average of 0.97 exacerbations (1 x 2 x 14 x 0.97)*

Table 118: Annual unit costs of 'intermittent' drug use

Drug	Preparation	Dose per unit	Number of units per pack	Cost per pack	Cost per unit	Annual number of units used	Annual cost
Budesonide	Dry powder inhaler	400 µg	50	£13.86	£0.28	47.32[a]	£13.25
						Total	£13.25

Source: NHS Drug Tariff

a) *Based on one 400 µg puff twice daily for 2 weeks per study-defined exacerbation and an average of 1.69 study defined exacerbations (1 x 2 x 14 x 1.69)*

The study gives no additional information that could be used to generate costs for healthcare utilisation.

Using information from the tables above the total annual cost of each intervention can be calculated along with the cost difference.

Table 119: Total annual costs of each intervention

Intervention	Drug cost	Healthcare utilisation cost	Annual cost
'Daily'	£50.82	NR	£50.82
'Intermittent'	£13.25	NR	£13.25
		Difference:	£37.57

Now the difference in costs between the two interventions has been established we need to evaluate the difference in health outcomes so that the cost effectiveness can be established.

According to the study there is a significant difference in linear growth (velocity, cm) between both interventions. This shows that the mean linear growth in the intervention group was 0.6 higher and a clinically important benefit for the treatment of intermittent ICS. No other suitable clinical outcomes were included in the study. Study-defined exacerbations could be used to calculate drug use but did not match the review protocol for inclusion as a clinical outcome.

Conclusions from the Turpeinen study

Intermittent use of ICS leads to lower costs (£37.57) to the NHS. The study also showed that daily ICS has a negative effect on mean linear growth and therefore intermittent ICS may have a positive impact on health. However, the study did not assess other health outcomes such as exacerbations or quality of life.

8.1.1.3.3 Adults over 16

The following section will evaluate the cost effectiveness of daily versus intermittent use of ICS in adults over 16 years old by attaching cost and health outcomes to the clinical outcomes presented in the paper by Boushey.

Cost effectiveness of intermittent vs daily use of ICS using data from Boushey 2005

In this study 250 µg beclometasone was administered twice daily for the 'daily' intervention. Then 100 µg of salbutamol as needed.

In the 'intermittent' intervention, people were administered 250 µg beclometasone and 100 µg of salbutamol in a single inhaler as needed.

Patients were instructed to use reliever therapy at any time it was needed to relieve symptoms.

The annual drug cost of these interventions is displayed in Table 120 and Table 121 below.

Table 120: Annual unit costs of 'daily' drug use

Drug	Preparation	Dose per unit	Number of units per pack	Cost per pack	Cost per unit	Annual number of units used	Annual cost
Beclometasone	Dose breath actuated inhaler CFC free	100 µg	200	£17.21	£0.09	769.7[(a)]	£66.23
Salbutamol	Dry powder inhaler	200 µg	100	£4.85	£0.05	32.95[(b)]	£1.60
						Total	£67.83

Source: NHS Drug Tariff

a) Based on cumulative dose of 76,970 µg

b) Based on cumulative dose of 6,590 µg

Table 121: Annual unit costs of 'intermittent' drug use

Drug	Preparation	Dose per unit	Number of units per pack	Cost per pack	Cost per unit	Annual number of units used	Annual cost
Beclometasone	Dose breath actuated inhaler CFC free	100 µg	200	£17.21	£0.09	184.8[(a)]	£15.90
Salbutamol	Dry powder inhaler	200 µg	100	£4.85	£0.05	36.95[(b)]	£1.79
						Total	£17.69

Source: NHS Drug Tariff

a) Based on cumulative dose of 18,480 µg

b) Based on cumulative dose of 7,390 µg

The study gives no additional information that could be used to generate costs for healthcare utilisation.

Using information from Table 120 and Table 121 the total annual cost of each intervention can be calculated along with the cost difference.

Table 122: Total annual costs of each intervention

Intervention	Drug cost	Healthcare utilisation cost	Annual cost
'Daily'	£27.64	NR	£67.83
'intermittent'	£6.28	NR	£17.69
		Difference:	£50.14

Now the difference in costs between the two interventions has been established we need to evaluate the difference in health outcomes so that the cost effectiveness can be established.

The study showed no significant difference in lung function between the two groups. However, the study did not report exacerbations or quality of life.

Conclusions from the Boushey study

Intermittent use of ICS leads to lower costs (£50.14) to the NHS whilst maintaining the same level of health as regular use. Therefore intermittent ICS could potentially be cost-effective at a £20,000 per QALY threshold.

8.1.1.4 Summary of study findings

All of the studies have shown that intermittent ICS is cost saving compared to daily use of ICS. The cost savings of each study have been summarised in Table 123 below.

Table 123: Study cost savings summary

Study	Age category	Total savings
Papi 2009	<5	£182.03

Study	Age category	Total savings
Turpeinen 2008	5–16	£37.57
Boushey 2005	>16	£50.14

The summary table shows that the largest cost saving is in the under 5s category at £182.03 and the smallest cost saving is in the 5–16 category at £37.57.

8.1.1.5 Evidence statements

8.1.1.5.1 Clinical

Over 16 years

- Intermittent ICS vs regular ICS resulted in a clinically important benefit for number of asthma exacerbations (1 study, 137 patients, Low quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for quality of life as measured by AQLQ (1 study, 137 patients, High quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for asthma control as measured by ACQ (1 study, 143 patients, High quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for rescue medication use (1 study, 234 patients, High quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for lung function as measured by % change in PEF (1 study, 136 patients, High quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for lung function as measured by absolute change in PEF (1 study, 234 patients, Very low quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for lung function as measured by % change in FEV_1 (1 study, 137 patients, Moderate quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for lung function as measured by absolute change in FEV_1(%predicted) (1 study, 234 patients, High quality evidence)

5–16 years

- Intermittent ICS vs regular ICS resulted in a clinically important harm for number of asthma exacerbations (1 study, 184 patients, Very low quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for linear growth (1 study, 184 patients, Low quality evidence)
- Intermittent ICS vs regular ICS resulted in a clinically important benefit for linear growth velocity (1 study, 98 patients, Very low quality evidence)

1 to <5 years

- Intermittent ICS vs regular ICS resulted in no clinically important difference for severe exacerbations (1 study, 278 patients, Very low quality evidence)
- Intermittent ICS vs regular ICS resulted in a clinically important harm for exacerbations requiring hospitalisation (1 study, 278 patients, Very low quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for rescue medication use as measured by daytime use (1 study, 220 patients, Moderate quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for rescue medication use as measured by night-time use (1 study, 220 patients, Moderate quality evidence)
- Intermittent ICS vs regular ICS resulted in no clinically important difference for rescue medication use as measured by % of days with SABA use (1 study, 278 patients, Low quality evidence)

- Intermittent ICS vs regular ICS resulted in no clinically important difference for linear growth (1 study, 278 patients, Low quality evidence)

8.1.1.5.2 Economic

- No relevant economic evaluations were identified.

8.1.1.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80
Relative values of different outcomes	The committee considered the following outcomes as critical or important for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee also considered the following additional outcomes: asthma control (as assessed by a validated questionnaire), hospital admission, SABA use, lung function (FEV_1 or morning PEF) and adverse events.
Trade-off between clinical benefits and harms	All the available evidence assessed the effectiveness of intermittent ICS treatment initiated for a short period when the person was symptomatic. The precise trigger for treatment varied between studies but was typically an increase or change in symptoms as identified by patients. In adults and people over 16 years old, evidence suggested fewer severe asthma exacerbations requiring OCS with intermittent ICS therapy compared to daily ICS therapy. However, this evidence was of Low quality and the committee did not consider the observed difference to be clinically important. There was also no clinically important difference between daily or intermittent ICS for the outcomes of quality of life, asthma control assessed using the ACQ, hospitalisations, rescue medication use or lung function. In the 5–16 age group the use of intermittent ICS was associated with a relative increase in severe exacerbations, and this difference appears clinically significant. Conversely, there was a clinically important benefit of using intermittent ICS for linear growth in the 5–16 age group, but that evidence was low quality. Furthermore, it is difficult to interpret this as a definite clinical benefit because other evidence in the literature suggests that the initial small deceleration in growth rate with daily ICS therapy is not maintained year on year.[24 ,80] As none of the studies were longer than one year, it is not known if this initial benefit of intermittent ICS is sustained for sufficient time to make an appreciable difference to final height. In children under 5 years old there was no clinically important difference between daily and intermittent ICS for the outcomes of severe exacerbations, mortality, rescue medication use or growth. There were more exacerbations requiring hospitalisation with the use of intermittent ICS. There was no evidence on infection or adrenal insufficiency, the two other adverse events potentially associated with daily ICS use. No evidence was found for children aged under 1. Across all three age groups the committee felt that there was generally insufficient high quality evidence with regards to any potential clinical harms of using intermittent ICS (exacerbations, hospitalisation) or any potential benefits of using intermittent ICS (reduced adverse events). Therefore, overall the committee felt there was insufficient evidence to confirm whether intermittent ICS was better, worse or equivalent to daily ICS. The committee felt therefore that they could not recommend a deviation from current practice, which is to offer ICS as part of a daily

	regimen and not on an intermittent basis.
Trade-off between net clinical effects and costs	No economic studies were included in this review. In the absence of economic evidence, unit costs of drugs and other healthcare resources were applied to resource use quoted in the included clinical studies. The analysis identified intermittent use of ICS as being cost saving compared to daily use of ICS for all age categories. The cost saving ranged from £37.57 to £182.03. The main reason for such a large range appeared to be the dose the individual was prescribed; the higher the dose the higher the saving appeared to be. A threshold analysis was undertaken using the identified cost savings to calculate the minimum required QALYs the use of daily ICS would need to obtain to be cost-effective at a £20,000 per QALY threshold. This is done by dividing the cost difference by £20,000. For example if an intervention cost an additional £20,000, if we used a £20,000 per QALY threshold then we would say the intervention would need to generate 1 additional QALY (20,000/20,000=1) to be considered cost effective. As the cost savings were small, the required QALYs needed for daily ICS to be cost-effective were also small (0.001 to 0.01 per year). However, as noted in the preceding section, the committee felt there was insufficient evidence to confirm whether intermittent ICS was better, worse or equivalent to daily ICS, so it was impossible to be certain whether intermittent ICS use is cost-effective As daily ICS use is prevailing practice and is known to be effective the committee felt that a recommendation concerning the use of intermittent ICS use could not be made until further research was gathered confirming its efficacy. Although it could be cost saving the potential clinical harm that would prevent it from being cost effective is very small.
Quality of evidence	The quality of evidence for the majority of outcomes was Low or Very Low. The exception was in adults and people over 16 years old, where some High quality evidence was available. However, only one study contributed to the evidence for all outcomes. The committee also discussed other limitations of the included studies which would not have been captured in the quality of the evidence. Both studies in children under 5 years used nebulised ICS which is not current routine clinical practice, and therefore the committee questioned the applicability of these studies. In particular, the use of nebulised beclometasone in one study was considered unusual and potentially ineffective. The committee sought the opinion of an external expert aerosol scientist who felt that there was still likely to be some pharmacological activity from the nebulised agent. As both arms in this study used nebulised agents and compared only with each other, the committee felt that it was therefore appropriate to include it in the review.
Other considerations	The patient representatives highlighted that many patients find courses of OCS unpleasant due to side effects. Before accepting an intermittent ICS regimen they would want reassurance that this is not associated with increased requirement for OCS courses, and the studies reviewed do not allow strong enough reassurance. No evidence was identified that assessed the effectiveness of intermittent ICS therapy initiated shortly prior to, and continued during, a period when the person was known to be at risk of an increase in symptoms or loss of asthma control (for example in hayfever season or during the winter months in those with known seasonal asthma). The committee noted this lack of evidence and felt the effectiveness of seasonal use of ICS for longer periods needs to be further investigated.

The committee also felt that it would be useful to know whether intermittent regimens made any difference to adherence to treatment.

9 Improving adherence to treatment

9.3 Introduction

It is well recognized that adherence to medications prescribed for long-term conditions is poor, with an estimated half of medication not taken as recommended (NICE, 2009).[65] Adherence to asthma medications is recognized to be between 20–70%.[89 ,167]However, estimates suggest that around 75% adherence to inhaled corticosteroid medication is needed to prevent exacerbations.[189] The National Review of Asthma Deaths recently identified poor adherence as a key factor contributing to asthma death, with underuse of inhaled corticosteroid a particular problem.[153] The report highlights the importance of monitoring and education in the management of asthmatic patients.

Some progress has been made in unravelling factors that influence adherence by applying behavioural models. For example, analyses using the Necessity and Concerns Framework show that the more a person views taking asthma medication as important (necessary) the more likely they are to adhere, whilst conversely the greater the concerns about adverse effects the less likely a person is to adhere.[69]

Being able to assess adherence accurately is important. Knowing whether a patient's poor asthma control reflects low adherence or ineffective medication is key to deciding whether to step up medication.[25] Electronic inhaler dosage monitoring suggests that subjective reports often overestimate adherence.[89]

Improving adherence is a challenge, particularly in some groups such as adolescents and young adults[34] where adherence is estimated at 20–35%.[9 ,30] In a systematic review of adherence across a wide range of medical conditions, a minority of interventions tested led to improvements; those that did were often complex and multifaceted, with only small improvements seen in adherence and outcomes.[65]

Novel and more effective interventions are urgently needed that lead to substantial and long-lasting improvements in asthma adherence. Digital reminder systems hold potential but current evaluations suggest impact wanes over time.[52] Incentivising adherence has proven effective in other long term conditions.[141](Brief and more effective educational interventions need to be developed and tested, perhaps combining health professional support with novel platforms such as smartphones.

This chapter aims to review the effectiveness of interventions to improve adherence that have been tested in randomised controlled trials.

9.1.1 Review question: What are the most clinically and cost-effective strategies to improve medicines adherence in children, young people and adults with asthma who are non-adherent to prescribed medicines?

For full details see review protocol in Appendix C.

Table 124: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma and have been prescribed regular preventer therapy but are non-adherent (taking <80% of their prescribed preventer medication). Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years **Exclusions:** People not on regular preventer medication People adherent to regular preventer medication
Interventions	• Asthma education (education intervention for people who are non-adherent) including individual and group education, nurse-led and other health professional consultations • More frequent asthma review (including telephone follow-up) or longer consultations • Inhaler alarms/alert to remind people to take regular therapy or inhalers that monitor use (including click inhalers, dose counters) • Behavioural change interventions (including motivational interviewing) • Usual care (at minimum including regular asthma review)
Comparison	All interventions will be analysed separately (compared against placebo/usual care and compared against each other).
Outcomes	All outcomes will only be included if reported at a minimum of 3 months following the end of the intervention. These interventions are aimed at promoting long- term behavioural change and hence any effects must persist after the cessation of the interventions themselves. **Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life • Adherence **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever/rescue medication use • Lung function (FEV_1 or morning PEF) • Adverse events: linear growth, infections (all respiratory), infections (serious respiratory), adrenal insufficiency.
Study design	RCT Systematic review of RCTs

9.1.1.1 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of strategies to improve medicines adherence in children, young people and adults with asthma who are non-adherent to prescribed medicines.

Six studies were included in the review; [44 55 93 135 156 186] these are summarised in Table 125 below. Evidence from these studies are summarised in the clinical evidence summary tables below (Table 126, Table 127,Table 128 and Table 129). See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Five studies included a population over the age of 16. One study included a population between the age of 5 and 16. No studies were identified that included a population under the age of 5. Three studies compared an education intervention to usual care, two studies compared a behavioural change intervention with usual care, and one study compared a medication alert system with usual care.

Table 125: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
van Es 2001 [44]	Education (n=58). Intervention group offered usual care from paediatrician every 4 months, plus additional education from the paediatrician around disease characteristics, triggers for airway obstruction, and treatment objectives, and sessions with an asthma nurse to reinforce this information. Group sessions were held by the asthma nurse to discuss how patients dealt with their asthma. Usual care (n=54). Control participants continued usual care from a paediatrician only every 4 months. The various sessions were spread out over the period of 1 year. During the second year, all participants in both groups received the same usual care.	Asthma diagnosis by a physician. Treatment prescribed by paediatrician with daily inhalations of prophylactic asthma medication. Non-adherent at baseline as defined by a mean baseline adherence score of 7.4 (scale 1–10, 1= never taking medication, 10 =always taking every dose). Age - Mean (SD): 13.7 (1.4)	• Adherence (1–10) ○ self-reported Follow up duration: 2 years	
Gamble 2011 [55]	Behavioural change (n=9). Intervention group offered up to 8 individualised visits based on the Compliance Therapy Model, within a 12-week period. Compliance Therapy Model encompassed the Theoretical Model of Change,	Adults attending the Northern Ireland Regional Difficult Asthma Service. Non-adherent (≤50% of prescription filling) despite concordance discussion and treatment plan to	• Quality of life (AQLQ) • Adherence (%) ○ prescription refills records • Asthma control score (ACQ) • Lung function – FEV_1 (%)	Two-phase study. Phase 1: 12-month observational study. Adherence recorded, concordance discussion and treatment plan to address poor adherence. Phase 2: 12-month intervention study.

Study	Intervention and comparison	Population	Outcomes	Comments
	Motivational Interviewing, and Cognitive Behavioural Therapy, using participants' reasons for non-adherence as a guide for intervention content. Usual care (n=11). Control participants continued usual care, comprising standard asthma care at the Difficult Asthma Service.	address poor adherence. Age - Mean (SD): 47.4 (9.9)	Follow up duration: 1 year	
Lavoie 2014 [93]	Motivational Interviewing (n=26). Three to four individual 15–30 minute sessions over a 4–6 week period. Explored ambivalence, self-efficacy, 'rolling with resistance', and 'change talk'. Usual care (n=28). Received whatever treatments their attending physician prescribed, which could have included ICS + reliever as needed, an asthma action plan for exacerbations, and/or referral to asthma education.	Adults with primary diagnosis of moderate to severe persistent asthma (bronchodilator reversibility in FEV_1 >20%). At baseline, participants were poorly controlled (ACQ ≥1.5) and non-adherent (filled <50% of ICS medication in last year) Age - Mean (SD): 50 (16)	• Quality of life (AQLQ) • Adherence (%) ○ prescription refill records • Asthma control (ACQ) • Asthma control (ACT) ` Follow up duration: 1 year	
Petrie 2012 [135]	Alerts/behavioural change (n=73). Baseline questionnaire to assess illness perceptions. Individually tailored text messages (selected from a bank of 166 text messages to target differing beliefs) based on their illness and medication belief over 18 weeks. Two messages per day from weeks 1–6, one per day	Adults, aged 16–45, diagnosed with asthma, who are not currently adhering (<80%) to their preventer medication as prescribed. Mean age not reported.	• Adherence (%) ○ self-reported Follow up duration: 9 months	Baseline self-reported adherence 55.26%

Study	Intervention and comparison	Population	Outcomes	Comments
	from weeks 7–12, and three per week from weeks 13–18. Usual care (n= 74). Usual care with no text messages.			
Schaffer 2004 [156]	Education (n=33). Education via 30-minute audiotape 'Bob's Lung Story' (focusing on basic asthma facts, roles of medications, psychomotor skills related to inhaler use and self-monitoring, environmental control measures, and when and how to take rescue actions), a 12-page booklet 'controlling your asthma' covering the same topics as the audiotape or both the audiotape and the booklet. Participants spent 30–60 minutes reviewing provided education materials before taking them home. Participants were not directed to review the material further. Usual care (n=13). Standard provider education; whatever education was provided by the participant's asthma care provider and was not assessed in this study.	Adults whose reported use of preventative medication for asthma during the 3 months prior to study indicated mild to moderate persistent asthma. Mean baseline pharmacy-verified adherence 50.46% Age - Mean (range): 37 (18–63)	• Quality of life (AQLQ) • Adherence (%) ○ prescription refills records • Asthma control (ACQ) Follow up duration: 9 months	Education intervention arms pooled
Wang 2010 [186]	Education (n=59). Nurse-led education programme, using a workbook prepared by chest physicians. Subset of participants also received pharmacist	Outpatient adults with confirmed diagnosis of bronchial asthma as determined by clinical features before treatment.	• Quality of life (AQLQ) • Adherence (4–16) ○ self-reported	Nurse education, and Nurse education plus pharmacist education data pooled.

Study	Intervention and comparison	Population	Outcomes	Comments
	counselling with education specific to medication. Three 1-hour sessions at months 1, 2, and 3. Usual care (n=32). Received routine care only.	Mean baseline adherence (using the Self-Assessment of Medication Adherence scale, range of 4–16 where 4 is always forgot and 16 is always remembered) of 9.65. Age - Mean (range): 25 (19–68)	Follow up duration: 6 months	

Table 126: Clinical evidence summary: Education compared to usual care for adults (>16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with Usual care	Risk difference with Education (95% CI)
Quality of life (AQLQ, 1–7, higher is better outcome)	137 (2 studies) 6–9 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the control groups was 4.88	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was 0.22 higher (0.15 lower to 0.6 higher)
Asthma control (ACQ, 0–6, higher is worse outcome)	46 (1 study) 9 months	VERY LOW[b,c] due to indirectness, imprecision	-	The mean asthma control (ACQ, 0–6, higher is worse outcome) in the control groups was 1.25	The mean asthma control (ACQ, 0–6, higher is worse outcome) in the intervention groups was 0.1 higher (0.56 lower to 0.76 higher)
Adherence (% - prescription refills records)	46 (1 study) 9 months	LOW[b,c] due to indirectness, imprecision	-	The mean adherence (%) in the control groups was 40%	The mean adherence (%) in the intervention groups was 28.21 higher (1.93 to 54.49 higher)
Adherence (self-reported, 4–16)	91 (1 study) 6 months	LOW[a,c] due to risk of bias, imprecision	-	The mean adherence (self-reported, 4–16) in the control groups was 12.6	The mean adherence (self-reported, 4–16) in the intervention groups was 0.91 higher

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Education (95% CI)
					(0.19 lower to 2.01 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 127: Clinical evidence summary: Behavioural change intervention compared to usual care for adults (>16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Behavioural change (95% CI)
Quality of life (AQLQ, 1–7, higher is better outcome)	72 (2 studies) 1 years	LOW[a,b] due to indirectness, imprecision	-	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the control groups was 4.45	The mean quality of life (AQLQ, 1–7, higher is better outcome) in the intervention groups was 0.33 higher (0.23 lower to 0.89 higher)
Adherence (% - prescription refills records)	74 (2 studies) 1 years	VERY LOW[a,b,c] due to indirectness, imprecision, inconsistency	-	Data given as mean difference	The mean adherence (%) in the intervention groups was 14.55 higher (0.98 to 28.12 higher)
Asthma control (ACQ, 0–6, higher is worse outcome)	72 (2 studies) 1 years	LOW[a,b] due to indirectness, imprecision	-	The mean asthma control (ACQ, 0–6, higher is worse outcome) in the control groups was 2.38	The mean asthma control (ACQ, 0–6, higher is worse outcome) in the intervention groups was 0.37 lower (0.88 lower to 0.13 higher)
Asthma control (ACT, 5–25,	54	LOW[b]	-	The mean asthma control (act, 5–25,	The mean asthma control (ACT, 5–25,

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Behavioural change (95% CI)
higher is better outcome)	(1 study) 1 years	due to imprecision		higher is better outcome) in the control groups was 18	higher is better outcome) in the intervention groups was 0 higher (2.7 lower to 2.7 higher)
Lung function - FEV_1 (% predicted)	18 (1 study) 1 years	VERY LOW[a,b] due to indirectness, imprecision	-	The mean lung function - FEV_1 (% predicted) in the control groups was 67.2 %	The mean lung function - FEV_1 (% predicted) in the intervention groups was 5.2 higher (18.96 lower to 29.36 higher)

a Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 or 2 increments because of heterogeneity, I^2=76%, p=0.04, unexplained by subgroup analysis

Table 128: Clinical evidence summary: Alerts/behavioural change compared to usual care for adults (>16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Alerts (95% CI)
Adherence (%, self-reported)	93 (1 study) 9 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean adherence (%) in the control groups was 43.2 %	The mean adherence (%) in the intervention groups was 14.6 higher (1.69 to 27.51 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 129: Clinical evidence summary: Education compared to usual care for young people (aged 5–16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Education (95% CI)
Adherence (self-reported, 1–10)	67 (1 study) 2 years	VERY LOW[a,b,c] due to risk of bias, due to indirectness, imprecision	-	The mean adherence (self-reported, 1–10) in the control groups was 6.7	The mean adherence (self-reported, 1–10) in the intervention groups was 1 higher (0.03 lower to 2.03 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

9.1.1.2 Economic evidence

Published literature

No economic evaluations were identified for this review.

See also the health economic study selection flow chart in Appendix F.

9.1.1.3 Evidence statements

9.1.1.3.1 Clinical

Education compared to usual care for adults (>16) with asthma

- No clinically important difference of education in terms of quality of life (AQLQ) from 2 studies with 137 participants, Very Low quality evidence due to risk of bias, indirectness and imprecision.
- No clinically important difference of education in terms of asthma control (ACQ) from 1 study with 46 participants, Very Low quality evidence due to indirectness and imprecision.
- Clinically important benefit of education in terms of adherence (% - prescription refills) from 1 study with 46 participants, Very Low quality evidence due to indirectness and imprecision.
- No clinically important benefit of education in terms of adherence (self-reported) from 1 study with 46 participants, Very Low quality evidence due to indirectness and imprecision.

Behavioural change intervention compared to usual care for adults (>16) with asthma

- No clinically important difference of education in terms of quality of life (AQLQ) from 2 studies with 72 participants, Low quality evidence due to indirectness and imprecision.
- Clinically important benefit of education in terms of adherence (% - prescription refills) from 2 studies with 74 participants, Very Low quality evidence due to indirectness, imprecision and inconsistency.
- No clinically important difference of education in terms of asthma control (ACQ) from 2 studies with 72 participants, Low quality evidence due to indirectness and imprecision.
- No clinically important difference of education in terms of asthma control (ACT) from 1 study with 54 participants, Low quality evidence due to imprecision.
- No clinically important difference of education in terms of lung function (FEV_1 - % predicted) from 1 study with 18 participants, Very Low quality evidence due to indirectness and imprecision.

Alerts/behavioural change compared to usual care for adults (>16) with asthma

- No clinically important benefit of education in terms of adherence (% - self-reported) from 1 study with 93 participants, Very Low quality evidence due to risk of bias, indirectness and imprecision.

Education compared to usual care for young people (aged 5–16) with asthma

- No clinically important benefit of education in terms of adherence (% - self-reported) from 1 study with 67 participants, Very Low quality evidence due to risk of bias, indirectness and imprecision.

9.1.1.3.2 Economic

- No economic evaluations were identified.

9.1.1.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80
Research recommendation	**4. What are the most clinically and cost-effective strategies to improve medicines adherence in adults, children and young people with asthma who are non-adherent to prescribed medicines?**
Relative values of different outcomes	The committee considered the following outcomes as critical for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality, quality of life, and adherence. The committee considered the following outcomes as important: asthma control (as assessed by a validated questionnaire), hospital admission, reliever medication use, lung function (FEV_1 or morning PEF) and adverse events.
Quality of the clinical evidence	The quality of the evidence ranged from Very Low to Low. No evidence was identified for severe exacerbations, mortality, hospital admission, reliever medication use, and adverse events. The evidence was generally downgraded for indirectness (the participants had not necessarily had their asthma diagnosis confirmed by objective measures) and imprecision. A number of studies reported adherence by way of a self-reported measure from participants, who were not blinded to whether they were receiving an active intervention (that is, education) or usual care. This evidence was subsequently downgraded for risk of bias.
Trade-off between clinical benefits and harms	All the available evidence assessed and compared the effectiveness of strategies to improve medicines adherence in children, young people and adults with asthma who are non-adherent to prescribed medicines. Educational intervention resulted in no clinically important difference in patients' quality of life or asthma control. Pharmacy-verified adherence was significantly improved following this intervention, but self-reported adherence showed no clinically important difference following education in both the adult (over 16) and young people (5–16) strata. Behavioural change interventions resulted in no clinically important difference in patients' quality of life, asthma control or lung function. Adherence, as measured by the per cent of prescription refills picked up, was clinically improved following behavioural change. Self-reported adherence showed no clinically important difference following behavioural change, motivational interviewing, or text message interventions. Due to the lack of quality and quantity of conclusive evidence, the committee were unable to make a recommendation on strategies to improve medicines adherence in asthma. Given the absence of evidence presented in this review and the accepted importance of medicine adherence, the committee referred to the recommendations made in the medicines adherence guideline. However, the committee recognise the importance of medicines adherence in asthma management. They considered that the evaluated studies show the potential value of strategies such as asthma education, more frequent asthma reviews, inhaler alarms/alerts, and behavioural change intervention. The committee are aware of ongoing studies in which objective measures of adherence are being used to assess the efficacy of adherence-improving interventions, and considered that similar

	research should be encouraged.
Trade-off between net clinical effects and costs	No economic evaluations were identified. The costs of interventions targeted at improving adherence are mostly determined by the additional healthcare professional time needed to conduct the intervention. In some of the clinical studies additional costs were also incurred through additional items given to the patients, such as reading supplements and dose alerts. Overall the clinical evidence was largely inconclusive regarding the efficacy of such adherence schemes with not a single study showing important clinical benefits. Given significant healthcare professional time needed to conduct a specific adherence intervention the committee agreed there was not sufficient evidence to make a recommendation. The committee acknowledged the importance of good adherence and the positive impact this could have on reducing unscheduled healthcare utilisation, therefore making a research recommendation a high priority.
Other considerations	The committee had some reservations over the inclusion of self-reported adherence as a clinical outcome, with questions over its reporting accuracy and susceptibility to bias. It was also noted that prescription refills, while having a greater validity than self-report, may not accurately report the actual amount of medication being taken. Objective measures of adherence such as electronic activation recording inhalers are considered more accurate measures of adherence, but even these can be manipulated. The committee accepted that there is no perfect way of measuring asthma medication adherence, and therefore included studies which used the aforementioned methods of measuring medicine adherence, with appropriate allowance for potential bias. The committee noted the paucity of High quality evidence assessing the benefit of education in addressing non-adherence. The committee agreed that education as part of a standard care package is an important part of addressing non-adherence, but they did not believe there was sufficient evidence to recommend a more intensive formal program of education specifically targeted at non-adherence.

10 Self-management plans

10.3 Introduction

It is estimated that 80–90% of all care for people with long-term conditions is undertaken by patients themselves and their families, highlighting the importance of self-management for these people. Self-management support can be viewed as a portfolio of techniques and tools to help people choose healthy behaviours, and as a fundamental transformation in the patient-caregiver relationship to one of a collaborative partnership. Self-management can cover a range of options including patient and carer education programmes, medicines management, use of telecare and telehealth to aid self-monitoring or psychological interventions. In asthma the most common form of self-management support offered is in the form of a Personal Asthma Action Plan (PAAP) and yearly asthma review, providing patient education and re-enforcing key aspects of self-management (for example inhaler technique).

BTS/SIGN guidance on the management of asthma has for many years recommended that all patients with asthma should be offered self-management education, including a PAAP, which is supported by regular professional review. However, the National review of Asthma Deaths highlighted that PAAPs were provided to only 44 (23%) of the 195 people who died from asthma and that 43% of patients who died had not had an asthma review at their GP surgery in the preceding year.

This review question focuses on the clinical and cost effectiveness of supported self-management in comparison to standard care for improving outcomes in patients with asthma.

10.1.1 Review question: What is the clinical and cost effectiveness of supported self-management (including self-management education, self-monitoring and a personalised asthma action plan, PAAP) in comparison to standard care (asthma review only), for improving outcomes for children, young people and adults with asthma?

For full details see review protocol in Appendix C.

Table 130: PICO characteristics of review question

Population	Children and adults with a clinician diagnosis of asthma. Population strata: • <1 year • 1 to <5 years • 5 to <16 years • ≥16 years
Intervention	Optimised self-management package (includes: self-management education, self-monitoring and a written personalised asthma action plan) in addition to standard care and alongside pharmacological therapy.
Comparison	Standard care: Regular review with a healthcare professional, alongside pharmacological therapy.

Outcomes	**Critical outcomes:** • Severe asthma exacerbations • Mortality • Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever medication use • Lung function (change in FEV_1 or morning PEF) Adverse events: • linear growth • all respiratory infections • serious respiratory infections • adrenal insufficiency
Study design	RCT Systematic review of RCTs

10.1.1.1 Clinical evidence

A search was conducted for randomised controlled trials (RCTs) and systematic reviews of RCTs investigating the benefit of formalised self-management packages in addition to regular reviews and pharmacological treatment in asthmatic children and adults. Only studies which reported packages including elements of self-management education, self-monitoring, and a written personalised asthma action plan (PAAP) were included. The committee agreed that the inclusion of minimal education in the control arm was permitted, in order to reflect current clinical practice. A true placebo group (absence of all elements of the package) would neither be ethical nor standard care. Studies that only assessed action plans without any training were excluded. The committee also agreed that proper inhaler technique should be encouraged in both arms. If the review reported people with either asthma or COPD, the evidence from the asthmatic population was included if both conditions were reported as separate strata.

Fourteen studies were included in the review;[20 ,23 ,29 ,37-39 ,42 ,46 ,70 ,86 ,98 ,104 ,149 ,166 ,176] these are summarised in Table 131 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 132, Table 133 and Table 134). See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Eight studies included a population over the age of 16. Five studies included a population aged 5–16. One study was identified that included a population of children aged 1–5.

One study was conducted in the UK, 4 studies elsewhere in Europe, 7 studies in North America, and 2 studies in South America.

Seven studies took place in primary care, 6 in secondary care and 2 studies in tertiary care.

Four studies only included people that had moderate to severe asthma; 1 study only included people with moderate asthma; a further 8 studies did not report the severity of asthma.

Table 131: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Bragt 2014[20]	Optimal supported self-management n=18 Patients used online Pelican instrument to assess asthma severity and knowledge. Patients were given a plan based on shared-decision making. Standard care n=20 Patients were reviewed by their GP or practice nurse.	Austria and The Netherlands Primary care Severity of asthma not reported. Stratum: 5 to <16 years Age (years) - Mean (SD): SM package - 8.4 (1.7); usual care - 8.7 (1.7). Inclusion criteria: Children aged 6–11 years with physician-diagnosed asthma, who had used asthma medication (that is, bronchodilators and/or inhaled corticosteroids) for at least 6 weeks during the previous year.	• Quality of life (PAQLQ) • Asthma control (ACT) Reported at 9 months	Study reported outcomes as medians and interquartile ranges (IQR), and could not been included in the meta-analysis.
Bruzzese 2011[23]	Optimal supported self-management n=175 Patients attended an 8-week intensive program which included individualised coaching sessions held weekly for one week. Their medical providers were sent relevant material and contacted to aid both the health provider and patient.	USA Primary care (school) Moderate to severe asthma Stratum: 5 to <16 years Age(years) - Mean (SD): 15.10 (0.86) Inclusion criteria: 9th and 10th grade high school students; moderate to severe persistent	• Quality of life (PAQLQ) Reported at 12 months • Hospitalisation Reported at 6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard care n=170 Patients were put on a 12-month waiting list, and their usual practices not interfered with. The study doesn't report that inhaler technique was taught.	asthma as defined by NHLBI guidelines; taking asthma medication prescribed by a medical provider in the last 12 months.		
Castro 2003[29]	Optimal supported self-management n=50 Patients were asked to record daily symptoms whilst still in hospital and this information was shared with their primary care doctor. Patients received a tailored education and action plan, monitored frequently by specialist nurses. Standard care n=46 On discharge from the ED, patients received some asthma education and discharge instructions (did not include an asthma action plan).	USA Secondary care Severity of asthma not reported. Stratum: ≥16 years Age (years) - Mean (SD): SM package - 35(11); usual care - 38(12). Inclusion criteria: Diagnosis of asthma of at least 12 months duration; age18–65 years; hospitalized at Barnes-Jewish Hospital; forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio less than 80%; history of one or more hospitalization in the 12 months prior to randomisation.	• Quality of life (AQLQ) ○ Reported at 6 months • Hospitalisation ○ Reported at 12 months	Study defined hospitalisations as: number of readmissions (and asthma-related admissions per patient).
Côté 1997[38]	Optimal supported self-management – Symptom-based plan n=45	Canada Tertiary care hospitals	• Severe asthma exacerbations • Hospitalisation	Reports two types of plan: symptom-based and peak-flow based. Study definition of

Study	Intervention and comparison	Population	Outcomes	Comments
	Patients kept a daily dairy of asthma symptom scores. This was reviewed at each follow-up appointment. Optimal supported self-management – peak-flow based plan n=50 Patients were asked to measure PEF twice daily and to adjust treatment according to a self-action plan based on the patient's PBV. Standard care n=54 Patients received minimal asthma education. All patients received a book entitled 'Understand and Control Your Asthma.	Moderate to severe asthma Stratum: ≥16 years Age (years) - Mean (SD): Usual care - 36 (22); PF plan - 37 (14.1); SB plan - 39 (13.4). Inclusion criteria: The presence of moderate to severe asthma, age 16 years or older, and the need to take daily anti-inflammatory agent (inhaled corticosteroids, cromoglicate, or nedocromil).	Reported at 12 months	severe exacerbation: number of oral corticosteroid courses.
Côté 2000[37]	Optimal supported self-management – Symptom-based plan n=45 Patients kept a daily diary of asthma symptom scores. This was reviewed at each follow-up appointment. Optimal supported self-management – peak-flow based plan n=50	Canada Tertiary care hospitals Moderate asthma Stratum: ≥16 years Age (years) - Mean (SD): SM package - 38(2); usual care - 36(3). Inclusion criteria: Presence of moderate asthma requiring daily treatment with inhaled	• Quality of life (AQLQ) Reported at 12 months	Reports two types of plan: symptom-based and peak-flow based.

Study	Intervention and comparison	Population	Outcomes	Comments
	Patients were asked to measure PEF twice daily and to adjust treatment according to a self-action plan based on the patient's PBV. Standard care n=54 Patients received minimal asthma education. Study involved a run-in period lasting from 2–6 weeks prior to randomisation, where medication was adjusted.	corticosteroids; PEF diurnal variation 15% or post-bronchodilator FEV_1 of 85% or greater of predicted (criteria of stability).		
Cowie 1997[39]	Optimal supported self-management – Symptom-based plan n=45 Plan included list of asthma symptoms, including waking at night and persistent cough. Optimal supported self-management – peak-flow based plan n=50 Patients were given plans that included peak flow measurements that were estimated from their measured and predicted peak expiratory flows. Standard care n=54	Canada Primary care (home) Severity of asthma not reported. Stratum: ≥16 years Age(years) - Mean (SD): Usual care - 36.4(12.76); PF plan - 39.1(14.1); SB plan - 36.8. Patients who received urgent treatment for their asthma in the preceding 12 months were invited to participate in the study.	• Hospitalisation • Serious exacerbations Reported at 6 months	Reports two types of plan: symptom-based and peak-flow based. Study defines serious exacerbations as: Total number of urgent treatments for asthma Urgent treatment was defined as treatment sought to provide immediate relief of asthma symptoms that were perceived to be severe and that failed to respond to the subjects' usual reliever medication.

Study	Intervention and comparison	Population	Outcomes	Comments
	Patients received minimal asthma education. Suggestions for adjustment of treatment were made to the patient's usual physician.			
De Oliveira 1999[42]	Optimal supported self-management n=26 Patients had their treatment plan adjusted at each follow-up appointment, according to their diary card. Standard care n=27 Patients received minimal education and attended regular review at an asthma clinic.	Brazil Secondary care (outpatient) Moderate to severe asthma Stratum: ≥16 years Age(years) - Mean (SD): SM package - 41 (15); usual care - 38 (17). Inclusion criteria: Asthma confirmed by history and airflow, obstruction according to the criteria of the ICRDMA were eligible to participate in the trial.	• Hospitalisation Reported at 6 months	
Farber 2004[46]	Optimal supported self-management n=28 Patients were given a written plan illustrated by coloured "traffic light" zones. Patients were followed up by telephone. Standard care n=28 Patients received	USA Secondary care Moderate to severe asthma Stratum: 5 to <16 years Age (years) - Mean (SD): SM package - 7.3 (4.3); usual care - 7.7 (4.2). Inclusion criteria: Age 2–18 years; has State of Louisiana	• Hospitalisation Reported at 6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	minimal asthma education and were referred back to their familial physician.	Medicaid insurance; has a telephone at home; has a history of asthma; has not been intubated or mechanically ventilated for asthma; does not have other clinically significant (that is, moderate to severe) chronic illness; presents to the ED when an investigator is available; has informed consent provided by parent or guardian; child voluntary assents to participation in study (if child is older than 12 years).		
Horner 2014[70]	Optimal supported self-management n=96 In addition to a written plan, patients were also given a home-management plan. Asthma education was delivered during school time. Standard care n=27 Patients were given the intervention at the end of the study.	USA Primary care (school) Severity of asthma not reported. Stratum: ≥16 years Age (years) - Mean (SD): 8.78 (1.24). Inclusion criteria: The parents reports the child has physician diagnosis of asthma; has had asthma symptoms in the previous 12 months; does not have significant comorbidity that would preclude participation in	• Quality of life (AQLQ) Reported at 7 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		classes (for example severe cerebral palsy, oxygen dependant conditions); speaks either English or Spanish.		
Khan 2014[86]	Optimal supported self-management n=45 Patients received a plan combing peak-flow measurements and symptoms, in a "traffic light" colour code system. Standard care n=46 Patients received moderate asthma education, as well as training on how to take PEFR measurements. Patients were allowed to take asthma education materials home.	Trinidad & Tobago Primary care Severity of asthma not reported. Stratum: 5 to <16 years Age (years) - Mean (SD): SM package - 5.67 (2.82); usual care - 6.35 (2.88). The main inclusion criterion was the ability of the child and/or parent to follow written directions. A history of presenting to the emergency room or paediatric clinic for acute treatment of bronchospasm in the preceding 6 months.	• Lung function (FEV_1 %predicted) Reported at 6 months	
Milenković 2007[104]	Optimal supported self-management n=40 Patients were trained on how to take PEFR measurements, and received a plan based on those measurements. Standard care	Serbia and Montenegro Secondary care (outpatient) Mild to severe asthma Stratum: ≥16 years Age (years) - Mean (SD): SM package - 49.1 (14.4); usual	• Severe asthma exacerbations (requiring OCS) • Hospitalisation • Lung function (FEV_1 %predicted) Reported at 12 months	Study defines serious exacerbations as: number of oral steroid courses per patient.

Study	Intervention and comparison	Population	Outcomes	Comments
	n=40 Patients received minimal education and regular review.	care - 44.9 (11.7) Inclusion criteria: Patients were aged between 18–60; had a continuous use of inhaled corticosteroids for at least 1 year; stable phase of disease during the last 3 months, were included in the study.		
Rikkers-Mutsaerts 2012[149]	Optimal supported self-management n=46 Patients received web-based asthma education and action plan, based on asthma symptoms and FEV_1 measurements. Standard care n=44 Patients received care from their usual health care professionals.	The Netherlands Primary care (35 GP practices) and secondary care (8 hospitals) Mild to severe asthma Stratum: 5 to <16 years Age (years) - Mean (range): SM package - 13.4 (12-17); usual care - 13.8 (12-17). Inclusion criteria: Doctor's diagnosis of mild to severe persistent asthma characterised by a prescription of ICS more than 3 months in the previous year; age 12–18 years; access to internet; understanding of the Dutch language.	• Quality of life • Asthma control • Serious exacerbations (requiring OCS) Reported at 12 months	Study defined severe exacerbations as: deterioration of asthma that required OCS for 3 days or more.

Study	Intervention and comparison	Population	Outcomes	Comments
Stevens 2002[166]	Optimal supported self-management n=99 Patients received: (1) a general education booklet about asthma in pre-school children (excluding babies); (2) a written guided self-management plan; (3) two 20-minute structured one-to-one education sessions	UK Secondary care Mild to severe asthma Stratum: 1–5 years Age (months) – Median (IQR): SM package – 32 (18–61); usual care – 32 (14–61). Inclusion criteria: aged 10 months to 5 years at the time of admission to a children's ward or attendance at either an accident and emergency (A&E) department or the children's (emergency) assessment unit (CAU at Leicester Royal Infirmary) with a primary diagnosis of acute severe asthma or wheezing.	• Number of inpatient admissions Reported at 12 months	
Thoonen 2003[176]	Optimal supported self-management n=98 Patients received individual training at their GP surgery. Presence of asthma symptoms and AM/PM peak –flow measurements were used within the action plan. Standard care n=95	The Netherlands Primary care Severity of asthma not reported. Stratum: ≥16 years Age - Mean (SD): SM package- 39.6 (11.2); usual care - 39.3 (12.0) Inclusion criteria: Treated for asthma by the GP; aged 16–60 years; FEV	• Severe asthma exacerbations (requiring OCS) • Quality of life (AQLQ) Reported at 24 months	Study defined severe exacerbations as: number of oral prednisolone courses per patient per 2 years.

Study	Intervention and comparison	Population	Outcomes	Comments
	Patients received usual care from their GP. Inhaler technique was assessed.	>40% of predicted value and >55% of predicted value 15 minutes after inhalation of 800 µg salbutamol metered dose inhaler or 6 weeks after inhalation of 800 µg budesonide twice daily; FEV_1 reversibility (after bronchodilation with 800 µg salbutamol metered dose inhaler or 8 weeks treatment with 800 µg budesonide twice daily) of at least 10% of the predicted value or PC20 histamine of 8 mg/mL		

10.1.1.1.1 *People aged over 16 years*

Table 132: Clinical evidence summary: Optimal self-management package versus standard care

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with Usual care (>16)	Risk difference with Self-Management package (95% CI)
Quality of life (AQLQ, 1–7, higher is better outcome)	215 (2 studies) 9 months	LOW[a] due to risk of bias	-	The mean quality of life (AQLQ) in the control groups was 4.65	The mean quality of life (AQLQ) in the intervention groups was 0.38 higher (0.32 to 0.45 higher)
Total number of serious exacerbations	324 (2 studies) 15 months	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 1.05 (0.72 to 1.52)	232 per 1000	12 more per 1000 (from 65 fewer to 121 more)
Total number of serious exacerbations per patient	223 (2 studies) 12 months	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	The mean serious exacerbations per patient in the control groups was 0.95	The mean serious exacerbations per patient in the intervention groups was 0.53 lower (0.84 to 0.22 lower)
Total number of hospital admissions	351 (4 studies) 9 months	MODERATE[b] due to inconsistency	RR 0.35 (0.21 to 0.58)	318 per 1000	207 fewer per 1000 (from 134 fewer to 251 fewer)
Total number of hospital admissions per patient	245 (2 studies) 12 months	VERY LOW[a,b] due to risk of bias, inconsistency	-	The mean total number of hospital admissions per patient in the control groups was 0.47	The mean total number of hospital admissions per patient in the intervention groups was 0.01 higher (0.09 lower to 0.1 higher)
% predicted FEV_1	74 (1 study)	VERY LOW[a,c] due to risk of bias,	-	The mean % predicted FEV_1 in the control groups was	The mean % predicted FEV_1 in the intervention groups was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care (>16)	Risk difference with Self-Management package (95% CI)
	12 months	imprecision		79	6.1 higher (2.67 lower to 14.87 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the measure if I^2 50–75%, downgraded by 2 increments if I^2 greater than 75%
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

10.1.1.1.2 People aged 5–16 years

Table 133: Clinical evidence summary: Optimal self-management package versus standard care

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care (5–16)	Risk difference with Self-Management package (95% CI)
Quality of life (PAQLQ, 1–7, higher is a better outcome)	588 (3 studies) 10.3 months	LOW[a,b] due to risk of bias, indirectness	-	-[e]	The mean quality of life in the intervention groups was 0.18 higher (0.03 to 0.34 higher)
Total number of hospital admissions	209 (2 studies) 6.5 months	VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision	RR 1.21 (0.44 to 3.13)	60 per 1000	13 more per 1000 (from 34 fewer to 128 more)
Total number of hospital admissions per patient	345 (1 study) 12 months	MODERATE[b] due to indirectness	-	The mean total number of hospital admissions per patient in the control groups was 0.23	The mean total number of hospital admissions per patient in the intervention groups was 0.19 lower

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care (5–16)	Risk difference with Self-Management package (95% CI)
					(0.37 to 0.01 lower)
Total number of serious exacerbations	90 (1 study) 12 months	VERY LOW[b,d] due to indirectness, imprecision	RR 0.82 (0.3 to 2.25)	159 per 1000	29 fewer per 1000 (from 111 fewer to 199 more)
Asthma control (ACQ, 0–6, higher is a worse outcome)	90 (1 study) 12 months	MODERATE[b] due to indirectness	-	The mean change in asthma control (ACQ) in the control groups was 0.79	The mean change in asthma control (ACQ) in the intervention groups was 0.04 higher (0.26 lower to 0.34 higher)
Peak expiratory flow rate	91 (1 study) 6 months	VERY LOW[b,d] due to indirectness, imprecision	-	The mean peak expiratory flow rate in the control groups was 83.3	The mean peak expiratory flow rate in the intervention groups was 1.97 higher (3.04 lower to 6.98 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment due to indirectness in the population or by 2 increments if further indirectness in the outcome
c Downgraded by 1 increment if I^2 50-75%, downgraded by 2 increments if I^2 greater than 75%
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
e Adjusted raw values not provided

One study, Bragt et al. 2014, was included but was not included in the meta-analysis. It reported the following quality of life measures: Overall paediatric asthma quality of life of life score at 9 months (median [IQR] SM package – 6.780.96]; usual care – 6.50.72]); asthma control measured by (ACQ) at 9 months (median [IQR] SM package – 0.1[0.5]; usual care 0.31[1.0]).

10.1.1.1.3 Children aged 1–5 years

Table 134: Clinical evidence summary: Optimal self-management package versus standard care

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care (< 5)	Risk difference with Self-management package (95% CI)
Total number of hospital admissions	187 (1 study) 12 months	LOW[a,b] due to risk of bias, imprecision	RR 1.4 (0.83 to 2.35)	211 per 1000	84 more per 1000 (from 36 fewer to 285 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

10.1.1.2 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review.[157] This is summarised in the health economic evidence profile below (Table 135) and the health economic evidence tables in Appendix I.

Two economic studies relating to this review question were identified but were excluded due to methodological limitations and the availability of more applicable evidence. [54 ,180] This is listed in Appendix M, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix F.

Table 135: Health economic evidence profile: Usual care versus self-management in adults

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Schermer 2002 [157] Netherlands	Partially applicable [(a)]	Potentially serious limitations [(b)]	CUA within-trial analysis (RCT) Population: People with asthma aged 16–60 years old who were being treated with inhaled steroids. Two comparators: 1) Usual care (no self-management) 2) Self-management package, education and review Time horizon: 2 years	**Total costs (mean per patient):** £146	**QALYs (mean per patient):** 0.015	£9,733 per QALY gained	Sensitivity analysis was undertaken from a societal perspective including productivity costs. Using a cost-effectiveness acceptability curve the study found that self-management is cost-effective 52% of the time compared to usual care.

Abbreviations: CUA: cost-utility analysis; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

(a) Costs and effects were not discounted. Time horizon only 2 years not capturing full effect. Rating scale, not using standard gamble or time-trade off approach, used to capture QALYs. Netherlands healthcare perspective

(b) Cost-effectiveness plane and probability intervention cost-effective using societal perspective only. QALYs only reported as final total rather than difference between baseline and follow-up scores

10.1.1.3 Evidence statements

10.1.1.3.1 Clinical

People aged over 16:

- An optimal self-management package versus usual care resulted in a clinically important benefit for the total number of serious exacerbations per patient (2 studies, Very Low quality); total number of hospital admissions (4 studies; Moderate quality); and % predicted FEV_1 (1 study, Very Low quality).
- An optimal self-management package versus usual care resulted in no clinically important difference for quality of life as measured by AQLQ (2 studies, Low quality); total number of serious exacerbations (2 studies, Very Low quality); and total number of hospital admissions (2 studies, Very Low quality).

People aged 5–16 years:

- An optimal self-management package versus usual care resulted in a clinically important benefit for the total number of serious exacerbations (1 study, Very Low quality).
- An optimal self-management package versus usual care resulted in a clinically important harm for the total number of hospital admissions (2 studies, Very Low quality).
- An optimal self-management package versus usual care resulted in no clinically important difference for quality of life as measured by PAQLQ (3 studies, Low quality); the total number of hospital admissions per patient (1 study, Moderate quality); asthma control as measured by ACQ (1 study, Moderate quality); and the peak expiratory flow rate (1 study, Very Low quality).
- Narrative evidence was presented for the following outcomes: quality of life as measured by PAQLQ (1 study at 9 months) and asthma control as measured by the ACQ (1 study at 9 months).

Children aged 1–5 years:

- An optimal self-management package versus usual care resulted in a clinically important harm in the total number of hospital admissions (1 study, Low quality).

10.1.1.3.2 Economic

- One cost–utility analysis found that supportive self-management asthma action plans were cost effective at a £20,000 per QALY threshold, relative to not using them (ICER: £9,733 per QALY). This analysis was assessed as partially applicable with potentially serious limitations.

10.1.1.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80

Research recommendation	5. What is the most clinically and cost-effective method of delivering an asthma self-management package?
Relative values of different outcomes	The committee considered the following outcomes as critical for this review: severe asthma exacerbations (defined as an asthma exacerbation requiring the use of oral corticosteroids), mortality and quality of life. The following outcomes were considered important: asthma control (as measured by a validated questionnaire), hospital admission, SABA use, lung function (FEV_1 or morning PEF) and adverse events (linear growth, infection, adrenal insufficiency, and infection [all or serious infections]).
Trade-off between clinical benefits and harms	In people aged 16 and over, an optimal self-management package (including asthma education, monitoring advice, inhaler technique and an individualised action plan) offered to people with a clinical diagnosis of asthma was considered to have a clinically important benefit for total number of serious exacerbations per patient; total number of hospital admissions; and % predicted FEV_1. No difference was seen in quality of life as measured by AQLQ; the total number of serious exacerbations; and the total number of hospital admissions. In young people and children aged 5–16 years, an optimal self-management package offered to people with a clinical diagnosis of asthma was considered to have a clinically important benefit for total number of serious exacerbations. There was no difference in quality of life as measured by the PAQLQ; total number of hospital admissions per patient; and asthma control as measured by ACQ. Clinical harm was seen in the total number of hospital admissions. In children aged 1–5 years, an optimal self-management package offered to the parents or carers of children with a clinical diagnosis of asthma was considered to have a clinically important harm for total number of hospital admissions. No evidence was found for the following outcomes: mortality, SABA use, and adverse events. The committee decided to make an 'offer' recommendation on the provision of self-management packages. They discussed the supposedly contradictory results around exacerbations and hospital admission. They recognised that the intervention itself was not harmful and that an increase in hospital admissions could be a result of parents being better educated, and therefore able to recognise signs of an exacerbation and when referral was necessary. The reverse is seen in adults and likewise the committee supposed this to be a result of increased confidence and patient autonomy. Although the quality of life did not improve directly as a result of offering the package, the committee reasoned that quality of life should increase indirectly as management of asthma improved; longer follow-up times in the studies may have captured this. The committee were concerned that the studies underpinning the recommendation were heterogeneous in the content of the package provided, the site of delivery and the person delivering the supportive care. They agreed that further research needs to be done to analyse the characteristics of the optimum package. Therefore, they put forward the above research recommendation. Research in this area would preferably be carried out in the UK to better reflect current practice across primary, secondary and tertiary sectors.

Trade-off between net clinical effects and costs	One economic study was identified as relevant. This showed that self-management was cost effective with an ICER below £20,000 per QALY. The committee noted that the makeup of the intervention within the study was very resource intensive, involving a high number of primary care visits. They felt that this was the top end of the spectrum of resource use associated with implementing self-management. The committee also noted the uncertainty around the quality of life measurements within the study. The committee noted that the main resource implication was within primary care. This would involve additional time to educate people about their PAAP from a GP or specialist asthma nurse. However, it may be possible to extend time at an annual asthma review to capture this in line with the annual review. The committee discussed the variability in self-management plans and inconsistency in how they are applied within current practice. They therefore noted that the resource use associated with self-management is also variable, leading to uncertainty around the cost effectiveness of how self-management plans are currently applied. They therefore decided to make a research recommendation to find the most cost-effective application of asthma self-management. However, the committee felt that the additional resource use in any self-management plan, increased primary care time and appropriate asthma medication, would be outweighed by clinical outcomes and is likely to be cost effective.
Quality of the clinical evidence	For the comparison of an optimal self-management package versus usual care, in people aged 16 and over, the quality of evidence ranged from Very Low to Moderate quality; the majority of the evidence being of Very Low quality. For the comparison of optimal self-management package versus usual care, in young people and children aged 5–16, the quality of the evidence range from Very Low to Moderate. For the comparison of optimal self-management package versus usual care, in children aged 1–5 years only one study of Low quality was available. No evidence was found for mortality, SABA use and adverse events; for all other outcomes at least one study was available. The committee noted that there was very little evidence available in the under 5 population. The committee felt that self-management packages are still likely to be beneficial in this population, although the degree of benefit may vary compared to the older populations. On the basis of this consensus the committee felt that it was appropriate to recommend the consideration of self-management packages in this age group.
Other considerations	The committee was concerned with the potential resource implications of offering an asthma action plan and reviewing the plan within the annual asthma review. The committee discussed the time currently allocated to conduct a review and was concerned that it may impact negatively on GP practice due to additional time pressures. Currently in practice, the attendance of the asthma annual review meeting is poor.[153] Increasing the length of the consultation may further reduce attendance. The committee also recognised that the standard of practice and resource use between asthma clinics, outpatient services and GP practices varies greatly. The committee noted that the burden of implementation would fall mostly on primary care. The committee also noted that although there may be increased upfront costs, there is potentially an offset in savings from the recommendation (for example a reduction in hospitalisations).

The committee discussed the way in which the package is offered, citing one included study[149] which delivered the package through an online interface. The committee felt that the information should be tailored according to the persons' needs, taking into consideration their capacity or ability to care for themselves. The committee noted that efforts would need to be made to address any possible inequalities arising for subgroups such as those with learning disabilities.

The committee noted that many of the included studies had populations of asthmatics with moderate to severe asthma and that the severity of asthma may influence the level of engagement in the package. The committee discussed this and agreed that some degree of benefit would be expected in all severities of asthma and there is insufficient evidence to justify separate recommendations for separate subgroups.

The committee noted that the weaker recommendation for using self-management packages in children was purely due to the weaker body of evidence. On the basis of their clinical experience the committee expected that self-management packages should have a similar risk to benefit profile for those under the age of5 as those over the age of 5. However the committee did not consider the body of evidence in these age groups to be of high enough quality to justify a strong recommendation.

The committee noted that there is evidence in other conditions that when people are supported to develop their own plans in partnership with healthcare professionals, they are more likely to follow the plans.

This section was partially updated in 2020. See (need to insert link) for the 2020 evidence review

11 Dose variation within self-management plans

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng80/evidence for the 2020 evidence review on increasing ICS treatment within supported self-management for children and young people.

11.3 Introduction

A key recommendation of the National Review of Asthma Deaths (Levy et al., 2014) report and British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) is that all patients with a confirmed clinical diagnosis of asthma should be offered a written personalised asthma action plan (PAAP). Asthma UK reported in 2015 that people with asthma are four times more likely to have an asthma attack requiring emergency hospital treatment if they do not have a PAAP. The body of evidence supporting self-management plans has been reviewed elsewhere in this guideline (see Chapter 10).

The aim of PAAPs is to enable patients with asthma to gain a better understanding and control of their asthma by recognising and avoiding known triggers where possible and to recognise, understand and safely titrate their treatment according to worsening or improving symptoms. A PAAP should be developed in conjunction with the clinician using the individual person's experience of their asthma symptoms to inform its content. Plans will differ from one individual with asthma to another. They should be reviewed annually with the clinician or when the person with asthma experiences uncontrolled symptoms of asthma, unscheduled secondary care or an asthma attack.

For a number of years people with asthma were encouraged, as part of their PAAP, to double their preventer inhalers for a limited period of time when their asthma becomes symptomatic. While the evidence in favour of self-management plans as a whole is favourable, some doubt has been cast on the benefit of this short-term increase. The aim of the current review is to assess whether this intervention is effective.

11.1.1 Review question: What is the optimal increase in ICS preventer therapy within supported self-management when control is lost?

For full details see review protocol in Appendix C.

Table 136: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma who are receiving preventer therapy as part of a personalised asthma action plan.
Interventions	Self-initiated increase in the dose of preventer ICS as part of a PAAP at the onset of asthma exacerbations • >1–2x increase in dose • >2–3x increase in dose • >3–4x increase in dose • >4x increase in dose
Comparison	Compared to any other increase or keeping the usual maintenance dose of ICS as part of a PAAP at the onset of asthma exacerbations.

Outcomes	**Critical outcomes:** • Subsequent asthma exacerbations • Treatment failures

	• Mortality • Quality of life **Important outcomes:** • Asthma control • Hospital admissions • Reliever medication use • Lung function • Adverse events
Study design	RCTs

11.1.1.1 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of varying levels of ICS dose increase within a personalised asthma action plan at the onset of an asthma exacerbation.

Studies implementing an adjustable maintenance dose (AMD) regimen were not included in this review due to their potential for ICS dosages to both increase and decrease at variable rates.

Studies randomised participants to plans which varied in their response to pre-specified signs of mild exacerbation. Outcomes were only extracted for those participants who experienced a mild exacerbation during the treatment period.

Six studies were included in the review; [120 51 49 64 ,148 193] these are summarised in Table 137 below. Three studies compared doubling ICS dose at the onset of an exacerbation to maintaining fixed dose in people over the age of 16; one study compared quadrupling ICS dose to maintaining fixed dose in people over the age of 16; one study compared quintupling ICS dose to maintaining fixed dose in people over the age of 16; and one study compared octupling, quadrupling and doubling ICS dose at the onset of an exacerbation for children and young people aged 5–16.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 138, Table 139, Table 140, Table 141, Table 142 and Table 143). See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Table 137: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
FitzGerald 2004[49]	Doubling dose: n=142, using low to moderate dose ICS daily; in response to PEF changes, increased bronchodilator use, or nocturnal awakenings – dose doubled for 14 days Fixed dose: n=148,	Age stratum: >16 ICS low to high dose at baseline 34% experienced PEF changes increased bronchodilator use, or nocturnal awakenings during study period	• Treatment failure – severe exacerbations (requiring OCS within 14 days of first mild exacerbation) • Treatment failure - (unscheduled visit/PEF remains low/symptoms persist at end of	

Study	Intervention and comparison	Population	Outcomes	Comments
	using low to moderate dose ICS daily; in response to exacerbation – addition of placebo inhaler to baseline ICS		14 days of treatment) • Exacerbations (subsequent exacerbation in 3 months after index) Followed up for 6 months	
Foresi 2000[51]	Quintupling dose: n=67, 100 ug budesonide twice daily with addition of 200 ug budesonide four times daily, for 7 days, in response to PEF changes Fixed dose: n=75, 100 ug budesonide twice daily with addition of placebo four times daily for 7 days, in response to PEF changes	Age stratum: >16 ICS moderate to high dose at baseline 25% experienced PEF changes during study period	• Exacerbation (subsequent exacerbation after index) Followed up for 6 months	
Harrison 2004[64]	Doubling dose: n=192, baseline dose from 100 to 2000 ug ICS per day, in response to PEF or symptom score changes, dose doubled for 14 days Fixed dose: n=198, baseline dose from 100 to 2000 ug ICS per day, in response to PEF or symptom score changes addition of placebo inhaler to baseline ICS	Age stratum: >16 ICS low to high dose at baseline 53% experienced PEF or symptom score changes during study period	• Severe exacerbations (subsequent exacerbation after index) Followed up for 12 months	
Oborne 2009[120]	Quadrupling dose: n=197, baseline dose from 200 to 1000 ug ICS per day,	Age stratum: >16 ICS low to high dose at baseline	• Severe exacerbations (subsequent exacerbation after	

Study	Intervention and comparison	Population	Outcomes	Comments
	in response to PEF changes, ICS dose quadrupled for 7 days, continued for additional 7 days if no return to baseline PEF Fixed dose: n=206, baseline dose from 200 to 1000 ug ICS per day, in response to PEF changes, addition of placebo inhaler to baseline ICS	23% experienced PEF changes during study period	index) Followed up for 12 months	
Rice-McDonald 2005 [148]	Doubling dose: n=18, in response to nocturnal awakenings, increased SABA use, symptoms necessitating cessation of usual activities of daily living, or PEF changes, doubling daily ICS dose for 14 days. Fixed dose: n=18, continuing usual ICS dose at the same number of inhalations with a placebo inhaler for 14 days.	Age stratum: >16 Data for those who underwent treatment period presented. Baseline ICS dose not reported	• Treatment failure - (PEF remains low/symptoms persist/withdrawal due to adverse event at end of 14 days of treatment) Follow up duration unclear	Cross-over trial
Yousef 2012[193]	Octupling dose: n=66, in response to PEF change or persistent cough/wheeze unresolved by SABA, dose octupled for 12 days Quadrupling dose:	Age stratum: 5–16 ICS/ICS+LABA low to high dose at baseline 42% experienced PEF change or persistent cough/wheeze unresolved by SABA during study period	• Severe exacerbations (requiring OCS following treatment period) Follow up duration unclear	Doubling dose upon PEF change or persistent cough/wheeze used as control.

Study	Intervention and comparison	Population	Outcomes	Comments
	n=70, in response to PEF change or persistent cough/wheeze unresolved by SABA, dose quadrupled for 12 days Doubling dose: n=61, in response to PEF change or persistent cough/wheeze unresolved by SABA, dose doubled for 12 days			

Table 138: Clinical evidence summary: Doubling compared to fixed dose for adults (>16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fixed dose	Risk difference with Doubling (95% CI)
Severe exacerbations (subsequent exacerbation after index)	207 (1 study) 12 months	VERY LOW[a,b,c] due to indirectness, imprecision	RR 0.76 (0.44 to 1.32)	227 per 1000	54 fewer per 1000 (from 127 fewer to 73 more)
Exacerbations (subsequent exacerbation in 3 months after index)	69 (1 study) 12 months	VERY LOW[c,d] due to risk of bias, imprecision	RR 0.86 (0.29 to 2.55)	171 per 1000	24 fewer per 1000 (from 122 fewer to 266 more)
Treatment failure (requiring OCS within 14 days of first mild exacerbation)	98 (1 study) 12 months	LOW[c] due to imprecision	RR 1.51 (0.70 to 3.25)	173 per 1000	88 more per 1000 (from 52 fewer to 389 more)
Treatment failure (unscheduled visit/PEF remains low/symptoms persist at end of 14 days of treatment)	98 (1 study) 12 months	LOW[c] due to imprecision	RR 0.66 (0.28 to 1.53)	231 per 1000	78 fewer per 1000 (from 166 fewer to 122 more)
Treatment failure (symptoms fail to improve/PEF remains low/withdrawal due to adverse event at 14 days)	36 (1 study) unclear	LOW[b] due to imprecision	RR 1 (0.59 to 1.68)	611 per 1000	0 fewer per 1000 (from 251 fewer to 416 more)

a Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis
b Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 139: Clinical evidence summary: Quadrupling compared to fixed dose for adults (>16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fixed dose	Risk difference with Quadrupling (95% CI)
Severe exacerbations (subsequent exacerbation after index)	94 (1 study) 12 months	MODERATE[a] indirectness	RR 0.43 (0.24 to 0.78)	500 per 1000	285 fewer per 1000 (from 110 fewer to 380 fewer)

a Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

Table 140: Clinical evidence summary: Quintupling compared to fixed dose for adults (>16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fixed dose	Risk difference with Quadrupling (95% CI)
Exacerbation (subsequent exacerbation after index)	36 (1 study) 6 months	VERY LOW[a,b,c,d] due to risk of bias, imprecision	RR 1.43 (0.57 to 3.57)	292 per 1000	125 more per 1000 (from 125 fewer to 750 fewer)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 or 2 increments because of heterogeneity, I^2>50%, p=0.03, unexplained by subgroup analysis.
c Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 141: Clinical evidence summary: Quadrupling compared to doubling dose for young people (aged 5–16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Doubling	Risk difference with Quadrupling (95% CI)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Doubling	Risk difference with Quadrupling (95% CI)
Severe exacerbations (subsequent exacerbations following index)	54 (1 study) follow-up unclear	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.8 (0.12 to 5.27)	83 per 1000	17 fewer per 1000 (from 73 fewer to 356 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 142: Clinical evidence summary: Octupling compared to doubling dose for young people (aged 5–16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Doubling	Risk difference with Octupling (95% CI)
Severe exacerbations (subsequent exacerbations following index)	54 (1 study) follow-up unclear	VERY LOW[a,b] due to risk of bias, imprecision	OR 0.11 (0.01 to 1.82)	83 per 1000	73 fewer per 1000 (from 82 fewer to 59 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 143: Clinical evidence summary: Octupling compared to quadrupling dose for young people (aged 5–16) with asthma

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Quadrupling	Risk difference with Octupling (95% CI)
Severe exacerbations (subsequent exacerbations following index)	58 (1 study) follow-up unclear	VERY LOW[a,b] due to risk of bias, imprecision	OR 0.14 (0.01 to 2.29)	67 per 1000	57 fewer per 1000 (from 67 fewer to 74 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Quadrupling	Risk difference with Octupling (95% CI)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

11.1.1.2 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix F.

11.1.1.3 Evidence statements

11.1.1.3.1 Clinical

Doubling compared to fixed dose in adults

- Clinically important benefit of doubling dose in terms of severe exacerbations (subsequent exacerbations after index) from 1 study with 207 participants, Very Low quality evidence due to indirectness and imprecision.
- Clinically important benefit of doubling dose in terms of exacerbations (subsequent exacerbations in 3 months after index) from 1 study with 69 participants, Very Low quality evidence due to risk of bias and imprecision.
- Clinically important harm of doubling dose in terms of treatment failure (requiring OCS within 14 days of first mild exacerbation) from 1 study with 98 participants, Low quality evidence due to imprecision.
- Clinically important benefit of doubling dose in terms of treatment failure (unscheduled visits/PEF remaining low/symptoms persisting after 14 days) from 1 study with 98 participants, Low quality evidence due to imprecision.
- No clinically important difference of doubling dose in terms of treatment failure (PEF remaining low/symptoms persisting/participants withdrawing due to symptoms or adverse event after 14 days) from 1 study with 18 participants, Low quality evidence due to imprecision.

Quadrupling compared to fixed dose in adults

- Clinically important benefit of quadrupling dose in terms of severe exacerbations (subsequent exacerbations after index) from 1 study with 94 participants, Moderate quality evidence due to indirectness.

Quintupling compared to fixed dose in adults

- Clinically important harm of quintupling dose in terms of exacerbations (subsequent exacerbations after index) from 1 study with 94 participants, Very Low quality evidence due to risk of bias and imprecision.

Quadrupling compared to doubling in young people and children aged 5–16

- Clinically important benefit of quadrupling dose in terms of severe exacerbations (subsequent exacerbations after index) from 1 study with 54 participants, Very Low quality evidence due to risk of bias and imprecision.

Octupling compared to doubling in young people and children aged 5–16

- Clinically important benefit of octupling dose in terms of severe exacerbations (subsequent exacerbations after index) from 1 study with 54 participants, Very Low quality evidence due to risk of bias and imprecision.

Octupling compared to quadrupling in young people and children aged 5–16

- Clinically important benefit of octupling dose in terms of severe exacerbations (subsequent exacerbations after index) from 1 study with 58 participants, Very Low quality evidence due to risk of bias and imprecision.

11.1.1.3.2 Economic

- No relevant economic evaluations were identified.

11.1.1.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80
Relative values of different outcomes	The committee considered the following outcomes as critical for this review: subsequent severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality, treatment failure and quality of life. The committee considered the following outcomes as important: asthma control (as assessed by a validated questionnaire), hospital admission, reliever medication use, lung function (FEV_1 or morning PEF) and adverse events.
Quality of the clinical evidence	The quality of evidence identified in the review ranged from Moderate to Very Low quality, and the majority of outcomes were Low or Very Low quality evidence. There was little information available for the majority of the pre-specified outcomes. In general the studies involved relatively small participant numbers; this is partly because only those whose asthma deteriorated during the study, and were therefore eligible for a brief increase in ICS dose, could contribute meaningful outcomes. The committee considered that the evidence was of sufficient quality to justify increasing ICS as part of a self-management plan. The committee noted there was less evidence to justify recommending a specific dose. There were no direct comparisons between different dose increases in the adult population. The committee noted that the majority of the evidence came from an adult population, but felt that it was reasonable to extrapolate this data to the younger population. There may be some non-specific benefits of having a PAAP and being enrolled in a study, irrespective of the ICS dose adjustment, for example better adherence to the daily fixed dose. This effect may lessen the observable difference between increasing

	dose and maintaining a fixed dose (where a placebo inhaler is used).
Trade-off between clinical benefits and harms	Generally across the studies included in this review there was a clinically important benefit in increasing ICS dose during periods of mild exacerbation in terms of both subsequent exacerbations (either severe or non-severe) and in terms of treatment failure rates. In children aged 5–16 years, there was a hint of a dose response effect with octupling dose appearing to be more effective than quadrupling dose, which was in turn more effective than doubling dose. No studies reported outcomes related to adverse events and harms of using higher ICS doses for short periods of time. The committee considered that the consistent direction of the evidence supported a recommendation to increase ICS dose within the context of a PAAP during times of mild exacerbation. The short-term increase in ICS dose was unlikely to have significant adverse events, and when compared with the potential exposure to the alternative, oral steroids, would be safer. However, it is important to emphasise the temporary nature of the increase in dose; people should not be left on these higher doses for prolonged periods without discussing with a healthcare professional. The evidence gathered used periods ranging from 7–14 days for their higher ICS dose episodes. The committee chose to recommend 7 days as they wanted to keep unnecessarily high dose to a minimum, and at the end of 7 days the potential for further management options could be reviewed. The committee noted that it would be appropriate to quadruple baseline ICS dose as part of a self-management plan. However the committee was keen to emphasise that the increase should not exceed licensing limits. Although these limits are intended for chronic use of inhalers, the body of evidence was not strong enough to justify a deviation from these limits even in the acute setting. With the restriction to maximum licensed dose and the short length of dose increase, the committee considered that quadrupling dose represented the best trade-off between practicality, benefits and potential harms.
Trade-off between net clinical effects and costs	No economic evaluations were identified for this review. The committee considered the cost implications of self-administered increases in ICS dose. The average cost of a puff from a 100 mcg ICS inhaler was found to be £0.05. An individual on a low dose ICS regimen would be on 400 mcg a day, meaning the cost per day would be £0.20. Quadrupling this dose would mean increasing this cost to £0.80 a day for 7 days, totalling an additional £4.20 on top of the £1.40 from regular therapy. The committee felt that without self-administered dose increases the individual would be much more likely to have an unscheduled GP appointment costing £37. They therefore felt the additional cost associated with medication could potentially be cost saving in reducing unscheduled resource utilisation and would also offer faster relief of symptoms, making it likely to be cost effective none the less. Limited evidence was available on efficacy of different dose increases and no formal economic evaluations were found. Therefore the committee chose to make a weaker recommendation on what the recommended dose increase should be.
Other considerations	The committee noted that due to the dose response curve of ICS in asthma, it may be expected that those using relatively low ICS doses at baseline may benefit more than those using relatively high ICS doses at baseline. The committee noted that one study[51] contained outcomes (for example total length of days on oral steroids) which were not presented in a way that met the review protocol but which supported a clinical benefit of increasing ICS dose as opposed to maintaining a fixed dose. The committee noted that self-management plans should contain some guidance to prevent people with asthma from taking repeated courses of increased doses of ICS

without discussing their condition with a healthcare professional.

12 Decreasing regular maintenance therapy

12.3 Introduction

Most current guidelines suggest that once a person's asthma has been well controlled for a period of time their treatment should be reduced, but often this process is not implemented. People with asthma are keen to be on the lowest level of therapy needed to control their asthma due to the potential dose-related side effects of therapy, particularly of inhaled corticosteroids and particularly in children. Healthcare professionals would also agree with this. However, there is also often concern from both healthcare professionals and patients about the risk of relapse into poor asthma control or recurrence of exacerbations.

A lack of clarity remains over when and how to step down therapy in a way which allows the lowest dose possible to maintain control, without relapse. Undoubtedly, the decision to step down should be made collaboratively between the healthcare professional and the patient with a clear plan for review as well as earlier escalation plans should asthma control deteriorate. The decision would ideally be based on proven indicators of disease stability, and the committee therefore wished to see whether there is any clinical research data which would allow reasonable prediction of successful treatment step-down.

12.1.1 Review question: What are the clinical features (symptoms and/or objective measures) which indicate that a step down in treatment is appropriate?

For full details see review protocol in Appendix C.

Table 144: Characteristics of review question

Population	People with a clinician diagnosis of asthma on regular preventer therapy that can be stepped down.
	
	Population strata:
	• Age:
	  ○ <1 years
	  ○ 1-5 years
	  ○ 5 to <16 years
	  ○ ≥16 years
	
	Evidence will be pooled together regardless of the starting step of preventer medication (in other words people stepped down from ICS therapy will be pooled with people stepped down from ICS+LABA therapy).

Prognostic variable/s under consideration	• Duration for which asthma has been controlled on current therapy • Recent asthma exacerbation versus no recent asthma exacerbation • Use of reliever medication • FeNO • ACQ score • ACT score
Confounding factors	All the other listed prognostic factors.
Outcomes	Step down successful (dichotomous outcome) – controlled according to BTS/SIGN

	guidelines after 4 weeks or more without the need to step back up or without asthma exacerbations. Statistical outputs may include: Sensitivity, specificity, PPV, NPV, AUC OR/RR/HR
Study design	Prospective cohorts, retrospective cohort, randomised trials (if appropriate, such as randomised to step down after >6 months control versus <6 months control) Systematic reviews of the above

12.1.1.1 Clinical evidence

A search was conducted for prospective cohort, retrospective cohort, and randomised trials to identify the clinical features associated with successful step down of treatment using a prognostic approach (association of the features with the outcome of successful step down or accuracy of using features to predict success or failure of step down).

No prognostic risk tool is known to exist for predicting the likelihood of successful step down of therapy in an individual with asthma. Therefore, the committee wished to know if certain factors are likely to influence prognosis, in order to recommend that step down of therapy is initiated in people with these factors (or clinical features). The aim is to estimate the prognostic value of the following factors:

- Duration for which asthma has been controlled on current therapy
- Recent asthma exacerbation versus no recent asthma exacerbation
- Use of reliever medication
- FeNO
- ACQ score
- ACT score

Four studies were included in the review; [88 ,95 ,143 ,196] these are summarised in Table 145. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 146, Table 147 and Table 148). See also the study selection flow chart in Appendix E, clinical evidence tables in Appendix H and excluded studies list in Appendix L.

Table 145: Summary of studies included in the review

Study	Population	Step-down method	Analysis	Prognostic variable(s)	Outcomes
Koskela 2016[88]	Single cohort of subjects with well controlled asthma; defined as no courses of oral corticosteroids or hospital admissions due to asthma within one year of trial. Physician diagnosis of asthma with objective diagnosis for at least 2 years and at least 6 months of combination therapy (ICS+LABA) at constant dose. n=55 Mean age: 58.8 Step-down failure (n): 29	2-week run-in phase during which combination asthma medication was maintained, followed by discontinuation of LABA (step one) and continuation of previously prescribed ICS for six weeks, followed by those with daily ICS dose of >400 ug budesonide or equivalent halving their dose (step two) and continuing for six weeks (those with daily dose of ≤400 ug budesonide progressed directly from step one to step 3); after this ICS was discontinued (step 3) and subjects were followed up for 6 weeks. (total step downs, n=126)	Risk prediction data presented; sensitivity/specificity PPV/NPV	Asthma control (ACQ-6) • Score of ≥0.15 versus score of <0.15 Asthma control (ACQ-7) • Score of ≥0.29 versus score of <0.29 Cut-off point for tests selected retrospectively from ROC curves	Exacerbation and failure of step-down therapy was defined as: awakening at night due to asthma symptoms during 2 consecutive nights; PEF less than 3 standard deviations from the mean value obtained during run-in on 3 consecutive days; bronchodilator use more than once on 3 consecutive days; if the subject felt his/her symptoms had clearly increased.
Li 2008[95]	Single cohort of children (aged 6–18) with stable asthma; defined as no disease exacerbations in the preceding 4 weeks necessitating oral corticosteroid or an increase in the dosage of ICS; and use	2-week run in phase during which asthma medication was maintained; followed by an ICS reduction phase where current ICS dose of subjects with stable asthma was halved every 8 weeks. ICS treatment was	Receiver operating characteristic (ROC) curve was used to examine which marker best predicted an asthma exacerbation, calculating the trade-offs between specificity and sensitivity at different cut-	FeNO • ROC curve – AUC Thresholds recorded • >82ppb • >108ppb • >137ppb	Exacerbation and failure of step-down therapy was considered to have occurred if the child had one or more of: daytime symptom score of >3 points or night-time score of >1 compared with baseline on

Study	Population	Step-down method	Analysis	Prognostic variable(s)	Outcomes
	of rescue treatment less than three times a week. Current therapy of ICS for at least 3 months preceding trial. n=50 Mean age: 11.8 Step-down failure (n): 11	discontinued when daily dose 200 ug BDP, or 100 ug FP was reached after successive reductions.	off values.		two consecutive days, or use of bronchodilator rescue medication <3 occasions per week for breakthrough asthma symptoms.
Rank 2015 [143]	Single cohort of patients identified using the Optum Labs Data Warehouse. Patients with a step-down of asthma medication and medical coverage overseeing 1 year before and 2 years following the step down. No stated restrictions on current preventer therapy. n=26,292 Step-down failure (n): 22,744	A step-down event was described as a ≥50% decrease in days supplied of controller medications from one 4-month evaluation period to the next (inclusive of step-down that occurred without healthcare provider guidance or as a consequence of medication adherence lapse).	Study outcome data used to calculate risk prediction; sensitivity/specificity* *risk prediction data not reported by study	Duration of asthma control • ≤3 months versus >3 months • ≤7 months versus >7 months • ≤11 months versus >11 months	Exacerbation and failure of step-down therapy was defined as an inpatient visit, ED visit, dispensing of a systemic corticosteroid linked to an asthma visit, having ≥2 rescue inhaler claims in a 4-month period, or returning to baseline controller therapy.
Zacharasiewicz 2005 [196]	Single cohort of children (aged 6–17) with paediatric respiratory physician diagnosis of asthma on a constant ICS dose. Stable asthma for >2 months; defined bronchodilator use <3 times a week for preceding 2 months. n = 40 Mean age: 12 Step-down failure (n): 15	ICS dose was reduced, and a follow-up visit was scheduled 2 months later unless an exacerbation or loss of asthma control occurred. In the majority of cases (85%) the dose was reduced by half, in some patients dose reduction steps were by 25% only, mainly due to a past history of severe exacerbations. Further reduction of ICS	Risk prediction data presented; sensitivity/specificity PPV/NPV	FeNO • ≥22ppb • ≥32ppb	Loss of asthma control was defined as the use of bronchodilators more than five times per week, (apart from use before, during or after exercise or with a viral cold) or the need for a course of oral corticosteroids.

Study	Population	Step-down method	Analysis	Prognostic variable(s)	Outcomes
		was attempted at 2-monthly intervals if bronchodilators were used less than three times per week. No treatment change was prescribed if bronchodilators were needed on a rescue basis 3–5 times per week.			

Table 146: Clinical evidence summary: FeNO for predicting step-down failure

Index test (threshold)	Number of Participants	Quality of the evidence	Sensitivity %	Specificity %	PPV	NPV	Area under ROC (95% CI)
FeNO, ppb	Total cohort n = 50	LOW due to indirectness, imprecision	-	-	-	-	0.81 (0.69-0.91)
FeNO, ppb	Total cohort n = 40	LOW due to risk of bias, imprecision	-	-	-	-	0.74 (0.61-0.87)
FeNO ≥22ppb versus <22ppb	Total cohort n = 40	LOW due to risk of bias	78.6%	68.6%	44%	92.5%	-
FeNO ≥32ppb versus <32ppb	Total cohort n = 40	LOW due to risk of bias	71.4%	82.4%	52.6%	91.3%	-

Table 147: Clinical evidence summary: Duration of asthma control for predicting step-down failure

Index test (threshold)	Number of Participants	Quality of the evidence	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
Duration of asthma control (≤3 months versus >3 months)	Total cohort n= 26292 ≤3=7668 (29%) >3=18624 (71%)	LOW due to indirectness	31.35% (31–32)	84.84% (84–86)	92.98%	16.16%
Duration of asthma control (≤7 months versus >7 months)	Total cohort n= 26292 ≤7=11901 (45%) >7=14391 (55%)	LOW due to indirectness	47.67% (47–48)	70.12% (69–72)	91.09%	17.29%
Duration of asthma control (≤11 months versus >11 months)	Total cohort n= 26292 ≤11=14796 (56%) >11=11496 (44%)	LOW due to indirectness	58.71% (58–59)	59.33% (58–61)	90.25%	18.31%

Table 148: Clinical evidence summary: Asthma control (ACQ-6) for predicting step-down failure

Index test (threshold)	Number of Participants	Quality of the evidence	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
ACQ-6 score (≥0.15 versus <0.15)	Total cohort n= 55 (total step downs, n=126)	VERY LOW due to risk of bias, imprecision	72% (53–87)	47% (37–58)	29%	85%

Index test (threshold)	Number of Participants	Quality of the evidence	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
ACQ-7 score (≥0.29 versus <0.29)	Total cohort n= 55 (total step downs, n=126)	VERY LOW due to risk of bias, imprecision	69% (49–85)	54% (43–64)	31%	85%

12.1.1.2 Economic evidence

Published literature

No relevant economic evaluations were identified.

One economic evaluations relating to this review question were identified but was excluded due to limited applicability. [124]These is listed in Appendix M, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix F.

12.1.1.3 Evidence statements

12.1.1.3.1 Clinical

- One study of 55 people with an asthma diagnosis showed that ACQ-6 had a sensitivity/specificity of 72/47 at a threshold score of ≥0.15; and that ACQ-7 had a sensitivity/specificity of 69/54 at a threshold score of ≥0.29. [Very Low quality]
- One study of 50 children with stable asthma indicated that FeNO measurement offers a high predictive value (AUC 0.81) for experiencing exacerbation following step-down in therapy, where high FeNO score represents a greater risk of step-down failure. [Low quality]
- One study of 40 children with stable asthma indicated that FeNO measurement offers a predictive value (AUC 0.74) for experiencing exacerbation following step-down in therapy, where high FeNO score represents a greater risk of step-down failure.[Low quality]
- One retrospective study of 26,292 people with an asthma diagnosis showed that duration of asthma control has a sensitivity/specificity of 31/85 at a threshold of ≥3months; 48/70 at a threshold of ≥7months; and 58/59 at a threshold of ≥11months for predicting step-down failure. [Low quality]
- No evidence was found for the prognostic factors of: recent asthma exacerbation versus no recent asthma exacerbation, use of rescue medication, or ACT score.

12.1.1.3.2 Economic

- No relevant economic evaluations were identified.

12.1.1.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80
Research recommendation	**6. In adults, children and young people with well controlled asthma, what are the objective measurements and prognostic factors that indicate**

	that a decrease in regular maintenance treatment is appropriate?
Relative values of different outcomes	The committee considered the following prognostic variables as potentially useful for this review: • Duration for which asthma has been controlled on current therapy • Recent asthma exacerbation versus no recent asthma exacerbation (defined as an exacerbation requiring OCS in the last year) • Use of reliever medication (SABA use) • FeNO • ACQ score • ACT score No evidence was identified for recent asthma exacerbation, use of rescue medication, ACQ score, or ACT score.
Trade-off between clinical benefits and harms	All the available evidence assessed the prognostic values of pre-specified clinical features in predicting success/failure of decreasing maintenance treatment in people taking regular preventer therapy. One study reported prognostic accuracy of duration of asthma control as a predictor of step-down failure rate. A very slight trend of increasing probability of step-down failure with lower duration of asthma control was noted, with positive predictive values ranging from 92.98%, 91.09%, and 90.25% for step-down failure at ≤3, ≤7 and ≤11 months of asthma control respectively, but these failure rates are all high and the committee were unable to use this evidence as the basis for a recommendation. Another study provided evidence for the prognostic value of FeNO in predicting exacerbations after step-down in asthma medication in children and young people. An AUC of 0.81 was reported, but only three FeNO thresholds were marked on the ROC curve: 82ppb, 108ppb, 137ppb. Given that these thresholds are all well above the normal range, and above the range expected with adequately treated asthma, the committee felt this might be more indicative of a high non-adherence rate in the study population. This could explain the reported exacerbation rate in the study, and raises doubts about the applicability of the study, given that the population in which clinicians would consider decreasing maintenance treatment would be those who were stable on regular preventer therapy. The committee felt that they were unable to use this evidence to recommend FeNO as a prognostic marker to predict success or failure of decreasing asthma medication. The final study reported prognostic accuracy outcomes for the use of ACQ (both ACQ-6 and ACQ-7). The committee noted that the sensitivity (69–72%) and specificity (47–54%) as predictors of step-down failure were relatively low for both versions of the questionnaire. These values were from thresholds chosen retrospectively from ROC curves. The committee felt that they would be unable to use this evidence to recommend ACQ as a prognostic marker.
Trade-off between net clinical benefits and costs	No economic studies were included in this review. It is likely that medication costs are cheaper on lower steps. Therefore decreasing maintenance treatment will be overall cost saving if the potential saving in medication costs outweighs any possible increase in resource utilisation. However, this will only be considered cost effective if there is also no significant clinical harm. It is therefore important that decreasing maintenance treatment is targeted at those in whom there is a reasonable chance of success, where it is more likely to be cost effective and have a positive impact on resource use.
Quality of evidence	All evidence presented was of Low quality. Both 'FeNO' and 'duration of asthma control' were downgraded for indirectness due to a lack of a physician's objective

	diagnosis of asthma. 'Duration of asthma control' was further downgraded for indirectness because the step-down process in this study was not regulated. It was a retrospective study based on pick up of prescriptions: step down occurred without healthcare provider guidance and it was not clear that the people with asthma had decided to stop treatment because they felt well-controlled or for some less clinically valid reason. In addition, it is not possible to be sure how frequently treatment was being taken even though prescriptions were being collected, and assessment of failure of step down was based on prescription data as opposed to more direct evidence of asthma control. The committee noted that in the study assessing the use ACQ-6/7 to predict success of decreasing maintenance treatment, the nature of the decrease was relatively drastic. Participants could have been taken from high dose ICS + LABA to no daily preventer therapy over the course of 18 weeks. The study did not report prediction outcomes categorised by stage of step down which limited the conclusions that the committee could reach. Due to the low quality of evidence presented the committee did not feel there was a sufficient evidence base to make specific recommendations on prognostic factors to support step down in preventer therapy. The committee therefore felt a research recommendation was appropriate, and offered a consensus opinion on current best practice.
Other considerations	The committee did not feel able to recommend the use of FeNO as a predictor of step-down failure/success based on the data provided here. They were also aware of the data from other studies of FeNO as part of routine monitoring of asthma (as detailed in the NICE Guideline on asthma diagnosis and monitoring)[110] which show mixed results in terms of benefit. However, the committee recognise the theoretical importance of airway inflammation, of which FeNO is a marker, in asthma control. They considered that there is potential value in measurement of airway inflammation, and did not feel that the evidence presented was of sufficient quality to make a recommendation against use of FeNO. The committee are aware of ongoing studies in which treatment is adjusted in response to changes in FeNO and other biological markers, and considered that similar research should be encouraged. Committee consensus was that despite the lack of supporting evidence, decreasing maintenance medication is an important process if safely achievable. It was emphasised that over-treatment with steroids holds the potential for harm in the long-run, particularly in younger people, and it is well recognised that symptoms change over time. It is therefore not the case that people should be kept on the same treatment indefinitely. The committee suggested that the possibility of decreasing maintenance treatment should be assessed at every clinical review (possibly annual review) in a patient with asthma. If a patient's asthma is deemed stable, both the clinician and the patient/carer should make an active decision based on current symptoms and lung function, but also considering any previous severe episodes of asthma, to either continue current levels of treatment or step down as a trial. There should be an active review process with follow up to determine if step down should be maintained, and there should be a clear self-management plan in place in case asthma control deteriorates. In terms of the specifics of how maintenance should be decreased, the committee did not feel it was appropriate to recommend a specific sequence but provided some general principles. The committee recommended that the choice of which maintenance treatment to stop or reduce in dose (in the case of ICS) should be made with the person with asthma and take into account the benefits and harms of each medication, as perceived by the person. The committee recommended that the last

	step of treatment reduction should be stopping ICS altogether, they did not think this would be appropriate for many people with asthma and should only be considered if the person has very little in the way of asthma symptoms on ICS low dose alone.

13 Breathing exercises in addition to pharmacological treatment

13.1 Introduction

Dysfunctional breathing is common in people with asthma. One primary care study carried out in the UK showed a prevalence of 29% of dysfunctional breathing in current asthmatics.[173] Behavioural techniques involving breathing exercises and dysfunctional breathing reduction techniques are offered as an adjunct to pharmacotherapy, alone or in addition to other complementary therapies including acupuncture and relaxation strategies. Breathing exercises vary, and may include encouragement of the daily practice of nose breathing, relaxation of the upper chest and diaphragmatic recruitment. These interventions serve to normalise breathing patterns and help to reduce hyperventilation.

Here, the evidence surrounding the clinical and cost effectiveness of breathing exercises in children, young people and adults is evaluated.

13.1.1 Review question: Are breathing exercises clinically and cost effective for children, young people and adults with asthma?

For full details see review protocol in Appendix C.

Table 149: PICO characteristics of review question

Population	People with a clinician diagnosis of asthma; in primary or secondary care **Population strata:** Age: • 5 to <16 years • ≥16 years **Exclusions:** • <5 years
Intervention	Breathing exercises: at least 1 course of treatment comprising breathing retraining/exercises. Intervention aims to control the hyperventilation symptoms of asthma, for example Papworth Method, the Buteyko breathing technique, yoga or similar intervention that manipulates breathing pattern.
Comparison	Control group: asthma education only or no intervention (additional interventions such as education should be the same in both arms of the trial, so the trial is only assessing the effect of breathing exercises).
Outcomes	**Critical outcomes:** • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥6 months) **Important outcomes:** • Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥6 months) • Hospital admissions (dichotomous outcome at ≥6 months) • SABA use (continuous outcome at ≥6 months) • Lung function (change in FEV_1, or morning PEF)(continuous outcome at ≥6 months)

	• Adverse events
Study design	RCT Systematic review

13.1.1.1 Clinical evidence

We searched for randomised trials comparing breathing exercises versus usual care in patients with a clinical diagnosis of asthma. A Cochrane systematic review was identified which reviewed studies comparing breathing exercises versus usual care.[53] As the Cochrane review also included studies with less than 6 months follow-up, only the relevant studies included in this Cochrane review were extracted and pooled with other relevant published studies. The committee chose to only include studies with follow-up of at least 6 months as the intervention in question requires several weeks to be taught and therefore the expected timescales for observable benefit are longer than for most pharmacological interventions.

Six studies were included in the review [1 ,60 ,68 ,172 ,174 ,175] all compared breathing exercises versus usual care, and are summarised in Table 150 below. Evidence from these studies is summarised in the evidence summary tables below (Table 151, Table 152 and Table 153). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

Five studies were downgraded for indirectness, due to uncertainty about whether or not the sample population had received objective testing to confirm diagnosis of asthma. Three papers involved breathing retraining interventions versus usual care, [60 ,172 ,174 ,175] one paper involved the Papworth method versus usual care, [68] and one paper involved yoga intervention versus usual care. [1]

Table 150: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes
Agnihotri 2016 [1].	Intervention (n=138): Yoga intervention (asanas, pranayama, and meditation) for 30 minutes per day, 5 days a week for 6 months. Control (n=138): usual care Follow-up: 6 months	Adults, Possible age range: 12–60 Physician diagnosis: Adult participants with mild to moderate persistent asthma. Demonstrates reversible airflow limitation with increase of >12% to post-bronchodilator FEV_1.	Lung function: FEV_1 % predicted at 6 months Lung function: PEF predicted at 6 months
Grammatopoulou 2011[60]	Intervention (n=20): breathing retraining: phase 1a) 60 minute small group session; phase 1b) 12 individual sessions (3 per week, 1 hour duration); phase 2) training at home (2/3 times per day, 20 minutes at least, for 5 months) Control (n=20): usual care	Adults, mean age: intervention 48.15 (14.63); control 45.45 (12.67) Physician diagnosis: Adult participants with stable, mild to moderate asthma [Downgraded for indirectness]	Quality of life: SF-36 physical component at 6 months Quality of life: SF-36 mental component at 6 months Asthma control: ACT at 6 months Lung function: FEV_1 % predicted at 6 months

Study	Intervention and comparison	Population	Outcomes
	Follow-up: phase 1: 1 month, phase 2: 5 months, total: 6 months	19/40 (52.5%) participants had the "hyperventilation syndrome" (Nijmegen questionnaire score ≥23) Greece	
Holloway 2007[68]	Intervention (n=39): five 60-minute sessions of treatment by the Papworth method between baseline and assessment Control (n=46): usual care Follow-up: assessments at 6 and 12 months	Adults, mean age: intervention 50.2 (14.0); control 49.3 (14.2) Physician diagnosis: Participants register on GP practice asthma register [Downgraded for indirectness] England	Quality of life: St George's Respiratory at 12 months Lung function: FEV_1 (L) at 12 months
Thomas 2003[174]	Intervention (n=17): breathing retraining with a physiotherapist, one 45-minute group session with 15-minute individual sessions 1 and 2 weeks after first session. Control (n=16): asthma education with an asthma nurse Follow-up: 6 months	Adults, 17–65 years old (mean age: intervention 48.8, control 48.9) Physician diagnosis: patients with a diagnosis of asthma who had received at least one prescription for an inhaled or oral bronchodilator or prophylactic anti-asthma medication in the previous year [Downgraded for indirectness] Nijmegen questionnaire score of 23 or more England	Quality of life: AQLQ at 6 months (median, interquartile range)
Thomas 2009a[175] Thomas 2009b[172]	Intervention (n=94): physiotherapist-supervised breathing training, one 60 minute group session	Adults (mean age: intervention 46.0, 33.0–57.3; control 46.0, 35.0–57.0)	Quality of life: AQLQ, between-group difference at 6 months

Study	Intervention and comparison	Population	Outcomes
	followed by two 40–45 minute individual sessions with 2–4 weeks between attendances. Control (n=89): asthma nurse-delivered asthma education Follow-up: 6 months	Physician diagnosis: patients treated for asthma in 10 UK primary care general practices [Downgraded for indirectness] Moderate impairment of asthma related health status (Asthma Quality of Life Questionnaire score <5.5) England	Asthma control: ACQ, between-group difference at 6 months SABA use: canisters used in 6-month period at 6 months (median, range)

Table 151: Clinical evidence summary: breathing exercise versus usual care

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with Usual care	Risk difference with Breathing exercise (95% CI)
Quality of life: AQLQ at 6 months. Scale from 1–7 (better indicated by higher values)	183 (1 studies) 6 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean change from baseline at 6 months in the control group was 0.74	The mean quality of life: AQLQ at 6 months in the intervention groups was 0.38 higher (0.08 higher to 0.68 higher)
Quality of life: SGRQ at 12 months, final score Scale from: 0–100 (better indicated by lower values)	72 (1 study) 12 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean quality of life: SGRQ at 12 months in the control groups was 16.7	The mean quality of life: SGRQ at 12 months in the intervention groups was 1.5 lower (6.71 lower to 3.71 higher)
Quality of life: SF-36 physical at 6 months Scale from: 0–100 (better indicated by higher values)	40 (1 study) 6 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean quality of life: SF-36 physical at 6 months in the control groups was 48.79	The mean quality of life: SF-36 physical at 6 months in the intervention groups was 3.51 higher (0.13 lower to 7.15 higher)
Quality of life: SF-36 mental at 6 month Scale from: 0–100 (better indicated by higher values)	40 (1 study) 6 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean quality of life: SF-36 mental at 6 months in the control groups was 48.04	The mean quality of life: SF-36 mental at 6 months in the intervention groups was 1.52 lower (7.54 lower to 4.5 higher)
Asthma control: ACQ at 6 months. Scale from: 0–6 (better	183 (1 study)	VERY LOW[a,b] due to risk of bias,	-	The mean change from baseline at 6 months in the control group	The mean asthma control: ACQ at 6 months in the intervention groups

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Breathing exercise (95% CI)
indicated by lower values)	6 months	indirectness		was -0.13	was 0.17 lower (0.38 lower to 0.04 higher)
Asthma control: ACT at 6 months, Scale from: 5–25 (better indicated by higher values)	40 (1 study) 6 months	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	-	The mean asthma control: ACT at 6 months in the control groups was 20.3	The mean asthma control: ACT at 6 months in the intervention groups was 1.7 higher (0.27 lower to 3.67 higher)
Lung function: FEV_1 (L)	85 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, indirectness	-	The mean lung function: FEV_1 (L) at 6 months, in the control groups was 2.7	The mean lung function: FEV_1 (L) in the intervention groups was 0.10 higher (0.26 lower to 0.46 higher)
Lung function: FEV_1 % predicted at 6 months	281 (2 studies) 6 months	VERY LOW[a,d] due to risk of bias, inconsistency	-	The mean lung function: FEV_1 % predicted at 6 months, in the control groups was 67.95 %	The mean lung function: FEV_1 % predicted at 6 months in the intervention groups was 12.86 higher (11.83 to 13.88 higher)
Lung function: PEF % predicted at 6 months	241 (1 study) 6 months	LOW[a] due to risk of bias	-	The mean lung function: PEF % predicted at 6 months in the control groups was 65.08 %	The mean lung function: PEF % predicted at 6 months in the intervention groups was 10.54 higher (9.48 to 11.6 higher)

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Breathing exercise (95% CI)
risk of bias [b] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgraded by 1 increment) or by a very indirect population (downgraded by 2 increments) [c] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDS [d] Downgraded by 1 or 2 increments because the point estimate and/or the confidence intervals varied widely across studies, unexplained by subgroup analysis					

Table 152: Clinical evidence summary: [Breathing exercise versus usual care] outcomes reported with median values – quality of life

Quality of life: AQLQ	
Thomas 2003 Median (interquartile range) change in AQLQ overall score at 6 months	intervention group, n=16: 0.79 (-0.09, 1.40); control group, n=12: 0.03 (-0.33, 0.47) [p=.0.065]

Table 153: Clinical evidence summary: [Breathing exercise versus usual care] outcomes reported with median values – SABA use

SABA use	
Thomas 2003 SABA canisters used in 6-month period at 6 months (median, range)	Intervention: 1 (0 to 6); Control: 1 (0 to 8)

13.1.1.2 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

This section calculates how much breathing exercises could cost the NHS. Table 154 outlines the appropriate unit costs and Table 155 takes the resource use from the studies identified in the clinical review and attaches unit costs.

Table 154: NHS physiotherapist and specialist asthma nurse costs

Session type	Cost per session
Physiotherapist, Adult, One-to-One	£52
Physiotherapist, Adult, Group	£41[(a)]
Physiotherapist, Child, One-to-One	£81
Physiotherapist, Child, Group	£89[(a)]
Specialist asthma nurse, Adult, Face-to-face	£79
Specialist asthma nurse, Child, Face-to-face	£131

Source: NHS reference costs 2013/14
(a) Cost per patient is dependent on the size of the group

Table 155: Included clinical study intervention costs

Study	Intervention	Cost breakdown	Total cost
Thomas 2003[174]	Breathing retraining with physiotherapist	One group session with a follow-up individual session	£60
Thomas 2009[175]	Breathing retraining with physiotherapist	One group session with a follow-up individual session	£60
Grammatopoulou 2011[60]	Breathing retraining	One group session and 12 individual sessions	£632
Holloway 2007[68]	Papworth method	Five individual sessions with physiotherapist	£260

(a) Assumes 5 individuals in the group

Economic considerations

A threshold analysis was undertaken using quality of life data included in the clinical review to help the committee consider cost effectiveness. A threshold analysis allows us to calculate how much the NHS would be willing to pay for an intervention at a £20,000 per QALY threshold. If we know how effective breathing exercises are, we can calculate how high the cost would need to be for breathing exercises to no longer be considered a cost-effective intervention at a £20,000 per QALY threshold.

$$£20{,}000 \times Change\ in\ QALYs = Maximum\ cost\ to\ remain\ cost\ effective$$

Taking the formula above, if an intervention generated 1 QALY then the intervention would be considered cost-effective at a £20,000 per QALY threshold if it cost no more than £20,000.

$$£20{,}000 \times 1 = £20{,}000$$

To calculate the QALY, quality of life data was extracted from the included studies and transformed to the preferred EQ-5D using published and validated mapping algorithms. The QALY is calculated by estimating what the quality of life benefit is and multiplying this over the time period the benefit lasts for. As the intervention is dependent on the individual performing the breathing exercises over time, it is likely that as time passes the individual will stop doing the exercises. An assumption was made that the benefit from breathing exercises would only occur if the individual continued to do them and therefore there was no lasting impact once the individual stopped. Therefore the QALY

was calculated under three assumptions, one where the benefit only lasts for 6 months, one where the benefit lasts 1 year and another where the benefit lasts for 5 years.

The estimated difference in QALYs was used in the equation above to obtain an incremental cost that the NHS would be willing to pay for. Cost effectiveness of the treatment was determined by comparing the estimated willingness to pay and cost of treatment, using the unit costs provided in Table 154.

Mapping algorithms were used to transform quality of life data into the preferred EQ-5D. Algorithms were taken from published studies included in the Health Economic Research Centre database of mapping studies. The mapping algorithm for each of the quality of life measures are detailed in Table 156.

Table 156: Quality of life mapping algorithms

Quality of life measure	Formula	Source	Notes
SF-36	EQ-5D=-0.18105 + 0.00781PF + 0.00213SF + 0.00022RE + 0.00599MH + 0.00472BP + 0.00064GH – 0.00069Age – 0.00004PF*PF – 0.00001SF*SF – 0.00003MH*MH – 0.00001BP*BP	Ara 2008[2] model 4	Mean scores reported in Ara 2008 based on asthma data sets used to determine overall SF-36 score where only PF and MH reported. It is assumed that unobserved components of the SF-36 remain constant over the duration of the study with changes to SF-36 from the PF and MH components only.
St. George's Respiratory Questionnaire (SGRQ)	(0.9617 - (0.0013 x SGRQ)) - (0.0001 x $SGRQ^2$) + (0.0231*male)	Starkie 2011[164]	Average EQ-5D scores were calculated using mean cohort quality of life weighted by male to female patient ratio in each treatment arm.

Abbreviations: BP: bodily pain; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); *GH: general health; MH: mental health; PF: physical functioning; RE: role-emotional; RP: role-physical; SF: social functioning; V: vitality*

Table 157: Threshold analysis using quality of life clinical evidence

Study	Study details	Reported QOL difference	EQ-5D difference	QALY difference[1)]	Maximum cost that would be considered	Estimated cost	Cost effectiveness
Grammatopoulou 2011 Time horizon: 6 months	Usual care versus Breathing retraining	**Difference in SF-36 PF:** Intervention 1: 0.64 Intervention 2: 3.83 Incremental (2−1): 3.19 **Difference in SF-36 MH:** Intervention 1: 2.49 Intervention 2: -1.14 Incremental (2−1): -3.63	0.0004	6 months: 0.0002 1 year: 0.0004 5 years: 0.002	6 months of benefit: £4.26 1 year of benefit: £8.52 5 years of benefit: £42.60	Intervention 1: £0 Intervention 2: £632 Incremental (2−1): £632	Breathing retraining not cost-effective at a £20,000 per QALY threshold for any length of benefit within 5 years.
Holloway 2007 Time horizon: 1 year	Usual care versus Papworth method	**Difference in SGRQ:** Intervention 1: -3 Intervention 2: -10 Incremental (2−1): -7	0.039	6 months: 0.017 1 year: 0.039 5 years: 0.193	6 months of benefit: £336 1 year of benefit: £771 5 years of benefit: £3,858	Intervention 1: £0 Intervention 2: £260 Incremental (2−1): £260	Papworth method cost-effective at a £20,000 per QALY threshold for any benefit lasting more than 6 months.

Abbreviations: EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); *MH: mental health; PF: physical functioning; SF-36: short form health survey (scale: 0 [maximum disability] to 100 [no disability]); SQRQ: St. Georges respiratory questionnaire (score: 0 [best] to 100 [worst]) ; QALY: quality adjusted life year; QoL: quality of life*

(a) Incremental cost=£20,000 / (change in QALYs)

1. *Assumed study treatment effect constant over six months, one year and five years*

13.1.1.3 Evidence statements

13.1.1.3.1 Clinical

- Breathing exercises versus usual care resulted in a clinically important benefit for quality of life as measured by the SF-36 physical component (1 study, n=40, Very Low quality); and FEV_1 % predicted (2 studies, n=281, Very Low quality); and PEF % predicted (1 study, n=241, Low quality) – all at ≥6 months.
- Breathing exercises versus usual care resulted in no clinically important difference for quality of life as measured by the AQLQ (1 study, n=183, Very Low quality), the SGRQ (1 study, n=72, Very Low quality), and SF-36 mental component (1 study, n=40, Very Low quality); asthma control as measured by the ACQ (1 study, n=183, Very Low quality), and the ACT (1 study, n=40, Very Low quality); and, lung function as both FEV_1 litres (1 study, n=85, Very Low quality) – all at ≥6 months.
- Narrative evidence was presented for the following outcomes: quality of life as measured by the AQLQ (1 study), and SABA use (1 study) – all at ≥6 months.

13.1.1.3.2 Economic

- No relevant economic evaluations were identified.

13.1.1.3.3 Recommendations and link to evidence

Research recommendation	7. What is the clinical and cost effectiveness of breathing exercises or breathing retraining in people with an objective diagnosis of asthma, with poor control on preventer treatment?
Relative values of different outcomes	The committee considered the following outcomes as critical or important for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee also considered the following additional outcomes: asthma control (as assessed by a validated questionnaire), hospital admission, SABA use, lung function (FEV_1 or morning PEF) and adverse events. These outcomes were considered important measures of asthma control for the patient.
Trade-off between clinical benefits and harms	Breathing exercises in people with a clinical diagnosis of asthma were considered to have a clinically important benefit for quality of life as measured by the SF-36 physical component. Evidence from one study of 40 participants suggested a small improvement in this particular domain of quality of life. Breathing exercises had a clinically important benefit for lung function (FEV_1 % predicted and PEF % predicted). There was no clinically important difference in quality of life as measured by the AQLQ, quality of life as measured by the St George's Respiratory Questionnaire, quality of life as measured by the SF-36 mental component, asthma control as measured by the ACQ, asthma control as measured by the ACT, or lung function measured as absolute FEV_1. For the majority of outcomes, evidence was only available from one study; and no evidence was available for the critical outcomes of severe asthma exacerbation and mortality, or the important outcomes of hospital admission, SABA use or adverse events. The committee felt that there was insufficient evidence available to fully assess the benefits and harms of breathing exercises. The committee discussed that this was due to a lack of high quality evidence, rather than a lack of effect of the intervention. There was also a lack of evidence of harm due to breathing exercises. Overall there was insufficient evidence to recommend that breathing exercises are either used or not used routinely. Targeted research in this area is required to identify whether breathing exercises may be of benefit to those patients with an objective diagnosis of asthma, and to determine whether there is a sub-set of people who will benefit. Those who will benefit are more likely to be found within the group who respond

	less well to pharmacological therapy. Therefore, the committee made a future research recommendation for the effectiveness of breathing exercises in people with poor control on preventer treatment. Research in this area would require a minimum duration of 6 months in order to detect any beneficial effect.
Trade-off between net clinical benefits and costs	No relevant economic evaluations were identified. In the absence of evidence, unit costs associated with breathing exercises were provided. Where possible, a threshold analysis was also undertaken using resource use and quality of life data from the included clinical studies. A threshold analysis could be undertaken for two studies included in the clinical review. It was explained to the committee that the nature of the analysis includes assumptions and uncertainty and should be considered only as a guide to aid cost-effectiveness considerations in the absence of evidence. The results outlined that breathing exercises provided a small benefit to quality of life and would therefore need to have low costs to be considered a cost effective use of NHS resources. Although the mapping algorithm showed that the benefits achieved by Holloway et al. would justify the cost of the intervention, this was not deemed sufficient evidence to base make recommendations on. Firstly, EQ-5D was not directly gathered and therefore the estimates generated from the mapping exercise are subject to uncertainty. Secondly, there were no data available on unscheduled resource utilisation or medication costs. If breathing exercises affected either of these then this would impact their cost effectiveness. The committee acknowledged the results of the economic analysis and unit costs provided alongside the clinical review. They felt that the results supported the need for further research into the clinical and cost-effectiveness of breathing exercises.
Quality of evidence	For the comparison of breathing exercises versus usual care, evidence for all outcomes was Low and Very Low quality. For all outcomes aside from lung function as FEV_1 % predicted, evidence was only available from one study with a mean follow-up of 6 months. The committee discussed the decision to downgrade the evidence quality if the studies include people with asthma without any objective diagnostic tests. It was considered to be particularly important here, as people with dysfunctional breathing are often misdiagnosed as having asthma. The committee reflected on the suitability of two studies[174 ,175] which both used some form of education in the control arm of the trial. The control groups had asthma education with a nurse. This was deemed by the authors to control for the professional attention aspect of the intervention. The intervention groups did not receive this asthma education, however the committee deemed the education to be non-specific and not personalised to the individual's asthma therapy, therefore these trials were still relevant to the review. The trials referenced a previous paper that showed this non-specific education to be ineffective on asthma outcomes. The committee questioned the applicability to real-world practice of an intervention implemented by one study, whereby participants attended a teaching hospital to perform yoga for 30 minutes, five times a week, for six months. The feasibility of such time demands was considered to be unrealistic. The committee discussed features of the populations in the included studies. Two studies included people with a Nijmegen questionnaire score of 23 or more. Populations with and without dysfunctional breathing could not be investigated further using the pre-specified subgroup analysis due to the lack of studies included in the meta-analysis for each outcome. The committee discussed whether people with asthma and dysfunctional breathing may benefit further from breathing exercises. It was highlighted that people with more severe asthma can also sometimes have other psychological problems and the additional sessions with a healthcare professional may help with multiple aspects of the disease. The

	committee highlighted that the Nijmegen questionnaire is not specifically validated in an asthma population. One study also included people with a moderate impairment of asthma-related health status (AQLQ score <5.5).
Other considerations	The committee agreed that these interventions would normally be performed in secondary care by a specialised physiotherapist, although there is no obvious reason why they could not take place in other settings as long as trained personnel are available. A committee member noted that a Cochrane review[53] looking at what patients want from future research has been published recently – for those patients with asthma, more research into breathing exercises was requested.

14 Managing patients in relation to risk of poor outcomes

14.1 Introduction

Targeting care at those at highest risk of an asthma attack is an attractive concept. Asthma attacks drive health care costs (largely via hospitalisation) and costs to society (for example, via loss of work),[5]and reducing hospitalisation is the key to reducing the overall costs of asthma care.[62] The concept of good asthma control fundamentally includes the notion of an individual's risk of experiencing an attack.[144]

Risk prediction is growing in importance — both to the individual and at the public health level. Risk scores already exist to predict, for example, the risk of future cardiovascular events,[67] (development of diabetes,[66] and lung cancer.[28]

Whilst there are numerous ways of predicting risk of an asthma attack, such as monitoring fluctuations in peak expiratory flow rate,[171]using symptoms and questionnaire scores,[8]or measuring biomarkers of inflammation, the important question we address here is whether targeting care stratified by risk is a cost-effective approach to organizing care.

14.1.1 Review question: What is the clinical and cost-effectiveness of delivering asthma care stratified according to risk of asthma attacks to improve outcomes for children, young people and adults with asthma?

For full details see review protocol in Appendix C.

Table 158: PICO characteristics of review question

Population	People with a diagnosis of asthma Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years
Interventions	• Asthma care of varying intensities stratified by risk of poor outcomes ○ Variation in intensity of care may include differing frequency of respiratory consultant reviews, differing frequency of medication reviews, differing frequency of peak flow/lung function testing etc. • Control group: regular best practice asthma care that is not stratified by risk of future attack
Comparison	Risk stratified asthma care versus usual care
Outcomes	**Critical outcomes:** • Severe asthma exacerbations • Mortality

	• Quality of life **Important outcomes:** • Asthma control assessed by a validated questionnaire • Hospital admissions • Reliever/rescue medication use • Lung function (FEV_1 or morning PEF) • Adverse events: linear growth, infections (all respiratory), infections (serious respiratory), adrenal insufficiency.
Study design	RCT Systematic review of RCTs

14.1.1.1 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of delivery of care according to stratified risk to usual care in people with a diagnosis of asthma.

One study was included in the review; [162] this is summarised in Table 159 below. Evidence from this study is summarised in the clinical evidence summary table below (Table 160). See also the study selection flow chart in Appendix E, forest plots in Appendix K, study evidence tables in Appendix H, GRADE tables in Appendix J and excluded studies list in Appendix L.

Table 159: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Smith 2012 [162]	Risk stratified care (participants=457, practices=14). Addition of electronic alerts, visible to all staff, to the computerised records of identified at-risk patients to flag their at-risk status at each contact. A one hour practice-based staff training session to support effective use of the alerts, which advised staff on how to engage with, and improve, the routine and emergency management of at-risk asthma patients. Standard care (participants=454, practices=15). Control practices continued usual care, comprising at least annual practice-based asthma reviews in nurse-led clinics, plus follow-up in secondary care outpatient clinics and emergency primary and secondary care for some patients as required.	At-risk asthma patients aged 5+ years. At risk defined as severe asthma and psychosocial problems. Severe asthma indicated by: in the last 2 years medications approximating to BTS/SIGN Step 4–5 treatment; asthma admission in the last 5 years; A&E visit in last year; Brittle asthma. Psychosocial problems based on clinician opinion. Factors taken into account include: adherence problems, failure to attend appointments, psychiatric illness, substance abuse, smoking, obesity, denial, learning difficulties, employment problems, social isolation, childhood abuse, severe domestic/marital/legal stress. Age - Mean (SD): 45.5 (21.9)	• Oral prednisolone course for asthma exacerbation • Hospitalisation for asthma exacerbation • Rate of SABA inhalers prescribed Follow up duration: 1 year	All participants were 'at-risk'. Actions following alerts to risk status of patients not specified; simply that training was provided for staff on how to respond to alerts, that is 'case examples used to highlight potential actions for receptionists, clinicians and dispensary teams'

Table 160: Clinical evidence summary: Care by risk stratification compared to usual care for people with asthma

Outcomes	Number of Participants	Quality of the evidence (GRADE)	Relative effect	Anticipated absolute effects

	(studies) Follow up		(95% CI)	Risk with Usual care	Risk difference with Care by risk stratification (95% CI)
Severe exacerbations (requiring OCS)	911 (1 study) 1 years	LOW[a,b] due to indirectness, imprecision	OR 1.28 (0.95 to 1.72)	469 per 1000	62 more per 1000 (from 13 fewer to 134 more)
Hospitalisations	911 (1 study) 1 years	LOW[a,b] due to indirectness, imprecision	OR 0.51 (0.26 to 1)	64 per 1000	30 fewer per 1000 (from 46 fewer to 0 more)
SABA use (rate of prescriptions)	911 (1 study) 1 years	MODERATE[a] due to indirectness	Rate Ratio 1.03 (0.91 to 1.17)	Median rate of SABA prescription 7 per year	

1 Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

14.1.1.2 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review. [162] This is summarised in the health economic evidence profile below (Table 161) and the health economic evidence table in Appendix I.

See also the health economic study selection flow chart in Appendix F.

Table 161: Health economic evidence profile: usual care versus risk stratification

Study	Applicability	limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Smith 2012 UK[162]	Partially applicable[(a)]	Potentially serious limitations[(b)]	Comparative costing Population: At-risk asthma patients aged 5+ years using British guideline criteria. Severe asthma indicated by: in the last 2 years medications approximating to BTS/SIGN Step 4–5 treatment; asthma admission in the last 5 years; A&E visit in last year; Brittle asthma. Two comparators: 1) Usual care 2) Risk stratification Time horizon: 1 year	-£88.91	none	n/a	Incorporating only the respiratory related resource use means that risk stratified care is no longer cost saving, costing an additional £62.03 per patient. Of the total cost difference £51.69 is associated with implementation and is therefore a one off cost that will decrease over time as more patients use the service. Each time a patient uses this service the £51.69 is not incurred, rather this is simply the implementation cost divided by total patients in the study.

(a) Quality of life was not assessed
(b) Potential inconsistencies with hospitalisations decreasing but asthma-related secondary care costs increasing

14.1.1.3 Evidence statements

14.1.1.3.1 Clinical

Care by risk stratification compared to usual care for people with asthma

- Care by risk stratification compared to usual care resulted in a clinically important harm for severe exacerbations (requiring OCS) (1 study, 911 patients, Low quality evidence)
- Care by risk stratification compared to usual care resulted in a clinically important benefit for hospitalisations (1 study, 911 patients, Low quality evidence)
- Care by risk stratification compared to usual care resulted in no clinically important difference for SABA use (rate of prescriptions) (1 study, 911 patients, Low quality evidence)

14.1.1.4 Economic

- One cost-comparison study found that risk stratification reduced costs to the health service by £88.91 when compared to usual care. This study was assessed as being partially applicable with potentially serious limitations.

14.1.1.4.1 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng80
Relative values of different outcomes	The committee considered the following outcomes as critical for this review: severe asthma exacerbation (defined as asthma exacerbation requiring oral corticosteroid use), mortality and quality of life. The committee considered the following outcomes as important: asthma control (as assessed by a validated questionnaire), hospital admission, reliever medication use, lung function (FEV_1 or morning PEF) and adverse events.
Quality of the clinical evidence	The quality of the evidence ranged from Low to Moderate. There was no evidence for mortality, quality of life, asthma control, lung function or adverse events. The evidence was generally downgraded for indirectness (the participants had not necessarily had their asthma diagnosis confirmed by objective measures) and imprecision. The committee noted that there was an apparent contradiction between the clinical and cost-effectiveness evidence from the included study, as outlined below. The committee took this into account when formulating their recommendation.
Trade-off between clinical benefits and harms	There was a clinically important harm in terms of increased severe exacerbations. There was a clinically important benefit in terms of reduced hospitalisations. There was no clinically important difference in terms of reliever medication use. The use of risk stratification appeared to cause harm in terms of leading to a greater number of exacerbations. However the committee did not think it was plausible that risk stratification had any impact on the occurrence of exacerbations. This apparent effect is more likely to be due to the greater vigilance and degree of monitoring for these at-risk participants. In the same way, the most likely explanation for the greater number of oral steroid courses in the intervention group was that the

	indications for steroids were more accurately being identified; as such this is likely to result in benefit and not harm. The benefit in terms of hospitalisations supports this suggestion as it is possible that the oral steroid courses help control exacerbations and prevent deterioration to the stage at which hospitalisation is required. The committee noted that there was only one included study and that the evidence ranged from Low to Moderate quality. However the committee decided that a recommendation to use risk stratification, based partly on consensus but informed by the included study, was appropriate as the potential benefits of risk stratification are likely to outweigh any potential harms. The committee noted that one potential harm of risk stratifying care involved the redistribution of resources away from those deemed to be at low risk. The included study only included participants at risk. There was no assessment of the impact of a risk stratification system on those people with asthma at the included practices who were not deemed at high risk. The committee noted that it was possible that this group may receive less intense resource use whilst efforts are targeted at the high risk population. However as the population is not reported on in this study, it is not possible to tell if they experienced adverse events as a consequence. The committee felt that if the basis for risk stratification is valid and the intervention focuses more on optimising care delivery for those at risk than redistributing resource, then the harm experienced by the low risk group was likely to be minimal.
Trade-off between net clinical effects and costs	One cost-comparison study was identified and included. This evaluation was part of the same study included in the clinical review with unit costs attached to resource use. The study showed that costs were largely similar between usual care and risk stratification. The main cost difference came from implementing the service, however the cost per patient associated with implementation will fall over time as more people use the service. Although the study showed that risk stratification was cost saving, the main cost savings came from reducing hospitalisations associated with non-respiratory related hospitalisations, which the committee found difficult to explain. The cost difference was also not of statistical significance. Overall the committee felt that the data presented in the study was not sufficient to base conclusive judgements on regarding the specific aspects of what risk stratification should look like, although the committee acknowledged that risk stratification was likely a cost effective intervention.
Other considerations	The committee noted that the intervention in the included study did not involve specific responses to people at risk. The entire practice staff attended a training session suggesting approaches that may be beneficial in the population (for example receptionists fast tracking clinical contact, GPs putting particular focus on psychosocial factors affecting asthma and the dispensary team being aware of adherence indicators). The committee noted that there is no universally accepted risk stratification system but that the criteria, a combination of pharmacological and psychosocial indicators, used in the included study were appropriate. By recommending risk stratification, the committee sought to promote the use of any appropriate system to identify the subgroup of people with asthma at higher risk of adverse outcomes and to adapt their care accordingly. The committee noted that the quality of evidence identified here and their own clinical experience was sufficient to recommend risk stratification as a strategy but not to define specific systems and response. The committee did want to emphasise that, as in the included study, assessment of risk should take into account a person's history of asthma exacerbations, their adherence to treatment

and psychosocial issues – all of which are likely to impact risk of adverse outcomes. The committee noted that there is growing research around the use of biomarkers to define risk. Although no studies were identified that used biomarkers (for example FeNO, sputum eosinophilia) to stratify risk and subsequently alter care delivery, this would certainly be an area of interest and a justifiable method for stratifying risk at least on the level of the more subjective assessment used in the study included in this review.

The committee noted that the included study was conducted in primary care. The committee felt that risk stratification could be equally appropriate in secondary care, but expected that the majority of people seen in secondary care would be deemed at high risk and therefore the actual impact of risk stratification may be lessened.

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16 Acronyms and abbreviations

Acronym or abbreviation	Description
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AMD	Adjustable maintenance dose
API	Asthma Predictive Index
AQLQ	Asthma Quality of Life Questionnaire
BDP	Beclometasone dipropionate
BDR	Bronchodilator reversibility
BNF	British National Formulary
BTS	British Thoracic Society
CCA	Cost consequences analysis
CI	Confidence interval
CUA	Cost-utility analysis
ED	Emergency department
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FSC	Fluticasone salmeterol combination
GC	Guideline Committee
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ICRDMA	International Consensus Report on Diagnosis and Management of Asthma
ICS	Inhaled corticosteroid
LABA	Long-acting beta-adrenoceptor agonist
LAMA	Long-acting muscarinic antagonists
LTA	Leukotriene antagonists
LTRA	Leukotriene receptor antagonists
MART	Maintenance and Reliever Therapy
MID	Minimally important difference
NGC	National Guideline Centre
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Care Excellence
OCS	Oral corticosteroid
OR	Odds ratio

Acronym or abbreviation	Description
PAAP	Personalised Asthma Action Plans
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PBV	Personal best value
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
QALY	Quality-adjusted life year
QOL	Quality of life
RR	Risk ratio
SABA	Short-acting beta agonist
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SMART	Single Maintenance and Reliever Therapy

17 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

17.3 Guideline-specific terms

Term	Definition
Adherence (to treatment)	The extent to which a patient's action matches the agreed recommendations.
Asthma	A common long-term incurable condition of unknown cause that affects people of all ages. The small tubes in the lungs (bronchi) become inflamed when the person encounters something that irritates their lungs (asthma triggers) causing the airways to become narrower and making it difficult to breathe. It can induce coughing, wheezing and tightness in the chest. Asthma is usually associated with an expiratory polyphonic wheeze. Severity of symptoms varies from person to person, and even in the same person at different times of the day or year. Worsening of symptoms can occur gradually or suddenly (known as an 'asthma attack' or 'asthma exacerbation').
Asthma attack	A worsening of asthma symptoms requiring the use of systemic corticosteroids to prevent a serious outcome.
Asthma exacerbation	See 'Asthma attack'.
Atopy	The genetic tendency to develop allergic diseases, for example atopic dermatitis (eczema), allergic rhinitis (hay fever) and asthma.
Bronchodilator	A drug that widens the airways making it easier to breathe.
Bronchodilator response	See 'bronchodilator reversibility'.
Bronchodilator reversibility	A measure of the ability (usually a physiological test) to reverse an obstruction in the airways using drugs that widen the airways (bronchodilators).
Controller medication	See 'Preventer medication'.
Exacerbation	See 'Asthma exacerbation'.
FeNO test	A test that measures the amount of nitric oxide (NO) present upon exhalation, generally expressed in parts per billion.
FEV_1	The amount of air you can blow out in one second with a forceful expiration from total lung capacity (forced expiratory volume in one second).
Forced vital capacity	The amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.
Inhaler	A portable device for administering an inhaled drug.

Term	Definition
Leukotriene antagonists (LTRA) (also known as leukotriene modifiers and leukotriene receptor antagonists)	A type of oral drug that blocks cysteinyl leukotrienes, used in the treatment of asthma and seasonal allergies.
Leukotriene receptor antagonists (LTA)	See 'Leukotriene antagonists'.
Leukotriene modifiers	See 'Leukotriene antagonists'.
Long-acting beta-adrenoceptor agonist (LABA)	A long-acting drug used to relax airways, smooth muscle and relieve symptoms of asthma.
Long-acting muscarinic antagonists (LAMA)	See 'Long-acting beta-adrenoceptor agonist'.
Maintenance and Reliever Therapy (MART)	A form of combined ICS + LABA treatment in which the a single inhaler, containing both ICS and a fast acting LABA, is used for both daily maintenance therapy and the relief of symptoms as required.
Peak expiratory flow rate	A measure of the maximum speed of expiration from total lung capacity, generally expressed in litres per minute.
Preventer medication (also known as controller medication)	Inhalers that are used regularly (at least daily) to reduce inflammation in the lungs, improve asthma control and prevent an asthma attack happening, reducing the need to use reliever inhalers.
Risk stratification	Risk stratification is a process of categorising a population by their relative likelihood of experiencing certain outcomes. In the context of this guideline, risk stratification involves categorising people with asthma by their relative likelihood of experiencing negative clinical outcomes (for example severe exacerbations or hospitalisations). Once the population is stratified, the delivery of care for the population can be targeted with the aim of improving the care of the strata with the highest risk.
Reliever medication	Inhalers that are used to relieve short-term symptoms. The medication delivered is usually a short-acting beta-agonist (SABA) which works by relaxing the muscles surrounding the narrowed airways, allowing them to open wider making breathing easier.
Rescue medication	Medication used to treat an asthma attack, usually oral corticosteroids and inhaled β-2 agonists.
Spirometry	A test that measures how a person forcibly exhales volumes of air as a function of time.
Suspected asthma	A term used to describe a potential diagnosis of asthma based on symptoms and response to treatment that has not yet been confirmed with objective tests.
Uncontrolled asthma	A term used typically to describe when asthma is having an impact on a person's lifestyle or is restricting their normal activities. Symptoms such as coughing, wheezing, shortness of breath and chest

Term	Definition
	tightness associated with uncontrolled asthma can significantly decrease a person's quality of life and may lead to a medical emergency. This can be quantified by a number of questionnaires. This guideline uses the following pragmatic thresholds to define uncontrolled asthma: 3 or more days a week with symptoms, or 3 or more days a week with required use of a SABA for symptomatic relief, or 1 or more nights a week with awakening due to asthma.

17.4 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it

Term	Definition
	does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the

Term	Definition
	'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs

Term	Definition
	and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Economic evaluation	An economic evaluation is used to assess the cost-effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data

Term	Definition
	are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more

Term	Definition
	predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN/(TN+FN)
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Non-randomised intervention study	A quantitative study investigating the effectiveness of an intervention that does not use randomisation to allocate patients (or units) to treatment groups. Non-randomised studies include observational studies, where allocation to groups occurs through usual treatment decisions or people's preferences. Non-randomised studies can also be experimental, where the investigator has some degree of control over the allocation of treatments. Non-randomised intervention studies can use a number of different study designs, and include cohort studies, case-control studies, controlled before-and-after studies, interrupted-time-series studies and quasi-randomised controlled trials.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for

Term	Definition
	non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP/(TP+FP)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.

Term	Definition
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial	A study in which a number of similar people are randomly assigned to 2

Term	Definition
(RCT)	(or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months

Term	Definition
	pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: manufacturers of drugs or equipment national patient and carer organisations NHS organisations organisations representing healthcare professionals.
State transition model	See Markov model
Systematic review	A review in which evidence from scientific studies has been identified,

Term	Definition
	appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).