National Guideline Centre

Final version

Chronic asthma management

Chronic asthma: management

NICE guideline NG80

Appendices A – S

November 2017

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

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.

Funding
National Institute for Health and Care Excellence

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Appendices

Appendix A: Scope

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline scope

Asthma: The management of asthma

Short title

Asthma management

Topic

The Department of Health in England has asked NICE to develop a clinical guideline on the management of asthma.

This guideline will be used to update the NICE quality standard for asthma.

Who the guideline is for

- People using services, families and carers and the public.
- Healthcare professionals in primary care.
- Healthcare professionals in secondary care.
- Healthcare professionals in tertiary care.
- Healthcare professionals in community care (including pharmacists).
- Local authorities.
- Commissioners of asthma clinics.
- Providers of asthma clinics.

It may also be relevant for:

- Private sector or voluntary organisations commissioned to provide services for the NHS or local authorities.
- People working in related services.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive.

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Equality considerations

NICE has carried out an equality impact assessment during scoping. The assessment:

- lists equality issues identified, and how they have been addressed
- explains why any groups are excluded from the scope, if this was done.

1 What the guideline is about

1.1 Who is the focus?

Groups that will be covered

- Adults, children and young people with a diagnosis of asthma.
- Specific consideration will be given to subgroups based on age, with proposed banding of children under 5 years; children aged 5-16; and adults and young people over 16 years of age. However, the age division may be adjusted for specific reviews according to the most appropriate age groupings to make different recommendations for the intervention in question.

1.2 Settings

Settings that will be covered

- All settings where NHS healthcare is provided or commissioned.

1.3 Activities, services or aspects of care

Key areas that will be covered

1. Pharmacological management of chronic asthma.
   Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.
2. Review of pharmacological therapy.
3. Non-pharmacological management of asthma (adherence, risk stratification, supported self-management and breathing exercises only).

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Areas that will not be covered

1. Non-pharmacological management of asthma (except as specified: adherence, risk stratification, supported self-management and breathing exercises)
2. Biologics (for example Omalizumab)
3. Comparison of drug-delivery devices (inhalers)
4. Bronchial thermoplasty
5. Management of acute asthma attacks by a healthcare professional
6. Service delivery for acute asthma attacks

1.4 Economic aspects

We will take economic aspects into account when making recommendations. We will develop an economic plan that states for each review question (or key area in the scope) whether economic considerations are relevant, and if so whether this is an area that should be prioritised for economic modelling and analysis. We will review the economic evidence and carry out economic analyses, using an NHS and a personal social services (PSS) perspective, as appropriate.

1.5 Key issues and questions

While writing this scope, we have identified the following key issues, and key questions related to them:

Pharmacological management of chronic asthma

People with asthma who are treatment-naive

1. What is the most clinically and cost effective drug class or combination of drug classes for the management of people with asthma who are not taking treatment for asthma?

People with asthma currently on an optimal single preventer (see previous question) (BTS/SIGN step 2)

1. What is the most clinically and cost effective sequence in which to introduce additional drugs or combination of drugs for the management of people with asthma who are currently taking an optimal single preventer (see previous question) (BTS/SIGN step 2) when this fails to provide adequate control?

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Review of pharmacological therapy

1 What are the clinical features (symptoms and/or objective measurements) which indicate that a step down in treatment is appropriate?

Non-pharmacological management of chronic asthma

Adherence to pharmacological therapy

1 What are the most clinically and cost effective strategies to improve medicines adherence in people with asthma?

Stratification of asthma management according to risk of asthma attack

1 What is the clinical and cost effectiveness of delivering asthma care stratified according to risk of asthma attacks to improve outcomes for people with asthma?

Supported self-management

1 What is the clinical and cost effectiveness of supported self-management for improving outcomes for people with asthma?

2 What is the optimal increase in preventer therapy within supported self-management when control is lost?

Breathing exercises

1 What is the value of breathing exercises in improving outcomes in people with asthma?

The key questions may be used to develop more detailed review questions, which guide the systematic review of the literature.

1.6 Main outcomes

The main outcomes that will be considered when searching for and assessing the evidence are:

1 Health-related quality of life
2 Asthma control assessed by a validated questionnaire (for example the Asthma Control Questionnaire)
3 Asthma attacks
4 Adverse events
5 Hospital admissions

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6 Unscheduled healthcare utilisation
7 Mortality

2 Links with other NICE guidance and NICE Pathways

2.1 *NICE guidance*

NICE guidance that will be updated by this guideline

- Quality standard for asthma (2013) NICE quality standard QS25

Related NICE guidance

- Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma (2000) NICE technology appraisal guidance TA10
- Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (2008) NICE technology appraisal guidance TA138
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years (2007) NICE technology appraisal guidance TA131
- Inhaler devices for routine treatment of chronic asthma in older children (aged 5-15 years) (2002) NICE technology appraisal guidance TA38
- Omalizumab for treating severe persistent allergic asthma (2013) NICE technology appraisal guidance TA278
- Bronchial thermoplasty for severe asthma (2012) NICE interventional procedure guidance IPG419
- Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath (2014) NICE diagnostics guidance DG12

Related NICE advice

- Asthma: tiotropium (Spiriva Respimat) (2015) NICE advice ESNM55
- Asthma in adults: beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) (2015) NICE advice ESNM53
- Asthma: beclometasone/formoterol (Fostair) for maintenance and reliever treatment (2013) NICE advice ESNM22
- Asthma: fluticasone furoate/vilanterol (Relvar Ellipta) combination inhaler (2014) NICE advice ESNM34

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- Asthma: fluticasone/formoterol (Flutiform) combination inhaler (2012) NICE advice ESNM3
- High-dose inhaled corticosteroids in asthma (2015) NICE advice KTT5
- The Airsonett temperature-controlled laminar airflow device for persistent allergic asthma (2014) NICE advice MIB8

NICE guidance about the experience of people using NHS services

NICE has produced the following guidance on the experience of people using the NHS. This guideline will not include additional recommendations on these topics unless there are specific issues related to asthma:

- Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes (2015) NICE guideline NG5
- Patient experience in adult NHS services (2012) NICE guideline CG138
- Service user experience in adult mental health (2011) NICE guideline CG136
- Medicines adherence (2009) NICE guideline CG76

NICE guidance in development that is closely related to this guideline

NICE is currently developing the following guidance that is closely related to this guideline:

- Asthma diagnosis and monitoring NICE guideline. Publication expected July 2015.
- Acute medical emergencies NICE guideline. Publication expected November 2016.

2.2 NICE Pathways

When this guideline is published, the recommendations will be added to NICE Pathways. NICE Pathways bring together all related NICE guidance and associated products on a topic in an interactive topic-based flow chart.

A draft pathway outline on asthma is included below – the recommendations from this guideline will be added to the 'management' section of the pathway. It will be adapted and more detail added as the recommendations are written during guideline development.

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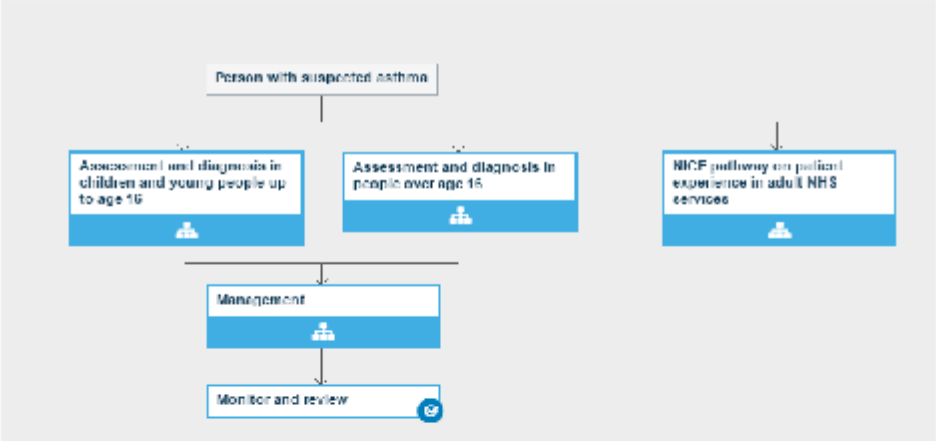
The guideline will overlap with the existing NICE guideline on asthma diagnosis and monitoring. The NICE Pathway will integrate the recommendations from both guidelines, showing clearly how they fit together.

Other relevant NICE guidance included in the NICE pathway on asthma:

- Omalizumab for treating severe persistent allergic asthma. NICE technology appraisal guidance 278 (2013)
- Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. NICE technology appraisal guidance 138 (2008)
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisal guidance 131 (2008)
- Inhaler devices for routine treatment of chronic asthma in older children (aged 5–15 years). NICE technology appraisal guidance 38 (2002)
- Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma. NICE technology appraisal guidance 10 (2000)
- Bronchial thermoplasty for severe asthma. NICE interventional procedure guidance 419 (2012)
- Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and Nobreath. NICE diagnostics guidance 12 (2014)
- Asthma quality standard. NICE quality standard 25 (2013)

Asthma overview



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3 Context

3.1 Key facts and figures

Asthma is a chronic disease of the lungs characterised by variable airflow limitation, inflammation and hyperactivity of the airways. It is estimated that between 3.1 million people (QOF 2011/2012) and 5.4 million (Asthma UK) people have asthma in the United Kingdom affecting in the region of 6% of the population.

The aims of asthma management are to optimise current control of symptoms and daily activities and prevent future risk of asthma attacks including hospital admission and death.

Despite available effective treatment, there are data to show that asthma is still poorly controlled. For example, 39% adult women and 30% men, 48% children had experienced an asthma attack in the previous 12 months (Health Survey for England 2010) with around 1000 deaths from asthma occurring each year in the UK (RCP NRAD 2014) and is a common cause for hospital admission (54,789 admissions in the UK in 2011/12 Department of Health). There is also some evidence to show that asthma control is worse in certain ethnic groups.

This guideline aims to give guidance on cost-effective management of asthma in children and adults to improve control of asthma and minimise future risk of asthma attacks.

3.2 Current practice

Most adults and children with asthma are managed in primary care by general practitioners, pharmacists and practice nurses with a few patients needing management in secondary care. Current guidelines (BTS/SIGN 2014) advise limiting exposure to known triggers, individualised self-management action plans and stepwise titration of preventive treatment tailored to the individual patient's severity of illness. Regular review and monitoring of symptoms and asthma attacks is advised in all patients with a diagnosis of asthma to identify poor control and poor adherence to treatment.

However, there is considerable variation in following these guidelines, highlighted in the National Review of Asthma Deaths by the Royal College of Physicians (RCP NRAD 2014). Deficiencies in health professionals' implementation of these guidelines were found in 46% of deaths. Only 23% of patients were provided with a personal

asthma action plan, 39% had excessive prescription of reliever medication, 80% had under-prescription of preventer treatment and 14% were prescribed a single component long acting beta agonist despite clear guidance not to. Avoidable patient factors contributing to asthma deaths included current tobacco smoking in 19%, poor recognition of the risk of adverse outcome in children and young people and psychosocial factors including depression, mental health issues and drug misuse in 26%.

People in whom there is diagnostic uncertainty or who have poor control despite apparent adequate treatment have their asthma managed in secondary care with specialist investigation and treatment. A small proportion of people with difficult to treat asthma have their asthma managed in tertiary centres with specialist investigations and treatment modalities. Referral to specialist care is recommended for people whose asthma is poorly controlled despite being on optimum therapy but the RCP NRAD 2014 findings that more than half the people who died were not under specialist care in the preceding 12 months suggests that this does not always happen.

In summary, the implementation of current guidelines for the management of asthma in children and adults is variable with the result that there is high proportion of people with poorly controlled asthma and there is a high preventable mortality rate from this condition.

4 Further information

This is the draft scope for consultation with registered stakeholders. The consultation dates are 15 April to 13 May 2015.

The guideline is expected to be published in 2017.

You can follow progress of the guideline.

Our website has information about how NICE guidelines are developed.

Appendix B: Declarations of interest

The September 2014 version of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

John Alexander (Chair)

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	In 2014 received payments from Abbvie for an advisory board and giving a talk.	Personal financial non-specific	Declared and participated
	JAl's Trust paediatric respiratory team had two time-out days on 10 July 2014 and 13 November 2014 which was facilitated by organisational development professionals from GSK.	Non-personal non-financial specific	Declared and participated
	Asked to give a talk on the management of life threatening asthma to the West Midlands Paediatric Respiratory forum aimed at DGH paediatricians. The forum is sponsored through an "arm's length" educational grant from GSK which pays for room hire and lunch. The money for the room hire went directly to the venue. There are no speaker fees or expenses paid.	Non-personal non-financial specific	Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No change to existing declarations.	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee	Chaired a clinical forum discussing the use of High Flow	Reasonable travel expenses	Declared and participated

Committee meeting	Declaration of interest	Classification	Action taken
meeting 16/02/2016	Nasal Cannula Oxygen treatment in children with respiratory distress. There were presentations and discussion from local and international experts. Travel Expenses (industry standard mileage) and hotel accommodation for all attendees was paid for by Fisher Paykel, one of the companies that manufacture devices that deliver High Flow oxygen. Did not receive any fees.		
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Noel Baxter

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	Executive member of PCRS-UK and an Asthma UK Council of Health Professionals member.	Personal non-financial specific	Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No change to existing declarations.	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Andrew Bush

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	Earns a small sum from book royalties.	Personal financial non-specific	Declared and participated
	Will cease to be Editor in Chief of Thorax, from which I have no personal gain, in 2015.	Personal non-financial specific	Declared and participated
	No financial contact with pharmaceutical companies.	N/A	N/A
	Inherited a small number of shares but none medically pertinent.	Personal financial non-specific	Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No change to existing declarations.	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
04/04/2016			
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Susan Frost

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	Chair of the National Paediatric Respiratory and Allergy Nurses Group (NPRANG). The NPRANG apply for annual educational grants from pharma companies, the last being from Novartis. SF is not a signatory for NPRANG funds – only the treasurer and vice treasurer are. Any grants/payments are paid to NPRANG to the treasurer. The NPRANG also holds annual conferences where pharmaceutical companies pay to have a stand to display to all	Non-personal financial specific	Declared and participated

Committee meeting	Declaration of interest	Classification	Action taken
	NPRANG members. An evidence review group member for the BTS/SIGN guidelines for asthma.	Personal non-financial specific	Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No change to existing declarations.	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	As Chair of National Paediatric Respiratory and Allergy Nurses Group (NPRANG) we are currently organising our next national conference. Pharma companies are being approached by one of our committee members who is responsible for pharma liaison. If they agree to sponsor our	Non-personal financial specific	Declared and participated

Committee meeting	Declaration of interest	Classification	Action taken
	conference, they are offered a stand at the event. This is purely an educational event – however as this is our 20th year celebrations Airsonett have given a donation towards our evening celebratory event where 80 Paediatric Respiratory and Allergy Nurses from across the UK will be attending for a pre-conference dinner. They have asked for a 10 minute session on the evening to talk about Airsonett. The other pharma companies' payments are pooled to fund the conference and will paid directly into NPRANG's bank account.		
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	Attended a SANN committee meeting and GSK brought the sandwich lunch and were present at lunch time. No other funding was provided by GSK.	Personal non-financial specific	Declared and participated

Chris Griffiths

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	Chair of an evidence review group on the BTS/SIGN guideline	Personal non-financial specific	Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
19/10/2015			
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Helen Haley

GC meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	None.	N/A	N/A
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No change to existing declarations.	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
02/09/2016			
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Val Hudson

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	In April 2015 VH was asked by Praxel if she would speak as a person with asthma about the challenges of using inhalers to Boehringer Ingelheim Respimat Consultancy Board Meeting in Amsterdam at very short notice because the Dutch patient had dropped out at the last minute. Praxel arranged standard class same day return flights for VH. VH was not expecting payment but received a large bouquet of flowers from Praxel the following week as a 'thank you'. Attended a similar event in Berlin in April 2014. Praxel arranged standard class flights and VH was accommodated in the conference venue. VH did not receive payment for this.	Reasonable travel expenses Reasonable travel expenses	Declared and participated Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No change to existing declarations.	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth	No change to existing	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
committee meeting 05/01/2016	declarations.		
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	On Monday 6th September I attended the ERS Annual Meeting as a delegate. My registration fee of 335 Euros was paid for by Owlstone Medical who asked me to attend their discussion on 'Contributing to the design of a clinical trial on stratification in asthma through breath analysis' as a patient representative. My accommodation and travel expenses were paid by Asthma UK as I attended other meetings outside the Conference Centre on their behalf.	Reasonable travel expenses	Declared and participated
Fourteenth committee	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
meeting 14/03/2017			

Matt Masoli

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	Preceptorship to attend Bronchial thermoplasty training at Wythenshaw Hospital Manchester with Dr R Niven in December 2014. Travel expenses supported by Boston Scientific.	Personal financial non-specific	Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	Involved as a local PI for a number of clinical trials in severe asthma including Mepolizumab, Benralizumab and lebrikizumab which are conducted by GSK, Astra-Zeneca and Roche respectively. Monies for trial involvement paid to the Trust R&D. Supported by Astra Zeneca to attend the European respiratory Society annual conference in September 2015.	Non-personal financial specific Reasonable travel expenses	Declared and participated Declared and particpated
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/09/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Nicola Mundy

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	None.	N/A	N/A
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No changes to existing declarations	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/05/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Prunella Neale

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	None.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No changes to existing declarations	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/05/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	No change to existing declarations.	N/A	N/A
Eleventh committee meeting 12/07/2016	Undertook: Ipsos MORI telephone interview on behalf of NHS England 21.6.2016 Subject: Recruitment and Retention of General Practice Nurses Fee : £50	Personal financial non-specific	Declared and participated
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth	No change to existing	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
committee meeting 04/10/2016	declarations.		
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Ellen Nicholson

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	None.	N/A	N/A
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No changes to existing declarations	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	Professional Educational funding from Boehringer Ingelheim for 2-day conference pass and associated travel to Winter British Thoracic Society Conference in London.	Reasonable expenses	Declared and participated
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
meeting 10/05/2016			
Tenth committee meeting 14/06/2016	Speaker at Teva Respiratory Masterclass on Diagnostic Tools for Respiratory Diseases 11/06/2016 at Hadley Wood, receiving no financial incentive for participation. Teva have combined this Masterclass with Napp Pharmaceutical Group Ltd.	Personal non-financial specific	Declared and participated
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Stephen Scott

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	Declared that he has no personal financial interests to declare.	N/A	N/A
	Principal investigator for multicentre clinical trials involving Astra Zeneca, Boehringer Ingelheim, Novartis. SS is not sole signatory as the funds go through the Hospital Trust R&D, but has arranged for another consultant to become the signatory.	Non-personal financial specific	Declared and participated
	Chair of the British Thoracic Society Asthma Specialist Advisory Committee.	Personal non-financial specific	Declared and participated

Committee meeting	Declaration of interest	Classification	Action taken
	Previously a member of the Evidence Review Group for "Delivery and Organisation of Care" as part of the BTS/SIGN Asthma Guidelines. Currently joint chair of the "Acute Management of Asthma" evidence review group for the BTS/SIGN Asthma Guidelines and therefore part of the steering committee.	Personal non-financial specific Personal non-financial specific	Declared and participated Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No changes to existing declarations	N/A	N/A
Fourth committee meeting 23/11/2015	No change to existing declarations.	N/A	N/A
Fifth committee meeting 05/01/2016	No change to existing declarations.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/05/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	I am secretary of the North West Thoracic Society. This position means I introduce speakers at the meetings for respiratory physicians in the North West. I have no direct	Personal non-financial specific	Declared and participated

Committee meeting	Declaration of interest	Classification	Action taken
	pecuniary benefit from this and it is a voluntary/nominated position. It is a purely educational meeting with no presentations or input from pharma into the content of the meeting. However Boehringer do provide funding for the venue and catering but have no input into the speakers who are decided on by the secretary team.		
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Lindsay Apps (co-opted member)

Committee meeting	Declaration of interest	Classification	Action taken
Tenth committee meeting 14/06/2016	None.	N/A	N/A

Charlotte Church (co-opted member)

Committee meeting	Declaration of interest	Classification	Action taken
Second committee meeting 02/09/2015	None.	N/A	N/A

Kevin Gruffydd-Jones (co-opted member)

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	In the last 12 months has acted as a consultant for, and received sponsorship to attend conferences from, various pharmaceutical companies.	Personal financial specific	Declare and withdraw from review questions on pharmacological management. Declare and participate for non-pharmacological management as co-opted expert adviser.
	Acted as an expert reviewer of the BTS/SIGN Asthma guideline.	Personal non-financial specific	Declare and participate
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/05/2015	No change to existing declarations.	N/A	N/A

NGC team

Committee meeting	Declaration of interest	Classification	Action taken
First committee meeting 07/07/2015	In receipt of NICE commissions.	N/A	N/A
	Bernard Higgins is the Chair of the British Thoracic Society.	Personal non-financial specific	Delcared and participated
	Bernard Higgins' Department takes part in multi-centre studies funded by various companies (over which he has no financial control).	Non-personal financial specific	Declared and participated
Second committee meeting 02/09/2015	No change to existing declarations.	N/A	N/A
Third committee meeting 19/10/2015	No change to existing declarations.	N/A	N/A
Fourth committee	No change to existing declarations.	N/A	N/A

Committee meeting	Declaration of interest	Classification	Action taken
meeting 23/11/2015			
Fifth committee meeting 05/01/2016	Bernard Higgins' term of office as Chair of the British Thoracic Society ended December 2015.	N/A	N/A
Sixth committee meeting 16/02/2016	No change to existing declarations.	N/A	N/A
Seventh committee meeting 04/04/2016	No change to existing declarations.	N/A	N/A
Eighth committee meeting 05/04/2016	No change to existing declarations.	N/A	N/A
Ninth committee meeting 10/05/2016	No change to existing declarations.	N/A	N/A
Tenth committee meeting 14/06/2016	Abigail Moore received a grant from Macmillan for a project on breathlessness in cancer patients.	Personal financial non-specific	Declared and participated
Eleventh committee meeting 12/07/2016	No change to existing declarations.	N/A	N/A
Twelfth committee meeting 02/09/2016	No change to existing declarations.	N/A	N/A
Thirteenth committee meeting 04/10/2016	No change to existing declarations.	N/A	N/A
Fourteenth committee meeting 14/03/2017	No change to existing declarations.	N/A	N/A

Appendix C: Clinical review protocols

C.1 Treatment in patients not on regular preventers

Table 1: Review protocol: PRN SABA versus regular ICS + PRN SABA

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)?**
Objectives	To compare SABA (as required) alone to the use of SABA (as required) plus a preventer drug for the management of people with asthma who are treatment naïve.
Review 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 years ○ 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.
Line of therapy	First-line treatment
Interventions and comparators: generic/class (specific/drug)	• SABA PRN (salbutamol, albuterol, terbutaline) • SABA PRN + 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) Note: ICS/LABA given as maintenance and reliever therapy will be considered as a separate intervention to ICS/LABA plus SABA PRN. **Exclusions:** Placebo/no treatment (without the use of SABA) as current practice is for people with asthma to be on at least a SABA, however, SABA + placebo versus SABA + preventer will be included. Comparisons of individual drugs/devices Comparisons of different preventer classes (SABA + any preventer) will be pooled in the analysis as the aim is to compare whether starting on a SABA plus any preventer is superior to starting on a SABA alone. Different preventer classes will be compared in the review of the most clinically and cost-effective first-line preventer drug.

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)?
	Strategy: All interventions will be combined within the drug class for analysis unless otherwise stated, regardless of delivery device
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 ≥3 months) **Important outcomes:** Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months) Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal results on short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted. Crossover studies are not appropriate for this question as the aim is to investigate the best first-line treatment for people who are treatment naïve. Previous preventer medication will affect the inflammation in the airways. A 'pseudo' treatment-naïve population of people who have not received asthma medication for at least a month is included to allow for the fact that people may have received medication intermittently in the past or during diagnosis.
Minimum duration of study	Minimum duration of studies should be 3 months in order to show a clinically relevant benefit or harm in even the most short-term outcomes.
Other exclusions	Non-randomised studies/observational studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Other stratifications	None
Subgroup analyses if there is heterogeneity	• Smoker versus non-smoker/ex-smoker (SABA+ICS might be more effective than SABA alone in smokers) • Recent asthma exacerbation (in the last year) versus no recent asthma exacerbation • Regular/daily symptoms or wheeze versus occasional symptoms or wheeze.
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results.

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)?
	Minimally important differences: Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review. Other: For the outcome of lung function by FEV_1, for the ≥16 age stratum, FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase and The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.2 Choice of first-line preventer in patients with poor asthma control

Table 2: Review protocol: First-line preventer

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)?

Objectives	To compare the preventer drug classes specified (or combination of drug classes) for the first-line management of people with asthma who have never been prescribed preventer medication (or have been preventer naïve for at least 1 month).
Review 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 should be uncontrolled on SABA alone as defined by the study (providing the definition is in line with either BTS/SIGN or GINA guidelines for uncontrolled) or, if not specified by the study, if it is clear that patients are 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 general asthma population on SABA with a mixture of people who are controlled and uncontrolled will only be included if at least 75% of people were uncontrolled on SABA. Studies recruiting a heterogeneous population of preventer-naïve (or no preventer for at least 1 month) and people on a preventer will only be included if at least 90% of the people were preventer-naïve (or no preventer for at least 1 month). Population strata: • Age: o <1 year o 1 to <5 years o 5 to <16 years o ≥16 years **Exclusions** People already on preventer treatment or previous use of preventer in the last 1 month (includes use of ICS, LABA, theophylline, cromolyns, leukotriene receptor antagonists or regular ipratropium in the last month [ipratropium used PRN as a reliever is acceptable]). Studies including a general asthma population on SABA with no breakdown of whether they were controlled or uncontrolled on SABA. Studies in which all people are on a preventer at enrolment and there is a wash-out period to destabilise the patient so they are uncontrolled.
Line of therapy	First-line preventer
Interventions and comparators: generic/class (specific/drug)	• Placebo/no treatment • Regular 'low dose' ICS (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) • Regular 'moderate dose' ICS (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) • Regular 'high dose' ICS (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone)

	• ICS+LABA (regular ICS+LABA with PRN SABA) • ICS+LABA (formoterol) used as maintenance and reliever therapy (for example SMART or MART therapy) • Leukotriene receptor antagonist (montelukast, zafirlukast) +/- ICS • Theophylline or aminophylline +/- ICS • Cromolyns (sodium cromoglicate, nedocromil) +/- ICS Note: ICS low, moderate and high dose as defined in the 2015 GINA guideline: see Appendix Q for details. **Exclusions:** Studies that start high ICS dose and titrate down to the same dose as the low dose arm within the study period. Comparisons of individual drugs/devices (not class effect for example ICS A in device A versus ICS B in device B) **Strategy:** All interventions will be combined within the drug class for analysis unless otherwise stated, regardless of delivery device All classes with be compared with each other, unless otherwise stated Patients may be on concurrent SABA as required (salbutamol, albuterol, terbutaline) – both arms of the trial should be on the same concurrent treatments (with the exception of when ICS/formoterol is also used as the reliever medication and no SABA is given)
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 ≥3 months) **Important outcomes:** Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months) Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal results on short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of	Minimum duration of studies should be 3 months, in order to show a clinically

study	relevant benefit or harm in even the most short-term outcomes.
Other exclusions	Non-randomised studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use and control status, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Other stratifications	None
Subgroup analyses if there is heterogeneity	• Prior asthma exacerbation in the last year versus no exacerbation in the last year (high doses may be more effective in people who have had a recent exacerbation) • Smoker versus non-smoker/ex-smoker (high doses might be more effective than low doses in smokers) • Completely preventer naïve versus previous preventer use (note: this preventer use would be more than 1 month ago to meet the protocol population)
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospiatlisations which are a separate outcome in this review. **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum, FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if

	that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.3 Escalating pharmacological treatment in patients poorly controlled on low dose ICS

C.3.1 Second-line preventer

Table 3: Review protocol: Second-line preventer

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?
Objectives	To compare the preventer drug classes specified (or combination of drug classes) for the second-line management of people with asthma who have never been prescribed a second-line preventer (or have not been prescribed a second-line preventer for at least 1 month).
Review population	People with a clinician diagnosis of asthma who are uncontrolled on low dose ICS. Population should be uncontrolled on low dose ICS as defined by the study (providing the definition is in line with either BTS/SIGN or GINA guidelines for uncontrolled) or, if not specified by the study, if it is clear that people are 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 general asthma population on low dose ICS with a mixture of people who are controlled and uncontrolled will only be included if at least 75% of people were uncontrolled on low dose ICS. Studies recruiting a heterogeneous population of people on low dose ICS and people on any additional or alternative preventers will only be included if at least 90% of the people are on low dose ICS only. Population strata: • Age: ○ <1 year ○ 1 to <5 years ○ 5 to <16 years ○ ≥16 years **Exclusions:** People already on second-line preventer treatment or previous use of second-line preventer within the month prior to trial (including use of ICS moderate dose, ICS high dose, theophylline, cromolyns, leukotriene receptor antagonists or regular ipratropium in the last month [ipratropium used PRN as a reliever is acceptable]).
Line of therapy	Second-line preventer
Interventions and comparators: generic/class	ICS + placebo or no increase in ICS dose – that is, staying on optimal single preventer therapy. Increasing dose of regular ICS to 'moderate dose' (budesonide, beclometasone

(specific/drug)	dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) Increasing dose of regular ICS to 'high dose' (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) ICS + LABA (salmeterol, formoterol, vilanterol) ICS + LABA (formoterol used also as the reliever medication for example SMART or MART therapy) ICS + LAMA (tiotropium) ICS + leukotriene receptor antagonist (montelukast, zafirlukast) ICS + theophylline or aminophylline ICS + cromolyns (sodium cromoglicate, nedocromil) Note: ICS low, moderate and high dose as defined in the 2015 GINA guideline: see Appendix Q for details. **Exclusions:** Comparisons of individual drugs/devices (not class effect for example ICS A in device A versus ICS B in device B) **Strategy:** All interventions will be combined within the drug class for analysis unless otherwise stated, regardless of delivery device All classes with be compared with each other, unless otherwise stated Patients may be on concurrent SABA as required (salbutamol, albuterol, terbutaline) – both arms of the trial should be on the same concurrent treatments (with the exception of when formoterol is also used as the reliever medication and no SABA is given)
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 ≥3 months) **Important outcomes:** Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months) Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal results on short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of	Minimum duration of studies should be 3 months in order to show a clinically

study	relevant benefit or harm in even the most short term outcomes.
Other exclusions	Non-randomised studies/observational studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use and control status, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Other stratifications	None
Subgroup analyses if there is heterogeneity	• Smoker versus non-smoker/ex-smoker (SABA+ICS might be more effective than SABA alone in smokers) • Recent asthma exacerbation (in the last year) versus no recent asthma exacerbation • Regular/daily symptoms or wheeze versus occasional symptoms or wheeze.
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review. **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum, FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase, The Cochrane Library.

	Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

Table 4: Review protocol: MART

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?
Objectives	To compare MART and ICS + LABA as preventer + SABA as reliever therapy for the management of people with asthma who are on ICS + LABA or require ICS + LABA.
Review population	People with a clinician diagnosis of asthma who are on ICS + LABA (alongside PRN reliever SABA therapy) or require ICS + LABA therapy according to the study. Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years
Line of therapy	Second to third-line preventer
Interventions and comparators: generic/class (specific/drug)	MART (maintenance and reliever therapy) with ICS + LABA (any dose, any specific ICS/LABA where the LABA has fast onset of action [for example formoterol]) versus ICS + LABA as preventer therapy + separate SABA as reliever inhaler Exclusions: Placebo/no treatment Comparisons in which the preventer dose of ICS + LABA varies between arms Any MART arms in which the reliever component does not consist of both ICS and LABA Within class comparisons of individual drugs/devices (not class effect, for example ICS A in device A versus ICS B in device B)
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 ≥3 months) **Important outcomes:** Total steroid dose (continuous outcome at ≥3 months) Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months)

	Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal results on short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Minimum duration of studies should be 3 months, in order to show a clinically relevant benefit or harm in even the most short-term outcomes.
Other exclusions	Non-randomised studies/observational studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Other stratifications	None
Subgroup analyses if there is heterogeneity	• Prior asthma exacerbation in the last year versus no recent exacerbation (regular ICS may be more effective than intermittent in people who have had a recent exacerbation) • Smoker versus non-smoker/ex-smoker (regular ICS may be more effective than intermittent in smokers) • People with seasonal or allergic asthma (intermittent ICS may be more effective in people with seasonal asthma) • Participants previously uncontrolled versus previously controlled
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures.[930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under.

	For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review. **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

Table 5: Review protocol: Third-line preventer

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?**
Objectives	What is the best preventer to add in (drug class or combination of drug classes) for the management of people with asthma who are currently taking optimal second-line preventer therapy but are not adequately controlled?
Review population	People with a clinician diagnosis of asthma who are uncontrolled on preventer therapy beyond ICS low dose. Population should be uncontrolled as defined by the study (providing the definition is in line with either BTS/SIGN or GINA guidelines for uncontrolled) or, if not specified by the study, if it is clear that people are 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 general asthma population with a mixture of people who are controlled and uncontrolled will only be included if at least 75% of people were uncontrolled. Studies recruiting a heterogeneous population of people on different lines of treatment will only be included if at least 90% of the people were on preventer therapy beyond ICS low dose. Studies will be analysed under the prior treatment stratum that best fits their baseline characteristics. Population strata: • Age: ○ <1 year ○ 1 to 5 year ○ 5 to <16 years ○ ≥16 years

	Prior treatment: • ICS moderate dose • ICS high dose • ICS + LABA • ICS + LTRA Exclusions Studies including a general asthma population on ICS low dose with no breakdown of whether they were controlled or uncontrolled.
Line of therapy	Third-line preventer
Interventions and comparators:	Addition of one of the following interventions to preventer therapy beyond ICS low dose: Placebo – that is, staying on previous preventer therapy Increasing ICS dose LABA + PRN SABA ICS + LABA as MART LAMA (tiotropium) LTRA Theophylline or aminophylline Cromolyns (sodium cromoglicate, nedocromil) Oral steroids Note: ICS low, moderate and high dose as defined in the 2015 GINA guideline see Appendix Q for details. **Exclusions:** Comparisons of individual drugs/devices (not class effect for example ICS A in device A vs ICS B in device B) – only MART therapy will be assessed at individual drug level. **Strategy:** All interventions will be combined within the drug class for analysis unless otherwise stated, regardless of delivery device. All classes with be compared with each other, unless otherwise stated. Patients may be on concurrent SABA as required (salbutamol, albuterol, terbutaline) – both arms of the trial should be on the same concurrent treatments (with the exception of when formoterol is also used as the reliever medication and no SABA is given).
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 ≥3 months) **Important outcomes:** Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months) Adverse events: linear growth (continuous outcome at ≥1 year), infections (all

	respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal results on short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Minimum duration of studies should be 3 months, in order to show a clinically relevant benefit or harm in even the most short term outcomes.
Other exclusions	Non-randomised studies/observational studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use and control status, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Subgroup analyses if there is heterogeneity	• Smoker versus non-smoker/ex-smoker (SABA+ICS might be more effective than SABA alone in smokers) • Recent asthma exacerbation (in the last year) versus no recent asthma exacerbation • Regular/daily symptoms or wheeze versus occasional symptoms or wheeze.
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures.[930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a

	separate outcome in this review. **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

Table 6: Review protocol: Intermittent ICS vs daily ICS

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?
Objectives	To compare regular and intermittent ICS therapy for the management of people with asthma who are on ICS only or require ICS only.
Review population	People with a clinician diagnosis of asthma who are on ICS only (alongside PRN reliever SABA therapy) or require ICS therapy according to the study (that is, uncontrolled on PRN SABA alone). Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years **Exclusions:** People who do not require ICS therapy (that is, controlled on SABA alone)
Line of therapy	First-line preventer
Interventions and comparators: generic/class (specific/drug)	Daily (all year round) 'low dose' ICS (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) Intermittent ICS (any dose): (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) Note: ICS low, moderate and high dose as defined in the 2015 GINA guideline: see Appendix Q for details. Intermittent may be: Symptomatic: studies initiating ICS for a short duration only when the person is symptomatic. Seasonal: studies initiating ICS for a defined period when the person is expected to have a worsening of their asthma (for example only during hayfever or mould season, or only during winter if prone to URTIs/viral colds).

	The above definitions of intermittent will be combined in the analysis. The intermittent arm may receive a higher ICS dose than the regular arm. **Exclusions:** Placebo/no treatment Within class comparisons of individual drugs/devices (not class effect for example ICS A in device A vs ICS B in device B) **Strategy:** All interventions will be combined within the drug class for analysis unless otherwise stated, regardless of delivery device All classes with be compared with each other, unless otherwise stated Patients will be on concurrent SABA as required (salbutamol, terbutaline) – both arms of the trial should be on the same concurrent treatments.
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 ≥3 months) **Important outcomes:** Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months) Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal results on short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Minimum duration of studies should be 3 months in order to show a clinically relevant benefit or harm in even the most short term outcomes.
Other exclusions	Non-randomised studies/observational studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Other stratifications	None
Subgroup analyses if there is heterogeneity	• Definition of intermittent (seasonal versus symptomatic) • Prior asthma exacerbation in the last year versus no recent exacerbation (regular ICS may be more effective than intermittent in people who have had a recent exacerbation) • Smoker versus non-smoker/ex-smoker (regular ICS may be more effective than intermittent in smokers)

	• People with seasonal or allergic asthma (intermittent ICS may be more effective in people with seasonal asthma).
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.5 Improving adherence to treatment

Table 7: Review protocol: Adherence

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?
Review 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
Line of therapy	Various
Interventions and comparators: generic/class (specific/drug)	• 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) Strategy: All interventions will be analysed separately (compared against placebo/usual care and compared against each other).
Outcomes	All outcomes are only to 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 (defined as asthma exacerbations requiring oral corticosteroid) (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 ≥3 months) Adherence (continuous outcome at ≥3 months) **Important outcomes**: Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). Adverse events: linear growth (continuous outcome at ≥1 year), infections (all

	respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Minimum follow-up duration for outcomes should be 3 months beyond the end of the intervention in order to show a clinically relevant benefit or harm maintained post-intervention.
Other exclusions	Non-randomised studies/observational studies Conference abstracts
Other stratifications	None
Subgroup analyses if there is heterogeneity	For the asthma education intervention – psychological interventions (for example cognitive behavioural therapy) versus other education interventions).
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review

	Other: For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase and The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.6 Self-management plans

Table 8: Review protocol: Self-management

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?**
Objectives	To evaluate the efficacy of supported self-management for people with asthma. Asthma reviews by a healthcare professional are already recommended in the NICE diagnosis and monitoring guideline, therefore the effectiveness of supported self-management should be in addition to asthma reviews by a healthcare professional (that is, both the control and intervention arms should be having an asthma review according to standard care, not no intervention at all).
Review population	Children and adults with a clinician diagnosis of asthma Setting – primary care and secondary care Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years Exclusions: People who are not being seen by a healthcare professional for reviews of their asthma
Line of therapy	Alongside pharmacological therapy
Interventions and comparators: generic/class (specific/drug)	Optimal supported self-management (only interventions including all these aspects: self-management education, self-monitoring and a written personalised asthma action plan, PAAP). Supported self-management should be on top of standard care (including asthma reviews by a healthcare professional) in order to investigate the added effect of supported self-management. Control group: standard care for asthma which should include regular asthma reviews by a healthcare professional, the control group may include some minimal elements of education (for example inhaler technique training) as this is considered standard practice. **Exclusions:** • PAAPs alone, outside the context of self-management • Self-management that does not include all these aspects: self-management

	education, self-monitoring and a PAAP **Definitions:** Patient asthma education: a programme that provides information about asthma and its management in one or more of the following forms: written, verbal, visual or audio. It may be interactive or non-interactive, structured or unstructured. Minimal education is characterised by the provision of written material alone or the conduct of a short unstructured verbal interaction between a healthcare provider and a patient where the primary goal is to improve patient knowledge and understanding of asthma. Maximal education provides information using both interactive and non-interactive methods. Self-monitoring: consists of the regular measurement of either peak expiratory flow or symptoms (whether or not recorded in a diary). Asthma review: consists of consultations with a healthcare provider during the intervention period for the purpose of reviewing the patient's asthma status and medications. This may occur either as a formal part of the intervention or the patient may be advised to see their own doctor on a regular basis. Interventions may be 'regular review' either inside the programme (if the patient is seen as a part of the programme) or outside the programme (if the patient is merely advised to seek regular medical review). Written action plan: an individualised written plan produced for the purpose of patient self-management of asthma exacerbations. The action plan is characterised by being individualised to the patient's underlying asthma severity and treatment and outlining: when and how to modify medications in response to worsening asthma; and how to access the medical system in response to worsening asthma.
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 ≥3 months) **Important outcomes:** Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Minimum duration of studies should be 3 months, in order to show a clinically relevant benefit or harm in even the most short-term outcomes.

Other exclusions	Non-randomised studies/observational studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Other stratifications	None
Subgroup analyses if there is heterogeneity	Primary versus secondary care/mixed/unclear
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase and The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.7 Dose variation within self-management plans

Table 9: Review protocol: Optimal increase in preventer therapy

Review question	What is the optimal increase in ICS preventer therapy within supported self-management when control is lost?
Objectives	To find the optimal increase in ICS dose within a personalised asthma action plan (PAAP).
Review population	People with a clinician diagnosis of asthma, using ICS preventer therapy, who are receiving supported self-management including a PAAP. Setting – primary care and secondary care Population strata: • Age: ○ <1 year ○ 1 to <5 years ○ 5 to <16 years ○ ≥16 years
Line of therapy	Various
Interventions and comparators: generic/class (specific/drug)	• Self-initiated increase in the dose of 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 • Keeping the usual maintenance dose of ICS as part of a PAAP at the onset of asthma exacerbations. Other co-interventions such as LABA, LTRA etc. could be given, providing that the dose is unchanged throughout the study. SABA medication may be increased or OCS given as part of an asthma exacerbation, providing the same procedure was followed in both arms of the trial. Different increases in dose will be kept separate and the evidence will be presented as multiple pairwise comparisons. Adjustable maintenance dosing (AMD) regimens are not included as they do not look only at how much to increase preventer therapy during exacerbation but also how much to taper it during periods without symptoms.
Outcomes	**Critical outcomes:** Subsequent asthma exacerbations (defined as per study, occurring after index exacerbation requiring treatment as per plan dichotomous outcome) Treatment failure (defined as per study, occurring after index exacerbation, requiring treatment as per plan, dichotomous outcome) Mortality (dichotomous outcome at ≥6 months) Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months)

Review question	What is the optimal increase in ICS preventer therapy within supported self-management when control is lost?
	Important outcomes: Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient
Crossover study	Permitted
Minimum duration of study	Minimum duration of study should be 3 months in order to allow for a reasonable proportion of participants to have experienced an exacerbation requiring the use of their PAAP.
Other exclusions	Non-randomised studies/observational studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Other stratifications	None
Subgroup analyses if there is heterogeneity	• Current smokers versus ex- or non-smokers • ICS dose prior to increase (low versus high) • Primary versus secondary care
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of

Review question	What is the optimal increase in ICS preventer therapy within supported self-management when control is lost?
	asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review. **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase and The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.8 Decreasing regular maintenance treatment

Table 10: Review protocol: Step down

Review question	What are the clinical features (symptoms and/or objective measures) which indicate that a step down in treatment is appropriate?
Objectives	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). 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 wishes 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

Review population	People with a clinician diagnosis of asthma on regular preventer therapy that can be stepped down.
	
	Population strata:
	• Age:
	  ○ <1 year
	  ○ 1–5 years

Review question	What are the clinical features (symptoms and/or objective measures) which indicate that a step down in treatment is appropriate?
	○ 5 to <16 years ○ ≥16 years Evidence will be pooled together regardless of the starting step of preventer medication (for example, people stepped down from ICS therapy will be pooled with people stepped down from ICS+LABA therapy).
Line of therapy	Various
Presence/absence of prognostic variable	Duration for which asthma has been controlled on current therapy (as defined by studies) Recent asthma exacerbation versus no recent asthma exacerbation (as defined by studies) Use of reliever medication (as defined by studies) FeNO (as defined by studies) ACQ score (as defined by studies) ACT score (as defined by studies)
Outcome	Step down successful (dichotomous outcome) – as defined by studies but in concordance with either being controlled according to BTS/SIGN guidelines after ≥4 weeks, without the need to step back up or without asthma exacerbations Statistical outputs may include: Sensitivity, specificity, PPV, NPV, AUC OR/RR/HR
Confounding factors	All other listed prognostic factors are key confounding factors
Study design	• Prospective cohorts, retrospective cohort, randomised trials (if appropriate, that is, randomised to step down after >6 months control versus <6 months control) • Systematic reviews of the above
Minimum duration of study	Minimum time period at which successful step down can be assessed: 4 weeks
Other exclusions	• Studies not considering the majority of key confounding factors in the multivariate analysis • Conference abstracts
Review strategy	A meta-analysis will be conducted if: • the clinical populations are comparable • the prognostic factors being evaluated in the different studies are the same in terms of having the same thresholds and the same referents • the outcomes are highly comparable • a similar array of other prognostic factors (that is, confounders) has been taken into account in the different studies • the measures of effect are the same (for example RR, OR or HR) If the above criteria are not met then the studies will be reported separately and not pooled. The committee will consider both evidence that reports on the association of the presence or absence of a prognostic factor with an eventual positive or negative outcome (in other words adjusted ORs/RRs/HRs for dichotomous data), and evidence that reports on the accuracy of using the presence or absence of a prognostic factors to predict the eventual occurrence of the outcome (in other words sensitivity, specificity, PPV, NPV and AUC).

Review question	What are the clinical features (symptoms and/or objective measures) which indicate that a step down in treatment is appropriate?
	Indirectness: In the ≥16 years and 5 to <16 years groups, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, include the study in the analysis strata for which the average age would fall under.
Search criteria	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only.

C.9 Breathing exercises in addition to pharmacological treatment

Table 11: Review protocol: Breathing exercises versus usual care

Review question	Are breathing exercises clinically and cost effective for children, young people and adults with asthma?
Objectives	To evaluate the efficacy of breathing exercises in the management of people with asthma

Review 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

Line of therapy	Alongside current pharmacological therapy (if on pharmacological therapy)
Interventions and comparators: generic/class (specific/drug)	• Breathing exercises: at least 1 course of treatment comprising of 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. • 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). **Exclusions:** Interventions that incorporate speech and language interventions for vocal cord dysfunction. If the intervention also involves a pharmacological component that is not given to the control arm (for example OCS given with Buteyko technique) or an additional educational component that is not given to the control arm.

	Strategy: All durations of therapy combined Patients may be on concurrent pharmacological therapy – both arms of the trial should be on the same concurrent treatments.
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 – any reported by study (dichotomous outcome at ≥6 months)
Study design	RCT Systematic review
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Minimum follow-up duration for outcomes should be 6 months in order to show a clinically relevant benefit or harm
Other exclusions	Non-randomised studies/observational studies Conference abstracts
Other stratifications	None
Subgroup analyses if there is heterogeneity	• Obese (≥30 BMI) versus non-obese (<30 BMI) – the intervention is expected to be more effective in people with obesity (in children, obesity is defined as a BMI at or above the 95th percentile for children and teens of the same age and sex). • Dysfunctional breathing versus people without dysfunctional breathing (for hyperventilation, dysfunctional breathing is assessed using the Nijmegen Questionnaire) – the intervention is expected to be more effective in people with asthma and dysfunctional breathing.
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used.

	Indirectness: In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

C.10 Managing patients in relation to risk of poor outcomes

Table 12: Review protocol for risk stratification

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?**
Objectives	To compare delivering asthma care to all patients similarly regardless of risk of attack with delivering care stratified by risk of attack.
Review population	People with a diagnosis of asthma Population strata: • Age: ○ <1 year ○ 1 to 5 years ○ 5 to <16 years ○ ≥16 years
Line of therapy	Any
Interventions and comparators:	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
Comparisons	Risk stratified asthma care versus usual care
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 ≥3 months) **Important outcomes:** Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) Hospital admissions (dichotomous outcome at ≥6 months) Reliever/rescue medication use (continuous outcome at ≥3 months) Lung function (change in FEV_1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months) Adverse events: linear growth (continuous outcome at ≥1 year), infections (all respiratory – dichotomous outcome at ≥3 months), infections (serious respiratory (including pneumonia and TB – dichotomous outcome at ≥3 months), adrenal insufficiency (as defined by study, including abnormal results on short synacthen test and morning cortisol, dichotomous outcome at ≥3 months)
Study design	RCT Systematic review of RCTs
Unit of randomisation	Patient or centre
Crossover study	Not permitted
Minimum duration of study	Minimum duration of studies should be 3 months, in order to show a clinically relevant benefit or harm in even the most short-term outcomes.
Other exclusions	Non-randomised studies Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. **Minimally important differences:** Mortality MID=any change; severe exacerbations MID= 0.9 to 1.1; hospitalisations MID=0.9 to 1.1 as per committee agreement. ACT MID=3.0; cACT=3.0; ACQ=0.5; pACQ=0.5; St George's respiratory questionnaire=4.0; AQLQ=0.5; miniAQLQ=0.5; parent/carerAQLQ=0.5 as per validation of these tools. FEV_1 0.23L; PEF 18.79L/min; SABA use -0.81 puffs/day as per published literature for these measures. [930] For all other outcomes, where established MIDs are not available, the NGC default MIDs will be used. **Indirectness:** In the ≥16 years and 5 to <16 years age strata, the quality of the evidence will be

	downgraded for indirectness if the study includes a population with 'a clinician diagnosis of asthma' only, without the use of objective tests in the diagnosis of asthma (for example bronchodilator reversibility, challenge tests, PEF variability, spirometry or FeNO). If the study includes a mixed population of adults and children (for example range 12–70 years) without a subgroup analysis, the study will be included in the analysis strata for which the average age would fall under. For the outcome of severe exacerbations requiring OCS, if a study reports the outcome of severe exacerbations as use of OCS, ED or hospitalisation, this outcome will be included as severe exacerbations but downgraded for indirectness as not all ED visits will require OCS use and some of the events will be hospitalisations which are a separate outcome in this review. **Other:** For the outcome of lung function by FEV_1, for the ≥16 age stratum FEV_1 % predicted will be extracted preferentially if both are reported, FEV_1 in L will be extracted if that is all that is available. For the <16 age strata only FEV_1 % predicted will be extracted.
Search criteria	The databases to be searched are Medline, Embase and The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.

Appendix D: Health economic review protocol

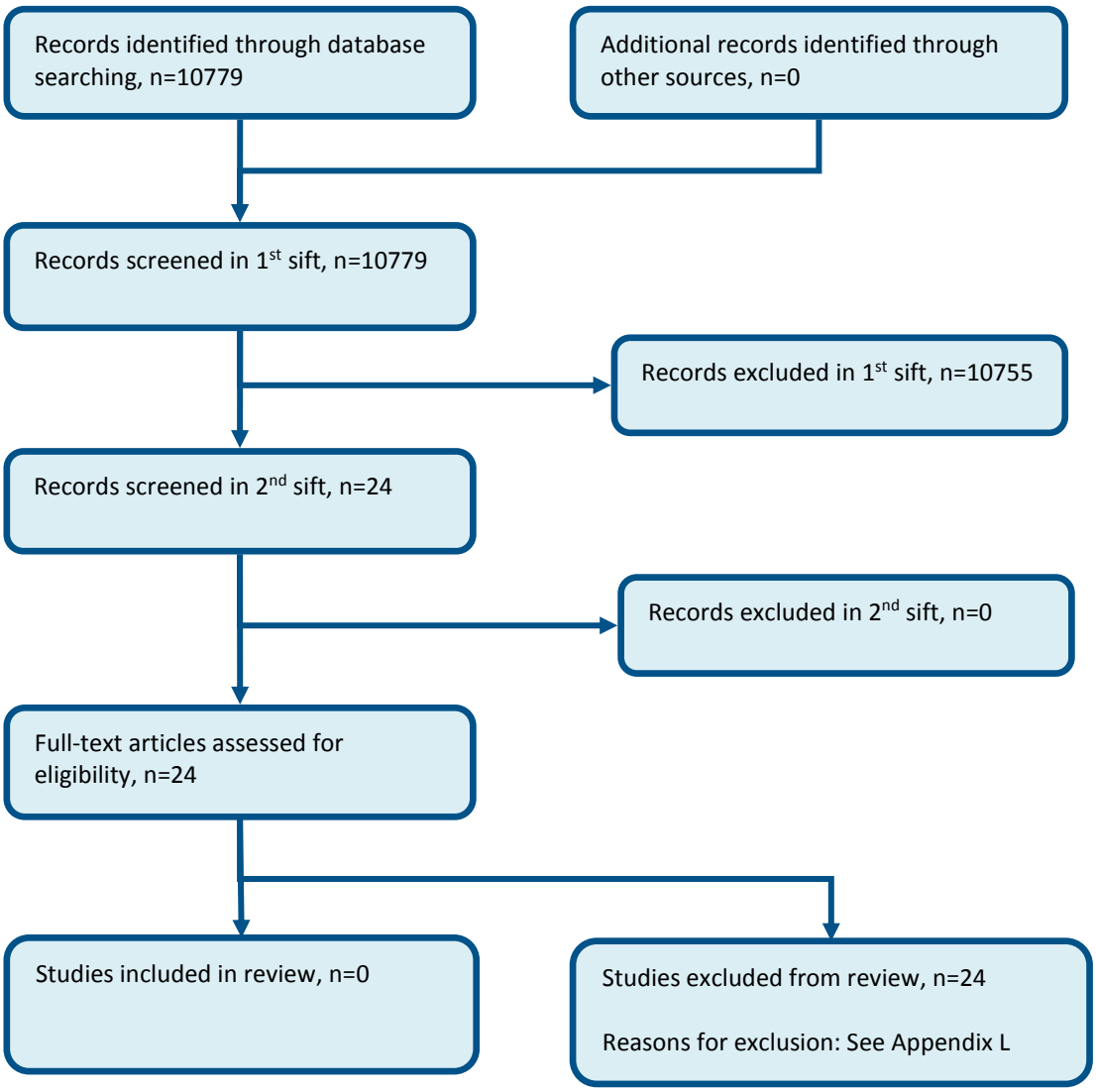
Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the individual review protocol above. Studies must be of a relevant economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	An economic study search will be undertaken which mirrors the clinical study search but with an economic study filter – see Appendix G.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 1999, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012). Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the committee if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example,

Review question	All questions – health economic evidence
	Switzerland). Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. Economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Quality and relevance of effectiveness data used in the economic analysis: The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix E: Clinical study selection

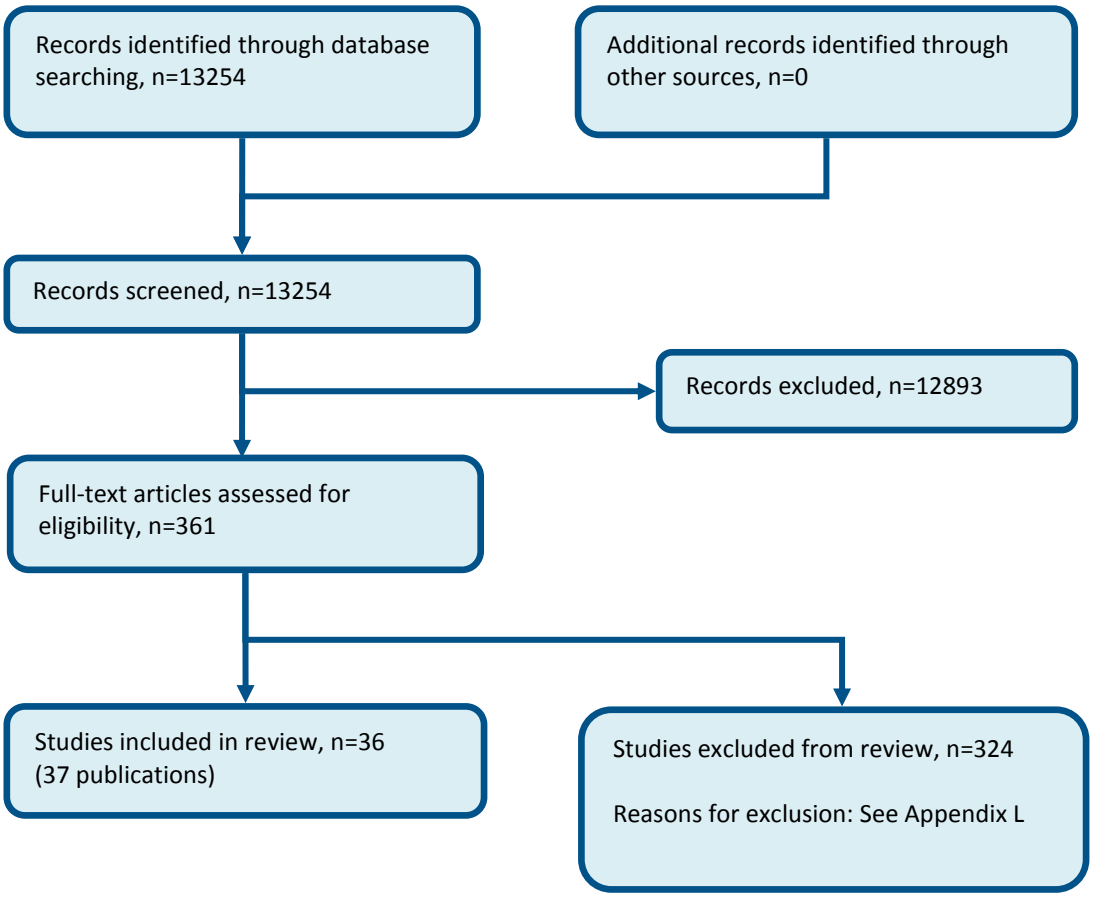
E.1 Treatment in patients not on regular preventers

Figure 1: Flow chart of clinical article selection for the review of Step 1



E.2 Choice of first-line preventer in patients with poor asthma control

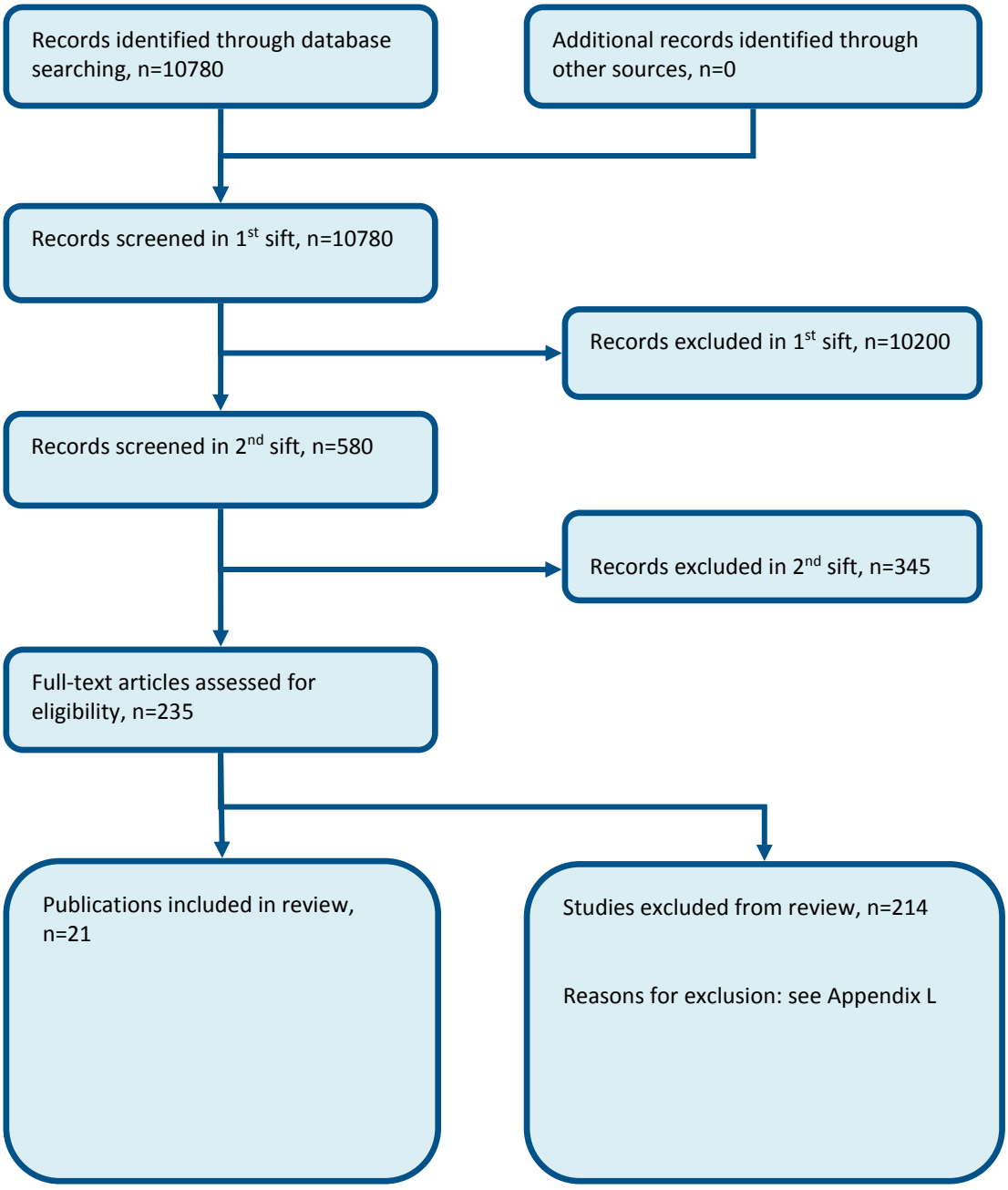
Figure 2: Flow chart of clinical article selection for the review of first-line preventer



E.3 Escalating pharmacological treatment in patients poorly controlled on low dose ICS

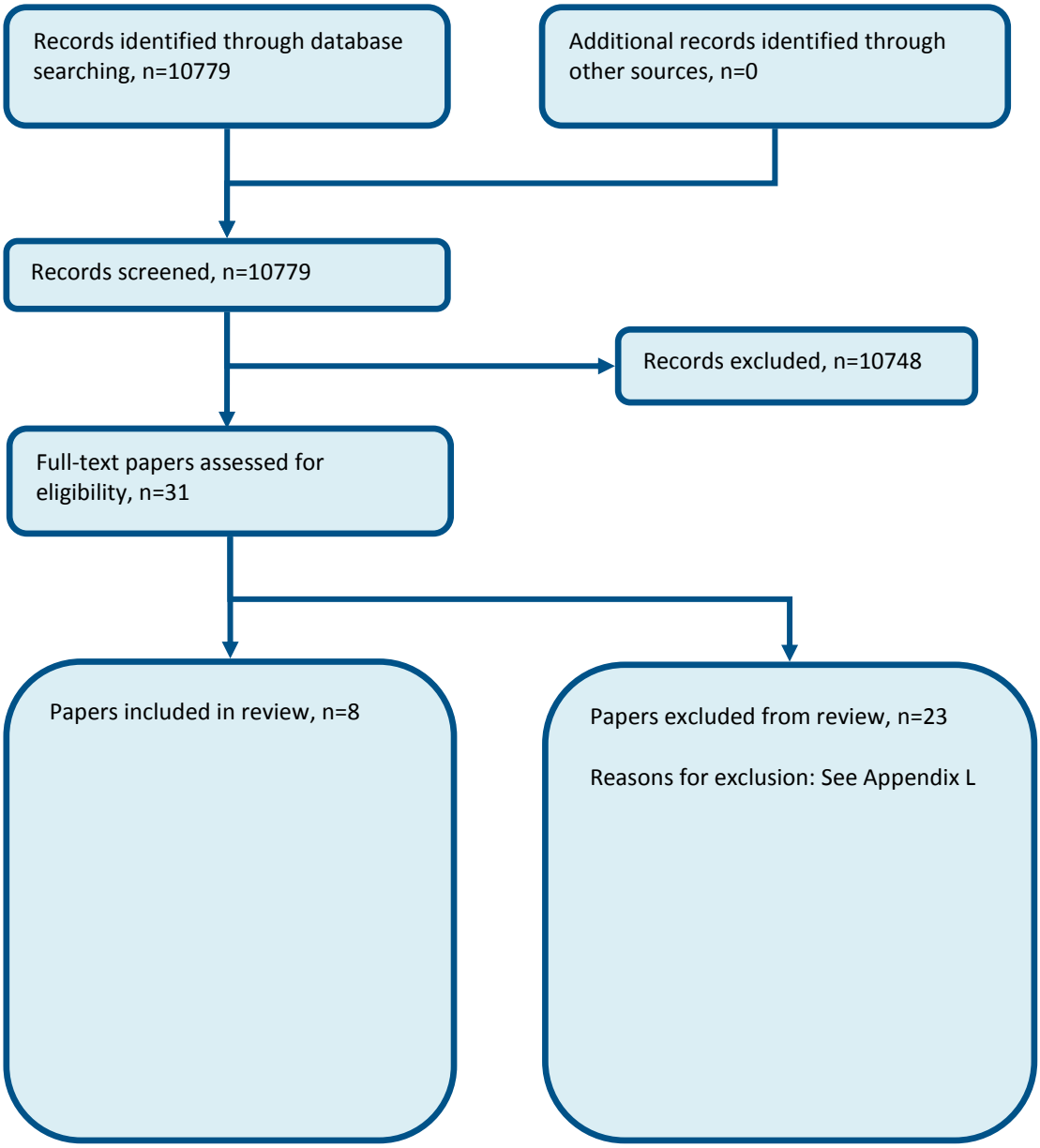
E.3.1 Second-line preventer

Figure 3: Flow chart of clinical article selection for the review of second-line preventers



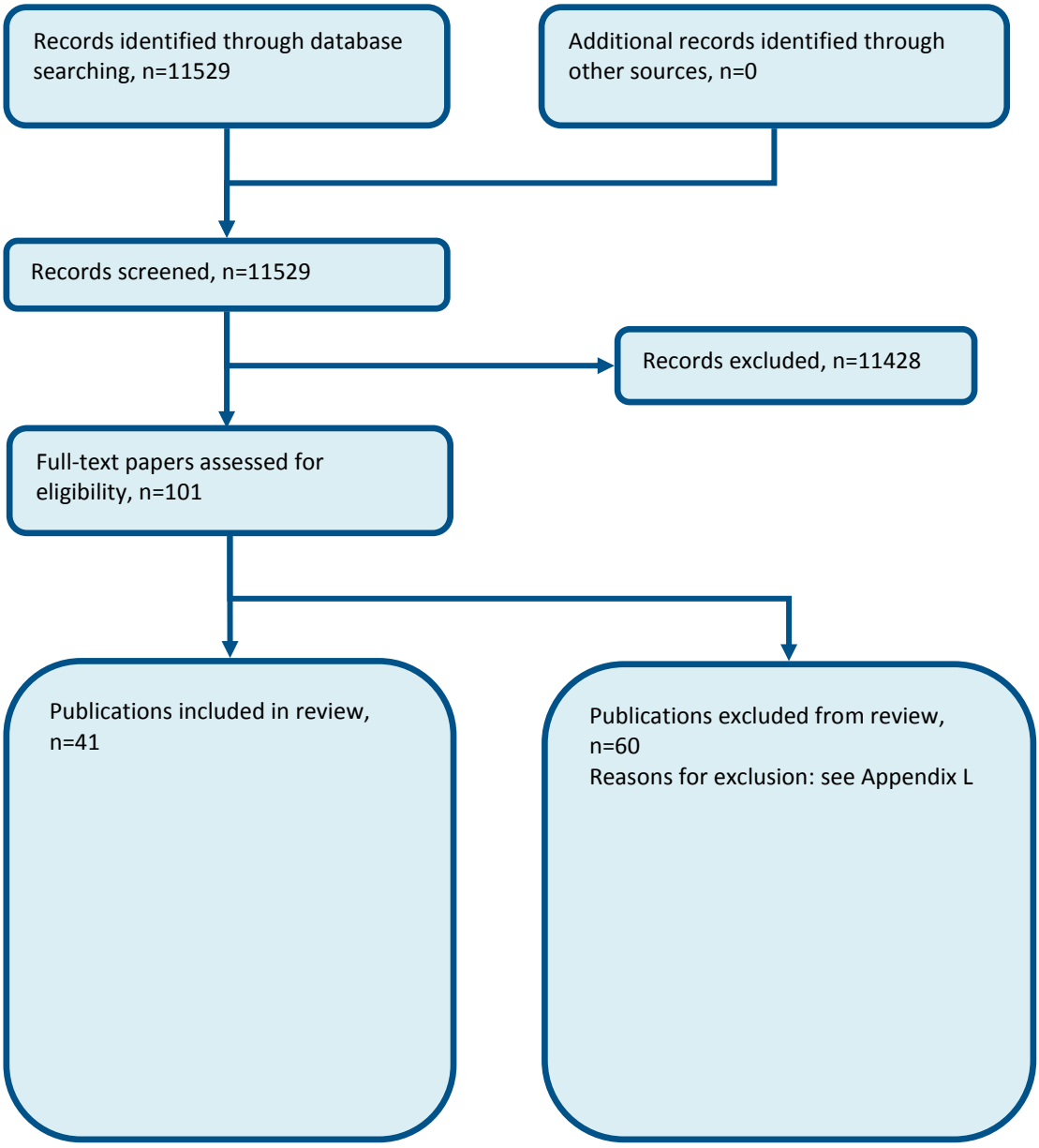
E.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

Figure 4: Flow chart of clinical study selection for the review of MART



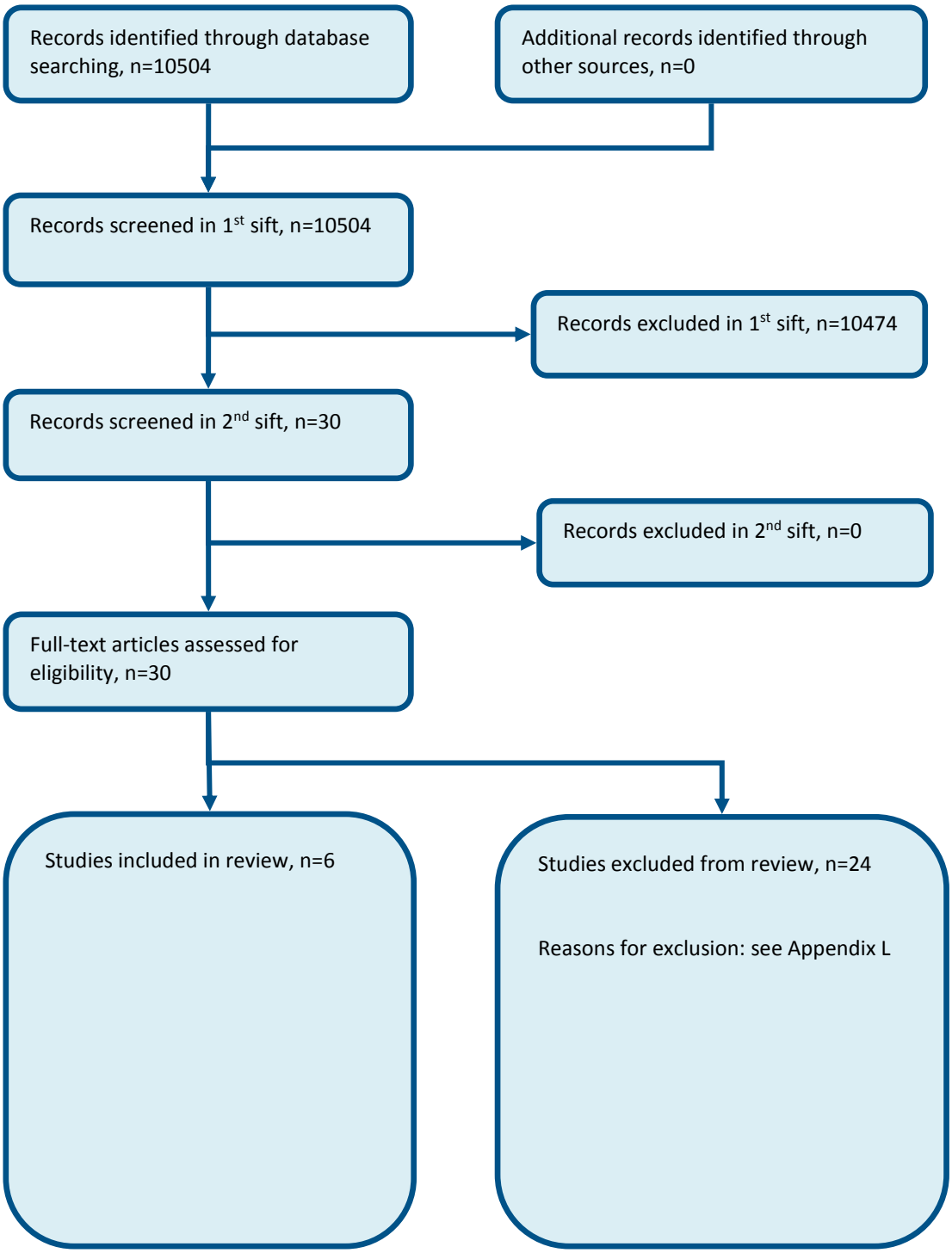
E.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

Figure 5: Flow chart of clinical study selection for the review of third-line preventer



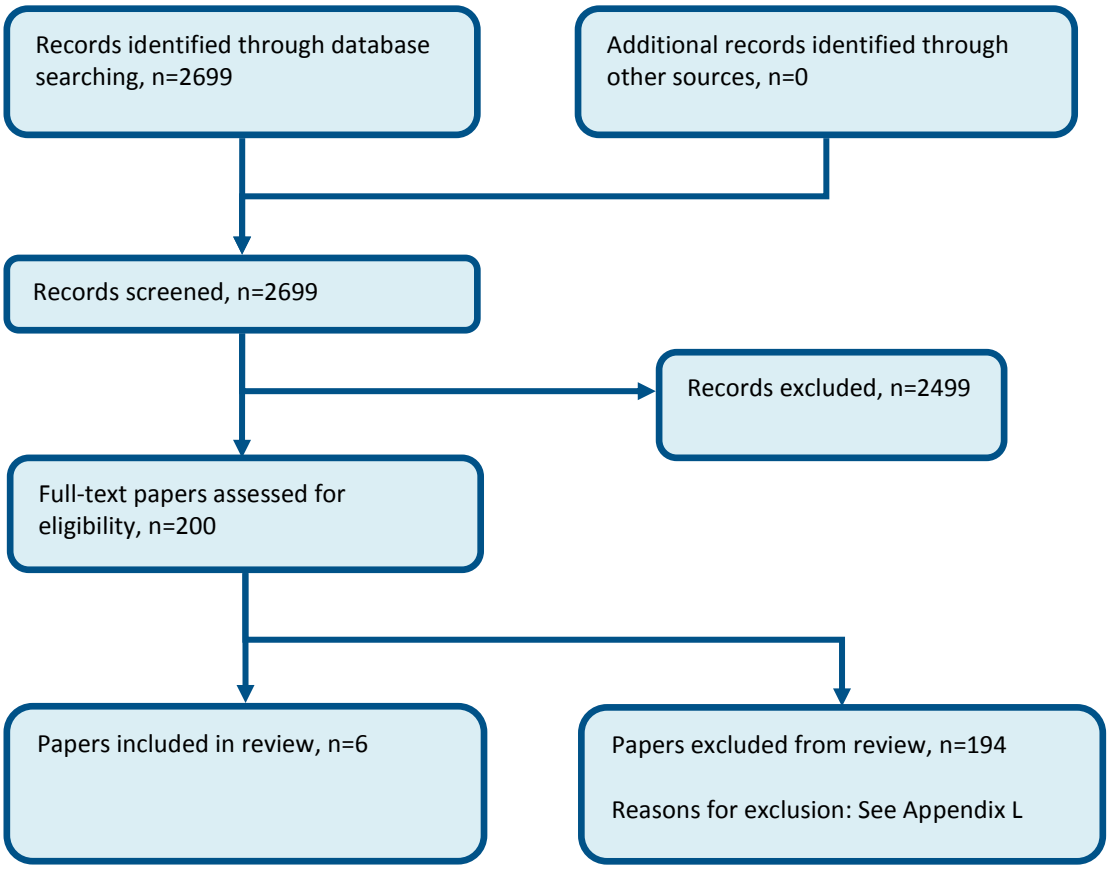
E.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

Figure 6: Flow chart of clinical article selection for the review of daily versus intermittent ICS



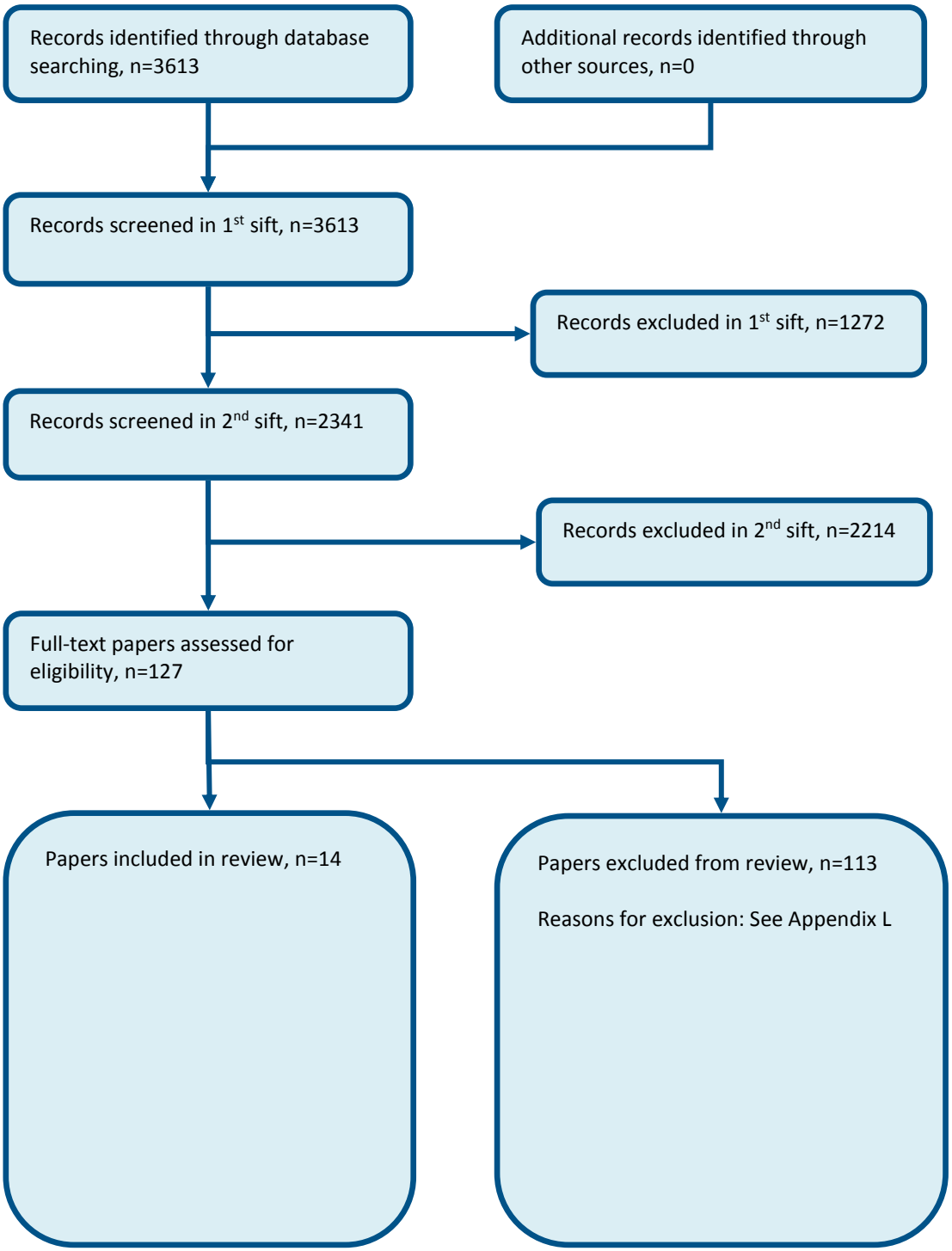
E.5 Improving adherence to treatment

Figure 7: Flow chart of clinical study selection for the review of adherence to treatment



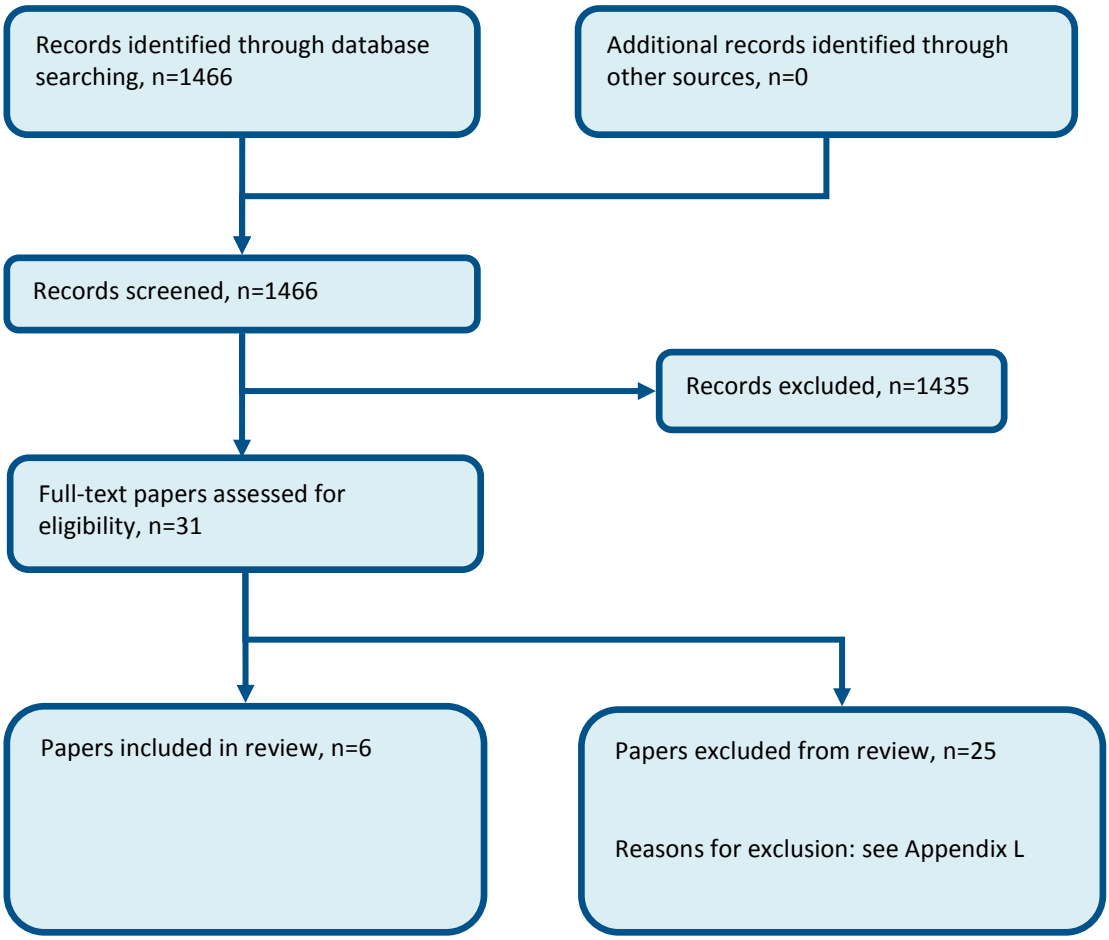
E.6 Self-management plans

Figure 8: Flow chart of clinical study selection for the review of optimal supported self-management



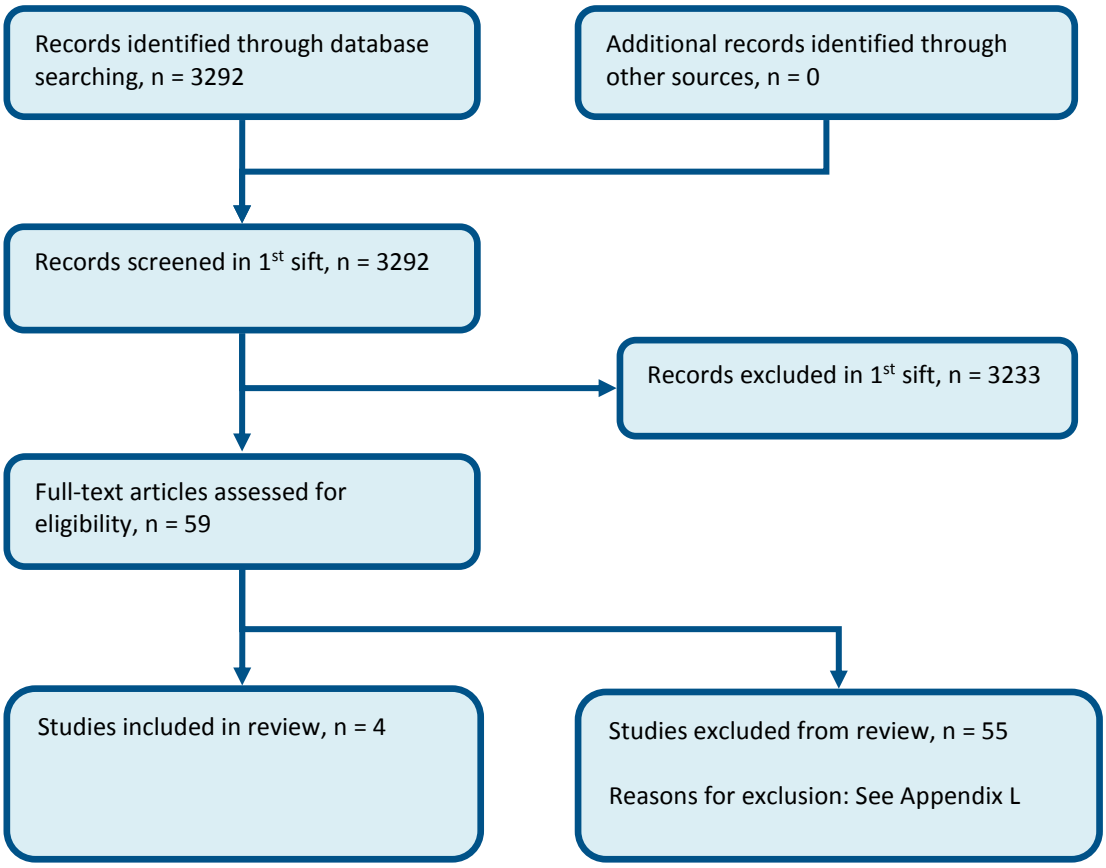
E.7 Dose variation within self-management plans

Figure 9: Flow chart of clinical study selection for the review of optimal increase within personalised asthma action plans



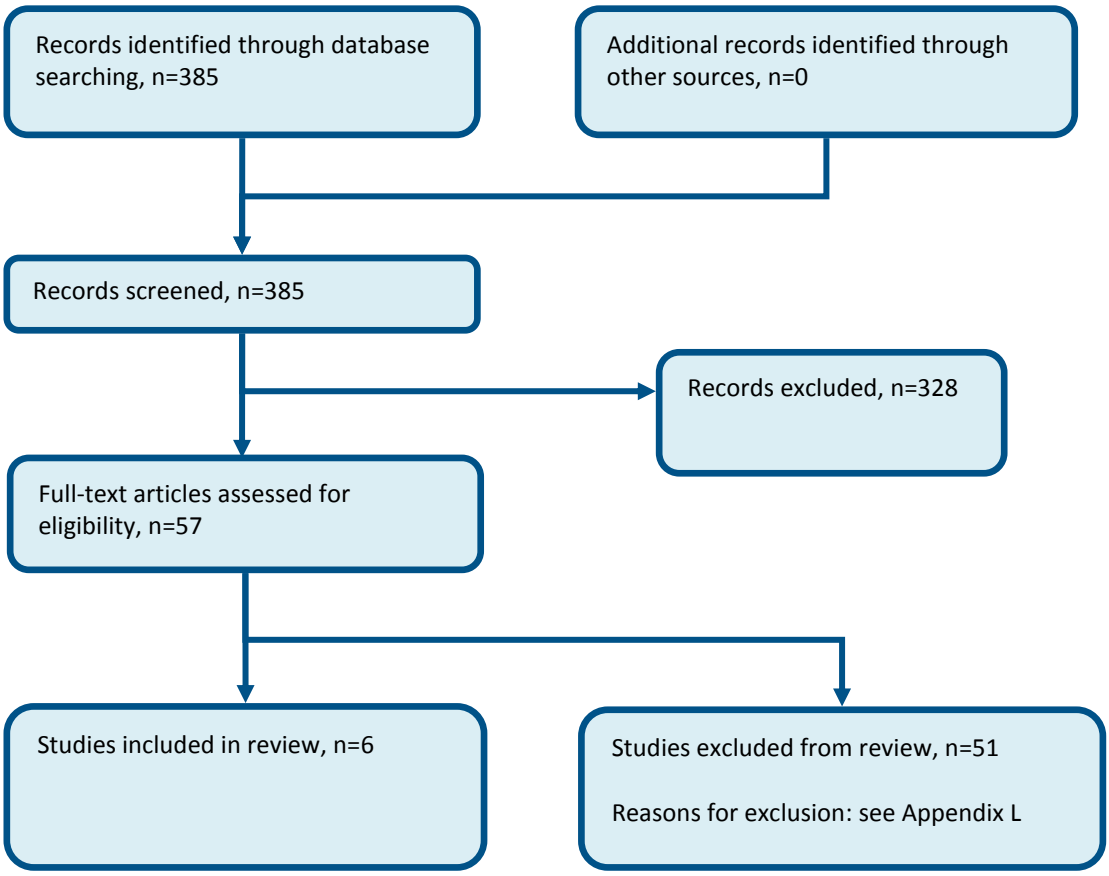
E.8 Decreasing regular maintenance treatment

Figure 10: Flow chart of clinical article selection for the review of decreasing maintenance treatment



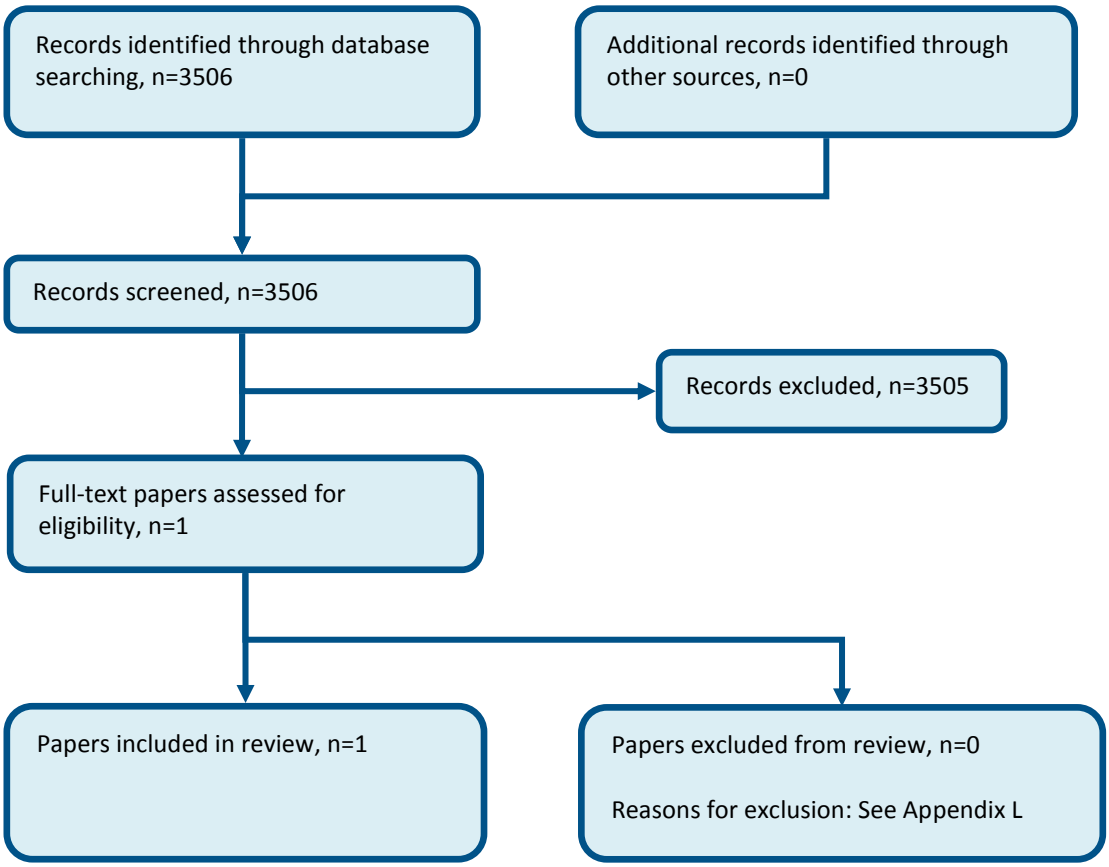
E.9 Breathing exercises in addition to pharmacological treatment

Figure 11: Flow chart of clinical article selection for the review of breathing exercises



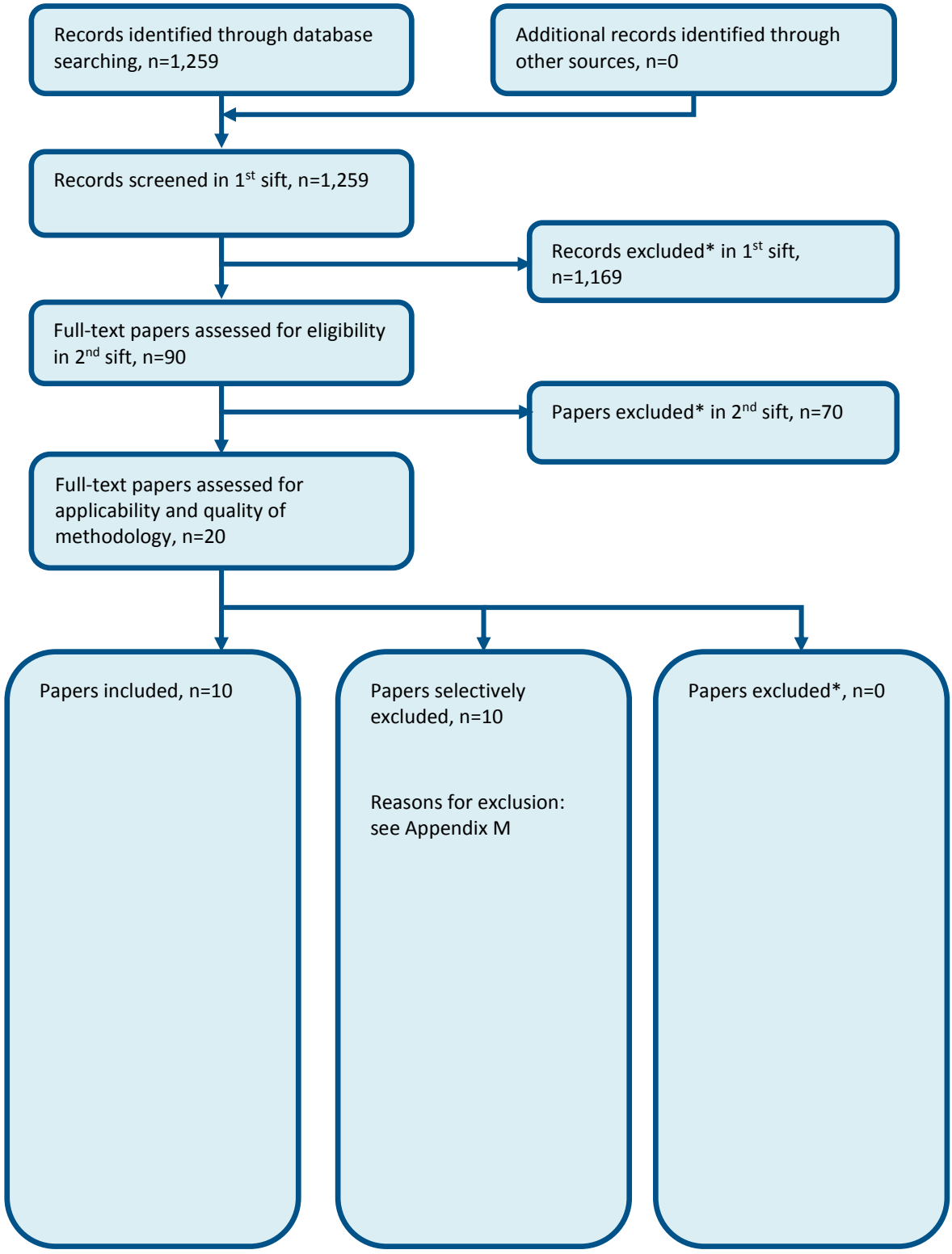
E.10 Managing patients in relation to risk of poor outcomes

Figure 12: Flow chart of clinical study selection for the review of risk stratification



Appendix F: Health economic study selection

Figure 13: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Literature search strategies

G.1 Contents

Search strategies used for the Asthma Management guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual (2014), available from https://www.nice.org.uk/article/pmg20/. All searches were run up to 12/09/2016 unless otherwise stated. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. Electronic, ahead of print or 'online early' publications are not routinely searched for. Where possible searches were limited to retrieve material published in English.

Table 13: Database date parameters

Database	Dates searched
Medline	1946 – 12 September 2016
Embase	1974 – 12 September 2016
The Cochrane Library	Cochrane Reviews to 2016 Issue 9 of 12 CENTRAL to 2016 Issue 9 of 12 DARE, HTA and NHSEED to 2015 Issue 2 of 4
AMED	Inception – 12 September 2016

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in AMED, Allied and Complementary Medicine (Ovid), see Table 14.

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Table 14: Databases searched

Question	Question number	Databases
Adherence	A.4.1	Medline, Embase, Cochrane Library
Breathing Exercises	A.4.2	Medline, Embase, AMED, Cochrane Library
PAAP - Personalised Asthma Action Plan	A.4.3	Medline, Embase, Cochrane Library
Pharma	A.4.4	Medline, Embase, Cochrane Library
Risk Stratification	A.4.5	Medline, Embase, Cochrane Library
Self- Management	A.4.6	Medline, Embase, Cochrane Library
Step Down	A.4.7	Medline, Embase, Cochrane Library
Health Economic Reviews	A.5.1	Medline, Embase, NHS EED, HTA
Quality of Life Review	A.5.2	Medline, Embase, NHS EED, HTA

Searches for the health economic reviews were run in Medline, Embase, the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD).

For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy. Searches in CRD were constructed using population terms only.

G.2 Population search strategies

G.2.1 Standard asthma management population

Medline, Embase and AMED search terms

1.	exp asthma/
2.	asthma*.ti.
3.	or/1-2

Cochrane search terms

#1.	MeSH descriptor: [asthma] explode all trees
#2.	Asthma*:ti
#3.	#1 or #2

CRD search terms

#4.	MeSH descriptor: [asthma] explode all trees
#5.	(Asthma*)

#6.	#1 or #2

G.3 Study filter search terms

G.3.1 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

AMED search terms

1.	case report/
2.	(letter or comment*).ti.
3.	or/1-2
4.	randomized controlled trials/ or random*.ti,ab.
5.	3 not 4
6.	animals/ not humans/
7.	(rat or rats or mouse or mice).ti.
8.	or/5-7

G.3.2 Randomised controlled trials (RCT)

Medline search terms

(Based on the sensitivity and precision maximising version reported in the Cochrane Handbook [http://handbook.cochrane.org/]).

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ti,ab.
4.	placebo.ab.
5.	randomly.ab.ti
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

G.3.3 Systematic reviews (SR)

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or

	cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

G.3.4 Health economic studies (HE)

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/

7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

G.3.5 Quality of life studies (QoL)

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	quality adjusted life year/
2.	"quality of life index"/
3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.

13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
22.	or/1-21

G.3.6 Observational studies (OBS)

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

G.4 Search Strategies for Specific Questions

G.4.1 Adherence

- 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?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	medication adherence/
6.	patient compliance/
7.	((adhere* or comply or complian* or complie*) adj4 (therap* or treat* or medicat* or drug* or dose* or medicine* or patient* or regimen)).ti,ab.
8.	(adhere* adj4 (improv* or increas* or enhanc* or strateg* or implement* or facilitat* or barrier* or manag*)).ti,ab.
9.	(adhere* adj3 (alert* or alarm* or review* or educat* or consult* or text* or app* or tool* or remind* or educat* or advice)).ti,ab.
10.	or/5-9
11.	(non-adhere* or non-complian* or nonadhere* or noncomplian*).ti,ab.
12.	((poor* or low* or lack*) adj3 (adhere* or complian*)).ti,ab.
13.	or/11-12
14.	10 or 13
15.	Study filters RCT (G.3.2) or SR (G.3.3) or OBS (G.3.6)
16.	4 and 14 and 15

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	medication compliance/
6.	patient compliance/
7.	((adhere* or comply or complian* or complie*) adj4 (therap* or treat* or medicat* or drug* or dose* or medicine* or patient* or regimen)).ti,ab.
8.	(adhere* adj4 (improv* or increas* or enhanc* or strateg* or implement* or facilitat* or barrier* or manag*)).ti,ab.
9.	(adhere* adj3 (alert* or alarm* or review* or educat* or consult* or text* or app* or tool* or remind* or educat* or advice)).ti,ab.
10.	or/5-9
11.	(non-adhere* or non-complian* or nonadhere* or noncomplian*).ti,ab.
12.	((poor* or low* or lack*) adj3 (adhere* or complian*)).ti,ab.
13.	11 or 12
14.	10 or 13
15.	Study filters RCT (G.3.2) or SR (G.3.3) or OBS (G.3.6)
16.	4 and 14 and 15

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	MeSH descriptor: [medication adherence] this term only
#3.	MeSH descriptor: [patient compliance] this term only
#4.	((adhere* or comply or complian* or complie*) near/4 (therap* or treat* or medicat* or drug* or dose* or medicine* or patient* or regimen)):ti,ab
#5.	(adhere* near/4 (improv* or increas* or enhanc* or strateg* or implement* or facilitat* or barrier* or manag*)):ti,ab
#6.	(adhere* near/3 (alert* or alarm* or review* or educat* or consult* or text* or app* or tool* or remind* or educat* or advice)):ti,ab
#7.	(or #2-#6)
#8.	(non-adhere* or non-complian* or nonadhere* or noncomplian*):ti,ab
#9.	((poor* or low* or lack*) near/3 (adhere* or complian*)):ti,ab
#10.	#8 or #9
#11.	#7 or #10
#12.	#1 and #11

G.4.2 Breathing Exercises

- Are breathing exercises clinically and cost effective for children, young people and adults with asthma?

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	breathing exercise/
6.	((breath* or respirat* or bronchial) adj1 (exercise* or train* or retrain* or technique* or manipulat* or rehab* or practice* or programme* or therap*)).ti,ab.
7.	(buteyko or papworth or pranayama or lotorp).ti,ab.
8.	yoga/
9.	(yoga or pilates or yogic breathing).ti,ab.
10.	((breath* or respirat* or bronchial) adj3 (physiotherap* or physical therapy or rehab*)).ti,ab.
11.	or/5-10
12.	4 and 11
13.	Study filters RCT (G.3.2) or SR (G.3.3)
14.	12 and 13

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	breathing exercises/
6.	((breath* or respirat* or bronchial) adj1 (exercise* or train* or retrain* or technique* or manipulat* or rehab* or practice* or programme* or therap*)).ti,ab.
7.	(buteyko or papworth or pranayama or lotorp).ti,ab.
8.	yoga/

9.	(yoga or pilates or yogic breathing).ti,ab.
10.	((breath* or respirat* or bronchial) adj3 (physiotherap* or physical therapy or rehab*)).ti,ab.
11.	or/5-10
12.	4 and 11
13.	Study filters RCT (G.3.2) or SR (G.3.3)
14.	12 and 13

AMED search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	breathing exercises/
5.	((breath* or respirat* or bronchial) adj1 (exercise* or train* or retrain* or technique* or manipulat* or rehab* or practice* or programme* or therap*)).ti,ab.
6.	(buteyko or papworth or pranayama or lotorp).ti,ab.
7.	yoga/
8.	(yoga or pilates or yogic breathing).ti,ab.
9.	((breath* or respirat* or bronchial) adj3 (physiotherap* or physical therapy or rehab*)).ti,ab.
10.	or/4-9
11.	3 and 10

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	MeSH descriptor: [breathing Exercises] this term only
#3.	((breath* or respirat* or bronchial) next/1 (exercise* or train* or retrain* or technique* or manipulat* or rehab* or practice* or programme* or therap*)):ti,ab
#4.	(buteyko or papworth method or pranayama or lotorp method):ti,ab
#5.	MeSH descriptor: [yoga] this term only
#6.	(yoga or pilates or yogic breathing):ti,ab
#7.	((breath* or respirat* or bronchial) near/3 (physiotherap* or physical therapy or rehab*)):ti,ab
#8.	(or #2-#7)
#9.	#1 and #8

G.4.3 PAAP – Personalised Asthma Action Plan

- What is the optimal increase in ICS preventer therapy within supported self- management when control is lost?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	self care/ or self administration/
6.	((self-manage* or self-monitor* or self-care) adj3 (strateg* or program* or guide* or information or educat* or plan* or paap or pap or diary or diaries or tool* or booklet* or manual* or pamphlet* or leaflet* or review*)).ti,ab.
7.	((supported or patient* or individualis* or individualiz*) adj3 (self-manage* or self manage* or self-care or self care or self-monitor* or self monitor* or plan* or paap or pap)).ti,ab.

8.	((patient* or individualis* or individualiz*) adj3 (diary or diaries or program* or tool* or educat*)).ti,ab.
9.	(dose* adj5 (doubl* or exacerbat* or maintenance* or maintain* or prevent* or reliev*)).ti,ab.
10.	or/ 5-9
11.	(inhaled corticosteroid* or ics).ti,ab.
12.	triamcinolone/
13.	budesonide/
14.	beclomethasone/
15.	(budesonide or beclomethasone* or ciclesonide or fluticasone* or flunisolide or triamcinolone or pulmicort flexhaler or qvar or formoterol or fostair or ciclesonide or alvesco or mometasone* or asmanex or aerobid).ti,ab.
16.	or/ 11-15
17.	10 and 16
18.	4 and 17

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	self care/ or drug self administration/
6.	((self-manage* or self-monitor* or self-care) adj3 (strateg* or program* or guide* or information or educat* or plan* or paap or pap or diary or diaries or tool* or booklet* or manual* or pamphlet* or leaflet* or review*)).ti,ab.
7.	((supported or patient* or individualis* or individualiz*) adj3 (self-manage* or self manage* or self-care or self care or self-monitor* or self monitor* or plan* or paap or pap)).ti,ab.
8.	((patient* or individualis* or individualiz*) adj3 (diary or diaries or program* or tool* or educat*)).ti,ab.
9.	(dose* adj5 (doubl* or exacerbat* or maintenance* or maintain* or prevent* or reliev*)).ti,ab.
10.	or/ 5-9
11.	(inhaled corticosteroid* or ics).ti,ab.
12.	*triamcinolone/
13.	*budesonide/
14.	*beclomethasone/
15.	(budesonide or beclomethasone* or ciclesonide or fluticasone* or flunisolide or triamcinolone or pulmicort flexhaler or qvar or formoterol or fostair or ciclesonide or alvesco or mometasone* or asmanex or aerobid).ti,ab.
16.	or/ 11-15
17.	10 and 16
18.	4 and 17

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	MeSH descriptor: [self care] this term only
#3.	MeSH descriptor: [self administration] this term only
#4.	((self-manage* or self-monitor* or self-care) near/3 (strateg* or program* or guide* or information or educat* or plan* or paap or pap or diary or diaries or tool* or booklet* or manual* or pamphlet* or leaflet* or review*)):ti,ab

#5.	((supported or patient* or individualis* or individualiz*) near/3 (self-manage* or self manage* or self-care or self care or self-monitor* or self monitor* or plan* or paap or pap)):ti,ab
#6.	((patient* or individualis* or individualiz*) near/3 (diary or diaries or program* or tool* or educat*)):ti,ab
#7.	(dose* near/5 (doubl* or exacerbat* or maintenance* or maintain* or prevent* or reliev*)):ti,ab
#8.	#2 or #3 or #4 or #5 or #6 or #7
#9.	(inhaled corticosteroid* or ics):ti,ab
#10.	MeSH descriptor: [Triamcinolone] this term only
#11.	MeSH descriptor: [Budesonide] this term only
#12.	MeSH descriptor: [Beclomethasone] this term only
#13.	(budesonide or beclomethasone* or ciclesonide or fluticasone* or flunisolide or triamcinolone or pulmicort flexhaler or qvar or formoterol or fostair or ciclesonide or alvesco or mometasone* or asmanex or aerobid):ti,ab
#14.	#9 or #10 or #11 or #12 or #13
#15.	#8 and #14
#16.	#1 and #15

G.4.4 Pharmacological

Searches for the following six questions were run as one search:

- 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)?
- 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)?
- 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?
- 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?
- 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?
- 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?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	adrenergic beta-2 receptor agonists/
6.	(adrenergic beta-2 receptor agonist* or saba or short acting beta agonist* or short-acting beta agonist* or short acting adrenoceptor agonist* or short-acting beta-adrenoceptor agonist* or short acting beta2 agonist* or short-acting beta-2 agonist*).ti,ab.
7.	albuterol/
8.	terbutaline/
9.	(albuterol or salbutamol or terbutaline).ti,ab.
10.	(airolin or airomir or asmasal or buventol or inspiryl or proventil or salamol or salbulin).ti,ab.

11.	(brethine or bricanyl).ti,ab.
12.	or/5-11
13.	(inhaled corticosteroid* or ics).ti,ab.
14.	triamcinolone/
15.	budesonide/
16.	beclomethasone/
17.	(budesonide or beclomethasone* or ciclesonide or fluticasone* or flunisolide or triamcinolone or pulmicort flexhaler or qvar or formoterol or fostair or ciclesonide or alvesco or mometasone* or asmanex or aerobid).ti,ab.
18.	or/13-17
19.	leukotriene antagonists/
20.	cromolyn sodium/
21.	theophylline/ or aminophylline/
22.	nedocromil/
23.	(leukotriene receptor antagonist* or leukotriene antagonist* or ltra or theophylline or aminophylline or cromolyn* or sodium cromoglicate or nedocromil or montelukast or zafirlukast or singulair or accolate).ti,ab.
24.	or/19-23
25.	((smart or mart or symbicort) adj1 therapy).ti,ab.
26.	(laba or long acting beta agonist* or long-acting beta agonist* or long acting adrenoceptor agonist* or long-acting beta-adrenoceptor agonist* or long acting beta2 agonist* or long-acting beta-2 agonist*).ti,ab.
27.	(salmeterol or formoterol or vilanterol or serevent or Seretide or foradil or atimos modulite or duaklir genuair or ANORO or relvar or fostair).ti,ab.
28.	or/25-27
29.	muscarinic antagonists/
30.	(long acting muscarinic antagonist* or muscarinic antagonist* or LAMA).ti,ab.
31.	ipratropium/
32.	(ipratropium or tiotropium or ATROVENT or SPIRIVA).ti,ab.
33.	or/29-32
34.	(cortisone acetate or dexamethasone or cortef or orapred or relone or OCS or oral corticosteroid* or delazacort).ti,ab.
35.	(betadexamethasone or betamethasone or celeston* or cellestoderm or flubenisolone or dexasone or dexpak or hexadrol or maxidex).ti,ab.
36.	(methylfluorprednisolone or millicorten or oradexon or cortifair or cortisol or cortril or epicortisol or hydrocortisone or medrol or methylprednisolone or metipred or urbason or predate or prednisolone or predonine or apo-prednisone or cortan or cortancyl or cutason or dacortin or decortin or decortisyl or dehydrocortisone or deltasone or encorton or encortone or enkortolon or kortancyl or meticorten or orasone or panafcort or panasol or predniment or prednison galen or prednison hexal or prednison acsis or prednisone or pronisone or rectodelt or sterapred or ultracorten or winpred or alpha fluorohydrocortisone or astonin or fludrocortisone).ti,ab.
37.	betamethasone/ or dexamethasone/ or methylprednisolone/ or prednisolone/ or prednisone/
38.	or/34-37
39.	12 or 18 or 24 or 28 or 33 or 38
40.	4 and 39
41.	Study filters RCT (G.3.2) or SR (G.3.3)
42.	40 and 41

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*beta 2 adrenergic receptor stimulating agent/
6.	(adrenergic beta-2 receptor agonist* or saba or short acting beta agonist* or short-acting beta agonist* or short acting adrenoceptor agonist* or short-acting beta-adrenoceptor agonist* or short acting beta2 agonist* or short-acting beta-2 agonist*).ti,ab.
7.	*salbutamol/
8.	*terbutaline/
9.	(albuterol or salbutamol or terbutaline).ti,ab.
10.	(airolin or airomir or asmasal or buventol or inspiryl or proventil or salamol or salbulin).ti,ab.
11.	(brethine or bricanyl).ti,ab.
12.	or/5-11
13.	(inhaled corticosteroid* or ics or icss).ti,ab.
14.	*triamcinolone/
15.	*budesonide/
16.	*beclometasone/
17.	(budesonide or beclomethasone* or ciclesonide or fluticasone* or flunisolide or triamcinolone or pulmicort flexhaler or qvar or formoterol or fostair or ciclesonide or alvesco or mometasone* or asmanex or aerobid).ti,ab.
18.	or/13-17
19.	*leukotriene receptor blocking agent/
20.	*cromoglicate disodium/
21.	*theophylline/
22.	*aminophylline/
23.	*nedocromil/
24.	(leukotriene receptor antagonist* or leukotriene antagonist* or ltra or theophylline or aminophylline or cromolyn* or sodium cromoglicate or nedocromil or montelukast or zafirlukast or singulair or accolate).ti,ab.
25.	or/19-24
26.	((smart or mart or symbicort) adj1 therapy).ti,ab.
27.	(laba or long acting beta agonist* or long-acting beta agonist* or long acting adrenoceptor agonist* or long-acting beta-adrenoceptor agonist* or long acting beta2 agonist* or long-acting beta-2 agonist*).ti,ab.
28.	(salmeterol or formoterol or vilanterol or serevent or seretide or foradil or atimos modulite or duaklir genuair or anoro or relvar or fostair).ti,ab.
29.	or/26-28
30.	*muscarinic receptor blocking agent/
31.	(muscarinic antagonist* or lama).ti,ab.
32.	*ipratropium bromide/
33.	(ipratropium or tiotropium or atrovent or spiriva).ti,ab.
34.	or/30-33
35.	(cortisone acetate or dexamethasone or cortef or orapred or prelone or ocs or oral corticosteroid* or delazacort).ti,ab.
36.	(betadexamethasone or betamethasone or celeston* or cellestoderm or flubenisolone or dexasone or dexpak or hexadrol or maxidex).ti,ab.

37.	(methylfluorprednisolone or millicorten or oradexon or cortifair or cortisol or cortril or epicortisol or hydrocortisone or medrol or methylprednisolone or metipred or urbason or predate or prednisolone or predonine or apo-prednisone or cortan or cortancyl or cutason or dacortin or decortin or decortisyl or dehydrocortisone or deltasone or encorton or encortone or enkortolon or kortancyl or meticorten or orasone or panafcort or panasol or predniment or prednison galen or prednison hexal or prednison acsis or prednisone or pronisone or rectodelt or sterapred or ultracorten or winpred or alpha fluorohydrocortisone or astonin or fludrocortisone).ti,ab.
38.	betamethasone/ or dexamethasone/ or methylprednisolone/ or prednisolone/ or prednisone/
39.	or/35-38
40.	12 or 18 or 25 or 29 or 34 or 39
41.	4 and 40
42.	Study filters RCT (A.3.2) or SR (A.3.3)
43.	41 and 42

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	MeSH descriptor: [adrenergic beta-2 receptor agonists] this term only
#3.	(adrenergic beta-2 receptor agonist* or saba or short acting beta agonist* or short-acting beta agonist* or short acting adrenoceptor agonist* or short-acting beta-adrenoceptor agonist* or short acting beta2 agonist* or short-acting beta-2 agonist*):ti,ab
#4.	MeSH descriptor: [albuterol] this term only
#5.	MeSH descriptor: [terbutaline] this term only
#6.	(albuterol or salbutamol or terbutaline):ti,ab
#7.	(airolin or airomir or asmasal or buventol or inspiryl or proventil or salamol or salbulin):ti,ab
#8.	(brethine or bricanyl):ti,ab
#9.	(or #2-#8)
#10.	(inhaled corticosteroid* or ics):ti,ab
#11.	MeSH descriptor: [triamcinolone] this term only
#12.	MeSH descriptor: [budesonide] this term only
#13.	MeSH descriptor: [beclomethasone] this term only
#14.	(budesonide or beclomethasone* or ciclesonide or fluticasone* or flunisolide or triamcinolone or pulmicort flexhaler or qvar or formoterol or fostair or ciclesonide or alvesco or mometasone* or asmanex or aerobid):ti,ab
#15.	(or #10-#14)
#16.	MeSH descriptor: [leukotriene antagonists] this term only
#17.	MeSH descriptor: [cromolyn sodium] this term only
#18.	MeSH descriptor: [theophylline] this term only
#19.	MeSH descriptor: [aminophylline] this term only
#20.	MeSH descriptor: [nedocromil] this term only
#21.	(leukotriene receptor antagonist* or leukotriene antagonist* or ltra or theophylline or aminophylline or cromolyn* or sodium cromoglicate or nedocromil or montelukast or zafirlukast or singulair or accolate):ti,ab
#22.	(or #16-#21)
#23.	((smart or mart or symbicort) next/1 therapy):ti,ab
#24.	(laba or long acting beta agonist* or long-acting beta agonist* or long acting adrenoceptor agonist* or long-acting beta-adrenoceptor agonist* or long acting beta2 agonist* or long-acting beta-2 agonist*):ti,ab
#25.	(salmeterol or formoterol or vilanterol or serevent or seretide or foradil or atimos modulite or

	duaklir genuair or anoro or relvar or fostair):ti,ab
#26.	(or #23-#25)
#27.	MeSH descriptor: [muscarinic antagonists] this term only
#28.	(long acting muscarinic antagonist* or muscarinic antagonist* or lama):ti,ab
#29.	MeSH descriptor: [ipratropium] this term only
#30.	(ipratropium or tiotropium or atrovent or spiriva):ti,ab
#31.	(or #27-#30)
#32.	(cortisone acetate or dexamethasone or cortef or orapred or prelone or ocs or oral corticosteroid* or delazacort):ti,ab
#33.	(betadexamethasone or betamethasone or celeston* or cellestoderm or flubenisolone or dexasone or dexpak or hexadrol or maxidex):ti,ab
#34.	(methylfluorprednisolone or millicorten or oradexon or cortifair or cortisol or cortril or epicortisol or hydrocortisone or medrol or methylprednisolone or metipred or urbason or predate or prednisolone or predonine or apo-prednisone or cortan or cortancyl or cutason or dacortin or decortin or decortisyl or dehydrocortisone or deltasone or encorton or encortone or enkortolon or kortancyl or meticorten or orasone or panafcort or panasol or predniment or prednison galen or prednison hexal or prednison acsis or prednisone or pronisone or rectodelt or sterapred or ultracorten or winpred or alpha fluorohydrocortisone or astonin or fludrocortisone):ti,ab
#35.	MeSH descriptor: [betamethasone] this term only
#36.	MeSH descriptor: [dexamethasone] this term only
#37.	MeSH descriptor: [methylprednisolone] this term only
#38.	MeSH descriptor: [prednisolone] this term only
#39.	MeSH descriptor: [prednisone] this term only
#40.	(or #32-#39)
#41.	(or #9, #15, #22, #26, #31, #40)
#42.	#1 and #41

G.4.5 Risk Stratification

- 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?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	delivery of health care/
6.	patient care/
7.	(deliver* adj3 (care or heathcare or service* or opportunistic or treatment or intervention* or therap*)).ti,ab.
8.	or/ 5-7
9.	((frequen* or sever* or risk* or control* or uncontrol* or reduce* or increase*) adj3 (attack* or exacerbat* or flare up*)).ti,ab.
10.	((frequen* or regular* or irregular* or urgent or emergenc* or routine or reduce* or increase*) adj3 (review* or respiratory consult* or refer* or hospitalis* or hospitaliz* or appointment* or visit*)).ti,ab.
11.	((reliever or rescue or emergenc* or increase*) adj3 (medicine or medication* or prescription*

	or dose* or dosage)).ti,ab.
12.	((lung function or peak flow) adj3 (test* or exam* or assess* or review* or score* or scoring* or screen*)).ti,ab.
13.	registries/
14.	risk assessment/
15.	*severity of illness index/
16.	or/ 9-15
17.	8 and 16
18.	((risk or at-risk or at risk) adj3 (register* or registr* or stratif* or assess* or model* or algorithm* or score* or scoring* or screen* or strateg* or index*)).ti,ab.
19.	(stratif* adj3 (organis* or manag* or care or healthcare or treatment* or approach*)).ti,ab.
20.	18 or 19
21.	4 and (17 or 20)

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	health care delivery/
6.	patient care/
7.	(deliver* adj3 (care or heathcare or service* or opportunistic or treatment or intervention* or therap*)).ti,ab.
8.	or/ 5-7
9.	((frequen* or sever* or risk* or control* or uncontrol* or reduce* or increase*) adj3 (attack* or exacerbat* or flare up*)).ti,ab.
10.	((frequen* or regular* or irregular* or urgent or emergenc* or routine or reduce* or increase*) adj3 (review* or respiratory consult* or refer* or hospitalis* or hospitaliz* or appointment* or visit*)).ti,ab.
11.	((reliever or rescue or emergenc* or increase*) adj3 (medicine or medication* or prescription* or dose* or dosage)).ti,ab.
12.	((lung function or peak flow) adj3 (test* or exam* or assess* or review* or score* or scoring* or screen*)).ti,ab.
13.	register/
14.	risk assessment/
15.	*severity of illness index/
16.	or/ 9-15
17.	8 and 16
18.	((risk or at-risk or at risk) adj3 (register* or registr* or stratif* or assess* or model* or algorithm* or score* or scoring* or screen* or strateg* or index*)).ti,ab.
19.	(stratif* adj3 (organis* or manag* or care or healthcare or treatment* or approach*)).ti,ab.
20.	18 or 19
21.	4 and (17 or 20)

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	MeSH descriptor: [delivery of health care] this term only
#3.	MeSH descriptor: [patient care] this term only

#4.	(deliver* near/3 (care or heathcare or service* or opportunistic or treatment or intervention* or therap*)):ti,ab
#5.	((future care or care or healthcare or treatment*) near/3 (organis* or stratif* or manag* or patient* or variation* or intensit* or approach*)):ti,ab
#6.	(or #2-#6)
#7.	((frequen* or sever* or risk* or control* or uncontrol* or reduce* or increase*) near/3 (attack* or exacerbat* or flare up*)):ti,ab
#8.	((frequen* or regular* or irregular* or urgent or emergenc* or routine or reduce* or increase*) near/3 (review* or respiratory consult* or refer* or hospitalis* or hospitaliz* or appointment* or visit*)):ti,ab
#9.	((reliever or rescue or emergenc* or increase*) near/3 (medicine or medication* or prescription* or dose or dosage)):ti,ab
#10.	((lung function or peak flow) near/3 (test* or exam* or assess* or review* or score* or scoring* or screen*)):ti,ab
#11.	MeSH descriptor: [registries] this term only
#12.	MeSH descriptor: [risk assessment] this term only
#13.	MeSH descriptor: [severity of illness index] this term only
#14.	(or #7-#13)
#15.	((risk or at-risk or at risk) near/3 (register* or registr* or stratif* or assess* or model* or algorithm* or score* or scoring* or screen* or strateg* or index*)):ti,ab
#16.	(stratif* near/3 (organis* or manag* or care or healthcare or treatment* or approach*)):ti,ab
#17.	(or #15-#16)
#18.	#6 and #14
#19.	#17 or #18
#20.	#1 and #19

G.4.6 Self-Management

- 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?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	self care/ or self administration/ or self medication/
6.	patient education as topic/
7.	pamphlets/
8.	((patient* or individualis* or individualiz*) adj4 (self-manage* or self manage* or self-care or self care or self-monitor* or self monitor* or action plan* or paap or train* or written plan* or verbal plan* or diary or diaries or program* or tool* or educat*)).ti,ab.
9.	or/ 5-8
10.	Study filters RCT (G.3.2) or SR (G.3.3) or OBS (G.3.6)
11.	4 and 9
12.	10 and 11

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	self care/
6.	patient education/
7.	((patient* or individualis* or individualiz*) adj4 (self-manage* or self manage* or self-care or self care or self-monitor* or self monitor* or action plan* or paap or train* or written plan* or verbal plan* or diary or diaries or program* or tool* or educat*)).ti,ab.
8.	((self-manage* or self manage* or self-monitor* or self monitor* or self-care or self care) adj4 (strateg* or program* or consult* or review* or guide* or support* or information or educat* or action plan* or paap or train* or teach* or written plan* or verbal plan* or diary or diaries or program* or tool* or instruct* or learn* or booklet* or manual* or pamphlet* or leaflet*)).ti,ab.
9.	or/ 5-8
10.	Study filters RCT (G.3.2) or SR (G.3.3) or OBS (G.3.6)
11.	4 and 9
12.	10 and 11

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	MeSH descriptor: [self care] this term only
#3.	MeSH descriptor: [patient education as topic] this term only
#4.	MeSH descriptor: [pamphlets] this term only
#5.	((patient* or individualis* or individualiz*) near/4 (self-manage* or self manage* or self-care or self care or self-monitor* or self monitor* or action plan* or paap or train* or written plan* or verbal plan* or diary or diaries or program* or tool* or educat*)):ti,ab
#6.	#2 or #3 or #4 or #5
#7.	#1 and #6

G.4.7 Step Down

- What are the clinical features (symptoms and/or objective measurements) which indicate that a step down in treatment is appropriate?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	(step* down or step* off or step-off).ti,ab.
6.	((stepwise or step-wise or step wise) adj3 (reduc* or discontin* or lower* or taper* or cut* or switch* or change* or stop*)).ti,ab.
7.	((reduc* or discontin* or lower* or taper* or cut* or switch* or change* or stop*) adj3 (therap* or treat* or dose* or drug* or medicat* or medicine* or asthma*)).ti,ab.
8.	or/ 5-7
9.	((duration or period* or current* or prolong* or month* or length) adj3 (control* or stable or stabilise* or stabilize*) adj3 (therap* or treat* or medicat* or drug* or dose* or medicine* or maintenance or maintain* or asthma*)).ti,ab.

10.	(rescue adj3 (therap* or treat* or dose* or drug* or medicat* or medicine* or SABA or short acting beta agonist* or short-acting beta agonist* or short acting adrenoceptor agonist* or short-acting beta-adrenoceptor agonist* or short acting beta2 agonist* or short-acting beta-2 agonist*)).ti,ab.
11.	(exacerbat* or attack* or flare* up or feno or Fractional exhaled nitric oxide level* or acq score or act score or asthma controlled questionnaire* or asthma controlled test*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	4 and 13

Embase search terms

1.	Standard population [A.2.1]
2.	Excluded study designs and publication types [A.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	(step* down or step* off or step-off).ti,ab.
6.	((stepwise or step-wise or step wise) adj3 (reduc* or discontin* or lower* or taper* or cut* or switch* or change* or stop*)).ti,ab.
7.	((reduc* or discontin* or lower* or taper* or cut* or switch* or change* or stop*) adj3 (therap* or treat* or dose* or drug* or medicat* or medicine* or asthma*)).ti,ab.
8.	or/ 5-7
9.	((duration or period* or current* or prolong* or month* or length) adj3 (control* or stable or stabilise* or stabilize*) adj3 (therap* or treat* or medicat* or drug* or dose* or medicine* or maintenance or maintain* or asthma*)).ti,ab.
10.	(rescue adj3 (therap* or treat* or dose* or drug* or medicat* or medicine* or SABA or short acting beta agonist* or short-acting beta agonist* or short acting adrenoceptor agonist* or short-acting beta-adrenoceptor agonist* or short acting beta2 agonist* or short-acting beta-2 agonist*)).ti,ab.
11.	(exacerbat* or attack* or flare* up or feno or Fractional exhaled nitric oxide level* or acq score or act score or asthma controlled questionnaire* or asthma controlled test*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	4 and 13

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	(step* down or step* off or step-off):ti,ab
#3.	((stepwise or step-wise or step wise) near/3 (reduc* or discontin* or lower* or taper* or cut* or switch* or change* or stop*)):ti,ab
#4.	((reduc* or discontin* or lower* or taper* or cut* or switch* or change* or stop*) near/3 (therap* or treat* or dose* or drug* or medicat* or medicine* or asthma*)):ti,ab
#5.	(or #2-#4)
#6.	((duration or period* or current* or prolong* or month* or length) near/3 (control* or stable or stabilise* or stabilize*) near/3 (therap* or treat* or medicat* or drug* or dose* or medicine* or maintenance or maintain* or asthma*)):ti,ab
#7.	(rescue near/3 (therap* or treat* or dose* or drug* or medicat* or medicine* or SABA or short acting beta agonist* or short-acting beta agonist* or short acting adrenoceptor agonist* or short-acting beta-adrenoceptor agonist* or short acting beta2 agonist* or short-acting beta-2

	agonist*)):ti,ab
#8.	(exacerbat* or attack* or flare* up or feno or Fractional exhaled nitric oxide level* or acq score or act score or asthma controlled questionnaire* or asthma controlled test*):ti,ab
#9.	(or #6-#8)
#10.	#5 and #9
#11.	#1 and #10

G.5 Health economics search

G.5.1 Health economic (HE) reviews

Economic searches were conducted in Medline, Embase, and CRD for NHS EED and HTA.

Medline & Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filter HE (G.3.4)
6.	4 and 5
	Date parameters: 2014 – 13 September 2016

CRD search terms

#1.	Standard population [G.2.1]
#2.	(#1) in NHSEED, HTA from 2014 to 2016

G.5.2 Quality of life (QoL) reviews

Economic searches were conducted in Medline and Embase only

Medline & Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filter QOL (G.3.5)
6.	4 and 5
	See table 13 for date parameters

Appendix H: Clinical evidence tables

H.1 Treatment in patients not on regular preventers

None.

H.2 Choice of first line preventer in patients with poor asthma control

Study	**Berger 2002[121]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=408)
Countries and setting	Conducted in USA; Setting: Clinic visits - secondary care. 48 centres in the Unites States.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12+, non-smokers, diagnosed with asthma requiring pharmacotherapy for at least 6 months, previously treated with B2-agonist only, FEV_1 of 60-85% of predicted, reversibility of airway obstruction shown as FEV_1 increase of 12% following 180 µg albuterol.
Exclusion criteria	History of life-threatening or unstable asthma or other severe uncontrolled diseases, hypersensitivity to sympathomimetic drugs, acute respiratory tract infections within the past 4 weeks, history of smoking. Excluded medications; oral or systemic corticosteroids, long-acting B2-agonist, cromolyn, nedocromil, leukotriene modifiers, or anticholinergics. No ICS within 1 month of the trial.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): FP: 33 (12-74) Placebo: 33 (12-69). Gender (M:F): 78/122. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated

	/ Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Diagnosed with asthma according to the American Thoracic Society criteria, FEV_1 of 60-85% of predicted, reversibility of airway obstruction shown as FEV_1 increase of 12% following 180 µg albuterol.
Indirectness of population	No indirectness
Interventions	(n=198) Intervention 1: ICS (low dose) - Fluticasone propionate. FP 250 µg in the morning. Duration 12 weeks. Concurrent medication/care: Inhaled albuterol as needed to relieve breakthrough symptoms. (n=210) Intervention 2: placebo / no intervention - placebo. Placebo via inhaler to match intervention. Duration 12 weeks. Concurrent medication/care: Inhaled albuterol as needed to relieve breakthrough symptoms.
Funding	Study funded by industry (GlaxoSmithKline Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE (LOW DOSE) versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Daily rescue albuterol use at 12 weeks ; Group 1: mean -1.6 Daily albuterol use (SD 2.8); n=170, Group 2: mean -0.9 Daily albuterol use (SD 1.4); n=174; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning FEV_1 (L not % of predicted) at 12 weeks ; Group 1: mean 0.23 L (SD 0.42); n=170, Group 2: mean 0.1 L (SD 0.43); n=174; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Morning PEF at 12 weeks ; Group 1: mean 34.3 L/min (SD 61.9); n=170, Group 2: mean 12.2 L/min (SD 46.4); n=174; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Boonsawat 2008[158]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=458)

Countries and setting	Conducted in multiple countries; Setting: Primary care and hospital outpatient settings.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-29 years, diagnosed with asthma for at least 6 months.
Exclusion criteria	ICS or leukotriene within 12 weeks of 2-week run-in period, treatment with LABA, sodium cromoglicate, nedocromil, anticholinergic bronchodilators within 2 weeks of run-in, respiratory tract infection within 4 weeks, accute exacerbation within 12 weeks, smoking history of >10 pack years, pregnant.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 34.02 (12-73). Gender (M:F): 219/239. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Prebronchodilator PEF >80% of predicted during run-in, diagnosis of asthma with positive BDR (increase in PEF of ≥15% following 400ug salbutamol), day-time symptom score of >1 on 3-6 of last 7 days.
Indirectness of population	No indirectness
Interventions	(n=149) Intervention 1: ICS+LABA - ICS + Salmeterol. SFC 50ug/100ug once daily via MDI on arising each morning. Duration 12 weeks. Concurrent medication/care: Salbutamol taken as needed as rescue medication. (n=154) Intervention 2: ICS (low dose) - Fluticasone propionate. FP 100ug once daily via MDI on arising each morning. Duration 12 weeks. Concurrent medication/care: Salbutamol taken as needed as rescue medication. (n=155) Intervention 3: placebo / no intervention - placebo. Placebo once daily via MDI on arising each morning. Duration 12 weeks. Concurrent medication/care: Salbutamol taken as needed as rescue medication.
Funding	Study funded by industry (GlaxoSmithKline)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE	

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Rescue free days (%) at 12 weeks; OR 0.56 (95%CI 0.34 to 0.9) (p value 0.018); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in morning PEF at 12 weeks; SMD 14 (95%CI 6.3 to 21.7) (p value 0.001); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Change in FEV_1 (L) at 12 weeks; SMD 0.18 (95%CI 0.093 to 0.257) (P value 0.001); Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Rescue free days (%) at 12 weeks; OR 0.19 (95%CI 0.12 to 0.32) (p value 0.001); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in morning PEF at 12 weeks; SMD 23 (95%CI 15 to 30.3) (p value 0.001); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Change in FEV_1 (L) at 12 weeks; SMD 0.21 (95%CI 0.112 to 0.276) (P value 0.001); Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus PLACEBO

Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning PEF at 12 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Change in morning PEF at 12 weeks; SMD 9 (95%CI 1 to 16.2) (P value 0.026); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Bousquet 2005[166]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=645)
Countries and setting	Conducted in multiple countries; Setting: 77 sites in 22 countries across Europe, South America and Asia.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	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 B-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 run in period.
Exclusion criteria	Treated in ED within 1 month, hospitalised for asthma within 3 months, URTI within 3 weeks. Excluded medications: any form of corticosteroid within 1 month; cromolyn, nedocromil, or leukotriene receptor antagonist within 2 weeks; theophylline or LABA within 1 week.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 36.3 (14.1). Gender (M:F): Define. Ethnicity: Caucasian 63%
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Diagnosis of asthma with a baseline FEV_1 value 80% of predicted, and either b-agonist reversibility of at least 12% or positive exercise challenge within the previous month.
Indirectness of population	No indirectness
Interventions	(n=325) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. Oral montelukast (10mg) once daily at bedtime. Duration 12 weeks. Concurrent medication/care: Rescue medication permitted as needed (n=320) Intervention 2: ICS (low dose) - Fluticasone propionate. Inhaled Fluticasone 100 µg twice daily. Duration 12 weeks. Concurrent medication/care: Rescue medication permitted as needed
Funding	Study funded by industry (Merck and Co. Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONTELUKAST versus FLUTICASONE PROPIONATE	

Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: Asthma specific quality of life at 12 weeks; Group 1: mean 0.66 (SD 0.97); n=208, Group 2: mean 0.83 (SD 1.06); n=237; Not reported Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Days with B-agonist use (%) at 12 weeks; Group 1: mean 28.6 Days (%) (SD 28.9); n=268, Group 2: mean 24.9 Days (%) (SD 31.1); n=281; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (% of predicted) at 12 weeks; Group 1: mean -2.02 FEV_1 (% of predicted) (SD 9.27); n=277, Group 2: mean 1.25 FEV_1 (% of predicted) (SD 9.2); n=284; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 22.8 L/min (SD 55.4); n=279, Group 2: mean 32.4 L/min (SD 49.2); n=291; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Busse 2001[207]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=533)
Countries and setting	Conducted in Unknown; Setting: Clinic visits
Line of therapy	1st line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 15 years and over, diagnosed with asthma for at least 6 months, use of SABA as needed for preceding 3 months, unmedicated FEV_1 of 50-80% of predicted.

Exclusion criteria	Use of inhaled corticosteroids within 2 months prior to the study. History of smoking 10 pack-years, hospital admission for asthma within 3 months, respiratory tract infections within previous 4 weeks, hypersensitivity to B2-agonist, sympathomimetic drug, leukotriene antagonist, or corticosteroid.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Mean (range): 34.9 (15-83). Gender (M:F): 239:294. Ethnicity: 83% white
Further population details	1. Previous asthma exacerbations: unclear 2. Prior medication: unclear 3. Smoking status: non/ex-smoker
Extra comments	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 albuterol 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.
Indirectness of population	No indirectness
Interventions	(n=271) Intervention 1: ICS (low dose) - Fluticasone furoate. FP 88µg bid (Flovent Inhalation Aerosol, GSK) two puffs of 44 µg strength plus placebo capsule. Duration 24 weeks. Concurrent medication/care: Inhaled albuterol as needed (n=262) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg (Singulair, Merck & Co.) in the evening, plus two puffs of placebo twice daily through MDI. Duration 24 weeks. Concurrent medication/care: Inhaled albuterol as needed
Funding	Study funded by industry (Glaxo Wellcome Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE FUROATE versus MONTELUKAST

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: AQLQ - Asthma Quality of Life Questionnaire at 24 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albuterol use, puffs/day at 24 weeks; Group 1: mean -3.1 puffs/day (SD 2.8); n=194, Group 2: mean -2.31 puffs/day (SD 2.75); n=187; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (given as L not % predicted) at 24 weeks; Group 1: mean 0.51 L (SD 0.49); n=194, Group 2: mean 0.33 L (SD 0.49); n=187; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for ≥16 years: Morning PEF at 24 weeks; Group 1: mean 68.5 L/min (SD 85.6); n=194, Group 2: mean 34.1 L/min (SD 68); n=187; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Calhoun 2001[222]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=423)
Countries and setting	Conducted in USA; Setting: 56 clinics across the United States
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 15+, asthma for at least 6 months, treated with an oral or inhaled SABA on a scheduled or PRN basis for at least 6 weeks (before screening period all oral and inhaled SABAs were replaced by inhaled albuterol), FEV_1 50-80% of predicted value, FEV_1 increase of 12%+ following 180 µg albuterol, requiring rescue albuterol on 5+ of 7 day run in period or a symptom score of more than or equal to 2 on three or more days for chest tightness, wheezing or shortness of breath (0-5 point scale with 0, no symptoms and 5, symptoms causing discomfort and preventing normal daily activities).
Exclusion criteria	Not given
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): FSC: 37 (16-72) Montelukast: 36 (15-66). Gender (M:F): 213:210. Ethnicity: 78% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	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 more than or equal to 2 on three or more days

Indirectness of population	Serious indirectness: Time period for which population are preventer naïve prior to study is unclear.
Interventions	(n=211) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone Propionate 100 µg + Salmeterol 50 µg, twice daily via Diskus device, plus placebo montelukast capsule once daily. Duration 12 weeks. Concurrent medication/care: Albuterol (Ventolin inhalation aerosol) as needed for rescue. (n=212) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg (Singlulair, Merk & Co.) once daily, placebo FSC twice daily. Duration 12 weeks. Concurrent medication/care: Albuterol (Ventolin inhalation aerosol) as needed for rescue.
Funding	Study funded by industry (GlaxoWellcome Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus MONTELUKAST

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albuterol use (puffs/day). UNCLEAR IF SD OR SE REPORTED at 12 weeks; Group 1: mean -3.3 puff/24 h (SD 2.9); n=213, Group 2: mean -1.9 puff/24 h (SD 2.9); n=213; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 only reported as L, not %predicted. UNCLEAR IF SD OR SE REPORTED at 12 weeks; Group 1: mean 0.54 L (SD 0.44); n=213, Group 2: mean 0.27 L (SD 0.44); n=213; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: morning PEF ("last post-baseline week" - so average over 7 days presumed). UNCLEAR IF SD OR SE REPORTED at 12 weeks; Group 1: mean 89.9 L/min (SD 97.3); n=211, Group 2: mean 34.2 L/min (SD 68.4); n=212; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Chavasse 2001[252]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52 [37 completed study])
Countries and setting	Conducted in United Kingdom; Setting: Community and outpatient care

Line of therapy	1st line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: Documented history of persistent wheeze or cough, personal history of eczema or family history of asthma or seasonal rhinitis in first degree relative.
Stratum	<1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	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 or seasonal rhinitis in first degree relative. Infants who had received a short course of oral steroid were not excluded, but recruitment was deferred until one month after the treatment course.
Exclusion criteria	History of preterm birth before 34 weeks, had required period of mechanical ventilation, major congenital malformation, already regularly using ICS.
Recruitment/selection of patients	Recruited from hospital outpatient clinics and by referral from general practitioners following a mail shot. Small number identified following admission to the ward with a wheezing illness.
Age, gender and ethnicity	Age - Mean (SD): ICS: 9.8 months (2.6) Placebo: 8.9 months (2.9). Gender (M:F): 77:23. Ethnicity: not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Not stated as uncontrolled, presenting symptoms indicating uncontrolled: 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).
Indirectness of population	Serious indirectness: Infants did not necessarily have a physician diagnosis of asthma
Interventions	(n=26) Intervention 1: ICS (low dose) - Fluticasone propionate. 150 µg (three activations, 50 µg each) twice daily via Babyhaler (small volume spacer and mask). Duration 12 weeks. Concurrent medication/care: Salbutamol inhaler 200-400 µg as needed if required (n=26) Intervention 2: placebo / no intervention - placebo. Three activations, twice daily. Duration 12 weeks. Concurrent medication/care: Salbutamol inhaler 200-400 µg as needed if required
Funding	Other (Rockinghorse Appeal)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for <5 years: Doses of salbutamol at 12 weeks; Group 1: mean -0.22 Doses (SD 0.57); n=19, Group 2: mean 0.12 Doses (SD 1.02); n=18; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events: linear growth at ≥1 year
- Actual outcome for <5 years: Length change at 12 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Chuchalin 2008[268]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2258)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-79, diagnosed with asthma for at least 6 months.
Exclusion criteria	Smoking history of ≥10 pack years, respiratory tract infection within 4 weeks of run in, or were pregnant. Use of any inhaled, oral, parenteral or depot corticosteroid or leukotriene receptor antagonist in the 12 week prior to run in period, or LABA, sodium cromoglicate, nedocromil, ketotifen, or B2-adrenoceptor agonist within 2 weeks of run in period.
Recruitment/selection of patients	Not reported

Age, gender and ethnicity	Age - Mean (range): Placebo: 35 (12-76); FP: 33.8 (12-76); SFC: 33.8 (12-75). Gender (M:F): 958:1300. Ethnicity: White 69%
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Systematic review: mixed (Smoking history (%): Placebo: never smoked (78), former smoker (14), current smoker (7); FP: never smoked (78), former smoker (15), current smoker (8); SFC: never smoked (77), former smoker (15), current smoker (9)).
Extra comments	Diagnosis of asthma with PEF ≥80% predicted, positive BDR (increase in PEF of ≥15%, following 400ug salbutamol), daytime asthma symptom score ≥1 on 3-6 of the previous 7 days.
Indirectness of population	No indirectness
Interventions	(n=973) Intervention 1: ICS+LABA - ICS + Salmeterol. SFC 50ug/100 ug (Seretide/Advair, GSK) once daily in the morning and placebo in the evening. Duration 52 weeks. Concurrent medication/care: Salbutamol provided for symptomatic relief. (n=970) Intervention 2: ICS (low dose) - Fluticasone propionate. FP 100ug (Flixotide/Flovent, GSK) twice daily, morning and evening. Duration 52 weeks. Concurrent medication/care: Salbutamol provided for symptomatic relief. (n=315) Intervention 3: placebo / no intervention - placebo. Placebo twice daily, morning and evening. Duration 52 weeks. Concurrent medication/care: Salbutamol provided for symptomatic relief.
Funding	Study funded by industry (GSK Research and Development Ltd.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE

Protocol outcome 1: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: Median ACQ at endpoint at 52 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Daily rescue medication use (mean) at 52 weeks; MD 0.02 (P value 0.054); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning PEF (L/min) at 52 weeks; SMD -5.3 (95%CI -9.1 to -1.6) (P value 0.006); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: FEV_1 (L) at 52 weeks; SMD 0.027 (95%CI -0.011 to 0.066) (P value 0.165); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Connett 1993[282]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not reported
Stratum	<5 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 1-3 years with at least 6 months of troublesome asthma, thought by their parents to be responsive to bronchodilators.
Exclusion criteria	No clinical evidence of URTI and no treatment with inhaled or oral corticosteroids in the previous fortnight (before two-week run in period where treatment is stopped).
Recruitment/selection of patients	Referred from hospital.
Age, gender and ethnicity	Age - Mean (SD): 1.8 (0.6). Gender (M:F): 26:14. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Cough, wheeze, sleep disturbance, or limitation of activity recorded on at least 3 days/week for both run in weeks.
Indirectness of population	Serious indirectness: No physician diagnosis of asthma.
Interventions	(n=20) Intervention 1: ICS (high dose) - Budesonide. Budesonide 200-400 ug twice a day. Duration 6 months. Concurrent medication/care: Oral prednisolone given for acute exacerbations and nebulised terbutaline prescribed if symptom control was poor.

	(n=20) Intervention 2: placebo / no intervention - placebo. Placebo inhaler taken twice a day. Duration 6 months. Concurrent medication/care: Oral prednisolone given for acute exacerbations and nebulised terbutaline prescribed if symptom control was poor.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for <5 years: Night-time bronchodilator use (doses) at 6 months; Group 1: mean -0.5 doses (SD 0.6); n=17, Group 2: mean 1.2 doses (SD 0.6); n=19; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for <5 years: Daytime bronchodilator use (doses) at 6 months; Group 1: mean -0.1 doses (SD 0.6); n=17, Group 2: mean 1.5 doses (SD 0.7); n=19; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Fish 1997[391]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=762)
Countries and setting	Conducted in unknown multicentre; Setting: In the community and at testing clinics
Line of therapy	1st line
Duration of study	Intervention time: 13 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable

Inclusion criteria	Aged 12 years and over, non-smokers, unmedicated FEV_1 of at least 55% of predicted, diagnosis of asthma with positive BDR; increase in FEV_1 of 15% following bronchodilator therapy.
Exclusion criteria	Presence of acute illness or disease, history of drug or alcohol abuse, respiratory tract infections within the past 6 weeks, vaccination for influenza or hepatitis B within 6 weeks of screening, use of astemizole within previous 3 months, inhaled cromolyn or corticosteroid within 4 weeks of screening, or inhaled corticosteroid as long term therapy.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range: 12-76. Gender (M:F): 440:322. Ethnicity: Not stated
Further population details	1. Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Patients had positive BDR (increase in FEV_1 of 15% following bronchodilator therapy). 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.
Indirectness of population	No indirectness
Interventions	(n=514) Intervention 1: Leukotriene receptor antagonist (LTRA) - Zafirlukast. Zafilukast 20 mg bid. Duration 13 weeks. Concurrent medication/care: Albetrol (Ventolin) taken as needed (n=248) Intervention 2: placebo / no intervention - placebo. Placebo capsule to match intervention medication. Duration 13 weeks. Concurrent medication/care: Albetrol (Ventolin) taken as needed
Funding	Study funded by industry (Zeneca Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ZAFIRLUKAST versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albetrol use (puffs/day) at 13 weeks; Group 1: mean 3.14 puffs/day (SD 2.04); n=433, Group 2: mean 3.91 puffs/day (SD 2.05); n=195; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (given as L and not % predicted) at 13 weeks; Group 1: mean 3.03 L (SD 0.45); n=433, Group 2: mean 2.95 L (SD 0.47); n=195; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Morning PEF at 13 weeks; Group 1: mean 418.3 L/min (SD 52.1); n=433, Group 2: mean 404.7 L/min (SD 50.4); n=195; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Garcia garcia 2005[427]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=994)
Countries and setting	Conducted in multiple countries; Setting: Multiple sites
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6-14, history of asthma <12 months, step 2 of GINA guideline, FEV_1 >80% predicted
Exclusion criteria	Use of systemic corticosteroid, immunosuppressant within 1 month of study, antibiotics in >7 days during run in.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): 9 (5-15). Gender (M:F): 613/381. Ethnicity: White 63.5%
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Increase in FEV_1 or PEF of >12% after SABA, decrease in >15% after exercise challenge
Indirectness of population	No indirectness
Interventions	(n=495) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast (5mg) . Duration 1 year. Concurrent medication/care: SABA as needed (n=499) Intervention 2: ICS (low dose) - Fluticasone propionate. FP 100ug (two puffs of 50ug) twice daily. Duration 1 year. Concurrent medication/care: SABA as needed

Funding	Study funded by industry (Merck and Co.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONTELUKAST versus FLUTICASONE PROPIONATE Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for 5 to <16 years: AQLQ at 1 year; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Reliever medication use at ≥3 months - Actual outcome for 5 to <16 years: Reliever medication use (% of days) at 1 year; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: FEV_1 (% predicted) at 1 year; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Hoshino 1998[497]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in Unknown; Setting: In the community and hospital/clinic for testing
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients satisfied the American Thoracic Society Criteria for asthma.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult (aged 16-48) non-smoking asthmatics (according to American Thoracic Society Criteria for asthma), PEF/FEV_1 increase of 20% following B2-agonist.
Exclusion criteria	No ICS or anti-inflammatory drugs within previous 4 months, no URTI within two weeks of study.

Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): ICS: 29 (16-44) placebo: 27 (17-48). Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	All patients satisfied the American Thoracic Society Criteria for asthma and demonstrated positive BDR with a 20% improvement in PEF or FEV_1 following G2 agonist inhalation.
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: ICS (moderate dose) - Beclometasone dipropionate. BDP 400 µg twice daily via metered dose inhaler. Duration 6 months. Concurrent medication/care: Inhaled B2-agonist, as needed (n=15) Intervention 2: placebo / no intervention - placebo. Placebo to match intervention BDP, taken twice daily. Duration 6 months. Concurrent medication/care: Inhaled B2-agonist, as needed
Funding	Other (Schering-Plough Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: B2-agonist use at 6 months; Group 1: mean 2.4 puffs/day (SD 1.4); n=12, Group 2: mean 5.8 puffs/day (SD 1.6); n=12; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: PEF (recorded twice daily) at 6 months; Group 1: mean 505 L/min (SD 95.6); n=12, Group 2: mean 436.7 L/min (SD 77.1); n=12; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: FEV_1 % at 6 months; Group 1: mean 73.7 % of predicted value (SD 10.1); n=12, Group 2: mean 68.5 % of predicted value (SD 9.2); n=12; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Jones 1994[543]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=340)
Countries and setting	Conducted in United Kingdom; Setting: Community, local general practices
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-70 years with mild to moderate stable asthma and documented response to B-agonsit, PEFR >60%, demonstrate competence with the use of Turbohaler and peak flow meter.
Exclusion criteria	Had received long-term glucocorticosteroids in the previous 6 months, shorts course glucocorticosteroids by any route in the past 2 month, had exacerbation of asthma in past 2 months, used cromoglicate or nedocromil in the past 2 months, need for nebulised B2-agonist, current respiratory infection or one treated in the past 6 weeks, other concomitant respiratory condition, symptomatic allergy or predicted seasonal allergy during study.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Morning: 36 (16) Evening: 36 (17) BD: 36 (17) Placebo: 40 (18). Gender (M:F): 178:162. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear (None within past 2 months). 2. Prior medication: Not applicable / Not stated / Unclear (None within past 6 months but unclear how many people were completely ICS naïve). 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Patients 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. 4 arm trial - budesonide 400µg once daily in the evening, budesonide 400µg once daily in the morning, budesonide 200µg twice daily, placebo. FIRST 3 ARMS COMBINED FOR THIS REVIEW AS ALL ARE LOW DOSE ICS.
Indirectness of population	No indirectness
Interventions	(n=255) Intervention 1: ICS (low dose) - Budesonide. Budesonside 400 µg taken am/pm/200 µg bid. Duration 12 weeks. Concurrent medication/care: Short-acting B2-agonist taken as needed

	(n=85) Intervention 2: placebo / no intervention - placebo. Placebo taken twice daily. Duration 12 weeks. Concurrent medication/care: Short-acting B2-agonist taken as needed
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Reliever medication use during the day - doses per day at 12 weeks; Group 1: mean -1.14 Doses per day (SD 2.26); n=255, Group 2: mean -0.59 Doses per day (SD 1.94); n=85; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Reliever medication use at night - doses per night at 12 weeks; Group 1: mean -0.28 Doses per night (SD 1.28); n=255, Group 2: mean 0.13 Doses per night (SD 1.75); n=85; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 28 L/min (SD 49); n=255, Group 2: mean 6 L/min (SD 46); n=85; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Respiratory infection at 12 weeks; Group 1: 29/255, Group 2: 17/85; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Kemp 2000[568]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=306)
Countries and setting	Conducted in unknown multicentre; Setting: Community and test clinics
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	History of asthma for at least 6 months, using SABA for at least 2 weeks before screening visit, FEV_1 55-85% of norm after restriction from medication, FEV_1 increase of 12% or more of prebronchodilator value.
Exclusion criteria	Treated with ICS within past 3 months, more than 14 days exposure to systemic corticosteroid in previous 6 months, required daily nebulised B2-adrenergic agonist, required more than 12 inhalations of albuterol per day on any two occasions, hospitalised for asthma within previous 3 months, emergency hospital treatment for asthma twice within previous 6 months, required ventilatory support for asthma within 5 years, smoked within 6 months, respiratory diseases.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): ICS 200µg am: 32 (15) ICS 400µg am: 29 (11) ICS 200µg bid: 32 (14) Placebo: 32 (15). Gender (M:F): 152:154. Ethnicity: 81% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Not stated that uncontrolled, states using SABA for at least 2 weeks before screening visit?
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: ICS (low dose) - Mometasone furoate. Mometasone furoate taken 200 µg taken in the am (via DPI) . Duration 12 weeks. Concurrent medication/care: Supplementary albuterol taken as needed (n=74) Intervention 2: placebo / no intervention - placebo. Placebo taken via DPI. Duration 12 weeks. Concurrent medication/care: Supplementary albuterol taken as needed (n=153) Intervention 3: ICS (moderate dose) - Mometasone furoate. Mometasone furoate 400 µg (taken 200 µg twice daily and 400 µg once daily via DPI) . Duration 12 weeks. Concurrent medication/care: Supplementary albuterol taken as needed Comments: 74 took 200 µg twice daily, 79 took 400 µg once daily.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MOMETASONE FUROATE versus PLACEBO	

Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Albuterol use (inhalations per day) at 12 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (given in L not as % of predicted value) at 12 weeks; Group 1: mean 0.27 L (SD 0.53); n=67, Group 2: mean 0.14 L (SD 0.52); n=56; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 26 L/min (SD 61.4); n=67, Group 2: mean 23 L/min (SD 60.2); n=56; Risk of bias: Low; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MOMETASONE FUROATE versus MOMETASONE FUROATE Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Albuterol use (inhalations per day) at 12 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (given in L not as % of predicted value) at 12 weeks; Group 1: mean 0.27 L (SD 0.53); n=67, Group 2: mean 0.41 L (SD 0.48); n=140; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 26 L/min (SD 61.4); n=67, Group 2: mean 58.2 L/min (SD 61.3); n=140; Risk of bias: Low; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MOMETASONE FUROATE versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Albuterol use (inhalations per day) at 12 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (given in L not as % of predicted value) at 12 weeks; Group 1: mean 0.41 L (SD 0.48); n=140, Group 2: mean 0.14 L (SD 0.52); n=56; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 58.2 L/min (SD 61.3); n=140, Group 2: mean 23 L/min (SD 60.2); n=56; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Kerwin 2008[577]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=844)
Countries and setting	Conducted in multiple countries; Setting: 103 sites in the United States and 18 sites in Canada
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Medical history of asthma (as defined by the American Thoracic Society) requiring physician prescribed asthma therapy for at least 3 months duration. Demonstrating BDR at screening.
Stratum	≥16 years: ≥12 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (range): ICS/LABA 250/50 QD: 33.4 (12–73); ICS/LABA 100/50 BID: 33.5 (12–71); ICS 250 QD: 31.7 (12–85); placebo: 33.0 (12–73). Gender (M:F): Define. Ethnicity: 75-80% Caucasian, 10-15% African-American, 8% Hispanic, 1-3% Asian, 1-2% other.
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Use of preventer medication in the past (>1 month ago) 3. Smoking status: Non-smoker/ex-smoker
Extra comments	To be eligible for randomisation patients had to have during the 7 days prior to the randomisation visit: an asthma symptom score (combined daytime and nighttime) of ≥2 or used albuterol on ≥4 days, an evening PEF between 50% and 90% of predicted, and demonstrate an FEV_1 within ±15% of the pre-bronchodilation screening FEV_1 at the randomisation visit.
Indirectness of population	No indirectness
Interventions	(n=420) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone propionate + salmeterol via a single inhaler (arm 1: 250/50 mcg once daily in the evening; arm 2: 100/50 mcg twice daily). Two arms analysed separately in the study but combined for analysis in this review. Duration 12 weeks. Concurrent medication/care: SABA PRN (n=212) Intervention 2: ICS (low dose) - Fluticasone propionate. Fluticasone propionate 250µg once daily in the evening with placebo inhaler in the morning (via Diskus). Duration 12 weeks. Concurrent medication/care: SABA PRN

	(n=212) Intervention 3: placebo / no intervention - placebo. Placebo inhaler twice daily. Duration 12 weeks. Concurrent medication/care: SABA PRN
Funding	Study funded by industry (supported by a grant from GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE + SALMETEROL versus FLUTICASONE PROPIONATE

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: 24 hour Reliever medication use at 12 weeks; Group 1: mean -1.85 puffs/24 hour (SD 2.54); n=420, Group 2: mean -1.5 puffs/24 hour (SD 2.8); n=212; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: morning PEF averaged over weeks 1-12 at 12 weeks; Group 1: mean 54.4 L/min (SD 43.6); n=420, Group 2: mean 33.6 L/min (SD 43.7); n=212; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: morning FEV_1 (given as L not % predicted) at 12 weeks; Group 1: mean 0.485 L (SD 0.43); n=420, Group 2: mean 0.36 L (SD 0.44); n=212; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Upper respiratory tract infection at 12 weeks; Group 1: 23/353, Group 2: 6/182; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE + SALMETEROL versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: 24 hour reliever medication use at 12 weeks; Group 1: mean -1.85 puffs/24 hour (SD 2.54); n=420, Group 2: mean -0.4 puffs/24 hour (SD 2.2); n=212; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: morning PEF averaged over weeks 1-12 at 12 weeks; Group 1: mean 54.4 L/min (SD 43.6); n=420, Group 2: mean 12.6 L/min (SD 43.7); n=212; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: morning FEV_1 (given as L not % predicted) at 12 weeks; Group 1: mean 0.485 L (SD 0.43); n=420, Group 2: mean 0.18 L (SD 0.44); n=212; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Upper respiratory tract infection at 12 weeks; Group 1: 23/353, Group 2: 8/163; Risk of bias: Very high; Indirectness of outcome: No

indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: 24 hour Reliever medication use at 12 weeks; Group 1: mean -1.5 puffs/24 hour (SD 2.8); n=212, Group 2: mean -0.4 puffs/24 hour (SD 2.2); n=212; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: morning PEF averaged over weeks 1-12 at 12 weeks; Group 1: mean 33.6 L/min (SD 43.7); n=212, Group 2: mean 12.6 L/min (SD 43.7); n=212; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: morning FEV_1 (given as L not % predicted) at 12 weeks; Group 1: mean 0.36 L (SD 0.44); n=212, Group 2: mean 0.18 L (SD 0.44); n=212; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Upper respiratory tract infection at 12 weeks; Group 1: 6/182, Group 2: 8/163; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Kooi 2008[588]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Netherlands; Setting: Performed in a secondary care setting.
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	1 to <5 years
Subgroup analysis within study	Not applicable

Inclusion criteria	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.
Exclusion criteria	ICS or LTRA use was not allowed for a period of 4 weeks preceding the trial. Other exclusion criteria were: use of systemic corticosteroid in the last 2 months, hospitalisation for asthma-related symptoms in the last two weeks, respiratory disorders or poorly controlled systemic diseases.
Recruitment/selection of patients	Potential participants approached by paediatricians from three outpatient clinics in The Netherlands.
Age, gender and ethnicity	Age - Mean (SD): 3.8 (1.3). Gender (M:F): 39/24. Ethnicity: Not stated
Further population details	1. Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Required to have asthma symptoms on at least 4 days during the two week run in period.
Indirectness of population	Serious indirectness: No clinical or physician diagnosis of asthma
Interventions	(n=25) Intervention 1: ICS (low dose) - Fluticasone propionate. FP 100 µg twice from MDI daily via a plastic spacer device, plus chewable placebo tablet once daily. Duration 3 months. Concurrent medication/care: Permitted the use of 100 µg salbutamol as required. (n=18) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Mk 4mg chewable tablet once daily, plus placebo twice from MDI daily via a plastic spacer device. Duration 3 months. Concurrent medication/care: Permitted the use of 100 µg salbutamol as required. (n=20) Intervention 3: placebo / no intervention - placebo. Placebo chewable tablet once daily, plus placebo twice from MDI daily via a plastic spacer device. Duration 3 months. Concurrent medication/care: Permitted the use of 100 µg salbutamol as required.
Funding	Study funded by industry (Merck Sharp and Dohme)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus MONTELUKAST

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for <5 years: Rescue free days % at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events: infection at ≥3 months
- Actual outcome for <5 years: Upper respiratory tract infection (number of patients experiencing URTIs) at 3 months; Group 1: 6/21, Group 2: 6/17; Risk of bias: High;

Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for <5 years: Rescue free days % at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: infection at ≥3 months - Actual outcome for <5 years: Upper respiratory tract infection (number of patients experiencing URTIs) at 3 months; Group 1: 6/21, Group 2: 1/15; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONTELUKAST versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for <5 years: Rescue free days % at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: infection at ≥3 months - Actual outcome for <5 years: Upper respiratory tract infection (number of patients experiencing URTIs) at 3 months; Group 1: 6/17, Group 2: 1/15; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Maspero 2008[678]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=548)
Countries and setting	Conducted in multiple countries; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6 to 14 years, diagnosed with asthma for at least 6 months, 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.
Exclusion criteria	Hospitalised for asthma or received systemic corticosteroid in previous 3 months, ICS in the past month, LTRA in past 2 weeks, URTI in previous 2 weeks, FEV_1 <55% predicted.
Recruitment/selection of patients	Recruited from outpatient setting
Age, gender and ethnicity	Age - Mean (SD): SFC: 9.3 (2.2) MON: 9.3 (2.1). Gender (M:F): 335/213. Ethnicity: American Hispanic 84%
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Diagnosis of asthma with positive BDR (increase in FEV_1 of ≥12%)
Indirectness of population	No indirectness
Interventions	(n=281) Intervention 1: ICS+LABA - ICS + Salmeterol. SFC 50ug/100ug BID, via multidose dry powder inhaler, plus placebo tablet QD. Duration 12 weeks. Concurrent medication/care: SABA as needed (n=267) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 5mg QD plus placebo inhaler BID. Duration 12 weeks. Concurrent medication/care: SABA as needed
Funding	Study funded by industry (GlaxoSmithCline)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONTELUKAST versus ICS + SALMETEROL Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for 5 to <16 years: Paediatric Asthma Quality of Life Questionnaire at 12 weeks; MD -0.09 (95%CI -0.3 to 0.12); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Reliever medication use at ≥3 months - Actual outcome for 5 to <16 years: Rescue-free 24-hour periods at 12 weeks; OR 3.24 (95%CI 2.09 to 5.02) (p 0.001); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Meltzer 2002[705]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=522)
Countries and setting	Conducted in unknown multicentre; Setting: In the community and clinic visits.
Line of therapy	1st line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 15+, non-smokers, diagnosed with asthma for at least 6 months, unmedicated FEV_1 of 50-80% of predicted, FEV_1 increase of 15% following 180 µg albuterol, use of SABA as needed for preceding 3 months.
Exclusion criteria	History of life-threatening or unstable asthma or other severe uncontrolled diseases, hypersensitivity to sympathomimetic drugs, acute respiratory tract infections within the past 4 weeks, history of smoking. Excluded medications; inhaled or systemic corticosteroids, inhaled cromolyn or nedocromil, leukotriene modifiers, anticholinergics, and theophylline.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): FP: 36.2 (15-73) Montelukast: 35.4 (15-77). Gender (M:F): 242:280. Ethnicity: White 81%
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Demonstrate a need for additional asthma controller therapy at the end of run in period: unmediated FEV_1 of 50 – 80% and within 15% of FEV_1 obtained at initial screen, use of albuterol for at least 6 of the 7 days before randomisation during run-in, asthma symptom score of 2 or more (0-5 scale) on at least 4 of 7 days before randomisation.
Indirectness of population	Serious indirectness: Time period for which population are preventer naïve prior to study is unclear.
Interventions	(n=258) Intervention 1: ICS (low dose) - Fluticasone propionate. Fluticasone propionate 88 µg twice daily (Flovent Inhalation Aerosol, GSK) + placebo capsule . Duration 24 weeks. Concurrent medication/care: Supplementary Albuterol taken as needed (n=264) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg capsule (Singulair,

	Merck & Co. Inc) + placebo via metered dose inhaler twice daily. Duration 24 weeks. Concurrent medication/care: Supplementary Albuterol taken as needed
Funding	Study funded by industry (Glaxo Wellcome Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus MONTELUKAST Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbations at 24 weeks; Group 1: 19/198, Group 2: 21/197; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 2: Quality of life at ≥3 months - Actual outcome for ≥16 years: Asthma Quality of Life Questionnaire (AQLQ) at 24 weeks; Group 1: mean 1.3 (SD 1.4); n=198, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Albuterol use (puffs/day) at 24 weeks; Group 1: mean -3.21 puffs/day (SD 2.67); n=198, Group 2: mean -2.25 puffs/day (SD 2.39); n=197; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning FEV_1 (absolute change, L) at 24 weeks; Group 1: mean 0.48 L (SD 0.42); n=198, Group 2: mean 0.32 L (SD 0.42); n=197; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 24 weeks; Group 1: mean 63.7 L/min (SD 71.8); n=198, Group 2: mean 37.6 L/min (SD 64.6); n=197; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Nathan 1999[754]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=386)

Countries and setting	Conducted in USA; Setting: 25 centres in the United States
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12+, non-smokers, diagnosed with asthma as defined by ATS for at least 3 months, unmedicated FEV_1 of 65-90% of predicted, FEV_1 increase of 12% following 180 µg albuterol, on SABA as needed.
Exclusion criteria	ICS within 6 months of trial, decline in FEV_1 of more than or equal to 15% after saline inhalation, asthma instability (hospital admission within 30 days before screening or by requiring >12 puffs of SABA on 3 of the last 7 days of screening), hypersensitivity to sympathomimetic drugs or BDP, use of medication which may affect course of asthma or interact with sympathomimetic amines, abnormal ECG, evidence of significant concurrent disease.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Age (SE) - BDP: 29.9 (1.1), Placebo: 29.1 (1.1). Gender (M:F): 120:138. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Baseline data states that during the week before randomisation, the range of symptom free days was 17% to 20% (therefore all patients symptomatic at inclusion). Intranasal corticosteroids or intranasal cromolyn sodium were allowed only if the dose remained unchanged during the study.
Indirectness of population	No indirectness
Interventions	(n=129) Intervention 1: ICS (moderate dose) - Beclometasone dipropionate. BDP 84 µg (Beclovent Inhalation Aerosol, GSK) four times daily. Duration 6 months. Concurrent medication/care: Supplementary inhaled aluberol as needed. Intranasal corticosteroids or intranasal cromolyn sodium were allowed only if the dose remained unchanged during the study. (n=129) Intervention 2: placebo / no intervention - placebo. Placebo to match intervention group. Duration 6 months. Concurrent medication/care: Supplementary inhaled aluberol as needed. Intranasal corticosteroids or intranasal cromolyn sodium were allowed only if the dose remained unchanged during the study.
Funding	Study funded by industry (Glaxo Wellcome Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Asthma exacerbation treated with an OCS at 6 months; Group 1: 13/129, Group 2: 17/129; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albuterol-free days % at 6 months; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Albuterol-free nights % at 6 months; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (L) at 6 months; Group 1: mean 0.23 L (SD 0.45); n=106, Group 2: mean 0.08 L (SD 0.45); n=101; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Nayak 2002[756]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=353)
Countries and setting	Conducted in USA; Setting: 50 outpatient hospitals across the United States.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 5 to 12, diagnosed with asthma for at least 6 months and receiving short acting B2-agonist on an as needed basis, FEV_1 of 50-80% of predicted, reversibility of airway obstruction shown as FEV_1 increase of at least 12% following 400 µg

	pirbuterol.
Exclusion criteria	Any significant, non-reversible pulmonary disease other than asthma; evidence of any clinically significant immunologic, neoplastic, endocrine, haematologic, cardiac, hepatic, renal, GI, neurologic, or psychiatric abnormalities or illness; upper or lower respiratory tract infection within two or four weeks respectively; known hypersensitivity to BDP; use of injectable, oral, or inhaled corticosteroids within the previous 6 months, 8 weeks, and 6 weeks respectively; use of long acting B2 agonist or leukotriene receptors.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 9.2 (2). Gender (M:F): 224:129. Ethnicity: 77% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	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.
Indirectness of population	No indirectness
Interventions	(n=120) Intervention 1: ICS (low dose) - Beclometasone dipropionate. 80 µg HFA BDP - one puff bid from 40 µg strength inhaler. Duration 12 weeks. Concurrent medication/care: Short acting B2-agonist (pirbuterol) taken as needed (n=117) Intervention 2: ICS (moderate dose) - Beclometasone dipropionate. 160 µg HFA BDP - one puff bid from 80 µg strength inhaler. Duration 12 weeks. Concurrent medication/care: Short acting B2-agonist (pirbuterol) taken as needed (n=116) Intervention 3: placebo / no intervention - placebo. HFA placebo - one puff bid . Duration 12 weeks. Concurrent medication/care: Short acting B2-agonist (pirbuterol) taken as needed
Funding	Study funded by industry (3M Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE (LOW) versus BECLOMETASONE DIPROPIONATE (MODERATE)

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for 5 to <16 years: Daily B-agonist use (puffs) at 12 weeks; Group 1: mean -0.59 puffs/day (SD 1.3); n=105, Group 2: mean -0.84 puffs/day (SD 1.3); n=108; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: FEV_1 % predicted at 12 weeks; Group 1: mean 9.2 % of predicted value (SD 11); n=105, Group 2: mean 10 % of predicted value (SD

11); n=108; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months
- Actual outcome for 5 to <16 years: Upper respiratory tract infection (number of participants experiencing URTIs) at 12 weeks; Group 1: 34/105, Group 2: 24/108; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse events: adrenal insufficiency at ≥3 months
- Actual outcome for 5 to <16 years: Patients with abnormal response to low-dose ACTH stimulation at 12 weeks; Group 1: 0/105, Group 2: 1/108; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE (LOW) versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for 5 to <16 years: Daily B-agonist use (puffs) at 12 weeks; Group 1: mean -0.59 puffs/day (SD 1.3); n=105, Group 2: mean -0.22 puffs/day (SD 1.3); n=97; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: FEV_1 % predicted at 12 weeks; Group 1: mean 9.2 % predicted value (SD 11); n=105, Group 2: mean 3.9 % predicted value (SD 11); n=97; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Morning PEF at 12 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months
- Actual outcome for 5 to <16 years: Upper respiratory tract infection (number of participants experiencing URTIs) at 12 weeks; Group 1: 34/105, Group 2: 26/97; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse events: adrenal insufficiency at ≥3 months
- Actual outcome for 5 to <16 years: Patients with abnormal response to low-dose ACTH stimulation at 12 weeks; Group 1: 0/105, Group 2: 3/97; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE (MODERATE) versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for 5 to <16 years: Daily B-agonist use (puffs) at 12 weeks; Group 1: mean -0.84 puffs/day (SD 1.3); n=108, Group 2: mean -0.22 puffs/day (SD 1.3); n=97; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months

- Actual outcome for 5 to <16 years: FEV_1 % predicted at 12 weeks; Group 1: mean 10 % of predicted value (SD 11); n=108, Group 2: mean 3.9 % of predicted value (SD 11); n=97; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for 5 to <16 years: Morning PEF at 12 weeks; MD 21.6 (SE 8.3); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for 5 to <16 years: Upper respiratory tract infection (number of participants experiencing URTIs) at 12 weeks; Group 1: 24/108, Group 2: 26/97; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse events: adrenal insufficiency at ≥3 months - Actual outcome for 5 to <16 years: Patients with abnormal response to low-dose ACTH stimulation at 12 weeks; Group 1: 1/108, Group 2: 3/97; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year

Study	**Nelson 2003[761]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=283)
Countries and setting	Conducted in USA; Setting: 33 investigation sites across the United States
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12+ years with medical history of asthma, requiring pharmacotherapy for previous 6 months, FEV_1 40 - 85% of predicted value, treated during previous month with an as-needed short-acting B2-agonist. Diagnosis of asthma with positive BDR (increase in FEV_1 of 15% following 180µg albuterol).
Exclusion criteria	Exclusion criteria only stated to have been similar to previous studies for Advair Diskus

Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 32.4 (12-77). Gender (M:F): 149:134. Ethnicity: 78% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Patients must have demonstrated a total 24hr symptom score of 7 or 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).
Indirectness of population	No indirectness
Interventions	(n=95) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone Propionate 88 µg plus Salmetrol 42 µg via MDI (two inhalations of 44/21 µg strength; Flovent Inhalation Aerosol, GSK). Duration 12 weeks. Concurrent medication/care: Albuterol CFC (Ventolin Inhalation Aerosol; GSK) as needed (n=97) Intervention 2: ICS (low dose) - Fluticasone propionate. Fluticasone Propionate 88 µg via MDI (two inhalations of 44 µg strength; Flovent Inhalation Aerosol, GSK). Duration 12 weeks. Concurrent medication/care: Albuterol CFC (Ventolin Inhalation Aerosol; GSK) as needed
Funding	Study funded by industry (GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albuterol use, puffs/day at 12 weeks; Group 1: mean -2.4 puffs/24 hours (SD 3); n=86, Group 2: mean -1.8 puffs/24 hours (SD 2.1); n=89; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (given as L not as % predicted) at 12 weeks; Group 1: mean 0.69 L (SD 0.49); n=86, Group 2: mean 0.51 L (SD 0.49); n=89; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 66.5 L/min (SD 54.3); n=86, Group 2: mean 43 L/min (SD 51.9); n=89; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	OPTIMA trial: O'byrne 2001 [776]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1970)
Countries and setting	Conducted in multiple countries; Setting: Community and outpatients care
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Mild asthma. Randomised patients demonstrated a ≥ 15% variability in peak expiratory flows (PEF), or a ≥ 12% increase in FEV_1 after terbutaline
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	>12 yrs old, had used no ICS for >3 months, had an FEV_1 >80% predicted normal after inhaling 1mg terbutaline. Demonstrated symptoms during run-in consistent with being "uncontrolled".
Exclusion criteria	Define
Recruitment/selection of patients	Recruited from 198 centers in 17 countries
Age, gender and ethnicity	Age - Range of means: 30.6-31.2. Gender (M:F): 178:281. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Randomised 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".
Indirectness of population	No indirectness
Interventions	(n=228) Intervention 1: ICS (low dose) - Beclometasone dipropionate. 100µg budesonide BD via turbohaler. Duration 1 year. Concurrent medication/care: No other treatment allowed unless the patient had a severe exacerbation at which point medications could be added at the physician's discretion. (n=231) Intervention 2: ICS+LABA - ICS + Formoterol. 100µg budesonide + 4.5µg formoterol BD via turbohaler. Duration 1 year. Concurrent medication/care: No other treatment allowed unless the patient had a severe exacerbation at which point medications could be added at the physician's discretion.

	(n=239) Intervention 3: placebo / no intervention - placebo. Placebo. Duration 1 year. Concurrent medication/care: No other treatment allowed unless the patient had a severe exacerbation at which point medications could be added at the physician's discretion.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW DOSE STEROIDS versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Number of patients receiving systemic corticosteroids at Within the year; Group 1: 27/228, Group 2: 56/239; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Number of rescue inhalations per day per patient at Within the year; MD -0.24 (SE 0.07); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in FEV_1 predicted % from baseline to end of treatment at Within the year; MD 2.25 (SE 0.79); Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus LOW DOSE STEROIDS

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Number of patients receiving systemic corticosteroids at Within the year; Group 1: 34/231, Group 2: 27/228; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Number of rescue inhalations per day per patient at Within the year; MD 0 (SE 0); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in FEV_1 predicted % from baseline to end of treatment at Within the year; MD 1.83 (SE 0.8); Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Number of patients receiving systemic corticosteroids at Within the year; Group 1: 34/231, Group 2: 56/239; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Number of rescue inhalations per day per patient at Within the year; MD -0.24 (SE 0.07); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Change in FEV_1 predicted % from baseline to end of treatment at Within the year; MD 4.08 (SE 1.04); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Pearlman 2002** [824]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=432)
Countries and setting	Conducted in USA; Setting: 51 outpatient sites across the United States
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 15 years and over, diagnosed with asthma for at least 6 months, use of SABA as needed for preceding 6 weeks, unmedicated FEV_1 of 50-80% of predicted.
Exclusion criteria	History of life-threatening or unstable asthma or other severe uncontrolled diseases, asthma instability (hospital admission within 3 months), concurrent acute respiratory tract infections. Excluded medications; inhaled or parenteral

	corticosteroids, inhaled cromolyn or nedocromil, leukotriene modifiers, anticholinergics, and theophylline. No use of inhaled or parenteral corticosteroids for at least 6 weeks prior to the study.
Recruitment/selection of patients	Recruited via referral or from advertising.
Age, gender and ethnicity	Age - Mean (range): 35.5 (15-83. Gender (M:F): 196:236. Ethnicity: 84.5% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Patients considered symptomatic and thus eligible with unmediated FEV_1 of 50 – 80% of predicted, an objective diagnosis of asthma with positive BDR (increase in FEV_1 of 12% following 180µg albuterol), use of albuterol 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.
Indirectness of population	No indirectness
Interventions	(n=216) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone Propionate 100 µg plus Salmetrol 50 µg; twice daily via Diskus device plus placebo Montelukast once daily. Duration 12 weeks. Concurrent medication/care: Albuterol (Ventolin inhalation aerosol, GSK) taken as needed. (n=216) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg capsule (Singulair, Merk & Co) once daily plus placebo Fluticasone Propionate twice daily via Diskus device. Duration 12 weeks. Concurrent medication/care: Albuterol (Ventolin inhalation aerosol, GSK) taken as needed.
Funding	Study funded by industry (Glaxo Wellcome Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus MONTELUKAST

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: Asthma Quality of Life Questionnaire at 12 weeks; Group 1: mean 1.7 (SD 1.18); n=171, Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albuterol use, puffs/day at 12 weeks; Group 1: mean -3.6 puffs/day (SD 2.9); n=171, Group 2: mean -2.2 puffs/day (SD 2.9); n=183; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (given as L not as % predicted) at 12 weeks; Group 1: mean 0.61 L (SD 0.44); n=171, Group 2: mean 0.32 L (SD 0.44); n=183; Risk of

bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 81.4 L/min (SD 86.7); n=171, Group 2: mean 41.9 L/min (SD 70.5); n=183; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Pedersen 1996** [826]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in Unknown; Setting: In the community and testing clinics
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptoms and lung function parameters compatible with diagnosis of asthma, requirement of regular maintenance treatment, significant FEV_1 increase following B2-agnoist inhalation.
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): low-dose ICS: 46.8 (12.5) high-dose ICS: 46.1 (11.2) theophylline: 45.0 (13.7). Gender (M:F): 48:37. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Believed to require regular maintenance treatment due to attacks of dyspnea, cough, and wheezing, in addition to signs of air flow variability.
Indirectness of population	Serious indirectness: Time period for which population are preventer naïve prior to study is unclear. Asthma diagnosis

	also unclear.
Interventions	(n=29) Intervention 1: ICS (low dose) - Budesonide. Inhaled budesonide 400µg daily. Duration 9 months. Concurrent medication/care: Allowed medication with inhaled B2-agonist only on as-needed basis (n=29) Intervention 2: ICS (high dose) - Budesonide. Inhaled budesonide 1600µg daily. Duration 9 months. Concurrent medication/care: Allowed medication with inhaled B2-agonist only on as-needed basis (n=27) Intervention 3: Theophylline/Aminophylline - Theophylline. Oral theophylline 600 mg daily. Duration 9 months. Concurrent medication/care: Allowed medication with inhaled B2-agonist only on as-needed basis
Funding	Study funded by industry (Astra Darco AB)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus BUDESONIDE Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 % predicted at 9 months; Group 1: mean 74 % of predicted value (SD 53); n=29, Group 2: mean 82 % of predicted value (SD 51); n=29; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus THEOPHYLLINE Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 % predicted at 9 months; Group 1: mean 75 % of predicted value (SD 53); n=29, Group 2: mean 75 % of predicted value (SD 62); n=27; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus THEOPHYLLINE Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 % predicted at 9 months; Group 1: mean 82 % of predicted value (SD 51); n=29, Group 2: mean 75 % of predicted value (SD 62); n=27; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Reliever medication use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Price 1997 [867]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=123)
Countries and setting	Conducted in United Kingdom; Setting: In the community and testing centre
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Pre-pubertal children (4-10 years), 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).
Exclusion criteria	Inhaled prophylactic therapy for asthma within the last year, OCS within last 3 months, acute respiratory tract infections within the past 2 weeks, disease/medication which may affect growth.
Recruitment/selection of patients	Recruited at 15 hospital centres in the United Kingdom, from their asthma clinics or via primary care referral
Age, gender and ethnicity	Age - Mean (SD): FPr: 6.0 (1.4) SCG: 6.4 (1.6). Gender (M:F): 75:47. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	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.
Indirectness of population	Serious indirectness: No objective measure of asthma diagnosis
Interventions	(n=52) Intervention 1: ICS (low dose) - Fluticasone propionate. Fluticasone Propionate 50 µg twice daily (FPran) via dry powder inhaler (Diskhaler). Duration 12 months. Concurrent medication/care: Salbutamol 200 µg as needed, via Diskhaler. (n=70) Intervention 2: Cromolyns - Sodium cromoglicate. Sodium Cromoglicate 20 mg q.i.d. (SCG) via dry powder inhaler (Spinhaler). After 8 weeks, patients uncontrolled (morning PEF <80% baseline post beta-agonist value or symptoms on at least 6 of the last 14 days) were either switched to fluticasone (n=22) or withdrawn(n=21) (intention to treat analysis in

	randomised groups). Duration 12 months. Concurrent medication/care: Salbutamol 200 µg as needed, via Diskhaler.
Funding	Study funded by industry (Allen and Hanbury Ltd. (GSK))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus SODIUM CROMOGLICATE

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: required a short course of OCS at 12 months; Group 1: 5/52, Group 2: 5/70; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: Morning PEF at 12 months; MD 7.3 (95%CI 1.9 to 12.7) (P 0.01); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: linear growth at ≥1 year
- Actual outcome for 5 to <16 years: Height velocity (cm/year, mean adjusted for gender and age, SD adjusted for gender and obtained from standardised tables) at 12 months; Group 1: mean 6 cm/year (SD 0.1); n=34, Group 2: mean 6.5 cm/year (SD 0.5); n=26; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Reliever medication use at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Price 2011** [862]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=306)
Countries and setting	Conducted in United Kingdom; Setting: 53 primary care practices in the United Kingdom
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable

Inclusion criteria	Aged 12-80, physicians diagnosis of asthma, PEF >50% predicted after inhaled B2-agonist withheld for 4 hours, impaired asthma-related quality of life (score of <6 on miniAQLQ) or impaired asthma control (>1 on Asthma Control Questionnaire).
Exclusion criteria	Prior treatment of ICS within 12 weeks.
Recruitment/selection of patients	Symptomatic asthmatics recruited through acute and routine respiratory care visits, and by invitation letter sent by participating primary care practices.
Age, gender and ethnicity	Age - Mean (SD): LTRA: 47.6 (16.5) ICS: 44.1 (16.4). Gender (M:F): 150:156. Ethnicity: 97% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Mixed cohort: LTRA; smoker 25%, ex-smoker 37%, non-smoker 38%, ICS; smoker 19%, ex-smoker 35%, non-smoker 46%
Extra comments	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).
Indirectness of population	No indirectness
Interventions	(n=158) Intervention 1: ICS (moderate dose) - Beclometasone dipropionate. Beclomethasone (n=146), Budesonide (n=8), Fluticasone (n=3), doses not given; assumed to be moderate-dose. Duration 2 years. Concurrent medication/care: Rescue bronchodilator taken as needed. Comments: Treatment dose not given, population likely to be on varying doses. (n=148) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast (n=127), Zafirlukast (n=16), doses not given. Duration 2 years. Concurrent medication/care: Rescue bronchodilator taken as needed. Comments: Treatment dose not given, population likely to be on varying doses.
Funding	Academic or government funding (National Coordinating Centre for Health Technology Assessment U.K.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE, BUDESONIDE, OR FLUTICASONE versus MONTELUKAST, OR ZAFIRLUKAST

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Patients experiencing exacerbations (requiring OCS or hospitalisation) at 2 years; Group 1: 27/158, Group 2: 36/148; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Quality of life at ≥3 months

- Actual outcome for ≥16 years: MiniAQLQ at 2 years; Group 1: mean 5.65 (SD 1.16); n=120, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Eq-5D at 2 years; Group 1: mean 0.881 (SD 0.218); n=143, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months - Actual outcome for ≥16 years: Asthma Control Questionnaire at 2 years; Group 1: mean 1.08 (SD 0.9); n=119, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Puffs of reliever during the day at 2 years; Group 1: mean 1.24 puffs/day (SD 1.42); n=158, Group 2: mean 1.67 puffs/day (SD 1.7); n=148; Risk of bias: Very High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Puffs of reliever during the night at 2 years; Group 1: mean 0.48 puffs/night (SD 0.96); n=158, Group 2: mean 0.52 puffs/night (SD 0.79); n=148; Risk of bias: Very High; Indirectness of outcome: No indirectness Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 2 years; Group 1: mean 419.2 L/min (SD 137.8); n=158, Group 2: mean 412.4 L/min (SD 102.6); n=148; Risk of bias: Very High; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Respiratory tract infections at 2 years; Group 1: 79/158, Group 2: 70/148; Risk of bias: Very High; Indirectness of outcome: No indirectness Protocol outcome 7: Hospitalisations at ≥3 months - Actual outcome for ≥16 years: Hospitalisations at 2 years; Group 1: 4/151, Group 2: 2/151, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Reid 2008** [897]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in Unknown; Setting: In community and outpatient centres.
Line of therapy	1st line

Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: History of asthma symptoms treated with SABA alone, had to demonstrate BDR (15% increase in FEV_1 after 400 µg of salbutamol) or diurnal PEF variability (>15%) during 1 week run-in.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-smoking adults with history of asthma symptoms treated with SABA alone. All patients had an unmedicated FEV_1 >60% at baseline.
Exclusion criteria	History of an asthma exacerbation, upper respiratory tract infection or alteration of asthma therapy within 6 weeks, or use of OCS within previous three months. Received a long-acting β2-agonist (LABA), anticholinergic, cromone or theophylline during the six weeks prior to the study.
Recruitment/selection of patients	Recruited through adverts
Age, gender and ethnicity	Age - Median (range): 41 (21-69). Gender (M:F): 11:10. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra 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.
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Leukotriene receptor antagonist (LTRA) - Zafirlukast. Zafirlukast (Accolate®, Astra Zeneca) 20 mg, taken bid . Duration 12 weeks. Concurrent medication/care: Usual care - β2-agonists (n=7) Intervention 2: placebo / no intervention - placebo. Matching intervention, taken bid. Duration 12 weeks. Concurrent medication/care: Usual care - β2-agonists
Funding	Study funded by industry (Astra Zeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ZAFIRLUKAST versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: β2-agonist use per day at 12 weeks; Group 1: mean 0.2 use per day (SD 0.5); n=12, Group 2: mean -0.6 use per day (SD 0.5); n=5; Risk of

bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (mL) at 12 weeks; Group 1: mean 14.2 mL (SD 72); n=12, Group 2: mean -258 mL (SD 213); n=5; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean -3.2 L/min (SD 11.5); n=12, Group 2: mean 0.8 L/min (SD 7.5); n=5; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Renzi 2010** [901]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=664 screened [526 randomised])
Countries and setting	Conducted in Canada; Setting: 45 general practices and 15 specialist centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Documented history of asthma treated with SABA only and FEV_1 ≥80% predicted
Stratum	≥16 years: ≥12 years
Subgroup analysis within study	Not applicable
Inclusion criteria	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.
Exclusion criteria	Not reported
Recruitment/selection of patients	October 2002 to February 2004
Age, gender and ethnicity	Age - Median (range): ICS/LABA: 34.8 (12-76); ICS: 34.3 (12-77). Gender (M:F): Define. Ethnicity: 90% Caucasian, 10% Asian, Black or other
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Completely treatment naïve

	3. Smoking status: Non-smoker/ex-smoker
Extra comments	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.
Indirectness of population	Serious indirectness: No objective measure of asthma diagnosis
Interventions	(n=262) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone propionate/salmeterol xinafoate (FSC) 100/50 µg twice daily (administered via Diskus inhaler). Duration 24 weeks. Concurrent medication/care: SABA PRN (n=270) Intervention 2: ICS (low dose) - Fluticasone propionate. Fluticasone propionate 100 µg twice daily (administered via Diskus inhaler). Duration 24 weeks. Concurrent medication/care: SABA PRN
Funding	Study funded by industry (study was funded and sponsored by GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE

Protocol outcome 1: Mortality at ≥6 months
- Actual outcome for ≥16 years: Mortality considered related to study drug at 24 weeks; Group 1: 0/209, Group 2: 0/224; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Emergency room visits at 24 weeks; Group 1: 3/209, Group 2: 3/224; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Mean daily rescue use (inhalations) at 24 weeks; Group 1: mean -1.2 inhalations/day (SD 0.65); n=262, Group 2: mean -1 inhalations/day (SD 0.66); n=270; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: mean morning PEF (last 7 days of treatment) at 24 weeks; MD 15.0 (95%CI 6.3 to 23.6) (P value <0.001); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: morning clinic FEV_1 at 24 weeks; Group 1: mean 0.14 Litres (SD 0.03); n=253, Group 2: mean 0.08 Litres (SD 0.02); n=263; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3

	months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Rojas 2007** [918]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=362)
Countries and setting	Conducted in multiple countries; Setting: 52 investigative sites in 9 countries
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-80, asthma for at least 6 months, <10 pack-year smoking history, treated on SABA only, FEV_1 60-80% of predicted value, either reversibility of more than or equal to 15% in FEV_1 or a morning mean PEF during the last 7 days of run in. Required to have a daytime symptom score of more than or equal to 2 on at least four days of the last 7 days run-in.
Exclusion criteria	Respiratory tract infection or asthma exacerbation during run-in.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): Sal/FP: 40 (15-78) FP: 41 (12-74). Gender (M:F): 153:209. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker (less than 10 pack year smoking history).
Extra comments	Required to have a daytime symptom score of more than or equal to 2 on at least four days of the last 7 days run-in.
Indirectness of population	Serious indirectness: Time period for which population are preventer naïve prior to study is unclear.
Interventions	(n=182) Intervention 1: ICS (moderate dose) - Fluticasone propionate. Fluticasone proprionate 250 µg twice daily via Diskus inhaler. Duration 12 weeks. Concurrent medication/care: Salbutamol via metered dose inhaler, taken as needed (n=180) Intervention 2: ICS+LABA - ICS + Salmeterol. Fluticasone proprionate 250 µg / Salmetrol 50 µg twice daily via Diskus inhaler. Duration 12 weeks. Concurrent medication/care: Salbutamol via metered dose inhaler, taken as needed

Funding	Study funded by industry (GlaxoSmithKline Research & Development)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus ICS + SALMETEROL Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for ≥16 years: Number of people experiencing 100% rescue free days during the treatment period at 12 weeks; Group 1: 26/182, Group 2: 40/180; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Number of people experiencing 100% rescue free nights during the treatment period at 12 weeks; Group 1: 31/182, Group 2: 54/180; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF (mean over the 12 week study period) at 12 weeks; MD 21 (95%CI 11 to 31) (P <0.001); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Ruff 2003** [922]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=319)
Countries and setting	Conducted in USA; Setting: 26 testing centres in the United States
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 6-12, mild to moderate symptomatic asthma of at least 6 months, only pharmacotherapy being Short-acting B2-agonist on an as-needed basis, unmedicated FEV_1 of 50-85% of predicted, satisfactory inhaler technique.

Exclusion criteria	Any significant nonreversible disease other than asthma; evidence of any clinically significant immunologic, neoplastic, or psychiatric problems; upper respiratory tract infection within the previous 2 weeks; lower respiratory tract infection within previous 4 weeks; use of systemic or inhaled corticosteroid within 6 months or 6 weeks respectively.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 9.6 (1.8). Gender (M:F): 191/128. Ethnicity: 79% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Unmediated FEV_1 of 50 – 85% and within 15% of FEV_1 obtained at initial screen, diagnosis of asthma with positive BDR (increase in FEV_1 of 12% following 400µg pirbuterol), requiring B-agonist at least once a day on at least 10 of the last 14 days of the run in period.
Indirectness of population	No indirectness
Interventions	(n=108) Intervention 1: ICS (low dose) - Beclometasone dipropionate. 100 µg HFA-BDP (one inhilation twice daily from the 50 µg strength inhaler). Duration 12 weeks. Concurrent medication/care: Pirbuterol 200 µg (Maxair Autohaler) taken as needed (n=104) Intervention 2: ICS (moderate dose) - Beclometasone dipropionate. 200 µg HFA-BDP (one inhilation twice daily from the 100 µg strength inhaler). Duration 12 weeks. Concurrent medication/care: Pirbuterol 200 µg (Maxair Autohaler) taken as needed (n=107) Intervention 3: placebo / no intervention - placebo. HFA-Placebo (one inhalation twice daily). Duration 12 weeks. Concurrent medication/care: Pirbuterol 200 µg (Maxair Autohaler) taken as needed
Funding	Study funded by industry (3M Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE (LOW DOSE) versus BECLOMETASONE DIPROPIONATE (MODERATE DOSE)

Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: Morning PEF at 12 weeks; Group 1: mean 23.3 L/min (SD 39.5); n=105, Group 2: mean 16.1 L/min (SD 39.4); n=100; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: FEV_1 % predicted at 12 weeks; Group 1: mean 7.7 % predicted (SD 13.3); n=105, Group 2: mean 3 % predicted (SD 13); n=100; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events: infection at ≥3 months - Actual outcome for 5 to <16 years: Participants experiencing upper respiratory tract infection at 12 weeks; Group 1: 20/108, Group 2: 22/104; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE (LOW DOSE) versus PLACEBO Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: Morning PEF at 12 weeks; Group 1: mean 23.3 L/min (SD 39.5); n=105, Group 2: mean 5.5 L/min (SD 40.3); n=104; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for 5 to <16 years: FEV_1 % predicted at 12 weeks; Group 1: mean 7.7 % predicted (SD 13.3); n=105, Group 2: mean 2.5 % predicted (SD 13.3); n=104; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: infection at ≥3 months - Actual outcome for 5 to <16 years: Participants experiencing upper respiratory tract infection at 12 weeks; Group 1: 20/108, Group 2: 26/107; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE (MODERATE DOSE) versus PLACEBO Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: Morning PEF at 12 weeks; Group 1: mean 16.1 L/min (SD 39.4); n=100, Group 2: mean 5.5 L/min (SD 40.3); n=104; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for 5 to <16 years: FEV_1 % predicted at 12 weeks; Group 1: mean 3 % predicted (SD 13); n=100, Group 2: mean 2.5 % predicted (SD 13.3); n=104; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: infection at ≥3 months - Actual outcome for 5 to <16 years: Participants experiencing upper respiratory tract infection at 12 weeks; Group 1: 22/104, Group 2: 26/107; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Reliever medication use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Schokker 2008** [939]
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in Netherlands; Setting: Any of three research centres across the North of the Netherlands.
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	1 to <5 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 1-5 who presented with recurrent respiratory symptoms (cough, wheeze, and/or shortness of breath) whose GPs had considered prescribing ICS for asthma. Required to record symptoms on at least 7 of the 14 days during the run-in period.
Exclusion criteria	Treated with ICS or oral steroids 4 or 8 weeks prior to the study respectively, use of ICS/oral steroids during run-in period, other respiratory diseases, poorly controlled systemic diseases, inability of patients to fill in the study diary or to appropriately use the inhalation medication, participation in other trials.
Recruitment/selection of patients	182 participating GPs informed parents of children who presented with recurrent respiratory symptoms about the study.
Age, gender and ethnicity	Age - Mean (SD): 2.65 (1.21). Gender (M:F): 66/30. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	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.
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: ICS (low dose) - Fluticasone propionate. FP 100 µg (two puffs of 50 µg) twice daily from pMDI via plastic spacer device (Babyhaler, GSK). Duration 6 months. Concurrent medication/care: Participants permitted to use salbutamol 200 µg as required for symptom relief. (n=48) Intervention 2: placebo / no intervention - placebo. Placebo (two puffs to match intervention) twice daily from pMDI via plastic spacer device (Babyhaler, GSK). Duration 6 months. Concurrent medication/care: Participants permitted to use salbutamol 200 µg as required for symptom relief.
Funding	Study funded by industry (GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for <5 years: Rescue medication use during day at 6 months; Group 1: mean 0.37 Mean Reliever medication use during the day (SD 0.7); n=45, Group 2: mean 0.31 Mean Reliever medication use during the day (SD 0.49); n=43; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for <5 years: Rescue medication use during night at 6 months; Group 1: mean 0.11 Mean Reliever medication use during the night (SD 0.29); n=45, Group 2: mean 0.06 Mean Reliever medication use during the night (SD 0.13); n=43; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Sheffer 1996** [959]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=307)
Countries and setting	Conducted in Unknown; Setting: Clinic visits
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12 years and over with a history of asthma requiring pharmacotherapy for at least 3 months, unmedicated FEV_1 between 45 and 75% predicted value, increase in FEV_1 of 15% following albuterol.
Exclusion criteria	History of life-threatening asthma, long term oral steroids for more than one month or within the previous 2 years, use of intranasal, injectable, oral, topical, or inhaled corticosteroids or inhaled cromolyn sodium within 1 month prior to initiation of study.
Recruitment/selection of patients	Not stated

Age, gender and ethnicity	Age - Mean (range): 29.5 (12-72). Gender (M:F): 185/122. Ethnicity: 85% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Considered symptomatic and thus eligible with diagnosis of asthma with positive BDR (increase in FEV_1 of 15% following albuterol), one or more days with more than 8 puffs of albuterol during 7 run-in days, total weekly score of 7 or more on any asthma symptom.
Indirectness of population	No indirectness
Interventions	(n=234) Intervention 1: ICS (low dose) - Fluticasone propionate. FP administered as 25 µg bid (one FP 25 µg puff plus one placebo puff), 50 µg bid (one FP 50 µg puff plus one placebo puff), or 100 µg bid (two FP 50 µg puffs). Duration 12 weeks. Concurrent medication/care: Inhaled albuterol taken as needed (n=73) Intervention 2: placebo / no intervention - placebo. Placebo bid (two placebo puffs). Duration 12 weeks. Concurrent medication/care: Inhaled albuterol taken as needed
Funding	Study funded by industry (Glaxo Wellcome Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albuterol use (puffs/day) at 12 weeks; Group 1: mean -1.75 puffs/day (SD 3.17); n=147, Group 2: mean -0.28 puffs/day (SD 2.48); n=29; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 34.4 L/min (SD 53.5); n=147, Group 2: mean 12.5 L/min (SD 42.7); n=29; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Morning FEV_1 (given in L not as % of predicted) at 12 weeks; Group 1: mean 0.44 L (SD 0.59); n=147, Group 2: mean 0.14 L (SD 0.51); n=29; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Stelmach 2005 [992]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=51)
Countries and setting	Conducted in Poland; Setting: In the community and clinic centres
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6-11, with newly diagnosed asthma (diagnosed by experience of typical symptoms and >15% increase in prebronchdilator FEV_1 after salbutamol 200 µg).
Exclusion criteria	Subjects had not received corticosteroid and anti-leukotriene therapy prior to the study
Recruitment/selection of patients	Recruited from Clinic Centres in Zgierz, Poland.
Age, gender and ethnicity	Age - Mean (SD): 12.1 (1.1). Gender (M:F): 28:21. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	At baseline the mean symptom score out of 9 was 7.1 (SD 1.38) so 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 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.
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast (Singulair®) 5 mg tablet children 6-14 years / 10 mg tablets children 14+ years, plus budesonide placebo. Duration 6 months. Concurrent medication/care: Neta2-agonist (Ventolin) as-needed for symptomatic relief

	(n=16) Intervention 2: ICS (moderate dose) - Budesonide. 400 µg budesonide (Miflonide dry powder capsule). Duration 6 months. Concurrent medication/care: Beta2-agonist (Ventolin) as-needed for symptomatic relief (n=18) Intervention 3: ICS (high dose) - Budesonide. 400 µg budesonide (Miflonide dry powder capsule). Duration 6 months. Concurrent medication/care: Beta2-agonist (Ventolin) as-needed for symptomatic relief
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE (MODERATE DOSE) versus MONTELUKAST Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: FEV_1 % predicted at 6 months; Group 1: mean 93.4 % of predicted value (SD 3.6); n=15, Group 2: mean 90.9 % of predicted value (SD 2.1); n=16; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE (MODERATE DOSE) versus BUDESONIDE (HIGH DOSE) Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: FEV_1 % predicted at 6 months; Group 1: mean 93.4 % of predicted value (SD 3.6); n=15, Group 2: mean 93 % of predicted value (SD 2.5); n=18; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE (HIGH DOSE) versus MONTELUKAST Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: FEV_1 % predicted at 6 months; Group 1: mean 93 % of predicted value (SD 2.5); n=18, Group 2: mean 90.9 % of predicted value (SD 2.1); n=16; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Reliever medication use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Teper 2004** [1025]
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=34)
Countries and setting	Conducted in Argentina; Setting: In the community and clinic visits
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	<1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	Age <2 years, asthmatic symptoms (three or more episodes of wheeze, with clinical improvement after bronchodilator, as assessed by a physician), family history of asthma.
Exclusion criteria	History of severe respiratory infection, cystic fibrosis, aspirative pathology, pulmonary or airways anomalies, bronchopulmonary dysplasia, congenital heart disease, or previously received inhaled steroids or sodium cromoglicate.
Recruitment/selection of patients	Attended Respiratory Disease Center of the Ricardo Gutierrez Children's Hospital between March 1999 - March 2000
Age, gender and ethnicity	Age - Mean (SD): Placebo: 11.9 months (6.4) FP100: 13.1 (5.2) FP250: 14.2 (5.7). Gender (M:F): 18:12. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Patients considered symptomatic and thus eligible if recorded three or more episodes of wheeze, with clinical improvement after bronchodilator, as assessed by a physician.
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: ICS (low dose) - Fluticasone propionate. Fluticasone proprionate 100 µg via MDI. Duration 6 months. Concurrent medication/care: Relief medication if needed (n=11) Intervention 2: ICS (moderate dose) - Fluticasone propionate. Fluticasone proprionate 250 µg via MDI. Duration 6 months. Concurrent medication/care: Relief medication if needed (n=12) Intervention 3: placebo / no intervention - placebo. Placebo aerosol inhaler. Duration 6 months. Concurrent medication/care: Relief medication if needed
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE (LOW) versus FLUTICASONE PROPIONATE (MODERATE)

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for <5 years: Mean days of albuterol use at 6 months; Group 1: mean 6.5 number of days (SD 0.8); n=10, Group 2: mean 9.1 number of days (SD 0.8); n=10; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events: linear growth at ≥1 year
- Actual outcome for <5 years: Growth at 6 months; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE (LOW) versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for <5 years: Mean days of albuterol use at 6 months; Group 1: mean 6.5 number of days (SD 0.8); n=10, Group 2: mean 24.3 number of days (SD 1.3); n=10; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events: linear growth at ≥1 year
- Actual outcome for <5 years: Growth at 6 months; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE (MODERATE) versus PLACEBO

Protocol outcome 1: Reliever medication use at ≥3 months
- Actual outcome for <5 years: Mean days of albuterol use at 6 months; Group 1: mean 9.1 number of days (SD 0.8); n=10, Group 2: mean 24.3 number of days (SD 1.3); n=10; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events: linear growth at ≥1 year
- Actual outcome for <5 years: Growth at 6 months; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Teper 2005 [1026]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in Argentina; Setting: Testing took place at the Hospital de Ninos Ricardo Gutierrez, Argentina.
Line of therapy	1st line
Duration of study	6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	<1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6 to 20 months: asthmatic symptoms defined as three or more episode of wheeze with clinical improvement after bronchodilators as assessed by physician, together with a family history of asthma or any other clinical finding indicating atopy in one or both partents, decreased pulmonary function, defined as an SD score (Z score) of VmaxFRC lower than -1 according to the European Respiratory Society/American Thoracic Society Task Force on Standards for Infant Respiratory Function Testing.
Exclusion criteria	Any other chronic pulmonary illness. Z score of VmaxFRC higher than 1.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 13.4 months (4) . Gender (M:F): 21/5. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: unclear 2. Prior medication: unclear 3. Smoking status: unclear
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: ICS (moderate dose) - Fluticasone propionate. FP 250 µg (Fixotide) - 125 µg in the morning and 125 µg in the evening via pMDI by means of a spacer. Duration 6 months. Concurrent medication/care: Albuterol (Ventolin) as needed (n=15) Intervention 2: placebo / no intervention - placebo. Placebo via pMDI once in the morning and once in the evening. Duration 6 months. Concurrent medication/care: Albuterol (Ventolin) as needed
Funding	Equipmen /drugs provided by industry (GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus PLACEBO Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for <5 years: Days on albuterol (%) at 6 months; Group 1: mean 8.6 days on albuterol (%) (SD 6); n=14, Group 2: mean 16.3 days on albuterol (%) (SD 9); n=12; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: linear growth at ≥1 year - Actual outcome for <5 years: Mean growth velocity at 6 months; Group 1: mean 14.2 cm/year (SD 4); n=14, Group 2: mean 12.1 cm/year (SD 3); n=12; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Zeiger 2005[1137]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=380)
Countries and setting	Conducted in Unknown; Setting: Study sites - secondary care.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-85 years, with symptoms and albuterol use consistent with mild persistent asthma for at least 4 months as assessed by questionnaire, treatment with only SABA as needed, average FEV_1 during run-in of ≥80% predicted with no individual FEV_1 <70%, symptoms or use of albuterol on an average of 2-6 a week during the two week run-in period, positive BDR (increase in FEV_1 of ≥12%, following albuterol).
Exclusion criteria	Use of other asthma controller medication or systemic corticosteroids within the past month, or recent hospitalisation or urgent care for asthma.

Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 35.2 (14.4). Gender (M:F): 116/244. Ethnicity: 85% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Symptoms or use of albuterol on an average of 2-6 a week during the two week run-in period, positive BDR (increase in FEV_1 of ≥12%, following albuterol).
Indirectness of population	No indirectness
Interventions	(n=191) Intervention 1: ICS (low dose) - Fluticasone furoate. FP 88 µg twice daily via MDI, plus montelukast placebo capsule. Duration 12 weeks. Concurrent medication/care: Albuterol taken as needed (n=189) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg once nightly, plus FP placebo. Duration 12 weeks. Concurrent medication/care: Albuterol taken as needed
Funding	Study funded by industry (Merck & Co., Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE FUROATE versus MONTELUKAST

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Number of participants who required the use of oral steroids. at 12 weeks; Group 1: 4/177, Group 2: 5/173; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for ≥16 years: Asthma-specific Quality of Life Questionnaire at 12 weeks; MD 0.1 (95%CI -0.1 to 0.3) (SE 0.1) Asthma-specific quality of life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Number of patients seen in the emergency department or hospitalised at 12 weeks; Group 1: 0/173, Group 2: 0/177; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Reliever medication use at ≥3 months
- Actual outcome for ≥16 years: Albuterol use puffs/day at 12 weeks; MD -0.1 (95%CI -0.2 to 0.1) (SE 0.08); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months

- Actual outcome for ≥16 years: FEV_1 % predicted at 12 weeks; MD -2.9 (95%CI -4.46 to -1.33) (SE 0.8); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF (average over 3 days) at 12 weeks; MD 11.8 (95%CI -0.9 to 24.6) (SE 6.5); Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Zielen 2006[1143]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in Germany; Setting: Outpatient clinic of the University Hospital of Frankfurt
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	1 to <5 years
Subgroup analysis within study	Not applicable
Inclusion criteria	6-36 months with suspected asthma, history of three physician-diagnosed exacerbations of dyspnoea associated with wheezing during the past 12 months with at least one of those exacerbations within the past 3 months. Exacerbation defined as an increase in asthma symptoms requiring beta2-bronchodilator treatment for >2 days or systemic steroids.
Exclusion criteria	History of severe or unstable asthma, regular treatment with DSCG, ICS, or systemic steroid within the 4-weeks prior to enrolment, pre-term neonates, infants of low birth weight, those with major chronic conditions such as cardiac disease, chronic lung disease or cystic fibrosis.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 18 months (5.5). Gender (M:F): 55/23. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Three physician-diagnosed exacerbations of dyspnoea associated with wheezing during the past 12 months with at least one of those exacerbations within the past 3 months.

Indirectness of population	Serious indirectness - Unclear if population uncontrolled at baseline.
Interventions	(n=37) Intervention 1: ICS (moderate dose) - Budesonide. Nebulised BUD 0.5mg/2mL bid. Duration 3 months. Concurrent medication/care: Salbutamol taken as needed (n=41) Intervention 2: Cromolyns - Sodium cromoglicate. Disodium Cromoglicate (DSCG) 20mg/2mL tid. Duration 3 months. Concurrent medication/care: Salbutamol taken as needed
Funding	Study funded by industry (Astra-Zeneca)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus SODIUM CROMOGLICATE Protocol outcome 1: Reliever medication use at ≥3 months - Actual outcome for <5 years: Salbutamol use (puffs/day) at 3 months; Group 1: mean 0.35 puffs/day (SD 0.44); n=37, Group 2: mean 0.48 puffs/day (SD 0.61); n=41; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: linear growth at ≥1 year - Actual outcome for <5 years: Length (cm) at 3 months; Group 1: mean 85.2 cm (SD 5.9); n=37, Group 2: mean 83.7 cm (SD 4.7); n=41; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

H.3 Escalating pharmacological treatment in patients poorly controlled on first line preventer treatment

H.3.1 Second line preventer

Study	**Baraniuk 1999[83]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=680)
Countries and setting	Conducted in USA; Setting: Pulmonary medicine clinics

Line of therapy	2nd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged ≥12 years, had previously been using ICS for 3 months and underwent a 2 week run-in period on low dose ICS
Exclusion criteria	Pregnancy, use of inhaled cromolyn or nedocromil within 4 weeks prior to study, use of OCS within 4 weeks of study, concomitant illness.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 40 (12-79). Gender (M:F): 260/420. Ethnicity: 85% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Participants were included if they had an FEV_1 of 40-85% predicted and demonstrated reversibility of airway obstruction with ≥15% increase following albuterol.
Indirectness of population	No indirectness
Interventions	(n=231) Intervention 1: ICS+LABA - ICS + Salmeterol. FP 88 ug plus SL 42 ug and placebo TAA. Duration 12 weeks. Concurrent medication/care: SABA taken as required (n=449) Intervention 2: Placebo or ICS low dose (remain on optimal single preventer) - Fluticasone propionate. FP 220 ug plus placebo SL and placebo TAA / or TAA 600 ug plus placebo SL and placebo FP. Duration 12 weeks. Concurrent medication/care: SABA taken as required
Funding	Study funded by industry (Glaxo Wellcome)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE/TRIAMCINOLONE

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Reliever med use (puffs/day) at 12 weeks; Group 1: mean -2.9 puffs/day (SD 3.04); n=231, Group 2: mean -2.1 puffs/day (SD 3.01); n=449; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months

- Actual outcome for ≥16 years: Morning PEF (L/min) at 12 weeks; Group 1: mean 58 L/min (SD 91); n=231, Group 2: mean 32 L/min (SD 69); n=449; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: FEV_1 (L) at 12 weeks; Group 1: mean 0.58 L (SD 0.45); n=231, Group 2: mean 0.41 L (SD 0.45); n=449; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Bjermer 2003[144]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1490)
Countries and setting	Conducted in multiple countries; Setting: Community
Line of therapy	2nd line
Duration of study	Intervention + follow up: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: FEV_1 50-90% predicted, 12% improvement in PEFR with SABA
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 15-72, asthma for 1 year or longer, FEV_1 50-90% predicted, 12% improvement in PEFR with SABA, regular use of ICS, uncontrolled on low dose ICS during 4 week run-in period
Exclusion criteria	Used OCS in preceding month, chromones/LTRA/LABA/inhaled anticholinergics during preceding two weeks, received theophylline during week preceding first visit (note - 4 week run-in period on low dose ICS only)
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range of means: 41.0-41.2. Gender (M:F): 45:55. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=747) Intervention 1: ICS+LABA - ICS + Salmeterol. ICS low dose (fluticasone 100ug twice daily) + LTRA (montelukast 10mg once daily) + placebo inhaler. Duration 48 weeks. Concurrent medication/care: Usual care (n=743) Intervention 2: ICS+LABA - ICS + Salmeterol. ICS low dose (100ug fluticasone, twice daily) + LABA (salmeterol 50ug twice daily) + placebo tablets. Duration 48 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS LOW DOSE + LTRA versus ICS LOW DOSE + LABA	

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Worsening asthma requiring treatment with oral/IV/IM steroids at 48 weeks; Group 1: 118/747, Group 2: 107/743; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Quality of life at ≥3 months - Actual outcome for ≥16 years: Hospitalisation at 48 weeks; Group 1: 5/747, Group 2: 7/743; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: AQLQ - mean change from baseline at 48 weeks; Group 1: mean 0.71 (SD 1.09); n=747, Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Increase from baseline FEV_1 at 48 weeks; Group 1: mean 0.11 (SD 0.54); n=747, Group 2: mean 0.19 (SD 0.54); n=743; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Increase from baseline PEFR at 48 weeks; Group 1: mean 17.73 (SD 46); n=747, Group 2: mean 34.59 (SD 46); n=743; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Bouros 1999[163]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=132)
Countries and setting	Conducted in Greece; Setting: 11 centers across Greece
Line of therapy	2nd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	≥18 years, taking ICS for ≥1 month, symptom score (day and night) of ≥2 on ≥4 of the 7 days during second week of run-in period, FEV_1 40-85% of predicted, airway reversibility with FEV_1 increase of ≥15% following 200ug salbutamol.
Exclusion criteria	Pregnancy, taking β-blockers, received short course of OCS in previous 6 weeks or >3 courses of OCS in previous year.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 43 (14.9). Gender (M:F): 46/86. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: ICS+LABA - ICS + Formoterol. Formoterol fumarate 12ug bid +BDP 250ug bid. Duration 12 weeks. Concurrent medication/care: Salbutamol (n=65) Intervention 2: ICS (medium dose) - Beclometasone dipropionate. BDP 500ug bid. Duration 12 weeks. Concurrent medication/care: Salbutamol
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus BECLOMETASONE DIPROPIONATE Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months	

- Actual outcome for ≥16 years: Morning PEF (L/min) at 12 weeks; MD 20.36 (SE 8.7757); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	De blic 2009[315]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=321)
Countries and setting	Conducted in multiple countries; Setting: Community
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients had a reversibility of FEV_1 or PEF of at least 15%
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	FEV_1/PEF variability of at least 15%, asthma for 6 months, currently receiving ICS at 400ug/day BDP or equivalent, able to use a PEF meter, asthma was assessed as "not controlled" for at least 2 of the 4 weeks of the run-in period
Exclusion criteria	Respiratory tract infection or acute asthma exacerbation requiring emergency room treatment in previous 4 weeks or hospitalisation due to asthma or use of systemic corticosteroids in previous 12 weeks were excluded from the study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range of means: 8.0-8.1. Gender (M:F): 65:35. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=160) Intervention 1: ICS+LABA - ICS + Salmeterol. Salmeterol 50ug/fluticasone propionate 100ug twice a day via Diskus inhaler. Duration 12 weeks. Concurrent medication/care: Usual care, 4 weekly follow-up at respiratory clinic (n=161) Intervention 2: ICS (medium dose) - Fluticasone propionate. Fluticasone propionate 200ug twice a day, via Diskus inhaler. Duration 12 weeks. Concurrent medication/care: Usual care, 4 weekly follow-up in respiratory clinic
Funding	Study funded by industry (GSK)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SALMETEROL/FLUTICASONE COMBINATION (SFC) versus FLUTICASONE PROPIONATE (FP)	

Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: Mean change in PEFR from baseline at 12 weeks; Group 1: mean 27.7 litres per minute (SD 25.1); n=129, Group 2: mean 18.4 litres per minute (SD 2.14); n=136; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for 5 to <16 years: Mean change in PEFR from baseline at 12 weeks; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Greening 1994[451]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=429)
Countries and setting	Conducted in United Kingdom; Setting: 99 GP centres
Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic asthma (documented reversibility of at least 15% of peak expiratory flow (PEF) or forced expiratory volume in 1 s (FEV 1) to an inhaled beta2-agonist and period variation in PEF (over 1 week) of at least 15% (highest evening PEF minus lowest morning PEF as a percentage of the highest value).
Stratum	≥16 years: aged 18 years and over
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 years and over, symptomatic asthma despite maintenance treatment with 200 µg twice daily inhaled BDP, documented reversibility of at least 15% of peak expiratory flow (PEF) or forced expiratory volume in 1 s (FEV 1) to an inhaled beta2-agonist, period variation in PEF (over 1 week) of at least 15% (highest evening PEF minus lowest morning PEF as a percentage of the highest value), FEV, of at least 50% of predicted normal, symptoms on at least 4 of 7 days during the second baseline week.
Exclusion criteria	OCS during the previous 6 weeks or more than four short courses during the past year
Recruitment/selection of patients	May 1991 to January 1993
Age, gender and ethnicity	Age - Mean (SD): ICS/LABA: 48(15); moderate dose ICS: 47(15). Gender (M:F): 187/239. Ethnicity: not reported
Further population details	1. Previous asthma exacerbations: no asthma exacerbation in the previous year (around 97% had no hospital visits for asthma in the previous year and around 85-90% had no courses of OCS in the previous year). 2. Smoking status: Not applicable / Not stated / Unclear (Around 27% current smokers, the remaining were previous smokers or non-smokers).
Extra comments	Symptoms on at least 4 of 7 days during the second baseline week (during which patients continued to take inhaled BDP therapy (200 mcg twice daily), while bronchodilators were replaced with salbutamol)
Indirectness of population	No indirectness
Interventions	(n=220) Intervention 1: ICS+LABA - ICS + Salmeterol. BDP (200 µg twice daily by MDI) plus salmeterol (50 µg twice daily by Diskhaler). Duration 6 months. Concurrent medication/care: During 2 week run-in, bronchodilators were replaced with salbutamol (by Diskhaler, Glaxo Pharmaceuticals, Ware, UK) to be used for relief of symptoms as required. All other treatment remained constant where possible: use of asthma drugs other than the study treatments did not

	preclude continued participation in the study (n=206) Intervention 2: ICS (medium dose) - Beclometasone dipropionate. BDP (500 µg twice daily by MDI) plus placebo. Duration 6 months. Concurrent medication/care: During 2 week run-in, bronchodilators were replaced with salbutamol (by Diskhaler, Glaxo Pharmaceuticals, Ware, UK) to be used for relief of symptoms as required. All other treatment remained constant where possible; use of asthma drugs other than the study treatments did not preclude continued participation in the study.
Funding	Study funded by industry (Clinical Research Department, Allen and Hanburys Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus MEDIUM DOSE ICS

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: asthma exacerbation requiring a short course of OCS at 21 weeks; Group 1: 18/220, Group 2: 19/206; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: severe exacerbation requiring hospitalisation at 21 weeks; Group 1: 1/220, Group 2: 0/206; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: SABA use at ≥3 months
- Actual outcome for ≥16 years: daytime doses per patient not reported with variance at 21 weeks; MD 0 (SE 0); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: night time doses per patient not reported with variance at 21 weeks; MD -0.2 (SE 0.12); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: mean morning PEF during week of assessment not reported with variance at 21 weeks; MD 21.5 (SE 6.46); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Ilowite 2004[513]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1473)
Countries and setting	Conducted in multiple countries; Setting: Community
Line of therapy	2nd line
Duration of study	Intervention + follow up: 48 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: FEV_1 between 50-90% predicted, 12% FEV_1 improvement post SABA
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 14-73, FEV_1 between 50-90% predicted, 12% FEV_1 improvement post SABA, history of asthma for at least 1 year, uncontrolled during run-in, used ICS daily for at least 8 weeks prior to study
Exclusion criteria	Treated in ED within 1 month, hospitalised for asthma within 3 months, URTI within 3 weeks of first visit, taken systemic steroids within 1 month, cromones/LTRAs/LABAs/LAMAs within 2 weeks or theophylline within 1 week of first visit (followed by 4 week run-in on ICS low dose alone)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range of means: 38.1-39.0. Gender (M:F): 40:60. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=743) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. ICS low dose (fluticasone 220ug/d) + LTRA (montelukast 10mg/d) + placebo inhaler. Duration 48 weeks. Concurrent medication/care: Usual care (n=730) Intervention 2: ICS+LABA - ICS + Salmeterol. ICS low dose (fluticasone 220ug/d) + LABA (salmeterol, 42ug twice daily) + placebo tablets. Duration 48 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS LOW DOSE + LTRA versus ICS LOW DOSE + LABA	

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Exacerbations requiring OCS at 48 weeks; Group 1: 123/734, Group 2: 102/718; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Quality of life at ≥3 months - Actual outcome for ≥16 years: Change in AQLQ at 48 weeks; Group 1: mean 0.78 (SE 0.03); n=743, Group 2: mean 0.90 (SE 0.03); n=718 Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Hospitalisation at 48 weeks; Group 1: 3/734, Group 2: 5/718; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: SABA use at ≥3 months - Actual outcome for ≥16 years: Total SABA use, puffs per day, change from baseline at 48 weeks; Group 1: mean -1.15 (SE 0.06); n=743, Group 2: mean -1.66 (SE 0.06); n=730; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Lung function (FEV1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF, change from baseline at 48 weeks; Group 1: mean 40.8 (SE 2.8); n=743, Group 2: mean 55 (SE 2.8); n=730; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: pre-SABA FEV_1%predicted, change from baseline at 48 weeks; Group 1: mean 3.14 (SE 0.35); n=743, Group 2: mean 5.12 (SE 0.35); n=730; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Kuna 2006[603]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=617)
Countries and setting	Conducted in multiple countries; Setting: Community
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Baseline FEV_1 of 60-90% of predicted, reversibility of FEV_1 of at least 12%
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of asthma for at least 6 months, not optimally controlled despite ICS of 200-500ug for at least 30 days before entry, FEV_1 60-90%, FEV_1 reversibility of at least 12%
Exclusion criteria	Used systemic corticosteroids within the previous 30 days, seasonal asthma, respiratory infection in the 4 weeks before study, a severe cardiovascular disease, beta blocker therapy or history of heavy smoking, unable to use a PEF meter or complete diary card during 7 or more of last 10 days of run-in period
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range of means: 43.9 to 45.8. Gender (M:F): 41:59. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=409) Intervention 1: ICS+LABA - ICS + Formoterol. Combination of two arms from the study, arm 1 - budesonide 80ug/formoterol 4.5ug two inhalations, once in the evening, arm 2 - budesonide 80ug/formoterol 4.5ug one inhalation, twice daily. Medication as "symbicort" in a turbuhaler. Duration 12 weeks. Concurrent medication/care: Usual care, respiratory clinic visits every 4 weeks, double dummy design to ensure all patients took the same number of inhalers each day (n=207) Intervention 2: Placebo or ICS low dose (remain on optimal single preventer) - Budesonide. Budesonide 200ug, one inhalation, once daily in the evening. Duration 12 weeks. Concurrent medication/care: Usual care, respiratory clinic visits every 4 weeks, double dummy design to ensure all patients took the same number of inhalers each day
Funding	Study funded by industry (AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE + FORMOTEROL versus BUDESONIDE Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Mean reliever-free days over treatment period at 12 weeks; Group 1: mean 64.1 % (SD 26.6); n=409, Group 2: mean 55.5 % (SD 26.1); n=207; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Increase in morning PEF from baseline at 12 weeks; Group 1: mean 23.75 l/min (SD 37.45); n=409, Group 2: mean 5.5 l/min (SD 37.8); n=207; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Respiratory infections at 12 weeks; Group 1: 55/409, Group 2: 25/207; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Laviolette 1999[614]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=393)
Countries and setting	Conducted in multiple countries; Setting: 70 study centers, in 18 countries in North America, Europe, Africa, Australia, and Asia.
Line of therapy	2nd line
Duration of study	Intervention + follow up: 16 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: A history of at least 1 year of intermittent or persistent asthma symptoms, at end of run-in FEV_1 between 50-85% predicted, 15% increase in FEV_1 following SABA use
Stratum	≥16 years: 15 years or older
Subgroup analysis within study	Not applicable
Inclusion criteria	Healthy, non-smoking, male and female patients (age 15 years and older), with a history of at least 1 year of intermittent or persistent asthma symptoms treated with ICS for at least 6 weeks (equal or comparable to 400 to 500 mcg of beclometasone). Incompletely controlled with inhaled beclometasone, 200 mcg twice daily during the 4-week run-in period. On at least two of the four visits during run-in, an FEV_1 between 50 and 85% of the predicted value after withholding inhaled beta-agonist and antihistamine for at least 6 and 48 h, respectively, and to show at least a 15% increase in FEV_1 (absolute value) 20 to 30 min after inhaled beta-agonist administration. Also, at least a minimum total daytime asthma symptom score (64 out of a possible 336 score) and daily average beta-agonist use (as needed) of at least 1 puff during the last 2 week.
Exclusion criteria	Had respiratory disorders other than asthma or had signs and symptoms of an upper respiratory infection within 3 weeks, pregnancy, oral and parenteral corticosteroids within 1 month, cromolyn and nedocromil within 2 week; theophylline (oral and intravenous), b-agonists (oral or long-acting inhaled), and anticholinergic agents within 1 week.
Age, gender and ethnicity	Age - Mean (range): Montelukast: 40(15-76); continue ICS: 39(15-78). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Incompletely controlled with inhaled beclometasone, 200 mcg twice daily during the 4-week run-in period.
Indirectness of population	No indirectness
Interventions	(n=193) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg once daily and inhaled beclometasone 200 mcg twice daily (Beclovent; Allen & Hanburys, Research Triangle Park). Duration 16 weeks. Concurrent medication/care: Patients used short-acting, inhaled b-agonist on an “as needed” basis (via metered-dose

	inhalers of albuterol/salbutamol, 100 mcg/actuation). (n=200) Intervention 2: Placebo or ICS low dose (remain on optimal single preventer) - Beclometasone dipropionate. Placebo tablets once daily and inhaled beclometasone 200 mcg twice daily (Beclovent; Allen & Hanburys, Research Triangle Park). Duration 16 weeks. Concurrent medication/care: Patients used short-acting, inhaled b-agonist on an "as needed" basis (via metered-dose inhalers of albuterol/salbutamol, 100 mcg/actuation).
Funding	--

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONTELUKAST+ICS versus CONTINUE LOW DOSE ICS

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: daily beta-agonist use (% change from baseline) at 16 weeks; Group 1: mean -5.51 % change from baseline (SD 71.1); n=193, Group 2: mean 6.04 % change from baseline (SD 70.9); n=200; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 reported as change from baseline in L and % change from baseline but not as %predicted at 16 weeks; Group 1: mean 0.14 L (SD 0.28); n=193, Group 2: mean 0.02 L (SD 0.29); n=200; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: morning PEF at 16 weeks; Group 1: mean 10.41 L/min (SD 29.1); n=193, Group 2: mean 2.65 L/min (SD 28.5); n=200; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: URTI at 16 weeks; Group 1: 70/193, Group 2: 79/200; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Lim 2000[632]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=155)
Countries and setting	Conducted in United Kingdom; Setting: Community
Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Baseline 15% variability in PEFR
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-smoking, treated with low dose ICS with or without SABA as required, symptoms on at least 3 of last 7 days of run-in period (on low dose ICS)
Exclusion criteria	Contraindications to use of theophylline, any other long term asthma therapy, no exacerbation of asthma in 6 weeks prior to starting trial
Recruitment/selection of patients	Recruited from GPs in the UK
Age, gender and ethnicity	Age - Mean (range): 36.5-40.5. Gender (M:F): 70:85. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Placebo or ICS low dose (remain on optimal single preventer) - Beclometasone dipropionate. 200ug BDP inhaled twice daily (daily dose 400ug). Duration 6 months. Concurrent medication/care: Placebo tablets (n=49) Intervention 2: Theophylline/Aminophylline - Theophylline. Low dose ICS (200ug inhaled, BD, total daily dose 400ug) plus low dose theophylline. Duration 6 months. Concurrent medication/care: Usual care (n=52) Intervention 3: ICS (high dose) - Beclometasone dipropionate. High dose ICS (500ug inhaled, BD, total daily dose 1000ug) plus placebo tablets. Duration 6 months. Concurrent medication/care: Usual care
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW DOSE ICS + THEOPHYLLINE versus LOW DOSE ICS + PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Exacerbations requiring OCS at 6 months; Group 1: 3/49, Group 2: 11/54; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in mean morning PEFR by end of study at 6 months; Group 1: mean 21.8 (SD 48); n=38, Group 2: mean 4.4 (SD 38); n=45; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Infections, all respiratory (bronchitis, pharyngitis, moniliasis) at 6 months; Group 1: 5/49, Group 2: 8/54; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSE ICS + PLACEBO versus LOW DOSE ICS + PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Exacerbations requiring OCS at 6 months; Group 1: 8/52, Group 2: 11/54; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in mean morning PEFR by end of study at 6 months; Group 1: mean 19.5 (SD 49); n=48, Group 2: mean 4.4 (SD 38); n=45; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Infections, all respiratory (bronchitis, pharyngitis, moniliasis) at 6 months; Group 1: 6/52, Group 2: 8/54; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSE ICS + PLACEBO versus LOW DOSE ICS + THEOPHYLLINE

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Exacerbations requiring OCS at 6 months; Group 1: 8/52, Group 2: 3/49; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in mean morning PEFR by end of study at 6 months; Group 1: mean 19.5 l/min (SD 49); n=47, Group 2: mean 21.8 l/min (SD 48); n=38; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events: infection at ≥3 months

- Actual outcome for ≥16 years: Infections, all respiratory (bronchitis, pharyngitis, moniliasis) at 6 months; Group 1: 6/52, Group 2: 5/49; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Malone 2005[663]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=203)
Countries and setting	Conducted in the USA
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: FEV_1 50-95% predicted, increase in FEV_1/PEF of 12% after SABA
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 4 to 11, asthma for at least 2 months, receiving ICS therapy (range of different ICS, restricted dose ranges in low to moderate range, mean dose in low 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.
Exclusion criteria	History of life-threatening asthma, hospitalisation due to asthma twice or more in the last year, significant concurrent disease, recent U/LRTI, not to have used OCS in last month before screening
Age, gender and ethnicity	Age - Range of means: 8-8.1. Gender (M:F): 64:36. Ethnicity: 70% White, 20% Black, remainder not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone propionate/salmeterol 100/50ug twice daily. Duration 12 weeks. Concurrent medication/care: Salbutamol as rescue (n=102) Intervention 2: Placebo or ICS low dose (remain on optimal single preventer) - Fluticasone propionate. FP 100 ug twice daily. Duration 12 weeks. Concurrent medication/care: Salbutamol as rescue medication
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE

Protocol outcome 1: Adverse events: infection at ≥3 months

- Actual outcome for 5 to <16 years: Infections (all respiratory) at 12 weeks; Group 1: 20/101, Group 2: 26/102; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	MASCOT trial: Lenney 2013[622]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63 randomised)
Countries and setting	Conducted in United Kingdom; Setting: Primary and secondary care
Line of therapy	2nd line
Duration of study	Intervention + follow up: 48 weeks
Method of assessment of guideline condition	Physician diagnosed asthma
Stratum	5 to <16 years: aged from 6 years to 14 years 11 months
Subgroup analysis within study	Not applicable
Inclusion criteria	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; symptoms resulting in nocturnal wakening in the last week and/or interference with usual activities in the last week and/or an exacerbation requiring OCS, unscheduled GP visit, ED visit or hospitalisation within the last 6 months. Remained uncontrolled during 4 week run-in period with inhaler technique training.
Exclusion criteria	Receiving LABA, LTRAs, regular theophylline therapy or high-dose ICSs (>1000 µg) and unlicensed beclometasone dipropionate or equivalent; other respiratory diseases, cystic fibrosis, cardiac disease or immunological disorders; asthma controlled after 4 week run-in period (defined as the absence of any symptoms of asthma [except cough alone] or when the symptoms of asthma had not interfered with usual activities in the last week).
Recruitment/selection of patients	Secondary care referrals and searching GP databases. Multicentre, England and Scotland.
Age, gender and ethnicity	Age - Mean (range): 10.4 (6.5-14.7). Gender (M:F): 40/23. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Uncontrolled during 4 week run-in period (consisting of expert inhaler technique training by the research nurse and fluticasone propionate 100 µg twice daily). Uncontrolled defined as symptoms resulting in nocturnal wakening in the last week and/or interference with usual activities in the last week.
Indirectness of population	No mention of objective tests
Interventions	(n=19) Intervention 1: Placebo or ICS low dose (remain on optimal single preventer) - Placebo. Fluticasone propionate 100 µg (Flixotide, GSK) twice daily plus placebo tablet once daily. Duration 48 weeks. Concurrent medication/care: SABA PRN

	(n=23) Intervention 2: ICS+LABA - ICS + Salmeterol. Fluticasone propionate 100 µg (Flixotide, GSK) and salmeterol 50 µg twice daily (combination inhaler) plus placebo tablet once daily. Duration 48 weeks. Concurrent medication/care: SABA PRN (n=21) Intervention 3: Leukotriene receptor antagonist (LTRA) - Montelukast. Fluticasone propionate 100 µg (Flixotide, GSK) twice daily plus montelukast 5-mg tablet once daily. Duration 48 weeks. Concurrent medication/care: SABA PRN
Funding	Academic or government funding (NIHR funded HTA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONTINUE ON LOW DOSE ICS versus ICS + SALMETEROL

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Exacerbations requiring a course of OCS at 48 weeks; Group 1: 1/11, Group 2: 5/15; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for 5 to <16 years: PAQLQ (NOTE: ADJUSTED MD ALSO PROVIDED BUT FINAL VALUES EXTRACTED FOR NMA) at 48 weeks; Group 1: mean 6.3 (SD 0.88); n=10, Group 2: mean 5.44 (SD 1.56); n=15; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Hospitalisation at ≥6 months
- Actual outcome for 5 to <16 years: Hospital admissions at 48 weeks; Group 1: 0/11, Group 2: 2/15; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: FEV_1 %predicted (final values also provided but extracted adjusted MD) at 48 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse events: infection at ≥3 months
- Actual outcome for 5 to <16 years: Infection or infestation (not respiratory specific) at 48 weeks; Group 1: 7/19, Group 2: 9/23; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONTINUE ON LOW DOSE ICS versus MONTELUKAST

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Exacerbations requiring a course of OCS at 48 weeks; Group 1: 1/11, Group 2: 1/12; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for 5 to <16 years: PAQLQ (NOTE: ADJUSTED MD ALSO PROVIDED BUT FINAL VALUES EXTRACTED FOR NMA) at 48 weeks; Group 1: mean 6.3 (SD 0.88); n=10, Group 2: mean 6.31 (SD 0.85); n=12; PAQLQ 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Hospitalisation at ≥6 months
- Actual outcome for 5 to <16 years: Hospital admissions at 48 weeks; Group 1: 0/11, Group 2: 0/11; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: FEV_1 %predicted (final values also provided but extracted adjusted MD) at 48 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse events: infection at ≥3 months
- Actual outcome for 5 to <16 years: Infection or infestation (not respiratory specific) at 48 weeks; Group 1: 7/19, Group 2: 7/21; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus MONTELUKAST

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Exacerbations requiring a course of OCS at 48 weeks; Group 1: 5/15, Group 2: 1/12; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for 5 to <16 years: PAQLQ (NOTE: ADJUSTED MD ALSO PROVIDED BUT FINAL VALUES EXTRACTED FOR NMA) at 48 weeks; Group 1: mean 5.44 (SD 1.56); n=15, Group 2: mean 6.31 (SD 0.85); n=12; PAQLQ 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Hospitalisation at ≥6 months
- Actual outcome for 5 to <16 years: Hospital admissions at 48 weeks; Group 1: 2/15, Group 2: 0/11; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: FEV_1 %predicted (final values also provided but extracted adjusted MD) at 48 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse events: infection at ≥3 months
- Actual outcome for 5 to <16 years: Infection or infestation (not respiratory specific) at 48 weeks; Group 1: 9/23, Group 2: 7/21; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Meltzer 2007[703]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=290)
Countries and setting	Conducted in USA; Setting: Community
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Required FEV_1 reversibility >12% and between 60-90% predicted
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 4 to 11, 6 month history of asthma, ICS for at least 30 days prior to screening, stable dose for at least 2 weeks, off other asthma medication for "specified period of time"
Exclusion criteria	Required daily therapy with SABA, 12 puffs/day for any 2 day period within screening, OCS within 1 month prior to screening, ventilatory support for asthma within previous 5 years
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range of means: 8.2-8.7. Gender (M:F): 59:41. Ethnicity: 60% Caucasian
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=97) Intervention 1: ICS (medium dose) - Mometasone furoate. 200ug mometasone furoate via Twisthaler DPI, once a day. Duration 12 weeks. Concurrent medication/care: Usual care, SABA reliever inhaler (n=100) Intervention 2: Placebo or ICS low dose (remain on optimal single preventer) - Mometasone furoate. Mometasone furoate 100ug via Twisthaler DPI, once a day. Duration 12 weeks. Concurrent medication/care: Usual care, SABA reliever medication
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS MODERATE DOSE versus ICS (LOW DOSE)	

Protocol outcome 1: SABA use at ≥3 months - Actual outcome for 5 to <16 years: Change in SABA use, puffs/day at 12 weeks; Group 1: mean -0.34 (SD 1.57); n=97, Group 2: mean -0.49 (SD 1.7); n=100; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: Change in FEV_1 % predicted at 12 weeks; Group 1: mean 5 % predicted (SD 14.7); n=97, Group 2: mean 5.74 % predicted (SD 18.2); n=100; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for 5 to <16 years: Change in PEF L/min at 12 weeks; Group 1: mean 15.76 (SD 58.9); n=97, Group 2: mean 25.81 (SD 60.6); n=100; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for 5 to <16 years: Oral candidiasis at 12 weeks; Group 1: 1/97, Group 2: 2/100; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Nabil 2014[745]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Egypt; Setting: Outpatient clinic
Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Moderate to severe persistent asthma, excluded if <12% reversibility of FEV_1
Stratum	≥16 years: >18 years old
Subgroup analysis within study	Not applicable
Inclusion criteria	Moderate to severe persistent asthma, uncontrolled on low doses of ICSs (budesonide or beclometasone dry powder inhaler, 400 mcg/day).
Exclusion criteria	Using systemic corticosteroids; respiratory infection in the previous 4 weeks, severe cardio-pulmonary disease or other concomitant disease and smoking patients
Recruitment/selection of patients	Attending the outpatient chest clinic in Fayoum Hospital University
Age, gender and ethnicity	Age - Range: 20-60 years. Gender (M:F): not reported. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	'Uncontrolled' on low dose ICS
Indirectness of population	No indirectness: no mention of objective tests during diagnosis but reversibility testing performed during screening using repeated neubilisation by 5 mg salbutamol and 500 mcg of ipratropium
Interventions	(n=30) Intervention 1: ICS+LABA - ICS + Formoterol. twice daily inhaled formetrol and budesonide in the form of DPI (aerolizer) in a dose of 12 mcg and 400 mcg. Duration 24 weeks. Concurrent medication/care: Treatment with systemic anti-histaminic or other anti-asthmatic products not permitted (n=30) Intervention 2: ICS (high dose) - Budesonide. Budesonide DPI (aerolizer) in a dose of 800 mcg/BID. Duration 24 weeks. Concurrent medication/care: Treatment with systemic anti-histaminic or other anti-asthmatic products not permitted

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH DOSE versus ICS + FORMOTEROL Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 UNITS UNCLEAR, % PREDICTED PRESUMED at 24 weeks; Group 1: mean 62 unclear (SD 4.5); n=30, Group 2: mean 65.7 unclear (SD 4.8); n=30; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Nelson 2000[758]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=447)
Countries and setting	Conducted in USA; Setting: Multicentre
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Only states 'patients with asthma' but required to show BDR at screeening
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 15 years and older, had asthma for at least 6 months and taking low or moderate dose ICS for at least 30 days (BDP 252 to 420 µg/d, budesonide 400µg/d, flunisolide 1000 µg/d, FP 176 to 220 µg/d, or triamcinolone acetonide 600 to 800 µg/d), FEV_1 between 50-80% predicted, and an increase in FEV_1 of at least 12% with albuterol.
Exclusion criteria	Pregnant or lactating female patients, life-threatening asthma, hospitalised for asthma in the previous 3 months, significant concurrent diseases including a recent upper or lower respiratory tract infection, oral or parenteral corticosteroid therapy within 30 days of screening, theophylline or other bronchodilators, other leukotriene modifiers, or cromolyn or nedocromil therapy.
Age, gender and ethnicity	Age - Mean (SD): ICS+LABA: 40.2 (14.4), ICS+montelukast: 43.0 (13.7). Gender (M:F): 79/121. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Only those patients who remained symptomatic (an average SABA use of 4 or more puffs per day; a symptom score of 2 or more [scale 0-5] on 3 or more days; or 3 or more nights when the patient awakened due to asthma) during the last 7 days of run-in (3-week run-in period, during which their prior ICS was switched to FP 100 µg twice daily).
Indirectness of population	No indirectness
Interventions	(n=222) Intervention 1: ICS+LABA - ICS + Salmeterol. FP/Salmeterol (100 µg / 50 µg BID) combination via the Diskus inhaler (Advair; Glaxo Wellcome Inc) plus placebo montelukast. Duration 12 weeks. Concurrent medication/care: SABA PRN (n=225) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. FP 100µg twice daily via the Diskus inhaler plus montelukast 10 mg (FP + montelukast). Duration 12 weeks. Concurrent medication/care: PRN SABA

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus ICS + MONTELUKAST Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: SABA use (puffs/day) at 12 weeks; Group 1: mean -1.55 puffs/day (SD 0.14); n=222, Group 2: mean -1.14 puffs/day (SD 0.12); n=225; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: morning PEF (mean over weeks 1-12 suggested but unclear) at 12 weeks; Group 1: mean 24.9 L/min (SD 2.1); n=222, Group 2: mean 13 L/min (SD 2.1); n=225; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: FEV_1 L at 12 weeks; Group 1: mean 0.34 L (SD 0.03); n=222, Group 2: mean 0.2 L (SD 0.02); n=225; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	OPTIMA trial: O'byrne 2001[776]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1970)
Countries and setting	Conducted in multiple countries; Setting: Community and outpatients care
Line of therapy	2nd line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	>12 years old, taking <400ug/d of budesonide or equivalent for >3 months, with a FEV_1 >70% predicted normal after terbutaline, need for two or more inhalations per week of rescue medication during the last 2 weeks of run-in, a >15% variability in PEF or a >12% increase in FEV_1 after terbutaline (consistent with definition of uncontrolled).
Exclusion criteria	Define
Recruitment/selection of patients	Recruited from 198 centers in 17 countries
Age, gender and ethnicity	Age - Range of means: 30.6-38.1. Gender (M:F): 286:360. Ethnicity: Not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=312) Intervention 1: Placebo or ICS low dose (remain on optimal single preventer) - Budesonide. 200ug budesonide BD. Duration 1 year. Concurrent medication/care: No other treatment allowed unless the patient had a severe exacerbation at which point medications could be added at the physician's discretion. (n=323) Intervention 2: ICS+LABA - ICS + Formoterol. 100ug budesonide BD + 4.5ug formoterol via turbohaler. Duration 1 year. Concurrent medication/care: No other treatment allowed unless the patient had a severe exacerbation at which point medications could be added at the physician's discretion.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONTINUE ON ICS LOW DOSE versus ICS + FORMOTEROL

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Asthma exacerbation (need for OCS as judged by doctor/admission/emergency treatment/decrease in morning PEF >25% from b/l on 2 consecutive days) at Within the year; RR 0.57 (95%CI 0.46 to 0.72); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: SABA use at ≥3 months
- Actual outcome for ≥16 years: Number of rescue inhalations per day per patient, insufficient information to extract correct comparison at Within the year; MD -0.09 (SE 0.07); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in FEV_1 predicted % from baseline to end of treatment, insufficient information to extract correct comparison at Within the year; MD 2.72 (SE 0.7); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Change in morning PEF L/min from baseline to end of treatment, insufficient information to extract correct comparison at Within the year; MD 13.4 (SE 3.4); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Hospitalisations at ≥6 months
- Actual outcome for ≥16 years: Patients hospitalised at Within the year; ICS (low) 9/615, ICS + LABA 5/618; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Paggiaro 2016[803]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=465)
Countries and setting	Conducted in Italy, United Kingdom
Line of therapy	2nd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-75, FEV_1 60-90% predicted, history of asthma for 3 months, symptomatic at screening and randomisation; mean ACQ-7 score of ≥1.5. FEV_1 reversibility of ≥12% after 400ug salbutamol.
Exclusion criteria	Smoking history of >10 pack years, diagnosis of COPD, concurrent use of anticholinergic bronchodilators and LABA therapy within 4 weeks of study.
Age, gender and ethnicity	Age - Mean (SD): 42.9 (13). Gender (M:F): 124/185. Ethnicity: NA
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=154) Intervention 1: LAMA - Tiotropium). 5ug tiotropium once daily in the evening. Duration 12 weeks. Concurrent medication/care: 200-400ug budesonide or equivalent daily (n=155) Intervention 2: Placebo or ICS low dose (remain on optimal single preventer) - Placebo. Placebo. Duration 12 weeks. Concurrent medication/care: 200-400ug budesonide or equivalent daily
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TIOTROPIUM) versus PLACEBO

Protocol outcome 1: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ-7 at 12 weeks; MD 0.61 (SE 0.067); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 % predicted at 12 weeks; MD 4.7 (95%CI 2.5 to 6.8); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Morning PEF at 12 weeks; MD 25.6 (95%CI 14.9 to 36.2); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Price 2011
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=352)
Countries and setting	Conducted in United Kingdom; Setting: 53 primary care practices in the United Kingdom
Line of therapy	2nd line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-80, physicians diagnosis of asthma, PEF >50% predicted after inhaled B2-agonist withheld for 4 hours, impaired asthma-related quality of life (score of <6 on miniAQLQ) or impaired asthma control (>1 on Asthma Control Questionnaire), had received inhaled glucocorticoid for at least 12 weeks prior to study.
Exclusion criteria	Treatment of LTRA or LABA within 12 weeks prior to study.
Recruitment/selection of patients	Symptomatic asthmatics recruited through acute and routine respiratory care visits, and by invitation letter sent by participating primary care practices.
Age, gender and ethnicity	Age - Mean (SD): LABA: 49.7 (16.1) LTRA: 51 (16). Gender (M:F): 132:220. Ethnicity: 98% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Deemed to have symptoms that required an increase in therapy; had impaired asthma-related quality of life (score of <6 on miniAQLQ) or impaired asthma control (>1 on Asthma Control Questionnaire).
Indirectness of population	No indirectness
Interventions	(n=182) Intervention 1: ICS+LABA - ICS + Salmeterol. Continue with current ICS treatment (451 ug/day ± 390), plus salmeterol (n=167), or formoterol (n=14), doses not given. Duration 2 years. Concurrent medication/care: Rescue bronchodilator taken as needed. Comments: Treatment dose not given, population likely to be on varying doses. (n=170) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Continue with current ICS treatment (551 ug/day ± 351), plus Montelukast (n=158), Zafirlukast (n=8). Duration 2 years. Concurrent medication/care: Rescue bronchodilator taken as needed.

	Comments: Treatment dose not given, population likely to be on varying doses.
Funding	Academic or government funding (National Coordinating Centre for Health Technology Assessment U.K.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL/FORMETROL versus ICS+ MONTELUKAST/ZAFIRLUKAST

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Patients experiencing exacerbations (requiring OCS or hospitalisation) at 2 years; Group 1: 66/182, Group 2: 58/170; Risk of bias: Very high; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for ≥16 years: MiniAQLQ at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: EQ-5D at 2 years; Group 1: mean 0.798 (SD 0.268); n=170, Group 2: mean 0.807 (SD 0.255); n=160; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: Asthma Control Questionnaire at 2 years; MD -0.04 (95%CI -0.22 to 0.15); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: SABA use at ≥3 months
- Actual outcome for ≥16 years: Puffs of reliever during the day at 2 years; Group 1: mean 1.49 puffs/day (SD 1.65); n=95, Group 2: mean 1.89 puffs/day (SD 2.31); n=84; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Puffs of reliever at night at 2 years; Group 1: mean 0.63 puffs/night (SD 0.87); n=87, Group 2: mean 0.69 puffs/night (SD 1.04); n=75; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning PEF at 2 years; MD 13.7 (95%CI 1.8 to 25.6); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Patients experiencing respiratory tract infections at 2 years; Group 1: 107/182, Group 2: 85/170; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Ringdal 2002[913]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=806)
Countries and setting	Conducted in multiple countries; Setting: 114 centers across 19 countries
Line of therapy	2nd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Had received ICS for ≥4 weeks, documented history of obstructive airway reversibility of ≥15% increase following salbutamol. During run in: mean PEF >50% and <85% of value following salbutamol, and cumulative symptoms score (day and night) of ≥8 during last 7 days, and symptoms on at least 4 of last 7 days.
Exclusion criteria	Change of medication, URTI, hospitalisation within previous 4 weeks. OCS with previous 4 weeks, or ≥2 occasions within previous 12 weeks. Smoking history of ≥10 pack years.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 43 (14-79). Gender (M:F): 329/396. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Systematic review: mixed
Indirectness of population	No indirectness
Interventions	(n=369) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. FP 100ug twice daily, plus oral montelukast 10mg once daily. Duration 12 weeks. Concurrent medication/care: Salbutamol for rescue use (n=356) Intervention 2: ICS+LABA - ICS + Salmeterol. SFC combination 50/100ug twice daily via Diskus inhaler, plus placebo oral placebo once daily. Duration 12 weeks. Concurrent medication/care: Salbutamol
Funding	Study funded by industry (GlaxoSmithKline)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS+LTRA versus ICS + SALMETEROL	

Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Reliever medication use (reliever free days) at 12 weeks; OR -0.2614 (SE 0.1188); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 weeks; MD -0.11 (SE 0.0255); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF (L/min) at 12 weeks; MD -17 (SE 2.55); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Infection (all respiratory) at 12 weeks; Group 1: 39/401, Group 2: 40/404; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	SOLTA trial: Pavord 2007[819]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in United Kingdom; Setting: not reported
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Only states asthma patients on ICS, but required to have positive challenge test as part of screening.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18–50 years; non-smokers; receiving a stable dose of up to 400µg of BDP a day or equivalent ICS, but requiring further therapy; a baseline FEV_1 of 61-85% predicted; PC20<8mg/ml with methacholine challenge; at least one of the following: diary card recording of symptoms (score of one or more for day and night combined) on ≥ 4 of the last seven days of the run-in period; SABA use on ≥2 different days during the last seven days of the run-in period; and a PEFv of ≥ 10% over the last seven days of the run in period. Run-in was 2 weeks on normal dose of ICS median BDP mcg equivalent 400 (range 200 to 400).
Exclusion criteria	Were taking or had previously taken additional asthma medication, other than an ICS or short acting β2-agonist or oral corticosteroids in the last three months; acute respiratory infection or exacerbation of asthma within four weeks of screening, any additional underlying lung disease, or any significant disease warranting exclusion; hospitalisation or emergency treatment (for > 24 hours) for acute asthma in the last 12 months; were a smoker, had smoked in the last six months, or had a smoking history of 10 pack years or more; pregnant or lactating women, or women of child-bearing potential not using adequate contraception; evidence of alcohol, drug, or solvent abuse; hypersensitivity to any component of the study formulations, or taking medication contraindicated in combination with the study formulations; and previous entry to the study or receipt of any investigational drugs within four weeks of screening.
Recruitment/selection of patients	May 2001 to August 2002
Age, gender and ethnicity	Age - Mean (SD): ICS + LABA: 36.3 (8.11); ICS + montelukast: 34.4 (7.71). Gender (M:F): 34/32. Ethnicity: not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	At least one of the following during the last 7 days of run-in (run-in could be repeated once if failed the first time): diary card recording of symptoms (score of one or more for day and night combined) on ≥ 4 days; SABA use on ≥2 different days; and a PEFv of ≥ 10%.

Indirectness of population	--
Interventions	(n=33) Intervention 1: ICS+LABA - ICS + Salmeterol. Seretide 50 (GlaxoSmithKline; salmeterol 25 µg/FP 50 µg) metered dose inhaler (MDI) two puffs twice daily (SFC) plus a placebo to montelukast once daily at night. Duration 12 weeks. Concurrent medication/care: SABA PRN (n=33) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. FP 50 µg MDI (Flixotide™, GlaxoSmithKline) two puffs twice daily plus montelukast 10 mg once daily at night. Duration 12 weeks. Concurrent medication/care: SABA PRN
Funding	Study funded by industry (GSK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus MONTELUKAST

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: % of rescue free nights at 12 weeks; MD 16.5 (95%CI 1.4 to 36.1) (SE 8.86); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: % of rescue free days at 12 weeks; Other: median ICS+LABA 73%, ICS + montelukast 70%; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: PEF (reported but unclear if a one off recording or an average over at least 7 days) at 12 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: FEV_1 L at 12 weeks; MD 0.11 (95%CI -0.1 to 0.32); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Vaessen-verberne 2010[1054]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=158)
Countries and setting	Conducted in Netherlands; Setting: Multicentre
Line of therapy	2nd line
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: moderate asthma with a history of BDR
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6-16 years, moderate asthma; a history of bronchial hyperresponsiveness; used ICS (maximum 250 mg fluticasone or equivalent); symptomatic during run-in.
Exclusion criteria	Not reported
Recruitment/selection of patients	June 2005 to October 2008
Age, gender and ethnicity	Age - Mean (SD): ICS + LABA: 9.4 (1.8); ICS: 9.3 (1.9). Gender (M:F): 91/67. Ethnicity: White 143, Asian 3, Black 4, Mixed 8
Further population details	1. Previous asthma exacerbations: no asthma exacerbation in the previous year (~90% had no asthma exacerbation (OCS course) in the previous year). 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	4 week run-in fluticasone propionate dry powder, 100 mcg twice a day by Diskus inhaler and considered symptomatic when they had a cumulative symptom score of greater than or equal to 14 for the last 14 days of the run-in period. Symptoms were separately scored for cough, wheeze, and shortness of breath, with a daily maximum score of 18.
Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: ICS+LABA - Fluticasone propionate + Salmeterol. Salmeterol/FP, 50/100 twice a day Diskus. Duration 26 weeks. Concurrent medication/care: SABA PRN (n=80) Intervention 2: ICS (medium dose) - Fluticasone propionate. FP, 200 mg twice a day Diskus. Duration 26 weeks. Concurrent medication/care: SABA PRN
Funding	Study funded by industry (GSK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE (MEDIUM DOSE)

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Defined as moderate or severe exacerbation (requiring OCS use, ED visit or hospitalisation) at 26 weeks; Group 1: 8/72, Group 2: 4/79; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: SABA use at ≥3 months
- Actual outcome for 5 to <16 years: % of days on which rescue medication used reported but not with p values at 26 weeks; MD 2 (SE 8.58); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: PEF reported but not an average over at least 7 days at 26 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: FEV_1 % predicted at 26 weeks; MD 1 (95%CI -2.2 to 4.1); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse events: linear growth at ≥1 year
- Actual outcome for 5 to <16 years: Reported at 26 weeks but does not meet protocol outcome duration of 1 year at 26 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Yurdakul 2003[1133]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in Turkey; Setting: Clinic visits and in the community
Line of therapy	2nd line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Mild persistent asthma, baseline FEV_1 at least 80% norm, FEV_1 increase of 15% after 400ug salbutamol, previously using inhaled budesonide 200 ug or equivalent for at least 2 months prior to study.
Exclusion criteria	Respiratory tract infection, smoked cigarettes or had a respiratory disorder other than asthma disease, had asthma exacerbations within the preceding 2 months, pregnant or lactating women or with hypersensitivity to sympathomimetic amines and women of childbearing potential who did not use a reliable contraceptive method.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): ICS: 35.9(5) LTRA: 34.3(5) Theophylline: 33.5 (5) . Gender (M:F): 15:59. Ethnicity: not stated
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Diagnosis of mild persistent asthma, baseline FEV_1 at least 80% norm, positive BDR with FEV_1 increase of 15% after 400ug salbutamol.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: ICS (high dose) - Budesonide. Budesonide 400 ug once daily. Duration 12 weeks. Concurrent medication/care: All patients given short acting b2-agonist (terbutaline) inhaler as needed. Concurrent use of any medications that could interact with the drugs used in the groups was not allowed. (n=25) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg once daily. Duration 12 weeks. Concurrent medication/care: All patients given short acting b2-agonist (terbutaline) inhaler as needed. Concurrent use of any medications that could interact with the drugs used in the groups was not allowed.

	(n=24) Intervention 3: Theophylline/Aminophylline - Theophylline. Theophylline 400 ug once daily. Duration 12 weeks. Concurrent medication/care: All patients given short acting b2-agonist (terbutaline) inhaler as needed. Concurrent use of any medications that could interact with the drugs used in the groups was not allowed.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus MONTELUKAST

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Rescue inhalations (puffs/day) at 12 weeks; Group 1: mean -0.6 puffs/day (SD 0.2); n=25, Group 2: mean -0.6 puffs/day (SD 0.2); n=25; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (% of predicted) at 12 weeks; Group 1: mean 0.9 % of predicted value (SD 4.2); n=25, Group 2: mean 4.8 % of predicted value (SD 6.1); n=25; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE versus THEOPHYLLINE

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Rescue inhalations (puffs/day) at 12 weeks; Group 1: mean 0.6 puffs/day (SD 0.2); n=25, Group 2: mean 0.6 puffs/day (SD 0.2); n=24; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (% of predicted) at 12 weeks; Group 1: mean 4.8 % of predicted value (SD 6.1); n=25, Group 2: mean 0.5 % of predicted value (SD 3.1); n=24; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONTELUKAST versus THEOPHYLLINE

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Rescue inhalations (puffs/day) at 12 weeks; Group 1: mean -0.6 puffs/day (SD 0.2); n=25, Group 2: mean -0.6 puffs/day (SD 0.1); n=24; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (% of predicted) at 12 weeks; Group 1: mean 0.9 % of predicted value (SD 4.2); n=25, Group 2: mean 0.5 % of predicted value (SD 3.1); n=24; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

H.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

Study	Atienza 2013[63]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2091)
Countries and setting	Conducted in multiple countries
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Sbgroup analysis within study	Not applicable
Inclusion criteria	Aged at least 16, asthma for at least 6 months supported by lung function testing, using ICS for at least 3 months, uncontrolled during run-in
Exclusion criteria	URTI within 4 weeks of entry, use of OCS within 4 weeks of entry, current or previous smoker with at least 10 pack years
Age, gender and ethnicity	Age - Mean (SD): 46 (15). Gender (M:F): 32:68. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=1049) Intervention 1: Daily ICS+LABA as preventer and ICS+LABA as reliever - ICS + formoterol. BUD/FORM 160/4.5ug 1 puff twice daily + BUD/FORM 160/4.5ug as needed. Duration 12 months. Concurrent medication/care: Usual care (n=1042) Intervention 2: Daily ICS+LABA as preventer with SABA as reliever - ICS + Formoterol. BUD/FORM 160/4.5ug 1 puff twice daily + PRN SABA. Duration 12 months. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART versus NON-MART

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Exacerbations at 12 months; Group 1: 130/1049, Group 2: 168/1042; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Mortality at ≥6 months - Actual outcome for ≥16 years: Mortality at 12 months; Group 1: 1/1049, Group 2: 1/1042; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months - Actual outcome for ≥16 years: Hospitalisations at 12 months; Group 1: 11/1049, Group 2: 33/1042; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: ACQ at 12 months; MD -0.124 (95%CI -0.179 to -0.069); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: SABA use at ≥3 months - Actual outcome for ≥16 years: Puffs/day at 12 months; MD -0.25 (95%CI -0.36 to -0.15); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.04 (95%CI 0.015 to 0.064); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: PEF (L/minute) at 12 months; MD 5.8 (95%CI 2.1 to 9.5); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: All respiratory infections at 12 months; Group 1: 60/1049, Group 2: 72/1042; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months; Hospitalisation at ≥6 months; Total steroid dose at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Bisgaard 2006[140]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=341)
Countries and setting	Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years: 4 to 11 year old population from larger trial
Subgroup analysis within study	Post-hoc subgroup analysis

Inclusion criteria	Aged 4-11, asthma for at least 6 months, one exacerbation in last 12 months, all used ICS at a constant dose for at least 3 months (200 to 500ug/d), FEV_1 60-100% of predicted, greater than 12% reversibility from baseline after SABA, 8 or more puffs of SABA in last 10 days of run-in
Exclusion criteria	Exacerbation or change in ICS required during run-in period
Age, gender and ethnicity	Age - Mean (range): 8 (4-11). Gender (M:F): 70:30. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: Daily ICS+LABA as preventer and ICS+LABA as reliever - ICS + formoterol. Budesonide/formoterol 80/4.5ug qd plus additional doses as needed. Duration 12 months. Concurrent medication/care: Usual care (n=117) Intervention 2: Daily ICS+LABA as preventer with SABA as reliever - ICS + Formoterol. Bud/form 80/4.5ug QD plus terbutaline 0.4mg for reliever medication use. Duration 12 months. Concurrent medication/care: Usual care
Funding	Other author(s) funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART versus ICS + LABA + PRN SABA

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Exacerbations requiring medical intervention (hospitalisation/ED treatment/OCS/increase ICS dose/additional treatment) at 12 months; Group 1: 10/118, Group 2: 36/117; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: SABA use at ≥3 months
- Actual outcome for 5 to <16 years: Puffs/day at 12 months; MD -0.18 (95%CI -0.34 to -0.02); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: FEV_1 (L) at 12 months; MD 0.16 (95%CI -0.04 to 0.36); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: PEF (L/minute) at 12 months; MD 13 (95%CI -10.5 to 36.5); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Total steroid dose at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	O'Byrne 2005
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2760)
Countries and setting	Conducted in Unknown; Setting: 246 centers in 22 countries
Line of therapy	3rd line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 4-80 years treated with 400 to 1000 ug/day of ICS for adults or 200-500 ug/day for children, one or more asthma exacerbations in the last year, constant dose of ICS for at least 3 months, 12 or more inhalations of as-needed medication during last 10 days of run-in period.
Exclusion criteria	10 or more inhalations of reliever on any one day during run-in or exacerbation during run-in period.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 36 (4-79). Gender (M:F): 1231/1529. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	FEV_1 60-100% of predicted with 12% or more reversibility.
Indirectness of population	No indirectness
Interventions	(n=925) Intervention 1: ICS+LABA (LABA also as the reliever medication, for example SMART or MART therapy) - ICS + Formoterol. bud/form 80/4.5ug twice a day plus bud/form 80/4.5ug as needed. Children were given half the maintenance dose once daily at night. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden). Duration 12 months. Concurrent medication/care: NA (n=909) Intervention 2: ICS+LABA - ICS + Formoterol. bud/form 80/4.5ug twice a day plus terbuline 0.4mg as needed. Children were given half the maintenance dose once daily at night. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden). Duration 12 months. Concurrent medication/care: NA

Funding	Study funded by industry (astrazeneca r&d)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus ICS + FORMOTEROL Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbations resulting in medical intervention (patients with event) at 12 months; Group 1: 102/925, Group 2: 191/909; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Reliever use (inhs/day) at 12 months; MD -0.11 (SE -0.033); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 12 months; MD 9 (SE 2.73); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.08 (SE 0.024); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Infections (respiratory infection) at 12 months; Group 1: 158/922, Group 2: 144/906; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Papi 2013[806]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=1714)
Countries and setting	Conducted in multiple countries
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 48 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years

Subgroup analysis within study	Not applicable
Inclusion criteria	18 and older, diagnosis of asthma for 6 months or more, FEV_1 of at least 60% predicted, 12% reversibility with SABA, at least one severe exacerbation in last year (but not in last month)
Exclusion criteria	Use of OCS in last month, other lung disease, use of LABA or ICS + LABA in the 24hrs before visit 1, LRTI in month prior to study
Age, gender and ethnicity	Age - Mean (range): 48 (18 to 83). Gender (M:F): 39:61. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=857) Intervention 1: Daily ICS+LABA as preventer and ICS+LABA as reliever - ICS + formoterol. Bud/form 100/6ug one puff, twice daily + additional inhalations PRN. Duration 48 weeks. Concurrent medication/care: Usual care (n=857) Intervention 2: Daily ICS+LABA as preventer with SABA as reliever - ICS + Formoterol. Bud/form 100/6ug one puff twice daily + PRN SABA. Duration 48 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART versus NON-MART

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Exacerbations requiring OCS at 48 weeks; Group 1: 89/852, Group 2: 143/849; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ at 48 weeks; MD -0.06 (95%CI -0.13 to 0.02); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Hospitalisations at 48 weeks; Group 1: 5/852, Group 2: 17/849; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: SABA use at ≥3 months
- Actual outcome for ≥16 years: Reliever use (puffs/day) at 48 weeks; MD -0.02 (95%CI -0.13 to 0.1); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: PEF (L/minute) at 48 weeks; MD 3.69 (95%CI -3.51 to 10.88); Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for ≥16 years: FEV_1 (L) at 48 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Total steroid dose at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Patel 2013**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=303)
Countries and setting	Conducted in New Zealand
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 16-65, diagnosis of asthma, current prescription for ICS, at least one exacerbation in last year
Exclusion criteria	Diagnosis or plausible diagnosis of COPD
Age, gender and ethnicity	Age - Mean (SD): 42 (14). Gender (M:F): 31:69. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness
Interventions	(n=151) Intervention 1: Daily ICS+LABA as preventer and ICS+LABA as reliever - ICS + formoterol. Two puffs of bud/form 200/6ug, twice daily + PRN for relief. Duration 24 weeks. Concurrent medication/care: Usual care (n=152) Intervention 2: Daily ICS+LABA as preventer with SABA as reliever - ICS + Formoterol. Two puffs of bud/form 200/6ug twice daily + PRN SABA. Duration 24 weeks. Concurrent medication/care: Usual care
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART versus NON-MART

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Exacerbations (hospitalisation, use of OCS >3days or via ED) at 24 weeks; Group 1: 28/151, Group 2: 50/152; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ at 24 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Hospitalisation at 24 weeks; Group 1: 2/151, Group 2: 2/152; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Total steroid dose at ≥3 months
- Actual outcome for ≥16 years: Total steroid dose at 24 weeks; Group 1: mean 793 (SD 893); n=151, Group 2: mean 772 (SD 1063); n=153; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 %predicted at 24 weeks; MD 2.5 (95%CI -2 to 7); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: FEV_1 L at 24 weeks; MD 0.15 (95%CI -0.06 to 0.36); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Rabe 2006[875]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=3394)
Countries and setting	Conducted in multiple countries
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	12 or older, one severe exacerbation in 12 months prior to entry, used ICS for at least 3 months and constant dose for at least 4 weeks, FEV_1 50-100% of predicted, 12% reversibility or more, used reliever medication on 5 or more of last 7 days of run-in
Exclusion criteria	Respiratory infection affecting asthma or use of OCS within 1 month of study
Age, gender and ethnicity	Age - Range of means: 42-43. Gender (M:F): 40:60. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=1113) Intervention 1: Daily ICS+LABA as preventer and ICS+LABA as reliever - ICS + formoterol. Bud/form 160/4.5ug one puff, twice a day + PRN bud/form 160/4.5ug. Duration 12 months. Concurrent medication/care: Usual care (n=1141) Intervention 2: Daily ICS+LABA as preventer with SABA as reliever - ICS + Formoterol. Bud/form 160/4.5ug one puff, twice a day + PRN SABA. Duration 12 months. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART versus NON-MART

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Exacerbations (emergency Tx/hospitalisations/need for OCS for at least 3 days) at 12 months; Group 1: 143/1107, Group 2: 245/1138; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ-5, change in at 12 months; MD -0.15 (95%CI -0.21 to -0.08); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: SABA use at ≥3 months
- Actual outcome for ≥16 years: puffs/day at 12 months; MD -0.2 (95%CI -0.28 to -0.11); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (L), change score at 12 months; MD 0.08 (95%CI 0.05 to 0.1); Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for ≥16 years: PEF (L/minute), change score at 12 months; MD 7.5 (95%CI 4.2 to 10.7); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: All respiratory at 12 months; Group 1: 22/1107, Group 2: 10/1138; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Hospitalisation at ≥6 months; Total steroid dose at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	**Ställberg 2008[988]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1776)
Countries and setting	Conducted in Sweden
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 12, diagnosis of asthma, using at least 400ug ICS per day for at least 1 month, using ICS + LABA in separate inhalers or symptomatic using ICS alone
Exclusion criteria	Use of fixed combination of bud/form or sal/flut in year prior to study, OCS within month of start, smoking history >10 pack years, individuals with disease that may be affected by study medication
Age, gender and ethnicity	Age - Other: Mean 44. Gender (M:F): 43:57. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Prior medication: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Indirectness of population	Serious indirectness
Interventions	(n=887) Intervention 1: Daily ICS+LABA as preventer and ICS+LABA as reliever - ICS + formoterol. Bud/form 160/4.5ug or 80/4.5ug depending on starting dose, two puffs, twice daily + additional inhalations as required. Duration 1 year. Concurrent medication/care: Usual care

	(n=456) Intervention 2: Daily ICS+LABA as preventer with SABA as reliever - ICS + Formoterol. Bud/form 160/4.5ug or 80/4.5ug, two puffs, twice a day + PRN SABA. Duration 1 year. Concurrent medication/care: Usual care
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART versus NON-MART Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Exacerbations (hospitalisation/ED visit/use of OCS) at 12 months; Group 1: 68/884, Group 2: 45/452; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Total steroid dose at ≥3 months; Adverse events: linear growth at ≥1 year; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Vogelmeier 2005[1085]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2143)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged at least 12, asthma for at least 6 months, using ICS at a moderate to high dose for at least 1 month (mean dose high), FEV_1 40-90% predicted, at least one severe exacerbation in last 12 months (but not within 2 weeks), used PRN SABA on at least 4 of last 7 days of run-in

Exclusion criteria	Bud/form or sal/flut within last 3 months
Age, gender and ethnicity	Age - Mean (range): 45 (12-84). Gender (M:F): 41:59. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=1067) Intervention 1: ICS+LABA (LABA also as the reliever medication, for example SMART or MART therapy) - ICS + Formoterol. Bud/form 160/4.5ug 4 puffs per day maintenance + as needed, after 4 weeks could vary maintenance dose down to 2 puffs per day. Duration 12 months. Concurrent medication/care: Usual care (n=1076) Intervention 2: ICS+LABA - ICS + Salmeterol. Sal/flu 50/250ug 2 inhalations per day + salbutamol as needed, could vary maintenance dose after 4 weeks altering total daily flu dose from baseline 500 down to 200 or up to 1000. Duration 12 months. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART (ICS MOD) versus ICS MOD + LABA

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: OCS courses at 12 months; Group 1: 132/1067, Group 2: 167/1076; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for ≥16 years: AQLQ (adj mean change from baseline) at 12 months; MD 0.03; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ-5 at 12 months; MD -0.08; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: SABA use at ≥3 months
- Actual outcome for ≥16 years: Puffs/day (average across treatment period) at 12 months; MD -0.35; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.03; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events:

	infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

H.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

Study	**Aubier 1999[66]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=503)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention + follow up: 28 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 12 years old, used high dose ICS for at least 4 weeks prior to run-in, symptom score at least 2 on at least 4 of last 7 days of run-in
Exclusion criteria	None
Age, gender and ethnicity	Age - Mean (range): 48 (12-79). Gender (M:F): 53:47. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=338) Intervention 1: ICS+LABA - ICS + Salmeterol. Continue on ICS high dose and add in LABA (salmeterol), pooled analysis of two trial arms (combination inhaler vs separate inhalers). Duration 28 weeks. Concurrent medication/care: Usual care (n=165) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Continue on ICS high and add placebo. Duration 28 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH + LABA versus ICS HIGH + PLACEBO Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Adjusted mean change from baseline in PEF at 12 weeks; Group 1: mean 34 (SD 40); n=338, Group 2: mean 15 (SD 40); n=165; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Barnes 2007[88]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=75)
Countries and setting	Conducted in Unknown; Setting: Multiple centres.
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-smokers aged 15-70, >year history of asthma symptoms, current treatment 600-1200ug/day budesonide. Remained symptomatic during final two weeks of 4 week run-in.
Exclusion criteria	Any other pulmonary disorder, emergency treatment for asthma within 1 month, hospitalisation within 2 months, URTI within 3 weeks.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): ICS+LTRA: 41 (11.7), ICS: 45 (14.2). Gender (M:F): 34/41. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Airway reversibility >12% (FEV1) or >15% (PEF), >50% predicted FEV_1/PEF.
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. 800ug budesonide + 10mg montelukast daily. Duration 12 weeks. Concurrent medication/care: Not reported (n=38) Intervention 2: ICS (high dose) - Budesonide. 1600 ug budesonide daily. Duration 12 weeks. Concurrent medication/care: Not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + MONTELUKAST versus BUDESONIDE	

Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: Asthma Specific Quality of Life at 12 weeks; MD -0.25 (95%CI -0.64 to 0.15); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 12 weeks; MD 0.6 (95%CI -29.4 to 30.6); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Bergmann 2004[127]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=365)
Countries and setting	Conducted in Unknown; Setting: 76 centres (private practices or outpatient clinics at hospitals)
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-70 years, asthma diagnosis for 6 months of moderate severity (symptoms less than once per day, not more than twice per week, FEV_1 50-80% predicted, increase in FEV_1 15% following 200ug salbutamol, treated with ICS (BDP or budesonide 800-1000ug/day, or fluticasone 800ug/day)
Exclusion criteria	Smokers, LABA or OCS in previous 4 weeks, URTI in previous 4 weeks.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 49.34 (14.05). Gender (M:F): 161/186. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Increase in FEV_1 15% following 200ug salbutamol
Indirectness of population	No indirectness
Interventions	(n=170) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone/salmeterol 250/50ug via Diskus inhaler. Duration 12 weeks. Concurrent medication/care: Salbutamol as needed (n=177) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Fluticasone 500ug via Diskus inhaler. Duration 12 weeks. Concurrent medication/care: Salbutamol as needed
Funding	Study funded by industry (Glaxo Wellcome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus ICS (MODERATE DOSE)	

Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Salbutamol use (puffs/day) at 12 weeks; Group 1: mean -1.6 puffs (SD 1.9); n=170, Group 2: mean -1 puffs (SD 2.2); n=177; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (%) at 12 weeks; Group 1: mean 86 % predicted (SD 22); n=170, Group 2: mean 83 % predicted (SD 27); n=177; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 52 L/min (SD 76); n=170, Group 2: mean 36 L/min (SD 65); n=177; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Bisgaard 2006[140]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=341)
Countries and setting	Conducted in Unknown; Setting: 41 centers in 12 countries
Line of therapy	3rd line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 4-11 years treated with 200-500 ug/day of ICS, one or more asthma exacerbations in the last year, constant dose of ICS for at least 3 months, 12 or more inhalations of as-needed medication during last 10 days of run-in period.
Exclusion criteria	10 or more inhalations of reliever on any one day during run-in or exacerbation during run-in period.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 8 (4-11). Gender (M:F): 237/104. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	FEV_1 60-100% of predicted with 12% or more reversibility.
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: ICS+LABA (LABA also as the reliever medication eg SMART or MART therapy) - ICS + Formoterol. bud/form 80/4.5ug once daily at night plus bud/form 80/4.5ug as needed. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden). Duration 12 months. Concurrent medication/care: NA (n=117) Intervention 2: ICS+LABA - ICS + Formoterol. bud/form 80/4.5ug once daily at night plus terbuline 0.4mg as needed. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden). Duration 12 months. Concurrent medication/care: NA (n=106) Intervention 3: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. bud 320ug once daily at night plus terbuline 0.4mg as needed. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden).

	Duration 12 months. Concurrent medication/care: NA
Funding	Study funded by industry (astrazeneca r&d)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus ICS + FORMOTEROL

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Severe exacerbations resulting in medical intervention (patients with event) at 12 months; Group 1: 10/118, Group 2: 36/117; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: SABA use at ≥3 months
- Actual outcome for 5 to <16 years: As-needed use (inhalations/24h) at 12 months; MD -0.18 (SE -0.054); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: Morning PEF at 12 months; MD 13 (SE 10.57); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: FEV_1 (L) at 12 months; MD 0.16 (SE 0.095); Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Severe exacerbations resulting in medical intervention (patients with event) at 12 months; Group 1: 10/118, Group 2: 21/106; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: SABA use at ≥3 months
- Actual outcome for 5 to <16 years: As-needed use (inhalations/24h) at 12 months; MD -0.16 (SE -0.097); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: Morning PEF at 12 months; MD 17 (SE 5.41); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: FEV_1 (L) at 12 months; MD 0.1 (SE 0.12); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse events: linear growth at ≥1 year
- Actual outcome for 5 to <16 years: Growth (cm) at 12 months; MD 1.0 (95%CI 0.3 to 1.7) (p 0.0054); Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for 5 to <16 years: Severe exacerbations resulting in medical intervention (patients with event) at 12 months; Group 1: 36/117, Group 2: 21/106; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for 5 to <16 years: As-needed use (inhalations/24h) at 12 months; MD 0.02 (SE 0.56); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: Morning PEF at 12 months; MD 4 (SE 2.06); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for 5 to <16 years: FEV_1 (L) at 12 months; MD -0.6 (SE -0.76); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse events: linear growth at ≥1 year - Actual outcome for 5 to <16 years: Growth (cm) at 12 months; MD 0.9 (95%CI 0.2 to 1.6) (p value 0.0099); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Bousquet 2007[165]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2309)
Countries and setting	Conducted in multiple countries; Setting: Community
Line of therapy	3rd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12 or older, treated with high dose ICS alone or moderate dose ICS + LABA for at least 3 months prior to study entry, lung function testing consistent with asthma, 1 or more exacerbations in previous 12 months, needed PRN SABA on at least 5 of previous 7 days of run-in on usual medication
Exclusion criteria	Exacerbation in last month, recent respiratory infection, smoking history >10 pack years
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range of means: 39-40. Gender (M:F): 38:62. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=1154) Intervention 1: ICS+LABA (LABA also as the reliever medication eg SMART or MART therapy) - ICS + Formoterol. Budesonide/formoterol, 2x 160/4.5ug, twice daily and as needed. Each participant given 1 inhaler with active preventer, 1 inhaler with placebo preventer, 1 inhaler with active reliever (in this case, same drug). Duration 6 months. Concurrent medication/care: Usual care (n=1155) Intervention 2: ICS+LABA - ICS + Salmeterol. Salmeterol/fluticasone 50/500ug BD plus terbutaline PRN, dummy inhalers to maintain blinding. Duration 6 months. Concurrent medication/care: Usual care
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART WITH MODERATE DOSE ICS + LABA versus ICS (HIGH DOSE) + LABA + PRN SABA	

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbations including OCS, hospitaliations and ER visits at 6 months; Group 1: 108/1151, Group 2: 130/1153; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months - Actual outcome for ≥16 years: ACQ-5, treatment effect at 6 months; MD -0.02 (95%CI -0.07 to 0.04); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: SABA use at ≥3 months - Actual outcome for ≥16 years: Total inhalations daily at 6 months; MD -0.04 (95%CI -0.12 to 0.04); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: PEF (L/min) at 6 months; Mean -0.8 (95%CI -4.4 to 2.8); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Boyd 1995[170]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=119)
Countries and setting	Conducted in United Kingdom
Line of therapy	3rd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years old, using high dose ICS, considered for OCS, 15% reversibity with SABA
Exclusion criteria	Concurrent uncontrolled systematic disease, URTI in last 2 weeks, FEV_1 <40% predicted
Age, gender and ethnicity	Age - Median (range): 47 (18-79). Gender (M:F): 43:57. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	--
Interventions	(n=55) Intervention 1: ICS+LABA - ICS + Salmeterol. Continue usual high dose ICS + salmeterol 100ug BD. Duration 12 weeks. Concurrent medication/care: Usual care (n=64) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Continue on usual high dose ICS + placebo BD. Duration 12 weeks. Concurrent medication/care: Usual care
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH DOSE + LABA versus ICS HIGH DOSE + PLACEBO

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: SABA use (puffs/day) at 12 weeks; Group 1: mean -5.1 (SD 4.7); n=53, Group 2: mean -2.5 (SD 4); n=62; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 weeks; MD 0.03 (95%CI -0.13 to 0.19); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: PEF (L/min) at 12 weeks; MD 22.4 (95%CI 6.7 to 38.2); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Chervinsky 2008[258]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=329)
Countries and setting	Conducted in Unknown; Setting: Conducted across 84 centres
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >12 with diagnosis of moderate to severe persistent asthma for 6 months, FEV_1 45-85% predicted, used medium to high doses of ICS alone or in combination with other maintenance medication for at least 4 weeks. Symptomatic on 3 or more of 7 consecutive days during run-in period.
Exclusion criteria	Asthma requiring hospitalisation within 6 months, SCS within 4 weeks, or smoking history of 10 pack years.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 42.45 (13.77). Gender (M:F): 120/209. Ethnicity: 79% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	FEV_1 reversibility of >12% following 200ug albuterol.
Indirectness of population	No indirectness
Interventions	(n=117) Intervention 1: ICS+LABA - ICS + Formoterol. Budesonide/Formoterol 320/9ug combination inhaler twice daily via pMDI. Duration 12 weeks. Concurrent medication/care: Albuterol taken as needed (n=102) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Budesonide 320ug twice daily. Duration 12 weeks. Concurrent medication/care: Albuterol taken as needed
Funding	Study funded by industry (AstraZeneca)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus ICS (MOD DOSE)	

Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: AQLQ at 24 weeks; MD 0.29 (95%CI 0.058 to 0.527); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Rescue medication use (puffs/day) at 24 weeks; MD -0.68 (95%CI -1.14 to -0.22); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Corren 2013[284]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=217)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12 years+, symptomatic asthma 12 months prior to screening, use if ICS for 4 weeks prior to study, FEV_1 between 40-80% predicted, use of rescue medication 2 or more times a day on any 7 consecutive days during 14 day run-in for 3 of the days.
Exclusion criteria	History of life threatening asthma, hospitalisation for asthma during previous 12 months, SCS in previous 3 months, LTRA within a week of screening, non-reversible pulmonary disease, RTI within previous 4 weeks, smoking history of 10 pack years.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): ICS+LABA: 44.8 (15.66), ICS: 41.9 (15.17). Gender (M:F): 96/127. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	FEV_1 reversibility of >14.5% following SABA within 12 months prior to study
Indirectness of population	No indirectness
Interventions	(n=110) Intervention 1: ICS+LABA - ICS + Formoterol. Fluticasone/Formoterol 250/10 ug b.i.d. Duration 12 weeks. Concurrent medication/care: SABA taken as needed (n=113) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Fluticasone 250 ug b.i.d. Duration 12 weeks. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (SkyePharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus FLUITICASONE Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Rescue medication use (puffs/day) at 12 weeks; Group 1: mean -1.188 puffs/day (SD 0.217); n=108, Group 2: mean -1.122 puffs/day (SD 0.207); n=109; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 weeks; Group 1: mean 0.184 L (SD 0.043); n=108, Group 2: mean 0.106 L (SD 0.041); n=110; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 28.367 L/min (SD 5.256); n=108, Group 2: mean 12.472 L/min (SD 5.052); n=110; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Infections and infestations (URTI) at 12 weeks; Group 1: 3/110, Group 2: 4/113; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	D'urzo 2001[301]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=911)
Countries and setting	Conducted in Unknown; Setting: 253 centres, mostly primary care.
Line of therapy	3rd line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Documented history of asthma, current and former smokers allowed to participate, demonstration of airflow obstruction reversibility (with no time restriction), receiving optimum doses of anti-inflammatory treatment while still requiring SABA.
Exclusion criteria	Uncontrolled pulmonary disease, psychological condition that precluded entry to study.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 46.2 (16.3). Gender (M:F): 417/494. Ethnicity: 95% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Systematic review: mixed
Indirectness of population	No indirectness
Interventions	(n=455) Intervention 1: ICS+LABA - ICS + Salmeterol. Salmeterol 50ug bid via MDI added to current ICS therapy. Duration 6 months. Concurrent medication/care: SABA taken as needed (n=455) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Placebo via MDI added to current ICS therapy. Duration 6 months. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (Glaxo Wellcome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus PLACEBO Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months	

- Actual outcome for ≥16 years: Morning PEF at 6 months; MD 10 (95%CI 2 to 17) (p 0.01); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Evans 1997[379]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=62)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Asthma according to ACS criteria, symptoms despite 800-1000ug BDP, FEV_1 >50% predicted. 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.
Exclusion criteria	No OCS 3 weeks before run-in, 3 courses of glucocorticosteroid in previous 6 months, exacerbation or theophylline within previous 3 weeks
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): ICS:39.5 (18-66), ICS + Theo: 38.1 (18-67). Gender (M:F): 25/36. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Airway reversibility >15% following 200ug albuterol.
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Theophylline/Aminophylline - Theophylline. 400 ug Budesonide plus 250 mg Theophylline (if <80kg) or 375 mg Theophylline (if >80kg). Duration 12 weeks. Concurrent medication/care: NA (n=33) Intervention 2: ICS (high dose) - Budesonide. 800 ug Budesonide plus placebo. Duration 12 weeks. Concurrent medication/care: NA
Funding	Study funded by industry (Byk Gulden)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE + THEOPHYLLINE versus BUDESONIDE	

Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 weeks; Group 1: mean 2.69 L (SD 0.16); n=31, Group 2: mean 2.61 L (SD 0.15); n=31; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 411 L/min (SD 19); n=31, Group 2: mean 405 L/min (SD 17); n=31; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Fish 2001[390]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=948)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >15 with diagnosis of asthma for at least 6 months, symptomatic despite receiving for 6 weeks prior to screening. In 7 days preceding randomisation, at least one of: use of an average of >3 puffs per day of albuterol, symptoms score of >1 on > 2 days, and >2 nights when the patient awakened due to symptoms.
Exclusion criteria	Concurrent use of theophylline or any other medication that could interact with sympathetic amines or montelukast were not allowed.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 40 (15-83). Gender (M:F): 368/580. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	Baseline FEV_1 of 50-80% predicted, airway reversibility 12% increase in FEV_1 following 180 ug albuterol.
Indirectness of population	No indirectness
Interventions	(n=472) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. Montelukast 10 mg (Singulair). Duration 12 weeks. Concurrent medication/care: Continue with ICS therapy - mean doses of: Fluticasone 497ug, Triamcinalone 557ug, Beclomethasone 261ug, Budesonide 588ug, Flunisolide 1036ug. (n=476) Intervention 2: ICS+LABA - ICS + Salmeterol. Salmeterol 50 ug bd (Serevent). Duration 12 weeks. Concurrent medication/care: Continue with ICS therapy - mean doses of: Fluticasone 468ug, Triamcinalone 548ug, Beclomethasone 269ug, Budesonide 714ug, Flunisolide 1117ug.
Funding	Study funded by industry (Glaxo Wellcome Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + MONTELUKAST versus ICS + SALMETEROL

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Total supplemental albuterol use (puffs/day) at 12 weeks; Group 1: mean -0.41 puffs/day (SD 0.05); n=448, Group 2: mean -1.9 puffs/day (SD 0.1); n=452; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 21.7 L/min (SD 5); n=472, Group 2: mean 30 L/min (SD 5); n=476; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Fitzgerald 1999[394]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=180)
Countries and setting	Conducted in Canada; Setting: 15 Canadian centres
Line of therapy	3rd line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-smoking adults with asthma, using ICS constant dose of 400-1200 ug/day and SABA for at least one month, reversibility of bronchoconstriction 15% increase following SABA, rescue use on at least 5 of the last 7 run-in days.
Exclusion criteria	URTI within 2 months of screening, exacerbation requiring ED visit within 3 months
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 36 (13). Gender (M:F): 80/100. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Reversibility of bronchoconstriction 15% increase following SABA
Indirectness of population	No indirectness
Interventions	(n=89) Intervention 1: ICS+LABA - ICS + Formoterol. Beclamethasone, budesonide, or flunisonide (400 to 1200 ug/day) plus formoterol furoate 12 ug twice daily. Duration 24 weeks. Concurrent medication/care: NA (n=91) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Beclamethasone, budesonide, or flunisonide (400 to 1200 ug/day). Duration 24 weeks. Concurrent medication/care: Albuterol taken as needed.
Funding	Study funded by industry (Novartis Pharma)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus PLACEBO	

Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Mean daytime rescue puffs at 24 weeks; MD -0.54 (p 0.05); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Mean night-time rescue puffs at 24 weeks; MD -0.41 (p 0.05); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 24 weeks; Group 1: mean 2.92 L (SD 0.8); n=89, Group 2: mean 2.68 L (SD 0.78); n=91; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 24 weeks; MD 27 (p 0.05); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Hamelmann 2016[474]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=272)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention time: 48 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12 to 17 documented history of asthma for 3 months, ACQ score ≥1.5, on maintenance therapy of ICS with or without LABA or LTRA for 4 weeks before screening, FEV_1 60-90% predicted, FEV_1 reversibility of 12% after 400mL salbutamol
Exclusion criteria	Diagnosis of any lung disease other than asthma, smoking history
Age, gender and ethnicity	Age - Mean (SD): 14.3 (1.7). Gender (M:F): 177/94. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear

Indirectness of population	No indirectness
Interventions	(n=134) Intervention 1: LAMA - Tiotropium). Tiotropium 5ug (2 puffs 2.5ug) once daily. Duration 48 weeks. Concurrent medication/care: ICS maintenance therapy 200-800ug budesonide (or equivalent), with or without LTRA (n=138) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Placebo tiotropium once daily. Duration 48 weeks. Concurrent medication/care: ICS maintenance therapy 200-800ug budesonide (or equivalent), with or without LTRA
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TIOTROPIUM versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for 5 to <16 years: Patients experiencing at least one severe exacerbation at 48 weeks; Group 1: 2/134, Group 2: 9/138; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for 5 to <16 years: AQLQ at 48 weeks; MD 0.03 (95%CI -0.138 to 0.198); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: SABA use at ≥3 months
- Actual outcome for 5 to <16 years: puffs/24hr at 48 weeks; Group 1: mean -0.648 puffs (SD 1.1201); n=123, Group 2: mean -0.372 puffs (SD 1.11); n=126; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: Trough FEV_1 (L) at 24 weeks; Group 1: mean 4 L (SD 4.66); n=129, Group 2: mean 2.83 L (SD 4.59); n=132; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Ind 2003[514]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=502)
Countries and setting	Conducted in multiple countries; Setting: Hospitals and primary care
Line of therapy	3rd line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 16-75 years with asthma, currently symptomatic on BDP 500-800ug twice daily (or equivalent), at least 2 documented asthma exacerbations in previous year, period variation in PEF of 15% over last 10 days of run-in.
Exclusion criteria	Receiving continuous OCS, uncontrolled systemic disease.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): FP/SM: 44.8, FP(mod): 45.7(15.2) FP(high): 43.9(14.9). Gender (M:F): 230/233. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: "Symptomatic" no objective diagnosis
Interventions	(n=171) Intervention 1: ICS+LABA - ICS + Salmeterol. SM/FP 250ug bd. Duration 24 weeks. Concurrent medication/care: Salbutamol as required (n=165) Intervention 2: ICS (high dose) - Fluticasone propionate. FP500ug b.d. Duration 24 weeks. Concurrent medication/care: Salbutamol as needed (n=160) Intervention 3: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. FP 250ug b.d. Duration 24 weeks. Concurrent medication/care: Salbutamol as needed
Funding	Study funded by industry (Glaxo Wellcome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus FLUTICASONE PROPIONATE	

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Exacerbations at 24 weeks; Group 1: 47/171, Group 2: 51/165; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 24 weeks; MD 25.5 (SE 7.68); Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus ICS (MODERATE DOSE) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Exacerbations at 24 weeks; Group 1: 47/171, Group 2: 56/160; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 24 weeks; Mean 25.1 (SE 7.56); Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUTICASONE PROPIONATE versus ICS (MODERATE DOSE) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Exacerbations at 24 weeks; Group 1: 51/165, Group 2: 56/160; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Jenkins 2000[533]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=353)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	3rd line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >12 years, history of airway obstruction, receiving ICS (budesondie or BDP 800-1200 ug/day or fluticason 400-600 ug/day) for 4 weeks before 2-week run-in period, >15% increase in FEV_1 following SABA, used salbutamol >2 times a day or daytime plus nigh-time symptom score of >1 on >3 of last 7 days during run-in period.
Exclusion criteria	4 weeks before run-in; hospitalisation, OCS or lower respiratory tract infection. LABA 2 weeks before run-in. Smoking history of 10 pack years.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 46.5 (14-80). Gender (M:F): 177/176. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	>15% increase in FEV_1 following SABA
Indirectness of population	No indirectness
Interventions	(n=180) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone propionate 250 ug plus salmaterol 50 ug twice daily by Diskus. Duration 24 weeks. Concurrent medication/care: Salbutamol as needed (n=173) Intervention 2: ICS (high dose) - Budesonide. Budesonide 800 ug twice daily by Turbohaler. Duration 24 weeks. Concurrent medication/care: Salbutamol as needed
Funding	Study funded by industry (Glaxo Wellcome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus BUDESONIDE	

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbations at 6 months; Group 1: 1/180, Group 2: 2/173; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Salbutamol free days (%) at 6 months; MD 24 (SE 9.64); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 6 months; MD 0.09 (95%CI 0 to 0.17); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF (L/min) at 6 months; Group 1: mean 406 L/min (SD 3.67); n=173, Group 2: mean 380 L/min (SD 3.81); n=160; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Jenkins 2006[531]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=456)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged at least 12, asthma for at least 6 months, used ICS at least moderate dose for at least 4 months, symptomatic during run-in
Exclusion criteria	Asthma deterioration requiring change in therapy
Age, gender and ethnicity	Age - Mean (range): 46 (13-79). Gender (M:F): 38:62. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=115) Intervention 1: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Continue on ICS high dose + placebo. Duration 12 weeks. Concurrent medication/care: Usual care (n=341) Intervention 2: ICS+LABA - ICS + Formoterol. Continue on ICS high dose and add LABA, pooled analysis of combination inhaler and separate inhaler arms where possible, where not possible only combination arm extracted. Duration 12 weeks. Concurrent medication/care: Usual care
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH + LABA versus ICS HIGH + PLACEBO

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: SABA puffs/day final value at 12 weeks: MD -0.64: Risk of bias: Low: Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: PEF (L/min) change score at 12 weeks; MD 32.9 (95%CI 23.5 to 42.3); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Infection (all respiratory) at 12 weeks; Group 1: 27/341, Group 2: 6/115; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Juniper 2002[549]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=144)
Countries and setting	Conducted in Unknown; Setting: Multicentre study
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >12 years, documented history of reversible airway obstruction, had received ~BDP 800-1200ug or equivalent for at least 4 weeks. FEV_1/morning PEF 50-85% predicted, total symptom score of >2 on >4 of the previous 7 evaluable days, use of SABA on >2 occasions per 24h on 4 of previous 7 evaluable days.
Exclusion criteria	URTI or acute exacerbation, changed medication or taken OCS in 4 weeks prior to study. Smoking history of 10 pack years.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 50.5 (15). Gender (M:F): 61/52. Ethnicity: 95% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Documented history of reversible airway obstruction, at baseline; increase in FEV_1 or PEF >15% following inhaled SABA
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: ICS+LABA - ICS + Salmeterol. Fluticasone/Salmeterol 250/50 ug via Diskus plus placebo twice daily (500/50ug). Duration 12 weeks. Concurrent medication/care: SABA taken as needed (n=58) Intervention 2: ICS (high dose) - Budesonide. Budesonide 800ug twice a day (Pulmicort). Duration 12 weeks. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (GlaxoSmithKline)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus BUDESONIDE	

Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: AQLQ at 12 weeks; Group 1: mean 0.89 (SD 0.11); n=55, Group 2: mean 0.44 (SD 0.1); n=58; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Kemp 1998[569]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=581)
Countries and setting	Conducted in USA; Setting: Not clear.
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Male or female patients (≥12 years of age) were eligible for enrolment if they met the criteria for asthma as defined by the American Thorarcic society. After a 2 week screening period, patients were eligible for randomisation if they: maintained their diary cards throughout the screening period and have symptomatic, but stable, asthma. Patients had to have an average symptom score for the screening period of at least 1 in at least one of the following four symptom categories: daytime symptoms of chest tightness, wheezing, and shortness of breath and sleep symptoms. Patients also had to have stable asthma that did not require excess albuterol use, which was defined as either more than 12 puffs daily or 12 puffs for 3 or more days per week. In addition, patients could not have required hospitalisation for asthma within 3 months, mechanical ventilation during an asthma exacerbation within 2 years, or more than 2 albuterol (or equivalent) inhalers per month within 3 months of screening.
Exclusion criteria	Patients were excluded if any of the following were present: tobacco use, oral corticosteroid therapy, immunotherapy requiring dosage change, inability to withdraw asthma/allergy medications before pulmonary function testing at

	screening (for example oral b2-agonists for 12 to 24 hours or xanthines for 12 to 48 hours) or at 4, 8, and 12 week visits (for example inhaled b2-agonists for 8 hours, anticholinergic eye drops for 24 hours, and antihistamines [except hydroxyzine and astemizole] for 48 hours), cystic fibrosis, chronic obstructive pulmonary disease, any significant uncontrolled disease state other than asthma, any other significant illness, pregnancy or lactation, contraindication to study medications, or inability to complete baseline quality-of-life assessment.
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Range: Salmeterol: 12-85; placebo: 12-78. Gender (M:F): 93/107. Ethnicity: Not reported.
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year (Patients could not have required hospitalisation for asthma within 3 months of the screening period). 2. Smoking status: Non-smoker/ex-smoker (Tobacco use was an exclusion criteria).
Indirectness of population	Serious indirectness: The age range of the patients does not match the strata in the protocol.
Interventions	(n=252) Intervention 1: ICS+LABA - ICS + Salmeterol. Salmeterol (Serevent; Glaxo Wellcome Inc.) was supplied as salmeterol xinafoate in a metered dose inhaler that delivered 21 mg (each actuation delivers 21 mg of salmeterol from the actuator) of salmeterol per inhalation (total dose, 42 mg). Patients were instructed to take two inhalations twice daily in the morning and evening (approximately 12 hours apart) and to continue to use albuterol on an as-needed basis to relieve breakthrough symptoms. Duration 12 weeks. Concurrent medication/care: Patients were stabilised on a fixed dose of inhaled corticosteroid that was within package insert guidelines (i.e., beclometasone dipropionate, 252 to 840 mg/day; flunisolide, 1000 to 2000 mg/day; or triamcinolone acetonide, 600 to 1600 mg/day). Patients were prescribed albuterol as a short acting beta agonist. (n=254) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Patients were given placebo, no additional information reported. Patients were stabilised on a fixed dose of inhaled corticosteroid that was within package insert guidelines (i.e., beclometasone dipropionate, 252 to 840 mg/day; flunisolide, 1000 to 2000 mg/day; or triamcinolone acetonide, 600 to 1600 mg/day). Patients were prescribed albuterol as a short acting beta agonist. Duration 12 weeks. Concurrent medication/care: None reported. Comments: N/A
Funding	Study funded by industry (Supported by a grant from Glaxo Wellcome, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus PLACEBO

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: Quality of life at 12 weeks; Group 1: mean 1.08 N/A (SD 243); n=252, Group 2: mean 0.61 N/A (SD 2.43); n=254; Asthma related Quality of Life Questionnaire 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Mean daytime supplemental albuterol use at 12 weeks; Group 1: mean -2.73 puffs/day (SD -6.31); n=252, Group 2: mean -1.06 puffs/day (SD -6.31); n=254; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: morning PEF at 12 weeks; Group 1: mean 47 L/min (SD 124.6); n=252, Group 2: mean 14 L/min (SD 124.6); n=254; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: FEV_1 at 12 weeks; Group 1: mean 0.42 L (SD 1.02); n=252, Group 2: mean 0.15 L (SD 1.02); n=254; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Kerstjens 2012[574]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	2 (n=912)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 to 75, asthma for at least 5 years, ACQ >1.5, FEV_1 <80% predicted, being treated with high dose ICS and LABA, at least one OCS exacerbation in last year, non-smokers or <10 pack years
Exclusion criteria	COPD, co-existing illnesses, previously using LAMAs
Age, gender and ethnicity	Age - Mean (SD): 53 (12). Gender (M:F): 40:60. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=456) Intervention 1: LAMA - Tiotropium). Continued on ICS high dose + LABA and added in 5ug tiotropium via respimat inhaler per day. Duration 48 weeks. Concurrent medication/care: Usual care (n=456) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Continue on ICS high dose + LABA and add in placebo. Duration 48 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH + LABA + LAMA versus ICS HIGH + LABA + PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Severe exacerbations at 48 weeks; Group 1: 112/453, Group 2: 149/454; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months - Actual outcome for ≥16 years: AQLQ at 24 weeks; MD 0.04, 0.18; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months - Actual outcome for ≥16 years: ACQ at 24 weeks; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: SABA use at ≥3 months - Actual outcome for ≥16 years: Puffs/day at 24 weeks; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 48 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: PEF (L/min) at 48 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: All respiratory at 48 weeks; Group 1: 21/456, Group 2: 16/456; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Serious respiratory - pneumonia at 48 weeks; Group 1: 12/456, Group 2: 7/456; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Kerstjens 2015[573]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=1581)
Countries and setting	Conducted in multiple countries; Setting: Multiple study sites
Line of therapy	3rd line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-75, diagnosed with asthma for at least 3 months, on stable medium dose ICS 400-800 ug budesonide or equivalent, symptomatic (ACQ mean score >1.5)
Exclusion criteria	Present or past COPD, smoking history of 10 pack years, current use of LABA within 4 weeks of screening.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 43.5 (12.85) years. Gender (M:F): 658/923. Ethnicity: Not reported
Further population details	Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Bronchodilator reversibility with FEV_1 increase >12% after 400 ug Salbutamol.
Indirectness of population	No indirectness
Interventions	(n=519) Intervention 1: LAMA - Tiotropium). Tiotropium 5ug once daily. Duration 24 weeks. Concurrent medication/care: Continue with maintenance ICS treatment (mean dose 663.9ug/day) (n=541) Intervention 2: ICS+LABA - ICS + Salmeterol. Salmeterol 50 ug twice daily. Duration 24 weeks. Concurrent medication/care: Continue with maintenance ICS treatment (mean dose 650.8 ug/day) (n=523) Intervention 3: Placebo (remain on optimal preventer therapy according to step 3). Duration 24 weeks. Concurrent medication/care: Continue with maintenance ICS treatment (mean dose 668.3ug/day)
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS+TIOTROPIUM versus ICS + SALMETEROL

Protocol outcome 1: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Infections (URTI) at 24 weeks; Group 1: 19/517, Group 2: 41/541; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS+TIOTROPIUM versus ICS+PLACEBO

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: AQLQ at 24 weeks; MD 0.041 (95%CI -0.054 to 0.137) (p 0.4); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ-7 at 24 weeks; MD -0.12 (SE 0.04); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (L) at 24 weeks; MD 0.185 (95%CI 0.146 to 0.223) (p value 0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Morning PEF at 24 weeks; MD 24.3 (95%CI 17.9 to 30.7) (p value 0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Infections (URTI) at 24 weeks; Group 1: 19/517, Group 2: 41/523; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus ICS+PLACEBO

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: AQLQ at 24 weeks; Mean 0.150 (95%CI 0.056 to 0.254) (p 0.0018); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ-7 at 24 weeks; MD -0.20 (SE 0.04); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (L) at 24 weeks; MD 0.196 (95%CI 0.158 to 0.234) (p value 0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Morning PEF at 24 weeks; MD 24.8 (95%CI 18.5 to 31.1) (p value 0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Infections (URTI) at 24 weeks; Group 1: 41/541, Group 2: 41/523; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Kuna 2007[604]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2212)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	3rd line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients over the age of 12, diagnosis of asthma for 6 months, using ICS for 3 months (≥500ug/day budesonide or fluticasone, or ≥1000ug of another ICS), using reliever medication on ≥5 of the last 7 days of 2-week run-in period.
Exclusion criteria	Using reliever medication on ≥10 in any day of 2-week ruin-in period. Use of SCS or experience URTI in 30 days preceding trial.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 38 (17). Gender (M:F): 927/1285. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	FEV_1 ≥50% predicted, ≥12% reversibility following terbutaline.
Indirectness of population	No indirectness
Interventions	(n=1107) Intervention 1: ICS+LABA (LABA also as the reliever medication eg SMART or MART therapy) - ICS + Formoterol. Budesonide/Formoterol 160/4.5 ug twice daily + as needed. Duration 6 months. Concurrent medication/care: NA (n=1105) Intervention 2: ICS+LABA - ICS + Formoterol. Budesonide/Formoterol 320/9 ug twice daily. Duration 6 months. Concurrent medication/care: Terbutaline as needed
Funding	Study funded by industry (AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL (SMART) versus ICS + FORMOTEROL Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbation, requiring hospitalisation, ED visit or OCS. at 6 months; Group 1: 94/1107, Group 2: 126/1105; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: As-needed medication (puffs/day) at 6 months; MD -0.03 (95%CI -0.12 to 0.06); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 6 months; MD 0.005 (95%CI -0.026 to 0.037); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 6 months; MD -0.7 (95%CI -4.5 to 3); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Mitchell 2003[721]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=203)
Countries and setting	Conducted in Australia; Setting: 16 centres across Australia
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18+ with moderate to severe asthma, FEV_1 >50% predicted, received treatment with ICS at a constant daily dose of 1000ug BDP or 800ug budesonide for at least one month before screening. The presence of at least 2 of the following on at least 2 of the last 7 days of run-in period: waking at least once a night due to asthma, asthma interfering with activities in the day, at least 4 puffs of salbutemol a day, PEF diurnal variation of 15%.
Exclusion criteria	Used LABA or OCS in previous month, unable to use inhaler.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 43.88 (15.15) years. Gender (M:F): 90/113. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Systematic review: mixed (ICS+LABA: Smoker (8), Ex-smoker (45), Never (49). ICS (high dose): Smoker (10), Ex-smoker (37), Never (54)).
Extra comments	FEV_1 increase in 15% following B-agonist use (or history of within previous year)
Indirectness of population	No indirectness
Interventions	(n=102) Intervention 1: ICS+LABA - ICS + Formoterol. BDP 500ug plus Formoterol 12ug twice daily (BDP/Fo 1000/24ug). Duration 12 weeks. Concurrent medication/care: SABA taken as needed (n=101) Intervention 2: ICS (high dose) - Beclometasone dipropionate. BDP 1000ug plus placebo twice daily (BDP 2000ug). Duration 12 weeks. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (Novartis Pharmaceuticals Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus BECLOMETASONE DIPROPIONATE Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Rescue medication use (puffs/day) at 12 weeks; Group 1: mean 0.93 puffs/day (SD 1.38); n=89, Group 2: mean 2.43 puffs/day (SD 2.43); n=89; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 386.7 L/min (SD 130); n=89, Group 2: mean 360.6 L/min (SD 109.7); n=89; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Molimard 2001[725]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=259)
Countries and setting	Conducted in France; Setting: Secondary care (outpatient clinics).
Line of therapy	3rd line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Asthma was defined according to the criteria of the American Thoracic Society. The FEV_1 had to be superior or equal to 60% of the predicted value.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female outpatients aged 18 years or over with moderate persistent asthma were eligible for inclusion.
Exclusion criteria	Patients were excluded if they presented one of the following criteria: known hypersensitivity to sympathic amines or to lactose; pregnancy or breast-feeding; women of child bearing potential who did not use a reliable contraceptive method; significant change in regular asthma medication, asthma exacerbation or respiratory tract infection in the month prior to the first visit; incapacity to use a metered-dose inhaler correctly or to complete the patient diary. Concomitant treatments with theophylline, anticholinergic bronchodilators and inhaled or oral beta-2-agonists other

	than the trial medications were not allowed.
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): ICS+ Formoterol - 38.5(14.9); ICS - 39.5(15.0). Gender (M:F): ICS + Formoterol - 38.5(14.9); ICS - 39.5(15.0). Ethnicity: Not reported.
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear (Not clearly reported.). 2. Smoking status: Systematic review: mixed (Non-smokers (formoterol - 91%; on-demand salbutamol - 88%), ex-smokers and current smokers were included in the study).
Extra comments	Baseline characteristics: Mean reversibility (% of predicted FEV_1): ICS + Formoterol - 15.1(5.6); ICS - 15.8 (7.8).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=130) Intervention 1: ICS+LABA - ICS + Formoterol. Patients took one dry-powder capsule containing 12 µg of formoterol fumurate every morning and evening (Foradil Novartis Pharma S.A.) with salbutamol as rescue medication, or on-demand salbutamol via a metered-dose inhaler (100 µg/puff). In addition to the above, patients had to take daily treatment with an inhaled corticosteroid (the same product at a stable dose for at least 1 month prior to the first visit) and require daily treatment with inhaled bronchodilators (taken regularly or on-demand). The inhaled corticosteroid was kept at a constant dose throughout the trial, up to the maximal daily dose permitted in moderate persistent asthma (ie. 1000 µg of beclometasone, 800 µg of budesonide, 500 µg of fluticasone). Duration 3 months. Concurrent medication/care: Background treatment apart from the trial medications was not permitted. Comments: N/A (n=129) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Patients were instructed to take on-demand salbutamol via a metered-dose inhaler (100 µg/puff). In addition to the above, patients had to take daily treatment with an inhaled corticosteroid (the same product at a stable dose for at least 1 month prior to the first visit) and require daily treatment with inhaled bronchodilators (taken regularly or on-demand). The inhaled corticosteroid was kept at a constant dose throughout the trial, up to the maximal daily dose permitted in moderate persistent asthma (ie. 1000 µg of beclometasone, 800 µg of budesonide, 500 µg of fluticasone). Duration 12 weeks. Concurrent medication/care: Background treatment apart from the trial medications was not permitted. Comments: N/A
Funding	Study funded by industry (The study was supported by a grant from Novartis pharma S.A.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus ICS ALONE

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: Quality of life at 3 months ; Group 1: mean -6.4 N/A (SD 10); n=128, Group 2: mean -3.5 N/A (SD 13.7); n=125; St George's Hospital Respiratory Questionnaire 0-100 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Mean number of puffs of salbutamol during the day at 3 months ; Group 1: mean 0.4 puffs (SD 0.65); n=128, Group 2: mean 1.1 puffs (SD 1.29); n=125; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 3 months ; Group 1: mean 25.7 L/min (SD 36.5); n=128, Group 2: mean 4.5 L/min (SD 32.7); n=125; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	O'byrne 2005[777]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2760)
Countries and setting	Conducted in Unknown; Setting: 246 centers in 22 countries
Line of therapy	3rd line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 4-80 years treated with 400 to 1000 ug/day of ICS for adults or 200-500 ug/day for children, one or more asthma exacerbations in the last year, constant dose of ICS for at least 3 months, 12 or more inhalations of as-needed medication during last 10 days of run-in period.
Exclusion criteria	10 or more inhalations of reliever on any one day during run-in or exacerbation during run-in period.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 36 (4-79). Gender (M:F): 1231/1529. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	FEV_1 60-100% of predicted with 12% or more reversibility.
Indirectness of population	No indirectness
Interventions	(n=925) Intervention 1: ICS+LABA (LABA also as the reliever medication eg SMART or MART therapy) - ICS + Formoterol. bud/form 80/4.5ug twice a day plus bud/form 80/4.5ug as needed. Children were given half the maintenance dose once daily at night. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden). Duration 12 months. Concurrent medication/care: NA (n=909) Intervention 2: ICS+LABA - ICS + Formoterol. bud/form 80/4.5ug twice a day plus terbuline 0.4mg as needed. Children were given half the maintenance dose once daily at night. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden). Duration 12 months. Concurrent medication/care: NA (n=926) Intervention 3: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Bud 320ug twice

	a day plus terbuline 0.4mg as needed. Children were given half the maintenance dose once daily at night. All medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden). Duration 12 months. Concurrent medication/care: NA
Funding	Study funded by industry (astrazeneca r&d)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus ICS + FORMOTEROL

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Severe exacerbations resulting in medical intervention (patients with event) at 12 months; Group 1: 102/925, Group 2: 191/909; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: SABA use at ≥3 months
- Actual outcome for ≥16 years: Reliever use (inhs/day) at 12 months; MD -0.11 (SE -0.033); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Reliever use (inhs/night at 12 months; MD -0.09 (SE -0.027); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning PEF at 12 months; MD 9 (SE 2.73); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.08 (SE 0.024); Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Severe exacerbations resulting in medical intervention (patients with event) at 12 months; Group 1: 102/925, Group 2: 176/926; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: SABA use at ≥3 months
- Actual outcome for ≥16 years: Reliever use (inhs/day) at 12 months; MD -0.3 (SE -0.091); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Reliever use (inhs/night at 12 months; MD -0.15 (SE -0.046); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Morning PEF at 12 months; MD 16 (SE 4.85); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.1 (SE 0.03); Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus PLACEBO

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbations resulting in medical intervention (patients with event) at 12 months; Group 1: 191/909, Group 2: 176/926; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Reliever use (inhs/day) at 12 months; MD -0.19 (SE -0.058); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Reliever use (inhs/night at 12 months; MD -0.06 (SE -0.02); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 12 months; Mean 7 (SE 2.12); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.02 (SE 0.012); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	O'byrne 2014[778]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=586)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	3rd line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >12 documented use of ICS, with or without LABA (FP/Salmeterol 250/50ug bd or equivalent) for at least 4 weeks. Asthma symptoms and/or daily SABA use on >3 or last 7 days of run-in period.
Exclusion criteria	History of life threatening asthma in previous 10 years, exacerbation requiring hospitalisation in previous 6 months, exacerbations requiring OCS in previous 12 weeks.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 45.2 (14.51). Gender (M:F): 241/345. Ethnicity: NA
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	FEV_1 40-90% of predicted FEV_1 reversibility of 12% on inhalation of SABA.
Indirectness of population	No indirectness
Interventions	(n=197) Intervention 1: ICS+LABA - ICS + Vilanterol. Fluticasone Furoate/Vilanterol 200/25 ug via DPI. Duration 24 weeks. Concurrent medication/care: SABA taken as needed (n=195) Intervention 2: ICS (high dose) - Fluticasone furoate. Fluticasone Furoate 500 ug twice daily via DPI. Duration 24 weeks. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (GlaxoSmithKline)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + VILANTEROL versus FLUTICASONE FUROATE	

Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: AQLQ at 24 weeks; Group 1: mean 0.93 (SD 0.065); n=197, Group 2: mean 0.9 (SD 0.068); n=194; AQLQ 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months - Actual outcome for ≥16 years: ACT at 24 weeks; Group 1: mean 5.5 (SD 0.28); n=197, Group 2: mean 4.7 (SD 0.29); n=194; ACT 5-25 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 24 weeks; Group 1: mean 0.394 L (SD 0.0302); n=187, Group 2: mean 0.183 L (SD 0.03); n=190; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 24 weeks; Group 1: mean 51.8 L/min (SD 2.94); n=197, Group 2: mean 18.8 L/min (SD 2.95); n=194; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Pavord 2009[820]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=127)
Countries and setting	Multiple centres
Line of therapy	3rd line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-65, using moderate dose ICS + LABA or ICS high dose, symptomatic (at least 4 of last 7 days with symptoms/SABA use), lung function testing consistent with asthma
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age – mean 40, range 19 to 65, Sex: 55:45 M:F
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=64) Intervention 1: MART (low dose ICS + LABA). Duration 52 weeks. Concurrent medication/care: Usual care (n=63) Intervention 2: ICS high dose + LABA + PRN SABA. Duration 52 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART versus ICS high + LABA

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Mean change in reliever medication use at 52 weeks; MD 0.04 (95%CI -0.47 to 0.55); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1%predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection at ≥3 months

Study	Peters 2008[835]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=708)
Countries and setting	Conducted in USA
Line of therapy	3rd line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 12 years old, using ICS (medium to high alone or low to medium + LABA) for at least 4 weeks, non-smokers, require at least 2 asthma controller medications or uncontrolled during week before screening
Exclusion criteria	Treated with OCS within 1 month of screening, other significant disease likely to impact trial
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range of means: 39-41. Gender (M:F): 31-37:69-63. Ethnicity: 87% White, 8% Black, 1% Asian
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=132) Intervention 1: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Continue on ICS moderate dose + LABA, budesonide/formoterol 320/9ug BD. Duration 52 weeks. Concurrent medication/care: Usual care, described as double blind, placebo/dummy not clear (n=443) Intervention 2: ICS+LABA - ICS + Formoterol. Budesonide/formoterol 640/18ug BD. Duration 52 weeks. Concurrent medication/care: Usual care (n=133) Intervention 3: ICS (high dose) - Budesonide. Stop LABA and increase ICS dose to high, budesonide 640ug BD. Duration 52 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH DOSE + LABA versus CONTINUE ON ICS MOD + LABA

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Use of OCS, hospitalisation or ED/urgent care visit at 52 weeks; Group 1: 54/443, Group 2: 19/132; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Hospitalisation at 52 weeks; Group 1: 2/443, Group 2: 2/132; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: SABA use at ≥3 months
- Actual outcome for ≥16 years: Puffs/day at 52 weeks; MD -0.16 (95%CI -0.37 to 0.06); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (L) at 52 weeks; MD 0.02 (95%CI -0.02 to 0.07); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: PEF (L/min) at 52 weeks; MD 6.67 (95%CI -0.99 to 14.32); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse events: infection at ≥3 months
- Actual outcome for ≥16 years: Respiratory infection (all) at 52 weeks; Group 1: 327/443, Group 2: 101/132; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH DOSE + LABA versus ICS HIGH DOSE ALONE

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Use of OCS, hospitalisation or ED/urgent care visit at 52 weeks; Group 1: 54/443, Group 2: 29/133; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Hospitalisation at 52 weeks; Group 1: 2/443, Group 2: 0/133; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: SABA use at ≥3 months
- Actual outcome for ≥16 years: Puffs/day at 52 weeks; MD -0.87 (95%CI -1.08 to -0.66); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (L) at 52 weeks; MD 0.11 (95%CI 0.06 to 0.16); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: PEF (L/min) at 52 weeks; MD 34.7 (95%CI 27.1 to 42.3); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse events: infection at ≥3 months

- Actual outcome for ≥16 years: Respiratory infection (all) at 52 weeks; Group 1: 327/443, Group 2: 105/133; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH DOSE ALONE versus CONTINUE ON ICS MOD + LABA Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Use of OCS, hospitalisation or ED/urgent care visit at 52 weeks; Group 1: 29/133, Group 2: 19/132; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 2: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Hospitalisation at 52 weeks; Group 1: 0/133, Group 2: 2/132; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: SABA use at ≥3 months - Actual outcome for ≥16 years: Puffs/day at 52 weeks; MD 0.72 (95%CI 0.45 to 0.98); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 52 weeks; MD -0.09 (95%CI -0.15 to -0.03); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: PEF (L/min) at 52 weeks; MD -28.04 (95%CI -37.51 to -18.56); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Respiratory infection (all) at 52 weeks; Group 1: 105/133, Group 2: 101/132; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Price 2003[865]
Study type	RCT(Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=889)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients enrolled in the study were non-smokers or ex-smokers (stopped for at least 6 months and <12 pack year history) diagnosed with asthma for >1 year, aged 15-75 years, who were not optimally controlled though already on a regular ICS prescription at doses of 600-1200 µg/day for budesonide, beclometasone, triamcinolone, flunisonide, and 300-800 µg/day for fluticasone.
Exclusion criteria	Patients were excluded if they had other active pulmonary disorders, respiratory infection within 3 weeks of visit 1 or during the run in period, treatment in an emergency setting within 2 months of visit 1, systemic corticosteroid treatment within 1 month, cromones or leukotriene receptor antagonists within 2 weeks, long acting antihistamine within 1 week (astemizole 3 months), or long acting β agonists or anticholinergic agents within 24 hours.
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): 43(14). Gender (M:F): % female - 60. Ethnicity: (%) White - 76.9; Black - 0.7; Asian - 4.9; and, other - 17.4.
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year (Reported as: number of visits with healthcare provider due to worsening asthma in previous year). 2. Smoking status: Non-smoker/ex-smoker (Inclusion criteria).
Extra comments	Baseline characteristics: Asthma duration (meanSD)) - 17(14) years.
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=448) Intervention 1: Leukotriene receptor antagonist (LTRA) - Montelukast. Patients received montelukast 10 mg/day (one tablet at bedtime) in addition to budesonide 800 µg/day. Patients were instructed to withhold inhaled β agonist (for 6 hours) and short acting antihistamines (within 48 hours) before clinic visits (every 4 weeks). Duration 12 weeks. Concurrent medication/care: None reported. Comments: Patients completed a 4 week run in period during which patients were switched to budesonide Turbohaler 800 µg/day (200 µg, two puffs twice daily). After 1 week, single blind montelukast placebo was added; β agonist use

	and daytime symptoms were assessed during this period to determine eligibility for randomisation. (n=441) Intervention 2: ICS (high dose) - Budesonide. Patients received budesonide 1600 µg/day (800 µg twice daily) while receiving oral placebo montelukast. Patients were instructed to withhold inhaled β agonist (for 6 hours) and short acting antihistamines (within 48 hours) before clinic visits (every 4 weeks). Duration 12 weeks. Concurrent medication/care: None reported. Comments: Patients completed a 4 week run in period during which patients were switched to budesonide Turbohaler 800 µg/day (200 µg, two puffs twice daily). After 1 week, single blind montelukast placebo was added; β agonist use and daytime symptoms were assessed during this period to determine eligibility for randomisation.
Funding	-- (The study was supported by a grant from Merck & Co Inc, Whitehouse Station, New Jersey, USA.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS MOD + LTRA versus ICS HIGH + PLACEBO Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: Change in quality of life at 10 weeks ; Group 1: mean 0.71 N/A (SD 1.06); n=448, Group 2: mean 0.59 N/A (SD 1.06); n=441; Asthma related Quality of Life Questionnaire 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Change in β agonist use (puffs/day) at 10 weeks ; Group 1: mean -0.78 puffs (SD 6.79); n=448, Group 2: mean -0.75 puffs (SD 6.79); n=441; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Change in morning PEF (L/min) at 10 weeks ; Group 1: mean 33.5 L/min (SD 67.3); n=448, Group 2: mean -0.75 L/min (SD 67.3); n=441; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Rabe 2006[875]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3394)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention + follow up: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	12 years or older, more than 1 severe asthma exacerbation in 12 months before entry, used ICS for at least 3 months, objective diagnostic tests supporting asthma diagnosis, used reliever medication on 5 or more of last 7 days of run-in on ICS low dose + LABA
Exclusion criteria	Respiratory infection or oral steroid use in 1 month prior to study start
Age, gender and ethnicity	Age - Range of means: 42-43. Gender (M:F): 40:60. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=1113) Intervention 1: ICS+LABA (LABA also as the reliever medication eg SMART or MART therapy) - ICS + Formoterol. ICS low dose + LABA daily + ICS low dose + LABA PRN (bud/form, 160/4.5ug). Duration 52 weeks. Concurrent medication/care: Usual care (n=1141) Intervention 2: ICS+LABA - ICS + Formoterol. ICS low dose + LABA + PRN SABA, bud/form 160/4.5ug BD + as needed terbutaline. Duration 52 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART (ICS LOW) versus ICS LOW + LABA + PRN SABA	

Protocol outcome 1: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months - Actual outcome for ≥16 years: Includes ED attendances as well as hospitalisations and OCS use at 12 months; Group 1: 143/1107, Group 2: 245/1138; Risk of bias: Low; Indirectness of outcome: Serious indirectness - Actual outcome for ≥16 years: ACQ-5 at 12 months; MD -0.15 (95%CI -0.21 to -0.08); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: Reliever use, puffs/24hrs at 12 months; MD -0.20 (95%CI -0.28 to -0.11); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.08 (95%CI 0.05 to 0.1); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF (L/min) at 12 months; MD 7.5 (95%CI 4.2 to 10.7); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: Infections (all respiratory) at 12 months; Group 1: 22/1107, Group 2: 10/1138; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Reid 2008[897]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in Australia
Line of therapy	3rd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Uncontrolled during screening on usual ICS of moderate to high dose
Exclusion criteria	History of exacerbation, URTI, change in medication in last 6 weeks, OCS within last 3 months
Age, gender and ethnicity	Age - Range of means: 37-45. Gender (M:F): 11:13. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Continue on ICS high dose + placebo. Duration 12 weeks. Concurrent medication/care: Usual care (n=16) Intervention 2: Leukotriene receptor antagonist (LTRA) - Zafirlukast. Continue on ICS high dose + LTRA. Duration 12 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH + LTRA versus ICS HIGH + PLACEBO Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: SABA puffs/day at 12 weeks; Group 1: mean -1.1 (SD 0.4); n=13, Group 2: mean -0.3 (SD 1); n=8; Risk of bias: High; Indirectness of outcome: No indirectness	

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 weeks; Group 1: mean 0.144 (SD 0.106); n=13, Group 2: mean -0.024 (SD -0.093); n=8; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: PEF (L/min) at 12 weeks; Group 1: mean 2.7 (SD 15.2); n=16, Group 2: mean 17.5 (SD 12.2); n=8; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Ringdal 2002[913]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=428)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 16-75, using high dose ICS, reversibility of >15% on FEV_1, symptoms or SABA use on at least 4 of the last 7 days of the run-in on usual ICS
Exclusion criteria	Changed ICS dose or added in LTRA in last 4 weeks, LABA in last 2 weeks
Age, gender and ethnicity	Age - Mean (SD): 47 (14). Gender (M:F): 45:55. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=216) Intervention 1: ICS+LABA - ICS + Formoterol. ICS high dose (800ug budesonide BD) + LABA (formoterol 12ug BD). Duration 12 weeks. Concurrent medication/care: Usual care (n=212) Intervention 2: ICS+LABA - ICS + Salmeterol. ICS moderate (fluticasone propionate 250ug BD) + LABA (salmeterol 50ug BD). Duration 12 weeks. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH + LABA versus ICS MOD + LABA

Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: Change in PEF (L/min) at 12 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events: infection at ≥3 months - Actual outcome for ≥16 years: All respiratory infections at 12 weeks; Group 1: 18/216, Group 2: 26/212; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Serious respiratory infections at 12 weeks; Group 1: 1/216, Group 2: 0/212; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

Study	Scicchitano 2004[945]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1890)
Countries and setting	Conducted in multiple countries; Setting: Centres across multiple countries
Line of therapy	3rd line
Duration of study	Intervention time: 12 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-80, diagnosis of asthma for at least 6 months, ≥1 clinically important exacerbation in previous year, 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.
Exclusion criteria	SCS 30 days prior to study, FEV_1 50-90% predicted, airway reversibility increase in FEV_1 15% following terbutaline sulphate 1mg, ≥ 3 courses of SCS in previous 6 months, smoking history of 10 pack years, ≥10 inhalations of as needed medication during run-in period.
Recruitment/selection of patients	Outpatients recruited from hospitals or primary care
Age, gender and ethnicity	Age - Mean (range): 43 (11-80). Gender (M:F): 798/1092. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	FEV_1 50-90% predicted, airway reversibility increase in FEV_1 15% following terbutaline sulphate 1mg.
Indirectness of population	No indirectness
Interventions	(n=947) Intervention 1: ICS+LABA (LABA also as the reliever medication eg SMART or MART therapy) - ICS + Formoterol. Budesonide/Formoterol 160/4.5 ug once daily in the evening with additional inhalations as needed. Duration 12 months. Concurrent medication/care: NA (n=943) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Budesonide 160ug 2 puffs twice daily (640ug/day). Duration 12 months. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + FORMOTEROL versus ICS (MODERATE DOSE) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbations (requiring OCS) at 12 months; Group 1: 170/947, Group 2: 259/943; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: As-needed free days (%) at 12 months; MD 11 (95%CI 8.2 to 13.8) (p 0.001); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at 12 months; MD 20.3 (95%CI 16.5 to 24.1) (p 0.001); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Shapiro 2000[955]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=168)
Countries and setting	Conducted in Unknown; Setting: Not reported
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12+, medical history of asthma of at least 6 months, FEV_1 40-85% predicted, >15% increase in FEV_1 following 180ug inhaled albuterol, received ICS for at least 12 weeks (patients screened had been treated with BDP 462-672 ug/day, triamcinolone acetonide 1100-1600 ug/day, flunisolide 1250-2000 ug/day, FP 440 ug/day). Stable asthma confirmed by diary cards at end of run-in period.
Exclusion criteria	History of life threatening asthma, smoking history of 10 pack years, ICS within previous month. Use of SABA more than 12 puffs daily during run in period.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 39 (12-69). Gender (M:F): 86/82. Ethnicity: 81% white
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: ICS+LABA - ICS + Salmeterol. FP 250 ug plus salmeterol 50 ug twice daily. Duration 12 weeks. Concurrent medication/care: SABA taken as needed (n=84) Intervention 2: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. FP 250 ug twice daily. Duration 12 weeks. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (Glaxo Wellcome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus ICS (MODERATE DOSE)	

Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Albuterol use (puffs/day) at 12 weeks; Group 1: mean -2.3 Puffs/day (SD 0.4); n=81, Group 2: mean -0.9 Puffs/day (SD 0.2); n=81; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 weeks; Group 1: mean 0.48 L (SD 0.05); n=81, Group 2: mean 0.25 L (SD 0.05); n=81; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Morning PEF at 12 weeks; Group 1: mean 53.5 L/min (SD 5.6); n=81, Group 2: mean 15.2 L/min (SD 4.6); n=81; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Van Noord 1999[1063]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=274)
Countries and setting	Conducted inNetherlands; Setting: Primary care.
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	≥16 years
Subgroup analysis withn study	Not applicable
Inclusion criteria	Patients should have been receiving 400-600 µg beclometasone dipropionate or 800-1200 µg budesonide daily. Patients were eligible for inclusion into the study if they successfully completed the 4 week run-in period and: (1) forced expiratory volume in one second (FEV_1) at least 50% of the predicted value at visit 3; (2) an increase in FEV_1 of at least 10% predicted FEV_1 from baseline after inhalation of 400 µg salbutamol from a metered dose inhaler or 800 µg from a dry power inhaler at visit 1,2 or 3, or during the month prior to run in period; (3) either a total daytime plus night time symptom score of ≥1, or a diurnal variation in peak expiratory flow (PEF) of at least 15%, or use of rescue salbutamol on two or more occasions per 24 hours on at least four days of the last two weeks of run in period.
Exclusion criteria	Patients were excluded if they had changed their asthma medication in the preceding 6 weeks, had used oral steroids

	in the previous three months, had been admitted to hospital for their asthma in the previous month.
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): ICS low - 46(15); ICS high - 47(14). Gender (M:F): 66/73. Ethnicity: Not reported.
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	N/A
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=139) Intervention 1: ICS+LABA - ICS + Salmeterol. Patients received fluticasone propionate (FP) in varying combinations: FP 100 µg (low dose) twice daily (open) + Salmeterol 50 µg twice daily (blind); FP 250 µg (high dose) twice daily (open) + salmeterol 50 µg twice daily (blind). All medications were inhaled via Diskhaler. Duration 12 weeks. Concurrent medication/care: Not reported. (n=135) Intervention 2: ICS (high dose) - Fluticasone propionate. Patients received fluticasone propionate (FP) in varying combinations: FP 100 µg (low dose) twice daily (open) + FP 100 µg twice daily (blind); FP 250 µg (high dose) twice daily (open) + 250 µg twice daily (blind). All medications were inhaled via Diskhaler. Duration 12 weeks. Concurrent medication/care: None reported.
Funding	Study funded by industry (The study was supported by Glaxo Wellcome BV, Zeist, The Netherlands)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus DOUBLE DOSE FLUTICASONE PROPIONATE Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: PEF (L/min) at 12 weeks ; Group 1: mean 386 L/min (SD 122); n=139, Group 2: mean 384 L/min (SD 120); n=135; Risk of bias: High; Indirectness of outcome: no indirectness	
Protocol oucomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Vaquerizo 2003[1068]
Study type	RCT (Patient randomisd; Pralel)
Number of studies (number of participants)	1 (n=639)
Countries and setting	Conducted in Spain; Setting: Secondary care (outpatients)
Line of therapy	3rd line
Duration of study	Intervention time: 16 weeks.
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients enrolled in the study were non-smoking male and female asthmatic outpatients aged 18-70 years who had been treated with inhaled corticosteroids at a clinically stable dose equivalent to budesonide 400-1600 µg/day for at least 8 weeks. Eligible patients had a forced expiratory volume (FEV_1) of at least 55% of the predicted value and evidence of reversible airway obstruction (increase of at least 12% in FEV_1 from the baseline value).
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Montelukast - 44(16) years; placebo - 42 (15). Gender (M:F): Montelukast - 202/124; placebo - 192/121. Ethnicity: Not reported.
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Extra comments	Baseline characteristics: Ex-smokers (%) - montelukast - 37; placebo - 30; mean (SD) duration of asthma (years) - montelukast - 13.8(11.4); placebo - 13.8(11.7).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=313) Intervention 1: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Patients were given a placebo version of montelukast 10mg film coated tablets, once daily at bedtime, irrespective of food. Duration 16 weeks. Concurrent medication/care: All patients received a constant dosage of inhaled budesonide (Budesonide Turbuhaler, Astra, Lund, Sweden; 400 - 1600 µg/day administered twice daily). Comments: The use of systemic corticosteroids, long acting antihistamines, and other anti-asthmatic medications was not permitted. (n=326) Intervention 2: Leukotriene receptor antagonist (LTRA) - Montelukast. Patients received 10mg film coated tablets to take once daily at bedtime. Duration 16 weeks. Concurrent medication/care: All patients received a constant

	dosage of inhaled budesonide (Budesonide Turbuhaler, Astra, Lund, Sweden; 400 - 1600 µg/day administered twice daily). Comments: The use of systemic corticosteroids, long acting antihistamines, and other anti-asthmatic medications was not permitted.
Funding	Study funded by industry (The study was supported by a grant from Merck Sharp & Dohme Spain)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONTELUKAST versus PLACEBO Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: Quality of life at 16 weeks ; Group 1: mean 0.52 N/A (SD 0.875); n=326, Group 2: mean 0.6 N/A (SD 0.875); n=313; Asthma Quality of Life Questionnaire 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: SABA use at ≥3 months - Actual outcome for ≥16 years: β agonist use (%) at 16 weeks ; Group 1: mean -17.26 % daily use (SD 78); n=326, Group 2: mean -4.92 % daily use (SD 78); n=313; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: morning FEV_1 (%) at 16 weeks ; Group 1: mean 2.63 % (SD 16.6); n=326, Group 2: mean 2.49 % (SD 16.6); n=313; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: morning PEFR (L/min) at 16 weeks ; Group 1: mean 16.86 L/min (SD 35.7); n=326, Group 2: mean 11.3 L/min (SD 35.7); n=313; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Vogelmeier 2005[1083]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2143)
Countries and setting	Conducted in multiple countries
Line of therapy	3rd line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged at least 12, asthma for at least 6 months, using ICS at a moderate to high dose for at least 1 month (mean dose high), FEV_1 40-90% predicted, at least one severe exacerbation in last 12 months (but not within 2 weeks), used PRN SABA on at least 4 of last 7 days of run-in
Exclusion criteria	Bud/form or sal/flut within last 3 months
Age, gender and ethnicity	Age - Mean (range): 45 (12-84). Gender (M:F): 41:59. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=1067) Intervention 1: ICS+LABA (LABA also as the reliever medication eg SMART or MART therapy) - ICS + Formoterol. Bud/form 160/4.5ug 4 puffs per day maintenance + as needed, after 4 weeks could vary maintenance dose down to 2 puffs per day. Duration 12 months. Concurrent medication/care: Usual care (n=1076) Intervention 2: ICS+LABA - ICS + Salmeterol. Sal/flu 50/250ug 2 inhalations per day + salbutamol as needed, could vary maintenance dose after 4 weeks altering total daily flu dose from baseline 500 down to 200 or up to 1000. Duration 12 months. Concurrent medication/care: Usual care
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MART (ICS MOD) versus ICS MOD + LABA Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: OCS courses at 12 months; Group 1: 132/1067, Group 2: 167/1076; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Quality of life at ≥3 months - Actual outcome for ≥16 years: AQLQ (adj mean change from baseline) at 12 months; MD 0.03; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months - Actual outcome for ≥16 years: ACQ-5 at 12 months; MD -0.08; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: SABA use at ≥3 months - Actual outcome for ≥16 years: Puffs/day (average across treatment period) at 12 months; MD -0.35; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (L) at 12 months; MD 0.03; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Wechsler 2015[1097]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1070)
Countries and setting	Conducted in USA; Setting:
Line of therapy	3rd line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Physician diagnosis of asthma
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Black patients aged 18-75 years, physician diagnosis of asthma, receiving combination ICS+LABA or taking ICS and

	having ACQ score >1.25.
Exclusion criteria	Current smokers, history of smoking 10-pack years, FEV_1 <40% predicted,exacerbation requiring OCS within previous 3 months.
Age, gender and ethnicity	Age - Mean (SD): 45.1(12.6). Gender (M:F): 257/1070. Ethnicity: Black
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: No objective diagnosis
Interventions	(n=532) Intervention 1: LAMA - Tiotropium). Once daily tiotropium (18 ug). Duration 18 months. Concurrent medication/care: Usual controller therapy (n=538) Intervention 2: ICS+LABA - ICS + Salmeterol. Twice daily LABA (either Salmeterol 50 ug or Formoterol 9ug). Duration 18 months. Concurrent medication/care: Usual controller therapy
Funding	Academic or government funding (Agency for Healthcare Research and Quality)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TIOTROPIUM) versus ICS + SALMETEROL

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Participants experiencing at least one exacerbation at 18 months; Group 1: 111/532, Group 2: 122/538; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months
- Actual outcome for ≥16 years: AQLQ at 18 months; Group 1: mean 1 (SD 1.9); n=349, Group 2: mean 0.93 (SD 2); n=371; AQLQ 0-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months
- Actual outcome for ≥16 years: ACQ at 18 months; MD -0.04 (95%CI -0.27 to 0.18); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: SABA use at ≥3 months
- Actual outcome for ≥16 years: Rescue med use (puffs/day) at 18 months; Group 1: mean -1.1 puffs/day (SD 5.55); n=349, Group 2: mean -1.05 puffs/day (SD 5.29); n=371; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months

- Actual outcome for ≥16 years: FEV_1 (L) at 18 months; MD -0.025 (95%CI -0.095 to 0.045); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Woolcock 1996[1122]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=738)
Countries and setting	Conducted in multiple countries; Setting: 72 centres across 14 countries
Line of therapy	3rd line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 17+ receiving 400-500ug bd BDP or equivalent. During run-in period, FEV_1 or PEF >50% predicted, 15% reversibility in FEV_1 with salbutemol, daytime plus night-time symptom score>2, diurnal variation of PEF >15%, rescue use >3 times /24hrs on 4 of 7 days prior to randomisation.
Exclusion criteria	Had changed asthma medication, hospitalised, or had URTI in month prior to trial.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 44 (17-79) . Gender (M:F): 385/353. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Not applicable / Not stated / Unclear
Extra comments	15% reversibility in FEV_1 with salbutemol.
Indirectness of population	No indirectness
Interventions	(n=487) Intervention 1: ICS+LABA - ICS + Salmeterol. BDP/Salmeterol 500/50ug and BDP/Salmeterol 500/100ug both taken twice daily (BDP/Salmeterol 1000/100ug and BDP/Salmeterol 1000/200ug) (data pooled). Duration 24 weeks. Concurrent medication/care: SABA taken as needed (n=251) Intervention 2: ICS (high dose) - Beclometasone dipropionate. BDP 1000ug twice daily (BDP 2000ug/day). Duration 24 weeks. Concurrent medication/care: SABA taken as needed
Funding	Study funded by industry (Glaxo Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS + SALMETEROL versus BECLOMETASONE DIPROPIONATE Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Mean predicted Morning PEF (%) at 24 weeks; Group 1: mean 92 % (SD 0.5); n=487, Group 2: mean 85 % (SD 0.57); n=251; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Predicted FEV_1 (%) at 24 weeks; Group 1: mean 8 % (SD 0.2); n=487, Group 2: mean 3 % (SD 0.2); n=251; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	**Yurdakul 2002[1132]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Turkey; Setting: Secondary care.
Line of therapy	3rd line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Study reports that despite treatment with inhaled corticosteroids, patients continued to display symptoms.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for randomisation after completion of a run-in period of ten days. No additional details regarding the inclusion criteria were reported.
Exclusion criteria	Patients were excluded if they had respiratory tract infection, smoked cigarettes or had a respiratory disorder other than asthma disease.
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): Formeterol - 38.3(6); Zafirlukast - 38.6(4); Theophylline - 37.7(7). Gender (M:F): Formeterol - 8/7; Zafirlukast- 6/13; Theophylline - 7/13. Ethnicity: Not reported.

Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear (Not reported). 2. Smoking status: Not applicable / Not stated / Unclear (Not reported).
Extra comments	N/A
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=25) Intervention 1: ICS+LABA - ICS + Formoterol. Patients received formoterol 9 µg twice daily, whilst taking budesonide 400 µg twice daily. Patients were given supplemental terbutalin as a short-acting beta-2 agonist. Duration 12 weeks. Concurrent medication/care: None reported. Comments: Patients took part in a ten day run-in period, but no details were given. (n=19) Intervention 2: Leukotriene receptor antagonist (LTRA) - Zafirlukast. Patients received zafirlukast 20 mg twice daily, whilst taking budesonide 400 µg twice daily. Patients were given supplemental terbutalin as a short-acting beta-2 agonist. Duration 12 weeks. Concurrent medication/care: None reported. Comments: Patients took part in a ten day run-in period before randomisation; no additional detail was reported. (n=20) Intervention 3: Theophylline/Aminophylline - Theophylline. Patients received a sustained-release preparation of theophylline 400 mg once daily, whilst taking budesonide 400 µg twice daily. Patients were given supplemental terbutalin as a short-acting beta-2 agonist. Duration 12 weeks. Concurrent medication/care: Not reported. Comments: Patients took part in a ten day run-in period before randomisation; no additional detail was reported.
Funding	Funding not stated (Not reported)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS MOD + FORMOTEROL versus ICS MOD + ZAFIRLUKAST

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Mean number of rescue inhalations at 12 weeks; Group 1: mean 0.2 puffs/day (SD 0.1); n=25, Group 2: mean 0.3 puffs/day (SD 0.1); n=19; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for ≥16 years: FEV_1 (% predicted) at 12 weeks; Group 1: mean 89.5 % predicted (SD 5.7); n=25, Group 2: mean 87.3 % predicted (SD 5.7); n=19; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS MOD + FORMOTEROL versus ICS MOD + THEOPHYLLINE

Protocol outcome 1: SABA use at ≥3 months
- Actual outcome for ≥16 years: Mean number of rescue inhalations at 12 weeks; Group 1: mean 0.2 puffs/day (SD 0.1); n=25, Group 2: mean 0.2 puffs/day (SD 0.1); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (% predicted) at 12 weeks; Group 1: mean 89.5 % predicted (SD 5.7); n=25, Group 2: mean 86.6 % predicted (SD 5.8); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS MOD + ZAFIRLUKAST versus ICS MOD + THEOPHYLLINE Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Mean number of rescue inhalations at 12 weeks; Group 1: mean 0.3 puffs/day (SD 0.1); n=19, Group 2: mean 0.2 puffs/day (SD 0.1); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (% predicted) at 12 weeks; Group 1: mean 87.3 % predicted (SD 5.7); n=19, Group 2: mean 86.6 % predicted (SD 5.8); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Zimmerman 2004[1145]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=302)
Countries and setting	Conducted in Canada
Line of therapy	3rd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6 to 11, using ICS for 3 months prior to entry, additional symptoms suggesting need additional therapy
Exclusion criteria	Smokers, deteriorating asthma, use of OCS or LTRA within 1 month, cromoglicate within 7 days, LABA within 72 hours, xanthines within 48 hours
Age, gender and ethnicity	Age - Median (range): 9 (6-11). Gender (M:F): 63:37. Ethnicity: Not reported
Further population details	1. Previous asthma exacerbations: Not applicable / Not stated / Unclear 2. Smoking status: Non-smoker/ex-smoker
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: Placebo (remain on optimal preventer therapy according to step 3) - Placebo. Continue on ICS high dose + placebo. Duration 12 weeks. Concurrent medication/care: Usual care (n=95) Intervention 2: ICS+LABA - ICS + Formoterol. Continue on ICS high dose and add in formoterol 9ug. Duration 12 weeks. Concurrent medication/care: Usual care
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ICS HIGH + LABA versus ICS HIGH + PLACEBO

Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months
- Actual outcome for 5 to <16 years: FEV_1 (%predicted) final vs change at 12 weeks; MD 3.63 (95%CI 0.72 to 6.55); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: PEF (L/min) treatment difference for baseline vs "mean across whole treatment period" at 12 weeks: MD 10.8 (95%CI 3.4 to 18.2);

Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: infection at ≥3 months - Actual outcome for 5 to <16 years: All respiratory infections at 12 weeks; Group 1: 31/95, Group 2: 36/101; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, STRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: adrenal insufficiency at ≥3 months

H.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

Study	Boushey 2005[164]	
Study type	RCT (Patient randomised; Parallel)	
Number of studies (number of participants)	1 (n=225 randomised, 199 completed study)	
Countries and setting	Conducted in USA; Setting: Patients were in the community but made regular study visits to the hospital, frequency is not clearly stated	
Line of therapy	1st line	
Duration of study	Intervention + follow up: 58 weeks	
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician diagnosed asthma + FEV_1 >70% expected + BDR at least 12% and 200ml after albuterol inhalation or a fall in FEV_1 of at least 20% following inhalation of 16mg methacholine.	
Stratum	≥16 years	
Subgroup analysis within study	Not applicable	
Inclusion criteria	Physician diagnosed asthma, age 18-65, FEV_1 >70% predicted (mild), BDR at least 12% and 200ml after albuterol inhalation or a fall in FEV_1 of at least 20% following inhalation of 16mg methacholine. Met further criteria during 4 week run-in (while not on ICS or zafirlukast): self-treatment with SABA more than 2 days per week, night-time 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 (i.e. daily self-treatment with SABA, night time awakenings once a week or more than 30% PEF variability).	
Recruitment/selection of patients	Patients were recruited from "pre-existing study populations and advertising"	
Age, gender and ethnicity	Age - Mean (SD): Regular ICS - 33.2 (9.5), intermittent ICS - 32.0 (10.5). Gender (M:F): 58:91. Ethnicity: 83-88% non-black	
Further population details	1. Allergic asthma status: Not applicable / Not stated / Unclear 2. Previous asthma exacerbations: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker	
Indirectness of population	No indirectness	
Interventions	(n=73) Intervention 1: ICS (regular low dose) - Budesonide. Twice daily oral placebo, twice daily inhalation of 200 micrograms of budesonide via Turbuhaler. Duration 52 weeks. Concurrent medication/care: Prior to starting 52 weeks of regular ICS, 14 day run-in of 0.5mg/kg/d prednisone orally, 800 micrograms twice daily and 20 mg of zafirlukast	

Study	Boushey 2005[164]	
	twice daily plus PRN albuterol (540 to 720 micrograms) to "eliminate any easily reversed causes of airflow obstruction affecting PEF or FEV_1". During the 52 weeks of regular ICS patients advised to take open label budesonide (800 micrograms twice daily) for 10 days OR oral prednisone (0.5mg/kg per day) for 5 days if their asthma symptoms worsened. Further details: 1. Definition of intermittent: Symptomatic (n=76) Intervention 2: ICS (intermittent for example initiated for a short duration only at the onset of exacerbations or seasonal administration) - Budesonide. During the 52 weeks of treatment patients were advised to take open label budesonide (800 micrograms twice daily) for 10 days OR oral prednisone (0.5mg/kg per day) for 5 days if their asthma symptoms worsened. Patients also took twice daily oral and inhaled placebo. Duration 52 weeks. Concurrent medication/care: Prior to starting 52 weeks of regular ICS, 14 day run-in of 0.5mg/kg/d prednisone orally, 800 micrograms twice daily and 20 mg of zafirlukast twice daily plus PRN albuterol (540 to 720 micrograms) to "eliminate any easily reversed causes of airflow obstruction affecting PEF or FEV_1". Further details: 1. Definition of intermittent: Symptomatic	
Funding	Academic or government funding (Astra Zeneca provided medication)	

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE (INTERMITTENT) versus BUDESONIDE (REGULAR)

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months

- Actual outcome for ≥16 years: Exacerbations requiring OCS (OCS was either self-administrated according to action plan or during an ED visit) at After 1 year of treatment; Group 1: 8/70, Group 2: 10/67; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life at ≥3 months

- Actual outcome for ≥16 years: AQLQ (average over all visits) at After 1 year of treatment; Group 1: mean 0.5 (SD 0.84); n=70, Group 2: mean 0.5 (SD 0.82); n=67; AQLQ 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months

- Actual outcome for ≥16 years: ACQ (average over all visits) at After 1 year of treatment; Group 1: mean -0.3 (SD 0.43); n=73, Group 2: mean -0.4 (SD 0.84); n=70; ACQ 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Boushey 2005[164]	
Protocol outcome 4: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Exacerbations requiring hospitalisation (asthma-related hospitalisations) at During 1 year of treatment; Group 1: 0/73, Group 2: 0/67; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: 2-week average of morning PEF (%) at After 1 year of treatment; Group 1: mean 7.1 % (SD 16.8); n=70, Group 2: mean 8.3 % (SD 15.4); n=66; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: FEV_1 (pre-bronchodilator) at After 1 year of treatment; Group 1: mean 0.7 % (SD 9.2); n=70, Group 2: mean 4 % (SD 1.2); n=67; Risk of bias: Low; Indirectness of outcome: No indirectness		
Protocol outcomes not reported by the study	Mortality at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months	

Study	Martinez 2011[675]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=843 enrolled, 288 randomised)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Follow up (post intervention): 44 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: History of mild persistent asthma during the previous 2 years
Stratum	5 to <16 years: 6 to 18 years
Subgroup analysis within study	Not applicable
Inclusion criteria	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); naïve to controller treatment and had a history of one to two exacerbations in the previous year, if they were treated for the previous 8 weeks with a monotherapy other than inhaled corticosteroids, or if 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 PRN SABA).

Study	Martinez 2011[675]
Exclusion criteria	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)
Recruitment/selection of patients	Recruited from 5 clinical centres
Age, gender and ethnicity	Age - Range of means: 10.4-11.4. Gender (M:F): 118:96, reported for specific treatment groups. Ethnicity: 70-80% white, varying between treatment groups
Further population details	1. Allergic asthma status: Not applicable / Not stated / Unclear 2. Previous asthma exacerbations: no asthma exacerbation in the previous year (Approximately 25-35% had one or more OCS course in the last year). 3. Smoking status: Not applicable / Not stated / Unclear (In children, likely to be non-smokers but certainly not exclusively).
Extra comments	History of mild persistent asthma during the previous 2 years (mild persistent asthma defined as having, on average, more than 2 days per week with symptoms, more than 2 days a week SABA use, or more than two awakenings at night per month when not using controller medication, or if they had to use daily controller treatment to keep their disorder well controlled).
Indirectness of population	Serious indirectness: No objective tests reported for asthma diagnosis
Interventions	(n=71) Intervention 1: ICS (regular low dose) - Beclometasone dipropionate. 40ug beclometasone twice daily with 180ug albuterol & 80ug beclometasone combined as rescue medication, referred to as "combined" group in paper. Duration 44 weeks. Concurrent medication/care: Nil else Further details: 1. Definition of intermittent: Symptomatic (n=72) Intervention 2: ICS (regular low dose) - Beclometasone dipropionate. 40ug beclometasone twice daily with 180ug albuterol & placebo combined as rescue medication, referred to as "daily" group in paper. Duration 44 weeks. Concurrent medication/care: Nil else Further details: 1. Definition of intermittent: Symptomatic (n=71) Intervention 3: ICS (intermittent for example initiated for a short duration only at the onset of exacerbations or seasonal administration) - Beclometasone dipropionate. No regular treatment (daily placebo). 180ug albuterol & 80ug beclometasone combined as rescue medication, referred to as "rescue" group in paper. Duration 44 weeks. Concurrent medication/care: Nil else Further details: 1. Definition of intermittent: Symptomatic
Funding	Academic or government funding (National Heart, Lung and Blood Institute)

Study	Martinez 2011[675]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BD BECLOMETASONE + PRN ALBUTEROL & BECLOMETASONE versus PRN ALBUTEROL & BECLOMETASONE Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for 5 to <16 years: Number of patients having exacerbations requiring oral steroids at 44 weeks; Group 1: 22/63, Group 2: 25/58; Risk of bias: Low; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BD BECLOMETASONE + PRN ALBUTEROL & PLACEBO versus PRN ALBUTEROL & BECLOMETASONE Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for 5 to <16 years: Number of patients having exacerbations requiring oral steroids at 44 weeks; Group 1: 20/63, Group 2: 25/58; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: linear growth at ≥1 year - Actual outcome for 5 to <16 years: Mean difference in growth at 44 weeks; Other: -0.8 (95%CI -1.54 to -0.05); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Papi 2007 [805]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=466 randomised)
Countries and setting	Conducted in multiple countries; Setting: Community and hospital outpatients appointments
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 44 weeks

Study	Papi 2007 [805]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: History of mild persistent asthma for at least 6 months, FEV_1 more than or equal to 75% predicted with either BDR or a positive methacholine challenge test
Stratum	≥16 years: Patients were aged 18-65
Subgroup analysis within study	Not applicable
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 more than or equal to 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 (250ug twice daily of inhaled beclometasone dipropionate and PRN SABA): 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 oral corticosteroids or hospitalisation from asthma during the previous year, regular treatment for >6 months with >500ug/day of beclometasone or equivalent
Age, gender and ethnicity	Age - Range of means: 36.8-40.6. Gender (M:F): 95:133. Ethnicity: Not stated
Further population details	1. Allergic asthma status: Not applicable / Not stated / Unclear 2. Previous asthma exacerbations: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker
Extra comments	Appears to exclude anyone who has ever visited ED due to asthma previously
Indirectness of population	No indirectness
Interventions	(n=124) Intervention 1: ICS (intermittent for example initiated for a short duration only at the onset of exacerbations or seasonal administration) - Beclometasone dipropionate. BD placebo + 250ug of beclometasone & 100ug of albuterol 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. Concurrent medication/care: Usual care Further details: 1. Definition of intermittent: Symptomatic (n=110) Intervention 2: ICS (regular low dose) - Beclometasone dipropionate. Twice daily 250ug beclometasone as needed 100ug of albuterol. Duration 6 months. Concurrent medication/care: Usual care Further details: 1. Definition of intermittent: Symptomatic
Funding	Study funded by industry (Funded by Chiesi Farmaceutici)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE + ALBUTEROL (AS NEEDED) versus BECLOMETASONE	

Study	Papi 2007 [805]
DIPROPIONATE (REGULAR) + PRN ALBUTEROL Protocol outcome 1: SABA use at ≥3 months - Actual outcome for ≥16 years: Rescue medication (puffs/day) at 6 months; Group 1: mean 0.5 puffs/day/patient (SD 0.78); n=124, Group 2: mean 0.44 puffs/day/patient (SD 0.73); n=110; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Morning PEF at end of study at 6 months; Group 1: mean 442.75 litres/min (SD 107.8); n=124, Group 2: mean 433.08 litres/min (SD 113.59); n=110; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: FEV_1 (% of predicted value) at 6 months; Group 1: mean 92.23 (SD 11.69); n=124, Group 2: mean 90.32 (SD 13.11); n=110; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Papi 2009 [808]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=276 randomised, 267 completed)
Countries and setting	Conducted in Unknown multicentre; Setting: Patients were in the community but made study visits to their respective clinics at weeks 2, 4, 8, and 12 of the study.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Documented history of at least three episodes of wheezing requiring medical attention in the previous 6 months
Stratum	<5 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 1-4 years, frequent wheeze (documented history of at least three episodes of wheezing requiring medical

Study	Papi 2009 [808]
	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 2500ug PRN).
Exclusion criteria	History of severe exacerbations requiring systemic glucocorticoid, a chest infection or hospitalisation for asthma or treatment with inhaled glucocorticoids or methyl-xanthine during the previous four weeks or with oral glucocorticoid in the previous 8 weeks.
Recruitment/selection of patients	Pre-school children who were referred to the centres because of further episodes of wheezing (in addition to the three episodes in the previous 6 months) were recruited.
Age, gender and ethnicity	Age - Mean (SD): Regular ICS 2.35 (0.81), Prn ICS 2.26 (0.79). Gender (M:F): 132:88. Ethnicity: Not stated
Further population details	1. Allergic asthma status: Not applicable / Not stated / Unclear 2. Previous asthma exacerbations: Not applicable / Not stated / Unclear 3. Smoking status: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: No doctor diagnosed asthma reported
Interventions	(n=110) Intervention 1: ICS (regular low dose) - Beclometasone dipropionate. 400ug/vial Beclomethasone (one vial bid/twice a day), plus Salbutamol 2500 ug/vial (one vial PRN/as needed). Duration 12 weeks. Concurrent medication/care: Usual care Further details: 1. Definition of intermittent: Symptomatic (n=110) Intervention 2: ICS (intermittent for example initiated for a short duration only at the onset of exacerbations or seasonal administration) - Beclometasone dipropionate. Placebo vial (one vial bid/twice a day), plus fixed combination of 800 ug Beclomethasone + 1800 ug Salbutamol/vial (one vial PRN/as needed). Duration 12 weeks. Concurrent medication/care: Usual care Further details: 1. Definition of intermittent: Symptomatic
Funding	Study funded by industry (Chiesi Farmaceutici SpA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BECLOMETASONE DIPROPIONATE (REGULAR) versus BECLOMETASONE DIPROPIONATE (INTERMITTENT)

Protocol outcome 1: SABA use at ≥3 months

- Actual outcome for <5 years: Daytime rescue medication required (no. of uses) at 12 weeks; MD 0 (95%CI -0.08 to 0.09); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for <5 years: Night-time rescue medication required (no. of uses) at 12 weeks; MD 0 (95%CI -0.04 to 0.04); Risk of bias: Low; Indirectness of outcome:

Study	Papi 2009 [808]
No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Turpeinen 2008 [1049]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=178 randomised)
Countries and setting	Conducted in Finland; Setting: Community and secondary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptoms suggestive of asthma for previous month AND evidence of 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 min after inhalation of SABA). According to the symptoms and lung-function tests, the majority of children could be categorised as having mild persistent asthma.
Stratum	5 to <16 years: 5-10 years
Subgroup analysis within study	Not applicable
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 min after inhalation of SABA)
Exclusion criteria	Acute asthma, FEV_1 <50%, treatment in the previous 2 months with ICS/cromones/LTAs/LABAs, total cumulative doses of previous ICS >36mg inhaled/>12mg nasal/>200mg oral prednisolone.
Recruitment/selection of patients	Single centre, no other information provided
Age, gender and ethnicity	Age - Range of means: 6.7-7.0. Gender (M:F): 72:44. Ethnicity: All Caucasian.
Further population details	1. Allergic asthma status: Systematic review: mixed 2. Previous asthma exacerbations: Not applicable / Not stated / Unclear 3. Smoking status: Non-smoker/ex-smoker (5-10 year olds, likely to be majority non-smoker but not

Study	Turpeinen 2008 [1049]
	necessarily).
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: ICS (regular low dose) - Budesonide. Months 6-18:100ug budesonide twice daily. During exacerbations:100ug budesonide replaced with 400ug budesonide twice daily for two weeks. Duration 12 months. Concurrent medication/care: Month 1:400ug budesonide twice daily. Months 2-5:200ug budesonide twice daily. Rescue:Terbutaline 0.25mg as needed. During exacerbations: study meds replaced with 400ug budesonide twice daily for two weeks Further details: 1. Definition of intermittent: (n=58) Intervention 2: ICS (intermittent for example initiated for a short duration only at the onset of exacerbations or seasonal administration) - Budesonide. Months 6-18:Placebo, twice a day, inhaled. During exacerbations:Placebo replaced with 400ug budesonide twice daily for two weeks. Duration 12 months. Concurrent medication/care: Month 1:400ug budesonide twice daily. Months 2-5:200ug budesonide twice daily. Rescue:Terbutaline 0.25mg as needed Further details: 1. Definition of intermittent:
Funding	Study funded by industry (Helsinki University hospital & AstraZeneca)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE & TERBUTALINE (INTERMITTENT) versus BUDESONIDE (REGULAR) + PRN HIGH DOSE BUDESONIDE & TERBUTALINE Protocol outcome 1: Adverse events: linear growth at ≥1 year - Actual outcome for 5 to <16 years: Growth over 18 months at 18 months; MD 0.6 (Standard error = 0.24); Risk of bias: Very high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Zeiger 2011[1138]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=278 randomised)
Countries and setting	Conducted in USA; Setting: Secondary care & community
Line of therapy	Mixed line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis
Stratum	<5 years
Subgroup analysis within study	Not applicable
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 they had fewer than 3 days per week of albuterol and fewer than 2 nights with awakening
Exclusion criteria	Received more than 6 courses of oral steroids or hospitalised more than two times for wheezing during the previous year
Recruitment/selection of patients	No information provided
Age, gender and ethnicity	Age - Range: 12-53 months. Gender (M:F): 192:86. Ethnicity: 59-66% white across groups
Further population details	1. Allergic asthma status: Not applicable / Not stated / Unclear 2. Previous asthma exacerbations: ≥1 asthma exacerbation in the previous year 3. Smoking status: Non-smoker/ex-smoker
Indirectness of population	Serious indirectness: No mention of doctor diagnosed asthma
Interventions	(n=139) Intervention 1: ICS (regular low dose) - Budesonide. 0.5mg once nightly nebulised budesonide (Pulmicort respules), maintained during periods of respiratory tract illness + placebo once in the morning for comparison with BD intermittent group. Duration 1 year. Concurrent medication/care: Open label rescue albuterol administered per protocol during respiratory tract illness Further details: 1. Definition of intermittent: Symptomatic (n=139) Intervention 2: ICS (intermittent for example initiated for a short duration only at the onset of exacerbations or seasonal administration) - Budesonide. 1.0mg budesonide BD, nebulised, only for 7 days 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". Duration 1 year. Concurrent medication/care: Open-label rescue albuterol was administered per protocol during a respiratory tract illness (4 times daily) and as needed. Further details: 1. Definition of intermittent: Symptomatic

Study	Zeiger 2011[1138]
Funding	Academic or government funding (National Lung, Heart and Blood Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDESONIDE (INTERMITTENT DOSE) versus BUDESONIDE (REGULAR LOW DOSE) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for <5 years: Time to first exacerbation at 1 year; HR 1.03 (95%CI 0.82 to 1.31) Reported; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality at ≥6 months - Actual outcome for <5 years: Mortality at 1 year; Group 1: 0/139, Group 2: 0/139; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Hospitalisation at ≥6 months - Actual outcome for <5 years: Hospitalisation for asthma exacerbations at 1 year; Group 1: 5/139, Group 2: 4/139; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: SABA use at ≥3 months - Actual outcome for <5 years: Days with SABA use at 1 year; MD 0.4 (95%CI -1 to 2); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse events: linear growth at ≥1 year - Actual outcome for <5 years: Change in height from baseline at 1 year; MD 0.26 (95%CI -0.17 to 0.68); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

H.5 Improving adherence to treatment

Study	Es 2001[376]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)

Countries and setting	Conducted in Netherlands; Setting: Six paediatric outpatient clinics
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 11-18, physician diagnosis of asthma, treatment prescribed by a paediatrician with daily inhalation of prophylactic asthma medication for at least 2 months prior to study start.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 13.7 (1.4). Gender (M:F): 58/54. Ethnicity: White: 77%
Indirectness of population	Serious indirectness: No objective diagnosis of asthma
Interventions	(n=58) Intervention 1: Asthma education. Intervention group offered usual care from paediatrician every 4 months, plus additional education from the paediatrician, and individual and group sessions with an asthma nurse. Duration 1 year. Concurrent medication/care: NA (n=54) Intervention 2: Usual care (regular asthma review). Control participants continued usual care from a paediatrician only every 4 months. Duration 1 year. Concurrent medication/care: NA
Funding	Academic or government funding (Netherlands Asthma Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASTHMA EDUCATION versus USUAL CARE (REGULAR ASTHMA REVIEW)

Protocol outcome 1: Adherence to regular preventer medication (as defined by study) at ≥3 months
- Actual outcome for 5 to <16 years: Adherence (self-reported, 1-10) at 2 years; Group 1: mean 7.7 (SD 2); n=33, Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥3 months;

Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (change in FEV_1; morning PEF) at ≥3 months; Adverse events linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months	

Study	Gamble 2011[425]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in United Kingdom; Setting: Northern Ireland Regional Difficult Asthma Service. ~60% are tertiary referrals
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: No objective diagnosis of asthma
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects attending the Northern Ireland Regional Difficult Asthma Service. Non-adherent (≤50% of prescription filling) despite patient concordance discussion and treatment plan to address poor adherence. Juniper asthma control score >3.
Exclusion criteria	Tobacco smoking, significant co-morbidity which may contribute towards respiratory symptoms. Patients who became adherent during phase 1 of study.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 47.4 (9.9). Gender (M:F): 3/17. Ethnicity: Not reported
Indirectness of population	Serious indirectness: No objective diagnosis of asthma
Interventions	(n=9) Intervention 1: Other intervention meeting protocol - Other. Intervention group offered up to 8 individualised visits based on the Compliance Therapy Model, within a 12 week period. Duration 12 weeks. Concurrent medication/care: NA (n=11) Intervention 2: Usual care (regular asthma review). Control participants continued usual care, comprising standard asthma care at the Difficult Asthma Service. Duration 12 weeks. Concurrent medication/care: NA
Funding	Academic or government funding (Research and Development Office, Northern Ireland)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEHAVIOURAL CHANGE versus USUAL CARE (REGULAR ASTHMA REVIEW)

Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: Quality of life (AQLQ) at 1 year; Group 1: mean 4.3 (SD 1.4); n=7, Group 2: mean 3.8 (SD 1.6); n=11; AQLQ 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥3 months - Actual outcome for ≥16 years: Asthma control score (ACQ) at 1 year; Group 1: mean 2.9 (SD 1.4); n=7, Group 2: mean 3.1 (SD 1.6); n=11; ACQ 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (change in FEV_1; morning PEF) at ≥3 months - Actual outcome for ≥16 years: FEV_1 (% predicted) at 1 year; Group 1: mean 72.4 % (SD 24.7); n=7, Group 2: mean 67.2 % (SD 26.7); n=11; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adherence to regular preventer medication (as defined by study) at ≥3 months - Actual outcome for ≥16 years: Adherence (%) at 1 year; MD 33.1 (95%CI 10.56 to 55.64) (SE 11.499); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Lavoie 2014[616]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=147)
Countries and setting	France
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Bronchodilator reversibility in FEV_1 >20%
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18+, with primary diagnosis of moderate-severe persistent asthma (bronchodilator reversibility in FEV_1 >20%). Poorly controlled (ACQ ≥1.5) non-adherent (filled <50% of ICS medication in last year)
Exclusion criteria	Comorbid medical condition, severe psychopathology, substance abuse, cognitive or language deficit, pregnant.
Recruitment/selection of patients	Recruited from outpatient asthma clinic at HSCM
Age, gender and ethnicity	Age - Mean (SD): 50 (16). Gender (M:F): 21/33. Ethnicity: Not reported
Indirectness of population	No indirectness: No objective diagnosis of asthma
Interventions	(n=26) Intervention 1: Other intervention meeting protocol - Other. Three to four individual 15-30 minute sessions over 4-6 week period. Explored ambivalence, self-efficacy, 'rolling with resistance', and 'change talk'. Duration 18 weeks. Concurrent medication/care: NA (n=28) Intervention 2: Usual care (regular asthma review). 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. Duration 18 weeks. Concurrent medication/care: NA
Funding	Study funded by industry (GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MOTIVAITONAL INTERVIEWING versus USUAL CARE (REGULAR ASTHMA REVIEW)

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: Quality of life (AQLQ) at 1 year: Group 1: mean 5 (SD 1.24): n=26, Group 2: mean 4.7 (SD 1.03): n=28; AQLQ 1-7 Top=High is good

outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥3 months - Actual outcome for ≥16 years: Asthma control (ACQ) at 1 year; Group 1: mean 1.7 (SD 0.99); n=26, Group 2: mean 2.1 (SD 1.03); n=28; ACQ 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Asthma control (ACT) at 1 year; Group 1: mean 18 (SD 4.95); n=26, Group 2: mean 18 (SD 5.16); n=26; ACT 5-25 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (change in FEV_1; morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adherence to regular preventer medication (as defined by study) at ≥3 months

Study	Petrie 2012[837]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=147)
Countries and setting	New Zealand
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 9 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 16-45, diagnosed with asthma, not currently adhering to their preventer medication as prescribed, own a mobile phone.
Exclusion criteria	Non-English speaking, diagnosis of COPD
Recruitment/selection of patients	Recruited using flyers dispensed with medication, and emails sent to members of a targeted marketing website.
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Indirectness of population	Serious indirectness: No objective diagnosis of asthma
Interventions	(n=73) Intervention 1: Inhaler alarms/alert or other method of alarm (for example text, app) to remind people to take regular therapy. Individually tailored text messages based on their illness and medication belief over 18 weeks. Two messages per day from weeks 1-6, one per day from weeks 7-12, and three per week from weeks 13-18. Duration 18 weeks. Concurrent medication/care: NA (n=74) Intervention 2: Usual care (regular asthma review). Usual care with no text messages. Duration 18 weeks. Concurrent medication/care: NA
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INHALER ALARMS/ALERT OR OTHER METHOD OF ALARM (EG TEXT, APP) TO REMIND PEOPLE TO TAKE REGULAR THERAPY versus USUAL CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Adherence to regular preventer medication (as defined by study) at ≥3 months	

- Actual outcome for ≥16 years: Adherence (%) at 9 months; Group 1: mean 57.8 % (SD 35.3); n=41, Group 2: mean 43.2 % (SD 26); n=52; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (change in FEV_1; morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Schaffer 2004[935]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=46)
Countries and setting	USA
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 9 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults whose reported use of preventative medication for asthma during the 3 months prior to study indicated mild to moderate persistent asthma.
Exclusion criteria	COPD, symptomatic cardiac disease
Recruitment/selection of patients	Using flyers posted through the health science centre campus.
Age, gender and ethnicity	Age - Mean (range): 37 (18-63). Gender (M:F): 15/31. Ethnicity: White 72%
Indirectness of population	Serious indirectness: No objective diagnosis of asthma
Interventions	(n=33) Intervention 1: Asthma education. Education via 30-minute audiotape (Bob's Lung Story), 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. Duration 1 hour. Concurrent medication/care: NA (n=13) Intervention 2: Usual care (regular asthma review). Standard provider education; whatever education was provided by the participant's asthma care provider and was not assessed in this study. Duration NA. Concurrent medication/care: NA
Funding	Academic or government funding (University of Florida College of Nursing Biobehavioural Research Centre)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASTHMA EDUCATION versus USUAL CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Quality of life at ≥3 months	

- Actual outcome for ≥16 years: Quality of life (AQLQ) at 9 months; Group 1: mean 5.24 (SD 0.93); n=33, Group 2: mean 4.87 (SD 1.2); n=13; AQLQ 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥3 months - Actual outcome for ≥16 years: Asthma control (ACQ) at 9 months; Group 1: mean 1.35 (SD 0.9); n=33, Group 2: mean 1.25 (SD 1.07); n=13; ACQ 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adherence to regular preventer medication (as defined by study) at ≥3 months - Actual outcome for ≥16 years: Adherence (%) at 9 months; Group 1: mean 68.2 % (SD 31.9); n=33, Group 2: mean 40 % (SD 44); n=13; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (change in FEV_1; morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

Study	Wang 2010[1091]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=91)
Countries and setting	Taiwan
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatient adults aged 18-80, good cognitive function, with confirmed diagnosis of bronchial asthma as determined by clinical features before treatment.
Exclusion criteria	Other medical conditions which could impact QoL or cognitive function
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 25 (19-68). Gender (M:F): 65/26. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Asthma education. Nurse led education programme, using a workbook prepared by chest physicians. Subset of participants also received pharmacist counselling with education specific to medication. Three 1-hour sessions at months 1, 2, and 3. Duration 3 months. Concurrent medication/care: NA (n=32) Intervention 2: Usual care (regular asthma review). Received routine care only. Duration 3 months. Concurrent medication/care: NA
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASTHMA EDUCATION versus USUAL CARE (REGULAR ASTHMA REVIEW)

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: Quality of life (AQLQ) at 6 months; Group 1: mean 5.05 (SD 0.98); n=59, Group 2: mean 4.88 (SD 1.05); n=32; AQLQ 1-7 Top=High is good outcome: Risk of bias: Low: Indirectness of outcome: No indirectness

Protocol outcome 2: Adherence to regular preventer medication (as defined by study) at ≥3 months - Actual outcome for ≥16 years: Adherence (self-reported 4-16) at 6 months; Group 1: mean 13.51 (SD 2.19); n=59, Group 2: mean 12.6 (SD 2.73); n=32; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (change in FEV_1; morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months

H.6 Self-management plans

Study	Agrawal 2005[15]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in India; Setting: Primary care/home
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Assessed according to the National Heart Lung and Blood Institute (NHLBI) guidelines.
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Those with uncontrolled medical conditions besides asthma and its causes
Recruitment/selection of patients	Consecutive recruitment
Age, gender and ethnicity	Age - Mean (SD): PAAP - 7.2 (2.2); usual care - 8.5 (2.8). Gender (M:F): Not reported. Ethnicity: Not reported.
Further population details	1. Setting: Primary care
Extra comments	Duration of asthma (years), mean(SD): PAAP - 4.09(1.5); usual care - 4.7 (2.4). No. of emergency visits per subject during the preceding year, mean(SD): PAAP - 0.9(0.3); usual care - 1.0(0.0). PEFR (% predicted), mean(SD): PAAP - 77.3 (4.8); usual care - 75.7 (7.5).
Indirectness of population	Serious indirectness: Method of diagnosis not reported.
Interventions	(n=35) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Patients received an individualised written home-management plan. The individualised action plans consisted of written guidelines for home management of asthma based on the assessment of asthma severity or peak expiratory flow rate depicted in a colour-coded chart. Duration 3 months. Concurrent medication/care: Patients received the intervention on top of usual care. (n=33) Intervention 2: Standard care (regular asthma review). All patients were given patient and parent education containing basic information about asthma and its causes, aggravating factors, purpose and effects of asthma therapy, and the principles of home monitoring and self-management of asthma. Patients and their parents were trained to perform peak expiratory flow rate (PEFR) measurements and record the best of three consecutive readings at 07.00

	hours daily. They were also taught to maintain an asthma symptom diary, consisting of six items to be scored: daytime or night-time cough, wheezing, difficulty in breathing, missing school, exercise intolerance and use of rescue mediation. Duration 3 months. Concurrent medication/care: None reported.
Funding	Funding not stated (Not reported.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OPTIMAL SUPPORTED SELF-MANAGEMENT versus STANDARD CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for 5 to <16 years: Acute asthma events per subject at 3 months; Group 1: mean 0.5 No units. (SD 0.71); n=32, Group 2: mean No units. (SD 0.61); n=28; Risk of bias: High; indirectness of outcome Very serious indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Bragt 2014[173]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Australia, Netherlands; Setting: Primary care
Line of therapy	Adjunctive to current care
Duration of study	Not clear: 9 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Patients with International Classification of Primary Care (ICPC) code - R96.
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
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.
Exclusion criteria	Patients with co-morbid conditions that significantly influence the HRQL (such as diabetes or congenital heart defects), not being able to attend a regular school class and insufficient skill in speaking and/or reading the Dutch language.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): SF group - 8.4 (1.7); Usual care - 8.7 (1.7). Gender (M:F): 18/11. Ethnicity: SM group: Caucasian - 14; African - 1. Usual care: Caucasian - 14.
Further population details	1. Setting: Primary care
Extra comments	Cluster-randomised trial. Baseline details: FEV_1 (% predicted), mean (SD): SF group - 111 (13.5); usual care - 101 (12.7).
Indirectness of population	Serious indirectness: Method of diagnosis not reported.
Interventions	(n=18) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Children received self-management support on top of usual care. Before each scheduled visit, children completed the online Pelican instrument. The child's selection of asthma-related problems was the starting point for a six-step individualised self-management intervention based on shared decision-making. Together with the patient and parent(s), a practice nurse discussed which selected problem would be subject of treatment (Step 1). When needed, details around a problem were discussed (step 2), a treatment goal was formulated (Step 3), a brainstorm session on solutions was held (step 4) and solutions that all involved agreed on were documented in a written action plan (step 5). Solutions could focus on education, inhalation technique, medication adjustments, therapy adherence, exercise, environment, social impact, self-efficacy and many other individual aspects. During the next visit, the results of the written action

	plan were evaluated (Step 6) and if the treatment goal was not achieved, the sixth step intervention was repeated. Telephone support was provided. Duration 9 months. Concurrent medication/care: None reported. (n=20) Intervention 2: Standard care (regular asthma review). Patients were given an assessment of their symptoms, medication use and exposure to triggers according to the guidelines of the Dutch College of General Practitioners every 3 months. Usual care was provided by the general practitioner (GP) or practice nurse. Usual care visits would last ~ 10 minutes - the standard length of a consultation in Dutch clinical practice. Duration 9 months. Concurrent medication/care: None reported.
Funding	Academic or government funding (The Dutch Lung Foundation (previously Dutch Asthma Foundation), NutsOhra foundation and a grant from the Nijemegen Centre of Evidence-Based Practice (RadboudUMC grant).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-MANAGEMENT GROUP versus USUAL CARE

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for 5 to <16 years: Health-related quality of life of the parent (PACQLQ) - Activities at 9 months; Other: SM group - 7.00(0.00); usual care - 7.00(0.25). Paediatric Asthma Caregiver's Quality of Life Questionnaire. 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: Serious indirectness
- Actual outcome for 5 to <16 years: Health-related quality of life of the parent (PACQLQ) - Emotions at 9 months; Other: SF group - 6.94(0.19); usual care - 6.78 (0.78). Paediatric Asthma Caregiver's Quality of Life Questionnaire 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Health-related quality of life (PAQLQ-s) - Activities at 9 months; Other: SM group - 7.00(1.00); usual care - 6.30(1.45). 1-7 Paediatric Asthma Quality of Life Questionnaire with standardised activities. Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Health-related quality of life (PAQLQ-s) - Emotions at 9 months; Other: SM group - 7.00(0.25); usual care - 7.00(0.38). Paediatric Asthma Quality of Life Questionnaire with standardised activities. 1-7 Top=High is good outcome; Risk of bias: Low Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Health-related quality of life (PAQLQ-s) - Symptoms at 9 months; Other: SM group - 6.70(1.20); usual care - 6.45 (0.75). Paediatric Asthma Quality of Life Questionnaire with standardised activities. 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Health-related quality of life (PAQLQ-s) at 9 months; Other: SM group - 6.78(0.96); usual care - 6.50(0.72). Paediatric Asthma Quality of Life Questionnaire with standardised activities. 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Health-related quality of life of the parent (PACQLQ) at 9 months; Other: SF group - 6.96(0.31); usual care - 6.85(0.54). Paediatric Asthma Caregiver's Quality of Life Questionnaire 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months
- Actual outcome for 5 to <16 years: Asthma control (C-ACT) at 9 months; Other: SM group - 26.0(4.5); Usual care- 29.0(2.0). Child Asthma Control Test 0-27 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Asthma control (ACQ) at 9 months; Other: (Change score)SM group - 0.1(0.5); usual care - 0.3(1.0). Asthma Control Questionnaire. 0-7 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Bruzzese 2011[190]
Study type	RCT (randomised; Parallel)
Number of studies (number ofparticipans)	1 (n=345)
Countries and setting	Conducted in USA
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: Up to 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	9th and 10th grade high school students; moderate to severe persistent asthma as defined by NHLBI guidelines; taking asthma medication prescribed by a medical provider in the last 12 months.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Participants were drawn from five participating high schools with a high proportion of Latino/a and African American students.
Age, gender and ethnicity	Age - Mean (SD): 15.10(0.86). Gender (M:F): 102/243. Ethnicity: Hispanic/Latino/a or Hispanic American (n) - 157; African American/African or Caribbean American/Caribbean (n) - 130; Mixed ethnicity (n) - 40; Other (n) - 18.
Further population details	1. Setting: Primary care
Extra comments	Baseline characteristics (n): NHLBI asthma classification, moderate persistent - 237; severe persistent - 108.
Indirectness of population	Serious indirectness: Method of diagnosis not reported.
Interventions	(n=175) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Students were enrolled in an 8-week intensive program for the students. The students attended three 45- to 60-minute group sessions, and individual tailored coaching sessions held at least once per week for 5 weeks. Sessions were delivered by trained health educators during the school day. They were taught asthma management skills and ways to cope with asthma, and were encouraged to see their medical provider for a clinical evaluation and treatment. Medical providers were first mailed a packet containing: a letter informing them that one of their patients was in the study and would be referred to him/her for a clinical evaluation; a blank asthma checklist the students complete throughout the intervention and bring to the visit with the provider; and a blank asthma action plan the provider was asked to complete. Within 2 weeks, a paediatric pulmonologist or adolescent medicine specialist called the students' medical providers to discuss the concepts presented in the program and to answer any questions regarding NHLBI Institute criteria for treating asthma. Students without a medical provider were given referrals to a primary care provider in

	their community, or if available, to the on-campus school-based health centre. Make-up sessions were offered to students who missed the group sessions; health educators were at school daily to conduct individual sessions and therefore were able to reach out multiple times to students who may have been absent on a given day. Duration 8 weeks. Concurrent medication/care: Not reported. (n=170) Intervention 2: Standard care (regular asthma review). Students were put on a 12-month waiting list and received the intervention after 12-month interviews had been conducted. Duration 12 months. Concurrent medication/care: Not reported.
Funding	Academic or government funding (Grant received from the National Heart, Lung, and Blood Institute grants R01HL067268; R01HL079953 and R01HL089493.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-MANAGEMENT PACKAGE versus USUAL CARE Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for 5 to <16 years: Quality of Life at 12 months ; SMD 0.3 (95%CI 0.09 to 0.5) Paediatric Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 2: Hospitalisation at ≥6 months - Actual outcome for 5 to <16 years: Hospitalisation at 12 months ; Group 1: mean 0.05 Days (SD 0.3); n=175, Group 2: mean 0.24 Days (SD 1.18); n=170; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Castro 2003[232]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in USA; Setting: Secondary care.
Line of thapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by physician.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of asthma of at least 12 months duration; aged from 18-65 years of age; hospitalised 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 hospitalisation in the 12 months prior to randomisation.
Exclusion criteria	Patients with a concomitant diagnosis of chronic bronchitis, emphysema, or congestive heart failure diagnosed by the primary physician; a terminal condition with anticipated survival of less than one year; dementia or serious psychiatric illness, such as schizophrenia or personality disorder; planned discharge to a long-term care facility, anticipated early discharge of less than 24 hours, not allowing enough time to complete the intervention; or refusal to participate by the patient or physician of record.
Recruitment/selection of patients	Patients admitted to Barnes-Jewish Hospital from September 1996 to July 1999.
Age, gender and ethnicity	Age - Mean (SD): SM group - 35(11); usual care - 38(12). Gender (M:F): 17/79. Ethnicity: (n) African American - 79; other - 17.
Further population details	1. Setting: Secondary care
Extra comments	Baseline details: FEV_1 (% Predicted): SM group - 57(18); usual care - 58(22).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=46) Intervention 1: Standard care (regular asthma review). Patients received the normal care provided by their private primary care physician. Asthma education was provided by the hospital respiratory therapist and nurse including asthma medication dosing, action and side effects, as well as inhaler technique and peak flow monitoring. Patients also received written discharge instructions from the hospital nurse stating the patient's discharge medications and physician follow-up information but did not include an asthma action or management plan. No nursing care was provided by the study nurses other than obtaining study data and the performance of baseline spirometry. Duration 6 months. Concurrent medication/care: None reported.

	(n=50) Intervention 2: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. The asthma nurse specialist reviewed the individual treatment plans with the patients. The nurse made suggestions to the primary physician regarding potential changes to the treatment plan, including simplification or consolidation, in accordance with the National Asthma Education and Prevention Program. Patients completed a daily "Asthma Care" flow sheet while in hospital which included a symptom score, pulmonary functions (including peak expiratory flow), current asthma medications, and any pertinent recommendations. This was shared with the patient's primary physician. Patients were provided with asthma education appropriate to the patient's education, motivation, and cultural beliefs. This included individual instruction using tailored asthma education which included identifying triggers, early and late warning signs, medications and delivery technique, use of a spacer, peak flow monitoring, how to implement environmental control measures, assessing need for allergy skin testing, smoking cessation counselling, and the importance of follow-up care. As many sessions as possible were provided to the patient until they were discharged. Patients were also provided with psychological support and screening for professional counselling. This was provided both verbally and written by an asthma nurse specialist. If there was important psychosocial issues that could interfere with asthma control and it was beyond the asthma nurses' expertise, the patient was referred to a social worker or psychiatric nurse specialist. Patients were given a written Asthma Self-Management plan. They were provided with social service professionals when necessary to facilitate discharge planning. Outpatient follow-up telephone contacts were made available to patients, as well as follow-up appointments with primary physician. The patient's asthma control was assessed at these subsequent contacts and the primary physician was contacted if necessary. A home visit was necessary for some patients who were unavailable by phone, to establish trust, and to evaluate for potential environmental or social factors which might be contributing to poor asthma control. Duration 6 months. Concurrent medication/care: None reported.
Funding	Academic or government funding (The Barnes-Jewish Hospital Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: USUAL CARE versus OPTIMAL SUPPORTED SELF-MANAGEMENT (INCLUDING SELF-MANAGEMENT EDUCATION, SELF-MONITORING AND A WRITTEN PERSONALISED ASTHMA ACTION PLAN, PAAP) IN ADDITION TO STANDARD CARE

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for ≥16 years: Asthma Quality of Life - Overall at 6 months; Group 1: mean 3.9 N/A (SD 1.5); n=33, Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Asthma Quality of Life - Activity at 6 months; Group 1: mean 4.2 N/A (SD 1.6); n=33, Group 2: mean 4.2 N/A (SD 1.4); n=33; Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for ≥16 years: Asthma Quality of Life - Symptom at 6 months; Group 1: mean 3.9 N/A (SD 1.6); n=33, Group 2: mean 4 N/A (SD 1.4); n=33; Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for ≥16 years: Asthma Quality of Life - Emotional at 6 months; Group 1: mean 3.8 N/A (SD 1.6); n=33, Group 2: mean 3.7 N/A (SD 1.5); n=33; Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Asthma Quality of Life - Environmental at 6 months; Group 1: mean 3.8 N/A (SD 1.6); n=33, Group 2: mean 3.9 N/A (SD 1.4); n=33; Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Hospital days at 12 months; Group 1: 53/46, Group 2: 129/50; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Hospital days at 12 months; Group 1: mean 2.8 Days (SD 5.9); n=46, Group 2: mean 1.1 Days (SD 2.4); n=50; Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocolutcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Cote 1997[287]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=149)
Countries and setting	Conducted in Canada; Setting: Primary/Secondary care
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 year + 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis was confirmed by either a documented reversibility greater than 15% in FEV_1 or a PC20 methacline ≤8 mg/ml when determind by the method described by Cockcroft and co-workers.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
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).
Exclusion criteria	All current or ex-smokers 40 years of age or older in whom the best FEV_1 after salbutamol was < 80% of predicted patients with significant concurrent diseases, those requiring > 7.5 mg/d of prednisolone to control asthma symptoms, and finally those having taken part in an asthma educational program.
Recruitment/selection of patients	Patients were recruited from tertiary care hospitals.
Age, gender and ethnicity	Age - Mean (SD): Usual care - 36 (22); PF plan - 37 (14.1); SB plan - 39 (13.4). Gender (M:F): 53/96. Ethnicity: Not reported.
Further population details	1. Setting: Not applicable / Not stated / Unclear
Extra comments	Baseline details: PEF morning (% predicted): usual care - 95(14.7); PF plan - 94 (21.2); SB plan - 91 (20.1).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=50) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Patients measured their PEF twice a day and kept a diary of results. PEF was measured using a portable device designed by Clement Clarke (UK). Every attempt was made to make sure patients knew how to interpret their results and respond to a change in PEF. At each follow-up appointment, the patient's diary card was reviewed, and if the action plan had not been implemented when required, further explanations were given regarding when treatment should be modified. Step 1 (green zone): morning pre-bronchodilator PEF values are > 85% of the PBV (personal best value): continue the same maintenance treatment. Step 2 (yellow zone): for past 24 hours, PEF values have been between 60 and 85% of the PBV: increase the dose of BDP to four puffs twice a day(2,000 µg/d) for a minimum of 10 days and the time required to return to

	PBV, then progressively reduce the dose of BDP to the initial level over 2 weeks. If 48 hours after increasing the dose of BDP, there is no increase in PEF values, proceed to Step 3. For patients with a maintenance dose of BDP > 1,000 µg per day, the action plan was modified as follows: the dose of BDP was increased as much as four puffs three times a day (3,000 µg/d).Step 3 (red zone): for the previous 12 hour, PEF values have been < 60 % of the PBV: advise personal physician and start using oral prednisolone by 5 mg/d every day. Step 4 (red extra zone): PEF values are < 50% of your PBV: visit your physician promptly or go directly to an emergency room. Duration 1 year. Concurrent medication/care: No. of patients using: (1) Theophyllines - 3; (2) Nedocromil - 3. Comments: These patients received the same care as the control group. They also received individual counselling with the specialised educator during a 1-hour session. A book entitled 'Understand and Control Your Asthma' was given to all the participants. Additional educational visits were scheduled if necessary. (n=45) Intervention 2: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Patients were asked to keep a daily diary of asthma symptom scores: breathlessness, wheezing, cough; using a scale of 0 (no symptoms) to 3 (night time asthma symptoms, severe daily symptoms preventing usual activities). They were also given this plan: Step 1 (green zone): not awakened at night by asthma, using the usual dose of B-agonist, able to perform usual activities without becoming short of breath: continue the same treatment. Step 2 (yellow zone): for the previous 24 hours, using twice as much B-agonist or awakening at night because of asthma, moderate exercise induces unusual breathlessness, B-agonist relieves respiratory symptoms for less than 4 hours: increase the dose of BDP as described for patients with the peak flow-based plan. Step 3 (red zone): for the previous 24 h, B-agonist has been relieving the asthma symptoms for less than 4 h, or using more than 10 puffs of B-agonist a day, or daily life activities causing shortness of breath, or breathlessness is present at rest: contact personal physician and start using oral prednisolone 30mg as described for the peak flow-based plan. Step 4 (red extra zone): difficulty talking, the B-agonist relieves the symptoms for 2 hours or less: advise personal physician if possible and go directly to an emergency clinic. Duration 1 year. Concurrent medication/care: No. of patients using: (1) Theophyllines - 4; (2) Nedocromil - 3. Comments: These patients received the same care as the control group. They also received individual counselling with the specialised educator during an 1 hour session. A book entitled 'Understand and Control Your Asthma' was given to all the participants. Additional educational visits were scheduled if necessary. (n=54) Intervention 3: Standard care (regular asthma review). The patients received instructions from their pulmonologists regarding medication use, and influence of allergenic and non-allergenic triggers. They were taught how to use their inhaler properly by the educator. A verbal action plan could be given by the physician. Duration 1 year. Concurrent medication/care: No. of patients using: (1) Theophyllines - 2; (2) prednisolone - 1.
Funding	Study funded by industry (A grant from Glaxo Canada, Mississauga (Ontario).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PEAK FLOW-BASED PLAN versus USUAL CARE

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Oral corticosteroid courses at 1 year; Group 1: mean 0.7 Courses (SD 1.4); n=50, Group 2: mean 0.5 Courses (SD 1.5); n=54; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Hospitalisation at 1 year; Group 1: mean 0.04 N/A (SD 0.28); n=50, Group 2: mean 0.04 N/A (SD 0.29); n=54; Risk of bias: High; Indirectness of outcome: Serious indirectness
- Actual outcome for ≥16 years: Emergency room visit at 1 year; Group 1: mean 0.7 N/A (SD 1.4); n=50, Group 2: mean 0.8 N/A (SD 1.5); n=54; Risk of bias: High; Indirectness of outcome: Serious indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYMPTOM BASED PLAN versus USUAL CARE

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months
- Actual outcome for ≥16 years: Oral corticosteroid courses at 1 year; Group 1: mean 0.9 Courses (SD 1.3); n=45, Group 2: mean 0.5 Courses (SD 1.5); n=54; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Hospitalisation at ≥6 months
- Actual outcome for ≥16 years: Hospitalisation at 1 year; Group 1: mean 0.09 N/A (SD 0.27); n=45, Group 2: mean 0.04 N/A (SD 0.29); n=54; Risk of bias: High; Indirectness of outcome: Serious indirectness
- Actual outcome for ≥16 years: Emergency room visit at 1 year; Group 1: mean 0.7 N (SD 1.3); n=54, Group 2: mean 0.8 N/A (SD 1.5); n=54; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Cote 2000[286]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=149)
Countries and setting	Conducted in Canada; Setting: Tertiary care.
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis confirmed by either a reversibility of greater than 15% in forced expiratory volume in 1 s (FEV_1) after salbutamol, or the concentration of methacholine that induces a 20% fall in FEV_1, of 8 mg/mL or more using American Thoracic Society criteria.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of moderate asthma requiring daily treatment with inhaled corticosteroids; PEF diurnal variation 15% or post bronchodilator FEV_1 of 85% or greater of predicted (criteriaf stability).
Exclusion criteria	Patients requiring more than 7.5mg/day prednisolone to control asthma and those with prior participation in an asthma education program.
Recruitment/selection of patients	Patients were recruited from three hospitals: L'hôpital Laval, Sainte-Foy; l'hôpital du Sacré-Coeur, Montréal; and l'hôpital du Saint-Sacrement, Québec city, Québec.
Age, gender and ethnicity	Age - Mean (SD): Self-management - 38(2); usual care - 36(3). Gender (M:F): 53/96. Ethnicity: Not reported.
Further population details	1. Setting: Not applicable / Not stated / Unclear
Extra comments	Baseline characteristics: Duration of asthma (years, mean ± SEM): Self-management group - 14(2); usual care - 12(2).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=50) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. In addition to usual care, patients were given individual counselling with a specialised educator for a 1 h session. Education was complemented at each follow-up visit. Patients were asked to measure PEF twice daily and to adjust treatment according to a self-action plan based on the patient's PBV. Duration 12. Concurrent medication/care: None reported. Comments: Patients were enrolled in a run-in period lasting from 2 to 6 weeks, prior to randomisation. Medication was adjusted according to the International Consensus Report on Diagnosis and Management of Asthma. All patients were given the book 'Understand and Control your Asthma'. (n=54) Intervention 2: Standard care (regular asthma review). Participants received instructions from their

	respirologist regarding dosage of medication to use, and influence of allergenic and non-allergenic triggers. They had to record asthma symptom score daily in the two weeks before each follow-up visit. Duration 12 months . Concurrent medication/care: None reported. Comments: Patients were enrolled in a run-in period lasting from 2 to 6 weeks, prior to randomisation. Medication was adjusted according to the International Consensus Report on Diagnosis and Management of Asthma. All patients were given the book 'Understand and Control your Asthma'. (n=45) Intervention 3: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. In addition to usual care, patients were given individual counselling with a specialised educator for a 1 h session. Education was complemented at each follow-up visit. Patients had to record their asthma symptom score daily. They were also asked to adjust their medication following action plan based on asthma symptom severity and bronchodilator use that consisted of four different steps. Duration 12 months. Concurrent medication/care: None reported. Comments: Patients were enrolled in a run-in period lasting from 2 to 6 weeks, prior to randomisation. Medication was adjusted according to the International Consensus Report on Diagnosis and Management of Asthma. All patients were given the book 'Understand and Control your Asthma'.
Funding	Study funded by industry (Supported by a grant from FRSQ-Glaxo Wellcome Canada, Mississauga, Ontario and Le Centre québécois d'excellence en santé respiratoire, Sainte-Foy, Québec.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PEAK-FLOW BASED PLAN versus USUAL CARE Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: Quality of life - Overall at 12 months; Group 1: mean 5.5 N/A (SD 0.15); n=50, Group 2: mean 5.3 N/A (SD 0.16); n=54; Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYMPTOM BASED PLAN versus USUAL CARE Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for ≥16 years: Quality of lif - Overall at 12 months; Group 1: mean 5.9 N/A (SD 0.17); n=45, Group 2: mean 5.3 N/A (SD 0.16); n=54; Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection

at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months	

Study	Cowie 1997[290]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Canada; Setting: Primary care/home.
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 6 months.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Methacholine challenge given by a physician.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants who had received urgent treatment for their asthma in the preceding 12 months.
Exclusion criteria	Subjects with written asthma management plans were ineligible.
Recuitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): Usual care - 36.4(12.76); PF plan - 39.1(14.1); Symptom plan - 36.8 (16.5). Gender (M:F): Define. Ethnicity: Not reported.
Further population details	1. Setting: Primary care
Extra comments	Baseline details - Duration of asthma, years, mean (SD): usual care - 16.8 (12.06); PF plan - 12.8 (10.08); symptom plan - 13.7 (12.14). FEV_1 % predicted, mean (SD): usual care - 78 (21.3); PF plan - 82 (20.5); symptom plan - 79 (18).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=48) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Patients were given a peak flow meter (Mini-Wright; Ferraris Medical, Inc; Holland, NY) and brief instructions in its use and in recording the data. Their action plan included peak flow measurements that were estimated from their measured and predicted peak expiratory flows. Peak flow readings at or below which each step should be initiated were written into each patient's action plan. Doubling of their inhaled corticosteroid was recommended when the peak expiratory flow < 70% of their estimated best reading or when the diurnal variation was ≥ 20%. Initiation of the third step (prednisolone) was advised at ≤50%, and the fourth step (urgent treatment in an emergency department) at ≤30% of their estimated best peak expiratory flow. Patients had their inhaler use checked and corrected when necessary. The role of medication to control asthma was emphasised and all subjects were given the general information that medication and dosage may need to be adjusted as asthma severity changed. Patients received a printed plan completed according to their current or recommended therapy. These patients were also given a prescription for prednisolone to enable them to utilise the third level of treatment recommended in their action plans. A letter was sent to each subject's family

	physician to inform them that their patient had been enrolled in the study. In those instances where the subject's prescribed medication (usually inhaled corticosteroid) was thought to be inadequate, a suggestion was made for an adjustment of therapy. Duration 60 minutes. Concurrent medication/care: None reported. Comments: The action plans had been modified from those of: 1. Charlton, Ian, et al. "Evaluation of peak flow and symptoms only self-management plans for control of asthma in general practice." Bmj 301.6765 (1990): 1355-1359. and, 2. Beasley, R., M. Cushley, and S. T. Holgate. "A self-management plan in the treatment of adult asthma." Thorax 44.3 (1989): 200-204. (n=52) Intervention 2: Standard care (regular asthma review). Patients had their inhaler use checked and corrected when necessary. The role of medication to control asthma was emphasised and all subjects were given the general information that medication and dosage may need to be adjusted as asthma severity changed. A letter was sent to each subject's family physician to inform them that their patient had been enrolled in the study. In those instances where the subject's prescribed medication (usually inhaled corticosteroid) was thought to be inadequate, a suggestion was made for an adjustment of therapy. Duration 60 minutes. Concurrent medication/care: None reported. Comments: Patients with peak flow meters were not excluded. (n=50) Intervention 3: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. The instructions for the symptom-based plan listed common symptoms of asthma, including waking at night or a persistent cough and symptoms of a common cold as indications for doubling their inhaled corticosteroid. The third step required the introduction of prednisolone if their relief following the use of a bronchodilator lasted ≤2 hours or if they became short of breath doing their normal daily activities. The fourth step required them to seek urgent treatment if their bronchodilator provided relief for ≤ 30 minutes or if their breathing made it difficult for them to speak. Patients had their inhaler use checked and corrected when necessary. The role of medication to control asthma was emphasised and all subjects were given the general information that medication and dosage may need to be adjusted as asthma severity changed. Patients received a printed plan completed according to their current or recommended therapy. These patients were also given a prescription for prednisolone to enable them to utilise the third level of treatment recommended in their action plans. A letter was sent to each subject's family physician to inform them that their patient had been enrolled in the study. In those instances where the subject's prescribed medication (usually inhaled corticosteroid) was thought to be inadequate, a suggestion was made for an adjustment of therapy. Duration 60 minutes. Concurrent medication/care: None reported. Comments: The action plans had been modified from those of: 1. Charlton, Ian, et al. "Evaluation of peak flow and symptoms only self-management plans for control of asthma in general practice." BMJ 301.6765 (1990): 1355-1359. and, 2. Beasley, R., M. Cushley, and S. T. Holgate. "A self-management plan in the treatment of adult asthma." Thorax 44.3 (1989): 200-204.

Funding	Academic or government funding (Grant from Foothills Hospital)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PEAK FLOW-BASED PLAN versus USUAL CARE Protocol outcome 1: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Total admissions for asthma at 6 months; Group 1: 2/46, Group 2: 12/48; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Total visits for urgent treatment of asthma at 6 months; Group 1: 5/46, Group 2: 55/48; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYMPTOM BASED PLAN versus USUAL CARE Protocol outcome 1: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Total admissions for asthma at 6 months; Group 1: 6/45, Group 2: 12/48; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Total visits for urgent treatment of asthma at 6 months; Group 1: 45/45, Group 2: 55/48; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not repoted by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Deoliveira 1999[316]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Brazil; Setting: Outpatient clinic
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 month
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not reported.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Asthma confirmed by history and airflow, obstruction according to the criteria of the ICRDMA were eligible to participate in the trial.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Patients were recruited from a computer database of asthma outpatients.
Age, gender and ethnicity	Age - Mean (SD): Self-management package - 41(15); usual care - 38(17). Gender (M:F): 5/37. Ethnicity: Not reported.
Further population details	1. Setting: Primary care
Extra comments	Baseline characteristics: Severe asthma % - Self management: 36; usual care - 35. Moderate asthma % - Self management: 64; usual care - 65.
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=26) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Patients assigned to the intervention were divided into four subgroups and each subgroup was scheduled for a monthly visit over a period of 6 months. On the first visit, the investigators explained the difference between relief and anti-inflammatory medications on an individual basis. Simple diary cards were given to the patients. At each follow-up visit the diary card was reviewed and discussed with the patient to stress the importance of management of the disease, and the treatment plan was readjusted according to the frequency of symptoms and the necessity of use of relief medication. The use of the metered dose inhaler (MDI) was checked and the patient retrained as necessary at each visit. Two 1-hour sessions were scheduled after the third and fourth monthly visits, in which the patients in each subgroup received information about the concept of asthma and its management. Patients were also encouraged to bring their medications to the clinic visits. Duration 6 months. Concurrent medication/care: None reported. (n=27) Intervention 2: Standard care (regular asthma review). The control followed the routine schedule of the

	Asthma Clinic, where their next follow-up appointment was determined by the attending physician according to individual patient needs. The number of visits for this group ranged from 2 to 5 and the therapy was personalised for each patient based on the ICRDMA recommendations. The control group only received instructions from the consulting physician. Regarding the use of medication and of the inhaler, they received only a verbal explanation. Duration 6 months. Concurrent medication/care: None reported.
Funding	Academic or government funding (The study was supported by: Conselho Nacional de Desenvolvimento Cientfico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-MANAGEMENT PACKAGE versus USUAL CARE Protocol outcome 1: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Hospital admissions at 6 months; Group 1: mean 0 N/A (SD 0); n=22, Group 2: mean 0.5 N/A (SD 0.8); n=20; Risk of bias: Very high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Farber 2004[383]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in USA; Setting: Primary and secondary care.
Line of therapy	Adjunctive to current care
Duration of study	Not clear: Not clearly reported.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not reported.
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 2-18 years; has State of Louisiana 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 emergency department 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).
Exclusion criteria	Not reported.
Recruitment/selection of patients	Patients were recruited sequentially from the paediatric ED of the University Hospital, Medical Center of Louisiana at New Orleans.
Age, gender and ethnicity	Age - Mean (SD): Intervention group - 7.3(4.3); control group - 7.7(4.2). Gender (M:F): Define. Ethnicity: Not reported.
Further population details	1. Setting: Secondary care
Extra comments	Baseline characteristics: Has beta-agonist medication (n): Self-management package- 23; usual care - 25.
Indirectness of population	Serious indirectness: Method of diagnosis not reported.
Interventions	(n=28) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Participants received basic asthma education; instruction on use of a metered-dose inhaler with holding chamber; a written asthma self-management plan illustrated by zones coloured green, yellow, and red; a sample age-appropriate holding chamber; and prescriptions for medication needed to implement the plan. Three brief follow-up phone calls were placed to patients in the intervention group 1-2 weeks, 4-6 weeks, and 3 months after enrolment. Return to a paediatrician or asthma specialist was suggested when asthma control was poor. Duration 3 months. Concurrent medication/care: None reported. (n=28) Intervention 2: Standard care (regular asthma review). Participants received routine care (consisting of referral back to community resources with no intervention from research staff) in the ED, hospital or both, from their treating

	physician. The asthma education provided in the ED as part of routine clinical practice was limited and brief. Follow up with their personal physician, local paediatric clinics, or both was encouraged by research staff. Duration 12 months. Concurrent medication/care: None reported.
Funding	Academic or government funding (Study was supported by a Louisiana Thoracic Society Lung Disease Research Grant and by support from the Tulane/Charity/Louisiana State University General Clinical Research Center (NIH Grant #5M01RR05096-08))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF MANAGEMENT PACKAGE versus USUAL CARE Protocol outcome 1: Hospitalisation at ≥6 months - Actual outcome for 5 to <16 years: Number of subjects with an asthma-related hospital-based event at 6 months; Group 1: 3/28, Group 2: 0/28; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Horner 2014[495]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=153)
Countries and setting	Conducted in USA; Setting: Primary care - Schools within Texas.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 5.5 weeks + 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	The parents report 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 classes (for example severe cerebral palsy, oxygen dependant conditions); speaks either English or Spanish.
Exclusion criteria	1. Improved health - the child had been symptom-free for more than 12 months; 2. family was planning on moving during the school year.
Recruitment/selection of patients	Patients selected from rural Texas communities of 1500 residents or less.
Age, gender and ethnicity	Age - Mean (SD): 8.78(1.24). Gender (M:F): Not reported. Ethnicity: Mexican American - 47%; White - 30%; African American - 22%; Other - 1%.
Further population details	1. Setting: Primary care
Extra comments	Baseline characteristics not reported.
Indirectness of population	Serious indirectness: Method of diagnosis not reported.
Interventions	(n=96) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. The intervention was designed to be delivered in 16 sequential sessions of 15 minute duration (4 hours in total), 3 days a week for 5.5 weeks, provided during the children's lunch break. Patients were given the 'Asthma Plan for Kids', a 7-step self-management plan. Session content covered the topics of recognising asthma symptoms, avoiding or reducing contact with asthma triggers, how healthy and asthmatic lungs work, how medications work, how to get help in different situations, responding to asthma symptoms, interpreting PFM scores, and talking to adults. Children practiced inhaler technique without a spacer using a placebo teaching inhaler during three of the sessions (session 7, 12, and 16). In the event a child missed a session, the instructor would keep the child after the group for a quick 5 minute intense review of the missed content. The treatment group parents received a Home Asthma Plan booklet with content related to daily care and emergency steps, and strategies for reducing contact with asthma triggers. One month after the intervention

	concluded, a home visit was made to provide individualised family education by reviewing pertinent asthma home management relevant to the child's asthma triggers and answering parents' questions. A written asthma action plan was filled in with the child's prescription and discussed with the parents. Duration 5.5 weeks. Concurrent medication/care: None reported. (n=82) Intervention 2: Standard care (regular asthma review). Details not reported. Participants were given the intervention at the end of the 12 month follow up. Duration 12 months. Concurrent medication/care: None reported.
Funding	Other (Grant received: R01NR007770)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-MANAGEMENT PACKAGE versus STANDARD CARE (REGULAR ASTHMA REVIEW)

Protocol outcome 1: Quality of life at ≥3 months
- Actual outcome for 5 to <16 years: Quality of life - Total score at 7 months ; Group 1: mean 1.74 N/A (SD 0.6); n=81, Group 2: mean 1.69 N/A (SD 0.6); n=72; Paediatric Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Quality of life - Activity limitations at 7 months ; Group 1: mean 2.04 N/A (SD 0.82); n=81, Group 2: mean 1.92 N/A (SD 0.84); n=72; Paediatric Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Quality of life - Emotional functioning at 7 months ; Group 1: mean 1.55 N/A (SD 0.71); n=81, Group 2: mean 1.48 N/A (SD 0.58); n=72; Paediatric Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Quality of life - Asthma symptoms at 7 months ; Group 1: mean 1.79 N/A (SD 0.66); n=81, Group 2: mean 1.74 N/A (SD 0.69); n=72; Paediatric Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for 5 to <16 years: Quality of life - Asthma severity at 7 months ; Group 1: mean 5.28 N/A (SD 1.42); n=81, Group 2: mean 5.25 N/A (SD 1.6); n=72; Paediatric Asthma Quality of Life 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Hospitalisation at ≥6 months
- Actual outcome for 5 to <16 years: Hospital day at 7 months ; Group 1: 5/81, Group 2: 6/72; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Khan 2014[583]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=91)
Countries and setting	Conducted in Trinidad and Tobago; Setting: Primary care
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	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 six months.
Exclusion criteria	Uncontrolled asthmatics, inability of child and/or parent to follow written directions, presence of co-morbid respiratory illness and previous enrolment in an asthma educational programme/study.
Recruitment/selection of patients	Patients recruited paediatric clinic at the Chaguanas Health Facility.
Age, gender and ethnicity	Age - Mean (SD): SM package - 5.67(2.82); usual care - 6.35(2.88). Gender (M:F): Self-management package - 24:21; usual care - 27:19. Ethnicity: Not reported.
Further population details	1. Setting: Primary care
Extra comments	Baseline characteristics: Duration of Asthma (years), mean(SD): SM package - 4.35(2.19); usual care - 4.58(2.86). Mean number of acute attacks per subject in the last six months: SM package - 2.08(1.46); usual care - 2.63(1.74).
Indirectness of population	Serious indirectness: Method of diagnosis not reported.
Interventions	(n=45) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. These participants received an individualised written asthma action plan in addition to usual care. The plan consisted of written guidelines for self-management of asthma based on the assessment of the severity of asthma symptoms or peak expiratory flow rates depicted in a traffic-light colour coded chart. Duration 6 months. Concurrent medication/care: None reported. (n=46) Intervention 2: Standard care (regular asthma review). Standard care included the issuance and explanation of asthma education material and scheduled clinic reviews. Written asthma action plans were not issued to those assigned to the control group, neither was information in the plan shared with them (verbal or written). Duration 6 months. Concurrent medication/care: Not reported.

	Comments: At the time of enrolment, all subjects were given patient and parent education consisting of written information about what happens in asthma, asthma triggers, proper use of a metred dose inhaler and spacer, and the purpose and effects of asthma therapy. Subjects older than 6 years and their parents were also trained to perform PEFR measurements. All children were on a treatment protocol receiving a moderate dose of inhaled corticosteroids with the option of using inhaled beta-2 agonist when required. This was done by the paediatrician and all subjects received the same asthma education material to take home. All patients were followed up monthly for six months (parents were contacted via telephone) and were seen at clinic on at least two subsequent occasions (two 3 monthly follow up visits).
Funding	No funding (The study was self-funded)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-MANAGEMENT PACKAGE versus USUAL CARE Protocol outcome 1: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: Mean PEFR at 6 months; Group 1: mean 85.27 % (SD 13.138); n=45, Group 2: mean 83.3 % (SD 11.154); n=46; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Milenkovic 2007[717]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and settng	Conducted in Serbia and Montenegro; Setting: Outpatient clinic (secondary care).
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis was confirmed according to national and international asthma guidelines.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were aged between 18-6; had a continuous use of inhaled corticosteroids for at least 1 year; stable phase of disease during the last 3 months.
Exclusion criteria	Patients who have a smoking history of 15 or more pack years; or had prior diagnosis of other diseases that could influence bronchial symptoms and/or lung function, were excluded.
Recruitment/selection of patients	Patients were entered into the trial in staggered intervals from September 1999 to September 2000.
Age, gender and ethnicity	Age - Mean (SD): SM program - 49.1 (14.4); usual care - 44.9 (11.7). Gender (M:F): 35/39. Ethnicity: Not reported.
Further population details	1. Setting: Secondary care
Extra comments	Baseline details: Smoking history (never/ex-/current): SM - 28/9/0; usual care - 26/11/0. Asthma duration (years), mean (SD): SM program - 10.3 (6.6); usual care - 11.2 (5.5).
Indirectness of population	Meets protocol.
Interventions	(n=40) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Patients were instructed to measure their PEF three times every morning using a peak flow meter (Vitalograph; Kansas, Birmingham, USA) provided to them. They recorded the highest reading in a diary as the morning PEF(MPEF). During the 2-week period , the patients' optimal MPEF (personal best) were measured. The individual written action plan was based on peak flow measurements. PEF values were divided into four zones with cut-off values of 80%, 60%, and 40% of personal best. Each zone required a specific therapeutic approach, including increasing inhaled corticosteroid dose or oral corticosteroids. In group A, the patients recorded daily symptom scores (based on presence of cough, expectoration, wheeze, breathing difficulties, and nocturnal awakenings) using a scale from 0 to 3, scale range: 0 = none, 3 = very severe). Patients were also asked to document if a supplement beta-2 agonist was used that day. Patients in the self-management group were carefully instructed on implementing their asthma action plan: how to compare the peak

	flow readings they obtained against the different treatment zones, how to match a given flow value and determine in which zone their value fell, and specifically how to act according to what the instructions were for that flow value. They were instructed how to record information on their asthma symptoms in a diary. Duration 1 year. Concurrent medication/care: None reported. (n=40) Intervention 2: Standard care (regular asthma review). Patients did not receive a peak flow meter. They were instructed to take reliever medication if their asthma symptoms deteriorated and to seek advice from their primary care physician regarding controller medication. During scheduled outpatient visits every 6 months, clinical state and course of treatment were evaluated by a physician as per routine clinical practice. Duration 1 year. Concurrent medication/care: None reported.
Funding	Funding not stated (Not reported)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OPTIMAL SUPPORTED SELF-MANAGEMENT (INCLUDING SELF-MANAGEMENT EDUCATION, SELF-MONITORING AND A WRITTEN PERSONALISED ASTHMA ACTION PLAN, PAAP) IN ADDITION TO STANDARD CARE versus STANDARD CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Exacerbations at 1 year; Group 1: 65/37, Group 2: 77/37; Risk of bias: High; Indirectness of outcome: Serious indirectness - Actual outcome for ≥16 years: Oral prednisolone courses at 1 year; Group 1: mean 0.3 N/A (SD 0.6); n=37, Group 2: mean 1.4 N/A (SD 1.1); n=37; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 2: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Hospitalisations at 1 year; Group 1: 1/37, Group 2: 1/37; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for ≥16 years: Lung function FEV_1 (% predicted) at 1 year; Group 1: mean 85.1 % (SD 17.2); n=37, Group 2: mean 79 % (SD 21.1); n=37; Forced expiratory volume in 1 second. 0 -100% Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Rikkers-mutsaerts 2012[912]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Netherlands; Setting: Primary and secondary care - 35 GP practices and 8 hospital clinics.
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
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.
Exclusion criteria	Patient's requiring oral steroids as maintenance; patients with relevant comorbidities.
Recruitment/selection of patients	Patients were identified via the registries of 35 practices from the Leiden University Medical Center (LUMC) general practice network and from hospital information systems of eight hospital outpatient clinics.
Age, gender and ethnicity	Age - Mean (range): SM group - 13.4(12-17); usual care - 13.8(12-17). Gender (M:F): Define. Ethnicity: Not reported.
Extra comments	Baseline details: FEV_1 (% predicted), mean(range): SM group - 88(49-151); usual care - 92(49-164).
Indirectness of population	Serious indirectness: Method of diagnosis not reported.
Interventions	(n=46) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Patients were provided with education in two ways: web-based, which included asthma information, news, frequently asked questions and interactive communication with a specialised nurse, and face-to-face group based education. Two asthma self-management education sessions were organised within 6 weeks after entering the trial. Information about asthma self-management was presented in response to participants' questions rather than in lectures. The first education session also included information on the pathophysiology of asthma, the web-based action plan, and on the inhalation technique. Patients were asked to record asthma control and FEV_1 every week for 1 year, and to report the results via the study website. They received instant feedback on their level of asthma control and advice on how to adjust their medication according to a predefined algorithm and personal treatment plan. A reminder was sent via text message if the weekly results were not reported. Patients were advised not to change their medication during the 4 weeks after their treatment had stepped up. Apart from the weekly assessments, patients could always report daily symptoms and lung function by a diary card or contract the asthma nurse, through the web or by phone. Patients attended their own physician, as they would normally do, every 3 - 6 months and extra if their asthma was

	deteriorating. Duration 1 year. Concurrent medication/care: Not reported. (n=44) Intervention 2: Standard care (regular asthma review). Patients received care by their physician according to the Dutch guidelines on asthma management in children in general practice and in hospitals. Duration 1 year. Concurrent medication/care: None reported.
Funding	Academic or government funding (Grant from the Netherlands Asthma Foundation (grant nrs. 3.4.03.157; 3.4.03.45))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF MANAGEMENT GROUP versus USUAL CARE Protocol outcome 1: Quality of life at ≥3 months - Actual outcome for 5 to <16 years: Paediatric Asthma Quality of Life at 12 months; Group 1: mean 5.93 No units. (SD 1.1); n=46, Group 2: mean 6.05 No units. (SD 1.1); n=44; Paediatric Asthma Quality of Life Questionnaire 1-7 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months - Actual outcome for 5 to <16 years: Asthma Control at 12 months; Group 1: mean 0.83 N/A (SD 0.73); n=46, Group 2: mean 0.79 N/A (SD 0.73); n=44; Asthma Control Questionnaire 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Lung function (FEV_1 %predicted or morning PEF) at ≥3 months - Actual outcome for 5 to <16 years: FEV_1 (L) at 12 months; Group 1: mean 3.08 Litres (SD 0.52); n=46, Group 2: mean 312 Litres (SD 0.52); n=44; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	**Stevens 2002[998]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in United Kingdom; Setting: Accident and emergency (A&E) department or the children's (emergency) assessment unit.

Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: Not reported.
Stratum	<5 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were included in the study if: aged between 18 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.
Exclusion criteria	Patients admitted during the weekends or when a specialist respiratory nurse was unavailable, were not included in the study.
Recruitment/selection of patients	Children were recruited over a period of 13 months and, following parental consent.
Age, gender and ethnicity	Age - Median (IQR): SM package - 32 (18-61) months; usual care - 32 (14-61) months. Gender (M:F): 65/34. Ethnicity: Not reported.
Further population details	1. Setting: Secondary care
Extra comments	N/A
Indirectness of population	Serious indirectness: Method of diagnosis not mentioned.
Interventions	(n=99) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. Children received: (1) a general education booklet about asthma in pre-school children (excluding babies); (2) a written guided self-management plan; and (3) two 20 minute structured educational sessions given on a one-to-one basis by a specialist respiratory nurse with a diploma in asthma care, to the parent(s) and child. Children recruited as inpatients received the first session on the ward on the day of discharge and returned to a special outpatient clinic 1 month later for the second session. Children recruited from A&E/CAU received their initial education session in the outpatient clinic within 2 weeks of attendance at A&E/CAU and returned 1 month later for their second visit. Those who failed to attend on any occassion were telephoned to arrange one further appointment. Patients were given a large volume spacer (Volumatic, GSK or Nebuhaler, Astra Zeneca) and metered dose inhaler (with or without facemask, depending on the age of the child). Duration 1 month. Concurrent medication/care: None reported. Comments: N/A (n=101) Intervention 2: Standard care (regular asthma review). Children assigned to the control group received usual care (a range of medical and nursing approaches used at present, according to the skills of the health professionals). Duration 12 months. Concurrent medication/care: None reported.

Funding	Academic or government funding (Funded by the NHS Executive Mother and Child Health Programme (MCH 16-15))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-MANAGEMENT PACKAGE versus STANDARD CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Hospitalisation at ≥6 months - Actual outcome for <5 years: No. of inpatient admissions at 12 months; Group 1: 26/97, Group 2: 19/91; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Thoonen 2003[1034]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=193 (Cluster randomised - GP practices))
Countries and setting	Conducted in Netherlands; Setting: Primary care.
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: GP assessed.
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Treated for asthma by the GP; aged 16-60 years; FEV >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.
Exclusion criteria	Smoking history of 15 or more pack years; serious diseases other than asthma with a low survival rate; exacerbation during the month before the start of the study; other diseases which influence bronchial symptoms and/or lung function such as heart failure, sarcoidosis; inability to inhale medication correctly or to measure and record peak flow adequately and unlikely that this can be taught.
Recruitment/selection of patients	Patients were identified by their GPS using problem list coding (ICPC).
Age, gender and ethnicity	Age - Mean (SD): Self-management - 39.6 (11.2); usual care - 39.3 (12.0). Gender (M:F): 74/119. Ethnicity: Not reported.
Further population details	1. Setting: Primary care
Extra comments	Baseline measurements: Smoking (never/former/current smokers), n: SM - 45/31/22; control - 54/21/21. FEV_1 (% predicted pre-bronchodilator), mean (SD): SM - 84.0(13.1); control - 86.9 (14.2).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=98) Intervention 1: Optimal supported self-management (including self-management education, self-monitoring and a written personalised asthma action plan, PAAP) in addition to standard care. The program started with four individual training visits of 30, 20 and 2 x 10 minutes, respectively, at the GP's surgery during a period of 3 months. These visits consisted of tailored education and instructions on how to use a personalised written self-treatment plan. Patient's weekly recorded morning and evening peak flow values and the presence of asthma symptoms. Three alarm symptoms were defined: waking at night because of asthma (yellow zone), use of bronchodilator > 4 times a day (red zone), and increased dyspnoea without exertion (purple zone). In the presence of alarm symptoms or a fall in peak

	flow values below 80%, 60%, or 40% of the personal best value, patients were instructed to start daily measurements of peak flow and symptoms. After the training visits biannual control visits were recommended over a follow up period of 21 months. At each control visit (10 minutes) GPs checked the patients' performance of the self-treatment instructions. It was left to the initiative of the GP and patient if and when these control visits took place. Training in the inhalation technique and peak flow measurement was repeated at each visit. Duration 3 months . Concurrent medication/care: None reported. Comments: Patients with a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of 80% predicted were treated with 800 µg budesonide twice daily during a 6 week run in period to obtain optimal asthma control at baseline and to enable proper assessment of the personal best peak flow of patients in the self-management group. (n=95) Intervention 2: Standard care (regular asthma review). GPs were instructed to treat all asthma patients as usual; for most GPs this was according to the guidelines of the Dutch College of Family physicians which recommend follow up visits (10 minutes) every 3 – 6 months. These national guidelines did not include self-management. At the start of the programme, one visit to the GP's surgery was scheduled to instruct patients on the use and dosage of their inhaled steroids (budesonide 200 µg Turbohaler). Duration 3 months. Concurrent medication/care: None reported. Comments: One
Funding	Study funded by industry (Project received research grants from The Netherlands Organization for Scientific Research (NWO) and ASTRAZeneca Pharmaceutica BV.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF MANAGEMENT PACKAGE versus STANDARD CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Oral prednisolone courses per patient per 2 years at 2 years; Group 1: 27/91, Group 2: 14/94; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Quality of life at ≥3 months - Actual outcome for ≥16 years: Asthma specific quality of life at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

H.7 Dose variation within self-management plans

Study	Fitzgerald 2004[392]
Study type	RCT (Patient randomised; Crossover)
Number of studies (number of participants)	1 (n=290)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >12, documented diagnosis of asthma in previous year; >12% reversibility in FEV_1 post bronchodilator, 20% diurnal variability in PEF, on stable dose of ICS (<1200 ug bdp) for one month before trial.
Exclusion criteria	Exacerbation in the previous month, history of near fatal asthma, hospitalisation due to asthma in previous 3 months, regular use of OCS.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 32.2 (13.2). Gender (M:F): 27/71. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Increasing ICS dose - Doubling dose. Second active inhaler taken in response to PEF changes, increased bronchodilator use, or nocturnal awakenings – dose doubled for 14 days. Duration 14 days. Concurrent medication/care: Maintenance dose of 100, 200, or 400 ug bdp or equivalent (n=52) Intervention 2: No increase in ICS dose/addition of placebo - Standard care (regular asthma review). In response to exacerbation – addition of placebo inhaler to baseline ICS. Duration 14 days. Concurrent medication/care: Maintenance dose of 100, 200, or 400 ug bdp or equivalent
Funding	Study funded by industry (AstraZeneca Canada)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOUBLING DOSE versus STANDARD CARE (REGULAR ASTHMA REVIEW)	

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Treatment failure (requiring OCS) at 14 days; Group 1: 12/46, Group 2: 9/52; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Treatment failure (unscheduled visit, persistently low PEF/raised symptom score) at 14 days; Group 1: 7/46, Group 2: 12/52; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: Exacerbation (following treatment success) at 3 months; Group 1: 5/34, Group 2: 6/35; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Treatment failure at Defined by study; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Foresi 2000[400]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=142)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Documented history of asthma, taking ICS (500 - 1000ug bdp) for at least 4 weeks before trial, aged 18-65, baseline FEV_1 >50 and <90% of predicted, PEF variability of >20% on 4 different days during 2-week run-in period, daily requirement on B-agonist, presence of wheeze, cough, chest tightness,
Exclusion criteria	OCS 1 month before trial, treated with high dose ICS (>1000ug bdp), seasonal asthma.
Recruitment/selection of patients	Recruited from 14 outpatient clinics
Age, gender and ethnicity	Age - Mean (SD): 39.5 (14.5). Gender (M:F): 68/74. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Increasing ICS dose - Quintupling dose. Budesonide 100 ug bid plus a course of budesonide 200 qid in case of an exacerbation (for 7 days). Duration 7 days. Concurrent medication/care: Oral prednisolone taken 3-10 days if PEF remained low for 2 consecutive days following 7-day treatment phase. (n=24) Intervention 2: No increase in ICS dose/addition of placebo - Standard care (regular asthma review). Budesonide 100 ug bid plus a course of placebo in case of an exacerbation (for 7 days). Duration 7 days. Concurrent medication/care: Oral prednisolone taken 3-10 days if PEF remained low for 2 consecutive days following 7-day treatment phase.
Funding	Study funded by industry (Astra Farmaceutici)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Quintupling DOSE versus STANDARD CARE (REGULAR ASTHMA REVIEW)	

Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe exacerbation (requiring OCS) at 7 days; Group 1: 5/12, Group 2: 7/24; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Treatment failure at Defined by study; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Harrison 2004[477]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=390)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 16+, clinical diagnosis of asthma, taking ICS (100 - 2000 ug/day) on regular basis, taken OCS or doubled ICS temporarily in previous 12 months to treat or prevent exacerbation.
Exclusion criteria	Smoking history of 10 pack-years, unstable asthma during 2-week run in period.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 49(13). Gender (M:F): 292/98. Ethnicity: Not reported
Indirectness of population	Serious indirectness: No objective diagnosis
Interventions	(n=110) Intervention 1: Increasing ICS dose - Doubling dose. Study inhaler (active) taken for 14 days in addition to usual treatment in response to PEF dropping by 15% or symptom score increased by 1 point - dose doubled for 14 days. Duration 14 days. Concurrent medication/care: Continued usual maintenance dose throughout study (n=97) Intervention 2: No increase in ICS dose/addition of placebo - Standard care (regular asthma review). Study inhaler (placebo) taken for 14 days in addition to usual treatment in response to PEF dropping by 15% or symptom score increased by 1 point. Duration 14 days. Concurrent medication/care: Continued usual maintenance dose throughout study
Funding	Academic or government funding (NHS executive)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOUBLING DOSE versus STANDARD CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months	

- Actual outcome for ≥16 years: Severe exacerbations (requiring OCS) at 14 days; Group 1: 19/110, Group 2: 22/97; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Treatment failure at Defined by study; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Rice-mcdonald 2005[906]
Study type	RCT (Patient randomised; Crossover)
Number of studies (number of participants)	(n=22)
Countries and setting	Conducted in Australia
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 3-15 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged ≥18, physician diagnosed asthma, reversible airway obstruction evidenced by ≥15% reversibility of FEV_1
Exclusion criteria	Mild asthma (exacerbation <80% unlikely), erroneous or falsified PEF recordings during run-in, asthma requiring continuous OCS
Age, gender and ethnicity	Age - Mean (range): 46.5 (32-64). Gender (M:F): 9/13. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Increasing ICS dose - Doubling dose. Doubling daily ICS dose; while continuing usual ICS dose at the same number of inhalations, plus placebo OCS - in response to nocturnal awakenings on 2/3 nights, SABA use 4 occasions in 24 hours more than run-in, symptoms necessitating cessation of usual activities of daily living, or PEF decrease below 80% of run-in. daily ICS dose for 14 days. Duration 14 days. Concurrent medication/care: As required rescue SABA (n=18) Intervention 2: No increase in ICS dose/addition of placebo - Standard care (regular asthma review). Placebo arm; continuing usual ICS dose at the same number of inhalations with a placebo inhaler, plus placebo OCS - in response to nocturnal awakenings on 2/3 nights, SABA use 4 occasions in 24hrs more than run-in, symptoms necessitating cessation of usual activities of daily living, or PEF decrease below 80% of run-in. daily ICS dose for 14 days. Duration 14 days. Concurrent medication/care: As required rescue SABA
Funding	Academic or government funding (Asthma Foundation of Queensland)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOUBLING DOSE versus STANDARD CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Treatment failure at Defined by study - Actual outcome for ≥16 years: symptoms fail to improve/PEF remains low/participant withdrawing due to uncontrolled symptoms or adverse events at 14 days; Group 1: 11/18, Group 2: 11/18; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbations (requiring OCS) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Oborne 2009[787]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=403)
Countries and setting	Conducted in United Kingdom
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Taking maintenance dose of ICS 200-1000 bdp or equivalent per day, have temporarily increased their dose of ICS or taken course of OCS within previous 12 months in response to worsening symptoms but not in the preceding 4 weeks, lowest morning PEF >90% of mean morning PEF during run-in period.
Exclusion criteria	Taking maintenance dose of OCS, clinically significant medical conditions, smoked for >20 pack-years.
Recruitment/selection of patients	Volunteer database and GP lists
Age, gender and ethnicity	Age - Mean (SD): 54 (14). Gender (M:F): 130/117. Ethnicity: Not reported
Indirectness of population	Serious indirectness: No objective diagnosis of asthma
Interventions	(n=56) Intervention 1: Increasing ICS dose - Quadrupling dose. Individualised asthma management plan. In response to morning PEF decreasing >15% on 2 consecutive days, 30% on 1 day from mean run-in morning PEF, ICS dose quadrupled for 7 days, continued for additional 7 days if no return to baseline PEF. Duration 1-2 week. Concurrent medication/care: Oral prednisolone 30mg if deterioration to point where participants would normally commence OCS treatment (n=38) Intervention 2: No increase in ICS dose/addition of placebo - Standard care (regular asthma review). In response to PEF changes, addition of placebo inhaler to baseline ICS. Duration 1-2 weeks. Concurrent medication/care: Oral prednisolone 30mg if deterioration to the point where participants would normally commence OCS treatment
Funding	Study funded by industry (Astra Zeneca, chiesi, GSK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: QUADRUPLING DOSE versus STANDARD CARE (REGULAR ASTHMA REVIEW) Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Severe asthma exacerbations (requiring OCS) at 1-2 weeks; Group 1: 12/56, Group 2: 19/38; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Treatment failure at Defined by study; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Study	Yousef 2012[1131]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=197)
Countries and setting	Conducted in USA; Setting: Tertiary care centre
Line of therapy	Mixed line
Duration of study	Not clear: Enrolled between Jan 2005 and Dec 2008
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	5 to <16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 2-17 years, clinical diagnosis of asthma, on ICS for at least 3 months, recurrent episodes of wheeze, cough, breathlessness, and chest tightness that were at least partially reversible with treatment of short-acting B2-agonist. Confirmed with a history of spirometry in children >5years. Asthma exacerbation in previous 12 months treated with OCS or increased ICS.
Exclusion criteria	Chronically unstable asthma, chronic lung conditions.
Age, gender and ethnicity	Age - Mean (SD): 5.83(3.42). Gender (M:F): 55/27. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Increasing ICS dose - Doubling dose. Participants instructed to contact investigators by telephone upon PEF change to 50-80% of best value, or persistent cough/wheeze unresolved by SABA; dose doubled for 12 days. Duration 12 days. Concurrent medication/care: SABA taken as needed (n=30) Intervention 2: Increasing ICS dose - Quadrupling dose. Participants instructed to contact investigators by telephone upon PEF change to 50-80% of best value, or persistent cough/wheeze unresolved by SABA; dose quadrupled for 12 days. Duration 12 days. Concurrent medication/care: SABA taken as needed (n=28) Intervention 3: Increasing ICS dose - Octupling dose. Participants instructed to contact investigators by telephone upon PEF change to 50-80% of best value, or persistent cough/wheeze unresolved by SABA; dose octupled for 12 days. Duration 12 days. Concurrent medication/care: SABA taken as needed
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOUBLING DOSE versus QUADRUPLING DOSE Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for 5 to <16 years: Required systemic corticosteroid at 12 days; Group 1: 2/24, Group 2: 2/28; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOUBLING DOSE versus OCTUPLING DOSE Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for 5 to <16 years: Required systemic corticosteroid at 12 days; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: QUADRUPLING DOSE versus OCTUPLING DOSE Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for 5 to <16 years: Required systemic corticosteroid at 12 days; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Treatment failure at Defined by study; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; Hospitalisation at ≥6 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

H.8 Decreasing regular maintenance treatment

Study	**Koskela 2016[590]**
Study type	Prospective cohort study. Sensitivity, specificity, NPV, PPV used to examine predictive value of ACQ in anticipating asthma exacerbation.
Number of participants	n=55
Country and setting	Finland

Study	Koskela 2016[590]
Funding	Kuopio University Hospital, Kuopion Hengityssaatio Foundation, Waino ja Laina Kivi Foundation.
Duration of study	6 week follow-up, following each step down.
Age, gender, ethnicity	Median age: 58.8 years Gender (m:f): 18:37
Patient characteristics	Subjects with well controlled asthma; defined as no courses of oral corticosteroids or hospital admissions due to asthma within one year of trial. People with a physician's diagnosis of asthma, with one of: at least 15% fall in FEV_1 after exercise challenge, at least 12% improvement in FEV_1 or FVC after bronchodilating drug, at least moderate degree of bronchodilatory hyperresponsiveness to metacholine or histamine, at least 20% diurnal variation in PEF on at least 3 days, at least 15% improvement in PEF after bronchodilating drug.
Index test	ACQ-6 - <0.15 ACQ-7 - <0.29
Target condition	Asthma control

Study	Koskela 2016[590]
Results:	ACQ-6 - <0.15 Sensitivity: 72% Specificity: 47% PPV: 29% NPV: 85% ACQ-7 - <0.29 Sensitivity: 69% Specificity: 54% PPV: 31% NPV: 85%
General limitations	Cut off point for tests selected retrospectively from ROC curves, exacerbation considered to have occurred if the subject felt his/her symptoms had clearly increased (subjective outcome).

Study	Li 2008[627]
Study type	Prospective cohort study. Receiver operating characteristic (ROC) curves were used to examine which marker best predicted as asthma exacerbation.
Number of participants	n=50
Country and setting	Not reported
Funding	Not reported
Duration of study	8 week follow-up, following each step down.
Age, gender, ethnicity	Median age: 11.8 years Gender (m:f): 30:20

Study	Li 2008[627]
	Ethnicity: Asian
Patient characteristics	Children aged 6-18 with stable asthma, who had been using only ICS for at least 3 months preceding the study were included. Stable asthma defined as those with no disease exacerbations in the preceding 4 weeks necessitating oral corticosteroid or an increase in the dosage of ICS; and use of rescue treatment less than three times a week. Those with the presence of concomitant chronic airway diseases such as bronchiectasis; use of any over-the-counter medication that could affect the course of asthma or its treatment; and involvement with any other asthma treatment trial were excluded. Children who attended a paediatric chest outpatient clinic were recruited for the study.
Index test	FeNO ROC curve: AUC Thresholds recorded - >82ppb - >108ppb - >137ppb
Target condition	Asthma control

Study	Li 2008[627]
Results:	AUC (95% CI): 0.81 (0.69-0.91), *P* = 0.002 >82ppb Sensitivity: ~75% Specificity: ~62% >108ppb Sensitivity: ~66% Specificity: ~71% >137ppb Sensitivity: ~55% Specificity: ~86% *sensitivity/specificity values read across from a graph
General limitations	Lack of physicians objective diagnosis of asthma

Study	Rank 2015[885]
Study type	Retrospective cohort study. Outcome data used to calculate risk prediction.
Number of participants	n=26,292
Country and setting	US claims database
Funding	Mayo Foundation for Medical Education and Research
Duration of study	Records between 2000 and 2012 analysed; ≥3 years follow up
Age, gender, ethnicity	Age (n): ≥65 years (1178); 18-64 years (19335); 5-17 years (4682); 0-4 years (1097)

Study	Rank 2015[885]
	Gender (m:f): 11797:14493 Race (n): White (18344); Black (2016); other (2303); unknown (3629)
Patient characteristics	Patients with continuous medical and pharmacy coverage for ≥3 years between 2000 and 2012, with a step-down of asthma medication (coverage overseeing one year before and two years following the step down) were included. Patients without controller medication claim, or with inconsistent medication filling patterns were excluded from the study. Study data was collected using Optum Labs Data Warehouse (OLDW), a longitudinal healthcare database containing de-identified data from >100million individuals enrolled in health insurance or Medicare Advantage plans.
Index test	Duration of asthma control - 0-3 months - 4-7 months - 8-11 months - ≥ 12 months
Target condition	Asthma control
Results:	>3 months Sensitivity: 31.35% (31-32) Specificity: 84.84% (84-86) >7 months Sensitivity: 47.67% (47-48) Specificity: 70.12% (69-72) >11 months Sensitivity: 58.71% (58-59) Specificity: 59.33% (58-61)
General limitations	Unclear whether the decision to step-down was made in consultation with a healthcare provider.

Study	Rank 2015[885]
	Lack of physicians objective diagnosis of asthma

Study	Zacharasiewicz 2005[1134]
Study type	Prospective cohort study. Receiver operating characteristic (ROC) curves and risk prediction (sensitivity/specificity, PPV/NPV) were used to examine FeNO as a guide for step down failure.
Number of participants	n=40
Country and setting	UK
Funding	Scholarship from the Gesellschaft
Duration of study	8 week follow-up, following each step down.
Age, gender, ethnicity	Median age: 12 years Gender (m:f): NA Ethnicity: NA
Patient characteristics	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.
Index test	FeNO ROC curve: AUC Thresholds recorded - >22ppb - >32ppb
Target condition	Asthma control

Study	Zacharasiewicz 2005[1134]
Results:	AUC (95% CI): 0.74 (0.61-0.87) >22ppb Sensitivity: 78.6% Specificity: 68.6% PPV: 44 NPV: 92.5 >32ppb Sensitivity: 71.4% Specificity: 68.6% PPV: 52.6 NPV: 91.3
General limitations	Potential attrition bias – participants opted out or chose to stop reduction after step-down while others initiated further step down.

H.9 Breathing exercises in addition to pharmacological treatment

Study	Agnihotri 2016[14]12
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=276)
Countries and setting	Conducted in India; Setting: Tertiary teaching hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: reversible airflow limitation of >12%
Stratum	≥16 years

Study	Agnihotri 2016[14]12
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-60, non-smokers or ex-smokers, mild to moderate persistent asthma, reversible airflow limitation of >12% and >200ml FEV1 to post-bronchodilator FEV1.
Exclusion criteria	Severe airflow limitation, pregnant, chronic respiratory disease
Recruitment/selection of patients	Recruited from outpatient clinics
Age, gender and ethnicity	Age - Other: Possible age range 12-60. Gender (M:F): NA. Ethnicity: Not reported
Further population details	1. Dysfunctional breathing: Not applicable / Not stated / Unclear 2. Obesity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=138) Intervention 1: Breathing exercises or retraining - Yoga. Yoga intervention (asanas, pranayama, and meditation) for 30 minutes per day, 5 days a week. Duration 6 months. Concurrent medication/care: Usual care (n=138) Intervention 2: Control group - Usual care. Usual care. Duration 6 months. Concurrent medication/care: NA
Funding	Academic or government funding (Indian Council of Medical Research)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: YOGA versus USUAL CARE Protocol outcome 1: Lung function (change in FEV1; PEF variability) at ≥6 months - Actual outcome for ≥16 years: FEV1 (% of predicted) at 6 months; Group 1: mean 78.39 % of predicted value (SD 4.55); n=121, Group 2: mean 65.18 % of predicted value (SD 3.64); n=120; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for ≥16 years: PEF (% of predicted) at 6 months; Group 1: mean 75.62 % of predicted value (SD 4.71); n=121, Group 2: mean 65.08 % of predicted value (SD 5.21); n=120; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Quality of life at ≥6 months; Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥6 months; Adverse events at ≥6 months

Study	Grammatopoulou 2011 [449]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Greece; Setting: Outpatient at asthma department, general hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: States diagnosed stable asthma but unclear if diagnosis confirmed with objective test
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants diagnosed with stable asthma, mild to moderate, under the same specialist's care
Exclusion criteria	60 years of age or over; smokers; using oral corticosteroids in the previous 3 months; suffered from heart failure; participated in a prior asthma education program.
Recruitment/selection of patients	Invitations to participate in a study of breathing retraining were sent to outpatients who attended the asthma department
Age, gender and ethnicity	Age - Mean (SD): Intervention: 48.15 (14.63). Control: 45.45 (12.67). Gender (M:F): 23/17. Ethnicity: Not stated
Further population details	1. Dysfunctional breathing: 19/40 (52.5%) participants had the “hyperventilation syndrome” (Nijmegen questionnaire score ≥23) 2. Obesity: Not stated
Indirectness of population	Serious indirectness: Unclear if participants diagnosis confirmed with objective test
Interventions	(n=20) Intervention 1: Breathing exercises or retraining - Other intervention that manipulates breathing pattern. Intervention group: breathing retaining sessions. Both groups were under the same specialist’s care, with regular follow-up visits and suggested to continue receiving regular asthma medication. In the case of asthma medicine modification, participants of both groups were withdrawn from the study. Duration 6 months. Concurrent medication/care: Phase one: (A) a 60-minute, small group session (five patients/group) structured according to the health belief model. During this session, patients were educated in (1) the “normal” breathing pattern as well as for the pattern during exacerbations, (2) recognising asthma symptoms, and (3) the comprehension of their ability to modify their breathing pattern targeting the self-management of the symptoms and expressed their perceived severity of asthma and the benefits and barriers of adapting a modified breathing patterns for a 6-month period. (B) 12 individual sessions (three/week) of nearly 1 hour duration each, comprised education and practice of: (1) diaphragmatic breathing, (2) nasal breathing, (3) short hold breath (2-3 seconds), and (4) adaption of the speech

	pattern (speaking, singing) in any position, during physical activity, and in asthma exacerbation. Phase two: the specific action plan included instructions regarding the duration (20 minutes at least) and frequency (2-3 times/day) of training at home for the remaining 5 months as well as for the adaption of the breathing behaviour in leisure-time physical activities (for example at home, when climbing stairs, carrying weights, at their respective free time, when walking, swimming, etc., throughout the day). (n=20) Intervention 2: Control group - Usual care. Both groups were under the same specialist's care, with regular follow-up visits and suggested to continue receiving regular asthma medication. The control group did not receive any additional treatment. In the case of asthma medicine modification, participants of both groups were withdrawn from the study. Duration 6 months. Concurrent medication/care: No other information provided
Funding	Study funded by industry (GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER INTERVENTION THAT MANIPULATES BREATHING PATTERN versus USUAL CARE

Protocol outcome 1: Quality of life at ≥6 months
- Actual outcome for ≥16 years: Quality of life: SF-36 physical component, final score at 6 months; Group 1: mean 52.3 (SD 5.4); n=20, Group 2: mean 48.79 (SD 6.31); n=20; SF-36 physical component 0-100 Top=High is good outcome; Risk of bias: high; Indirectness of outcome: Serious indirectness
- Actual outcome for ≥16 years: Quality of life: SF-36 mental component, final score at 6 months; Group 1: mean 46.52 (SD 12.24); n=20, Group 2: mean 48.04 (SD 6.25); n=20; SF-36 mental component 0-100 Top=High is good outcome; Risk of bias: high; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥6 months
- Actual outcome for ≥16 years: Asthma control: ACT, final score at 6 months; Group 1: mean 22 (SD 3.37); n=20, Group 2: mean 20.3 (SD 2.99); n=20; ACQ 5-25 Top=High is good outcome; Risk of bias: high; Indirectness of outcome: Serious indirectness

Protocol outcome 3: Lung function (change in FEV_1; PEF variability) at ≥6 months
- Actual outcome for ≥16 years: Lung function: FEV_1 % predicted, final score at 6 months; Group 1: mean 86.25 (SD 8.21); n=20, Group 2: mean 84.55 (SD 10.66); n=20; Risk of bias: high; Indirectness of outcome: Serious indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥6 months; Adverse events at ≥6 months

Study	Holloway 2007 [489]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in United Kingdom; Setting: Semi-rural GP practice in Welwyn, Hertfordshire England
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 8 intervention sessions and follow-up at 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants enrolled on the GP practice asthma register
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants included in the study had to be: aged 16-70 years; able to understand, read and write English; with a commitment to participant for possibly eight attendances; willing to give written informed consent and with no serious co-morbidity.
Exclusion criteria	None stated
Recruitment/selection of patients	All patients on the asthma register were initially approached to complete a postal survey about their condition. Those that responded were invited to attend a physiotherapy-orientated asthma assessment. Of those that attended, 85 met the criteria for the trial.
Age, gender and ethnicity	Age - Mean (SD): Intervention: 50.2 (14.0); Control 49.3 (14.2). Gender (M:F): 36/49. Ethnicity: Not stated
Further population details	1. Dysfunctional breathing: Not stated 2. Obesity: Not stated
Indirectness of population	Serious indirectness: Unclear if participants received objective test to confirm diagnosis
Interventions	(n=39) Intervention 1: Breathing exercises or retraining - Papworth method. Participants received 5x 60 minute individual treatments with the Papworth method (PM) from a respiratory physiotherapist. Duration 12 months. Concurrent medication/care: PM integrates five components, the principal one being specific breathing training. (1) Breathing training, including teaching of appropriate minute and tidal volume and the development of a pattern of breathing suitable to current metabolic activity. Elimination of dysfunctional breathing, including hyperinflation and hyperventilation patterns is discussed. A specific Papworth method diaphragmatic breathing technique is taught to replace the use of inappropriate accessory muscles of respiration. Emphasis, when relaxed, is placed on calm slow nasal expiration. Patients are encouraged to “nose-breathe” rather than “mouth-breathe” and eradication or reduction of habits such as yawning, sighing, etc. is taught and practiced. (2) Education, with the emphasis on the recognition and physical management of stress response and specifically the integration with breathing patterns. (3) Relaxation training, specific and general. (4) Integration of “appropriate” breathing and relaxation techniques into daily living activities. Initially the techniques are taught in a semi-recumbent position progressing to sitting, then

	standing and during daily living activities. Finally, the integration of breathing and relaxation techniques into speech is taught and practiced. (5) Home exercises with an audiotape or CD containing reminders of the breathing and relaxation techniques are supplied at the third treatment. Encouragement is given to practice at least once a day with the tape. Both groups continued to receive usual asthma care including medication and routine asthma education from a practice nurse. The usual care did not include advice about breathing exercises. (n=46) Intervention 2: Control group - Usual care. The control group received no additional treatment. Duration 12 months. Concurrent medication/care: Both groups continued to receive usual asthma care including medication and routine asthma education from a practice nurse. The usual care did not include advice about breathing exercises.
Funding	Other (Study was not sponsored but was undertaken as part fulfilment of a PhD degree at University College London, part funded by Cancer Research UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PAPWORTH METHOD versus USUAL CARE

Protocol outcome 1: Quality of life at ≥6 months
- Actual outcome for ≥16 years: Quality of life: St George's Respiratory Questionnaire (SGRQ) symptoms at 6 months; Group 1: mean 21.8 0-100 (SD 18.1); n=33, Group 2: mean 32.8 0-100 (SD 20.1); n=45; St George's Reparatory Questionnaire 0-100 Top=High is poor outcome; Risk of bias: very high; Indirectness of outcome: Serious indirectness
- Actual outcome for ≥16 years: Quality of life: St George's Respiratory Questionnaire (SGRQ) symptoms at 12 months; Group 1: mean 15.2 (SD 10.9); n=32, Group 2: mean 16.7 (SD 11.6); n=40; St George's Respiratory Questionnaire 0.100 Top=High is poor outcome; Risk of bias: very high; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Lung function (change in FEV_1; PEF variability) at ≥6 months
- Actual outcome for ≥16 years: Lung function - FEV_1 (l) (final score) at 6 months; Group 1: mean 2.9 (SD 0.8); n=32, Group 2: mean 2.8 (SD 0.9); n=41; Risk of bias: very high; Indirectness of outcome: Serious indirectness
- Actual outcome for ≥16 years: Lung function - FEV_1 (l) (final score) at 12 months; Group 1: mean 2.8 (SD 0.7); n=30, Group 2: mean 2.7 (SD 0.8); n=37; Risk of bias: very high; Indirectness of outcome: Serious indirectness

Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥6 months; Adverse events at ≥6 months

Study	Thomas 2003 [1032]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=33)
Countries and setting	Conducted in United Kingdom; Setting: Single semi-rural UK general practice of 7033 patients
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 2 week intervention & 6 month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 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; identified from medical records of general practice
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 17-65 years, 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; identified from medical records of general practice
Exclusion criteria	Not stated
Recruitment/selection of patients	All patients fulfilling the inclusion criteria were sent the Nijmegen questionnaire, a score of 23 or more suggests a diagnosis of dysfunctional breathing. All those with such score were invited to enter the RCT.
Age, gender and ethnicity	Age - Mean (SD): Intervention: 48.8 (10.9); Control: 48.9 (15.6). Gender (M:F): 7/26. Ethnicity: Not stated.
Further population details	1. Dysfunctional breathing: Not stated 2. Obesity: Not stated
Indirectness of population	Serious indirectness: Unclear if participants had objective test to confirm diagnosis
Interventions	(n=17) Intervention 1: Breathing exercises or retraining - Other intervention that manipulates breathing pattern. Breathing retraining with a physiotherapist. The physiotherapist saw patients initially in groups of 4-5 for a small group session for 45 minutes with individual 15 minute sessions 1 and 2 weeks later (total contact time 75 minutes). Duration 6 months. Concurrent medication/care: In these sessions, participants were informed that several symptoms including breathlessness can be produced by over-breathing or by abnormal breathing such as non-diaphragmatic breathing, and taught diaphragmatic breathing exercises using an established physiotherapy methodology emphasising slow regular breathing and the dominant use of diaphragmatic respiratory effort. Participants were encouraged to practice slow breathing for short (for example 10 minute) periods each day. (n=16) Intervention 2: Control group - Asthma education only (if education also given to intervention arm). Asthma education with an asthma nurse. Duration 6 months. Concurrent medication/care: The control group had a 60 minute

	small group session with the practice asthma nurses at which education on asthma was provided. They were also invited to attend for an individual asthma review with a nurse or doctor although only six of the 16 patients took up this offer.
Funding	Academic or government funding (Royal College of General Practitioners Scientific Foundation Board)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER INTERVENTION THAT MANIPULATES BREATHING PATTERN versus ASTHMA EDUCATION ONLY (IF EDUCATION ALSO GIVEN TO INTERVENTION ARM) Protocol outcome 1: Quality of life at ≥6 months - Actual outcome for ≥16years: Quality of life: AQLQ (median, interquartile (change score) at 6 months; Risk of bias: high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥6 months; Lung function (change in FEV_1; PEF variability) at ≥6 months; Adverse events at ≥6 months

Study (subsidiary papers)	Thomas 2009 (Thomas 2009) [1033]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=183)
Countries and setting	Conducted in United Kingdom; Setting: 10 UK primary care general practices in Leicester UK
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 4 weeks intervention & 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients treated for asthma in 10 UK primary care general practices
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients treated for asthma in 10 UK primary care general practices and having moderate impairment of asthma related health status (Asthma Quality of Life Questionnaire score <5.5)
Exclusion criteria	None stated
Recruitment/selection of patients	Invitations were sent to all adult patients with asthma in the participating centres
Age, gender and ethnicity	Age - Mean (range): Intervention: 46.0 (33.0-57.3). Control: 46.0 (35.0-57.0). Gender (M:F): 71/112. Ethnicity: Not stated
Further population details	1. Dysfunctional breathing: Not stated 2. Obesity: Not stated
Indirectness of population	Serious indirectness: Unclear if participants given objective test to confirm diagnosis
Interventions	(n=94) Intervention 1: Breathing exercises or retraining - Other intervention that manipulates breathing pattern. Three sessions of physiotherapist-direct breathing exercises. Duration 6 months. Concurrent medication/care: Study attendances for both groups consisted of three sessions, an initial 60 minute small group session (2-4 participants) followed by two individual sessions of 30-45 minutes with 2-4 weeks between attendances. In the BT group, explanation of normal breathing and possible effects of abnormal “dysfunctional breathing” such as over-breathing, mouth breathing and upper chest breathing was provided. In individual sessions, participants were taught appropriate regular diaphragmatic and nasal breathing techniques (similar to the Papworth method) and encouraged to practice these exercises for at least 10 minutes each day. (n=89) Intervention 2: Control group - Asthma education only (if education also given to intervention arm). Three sessions of nurse-provided asthma education. Duration 6 months. Concurrent medication/care: Study attendances for both groups consisted of three sessions, an initial 60 minute small group session (2-4 participants) followed by two individual sessions of 30-45 minutes with 2-4 weeks between attendances. Control participants had similar sessions, but with a health professional (asthma nurse) delivering asthma education. This intervention comprised information

	on the nature of asthma followed by individual sessions, presenting broad asthma and atopy concepts and explaining treatment rationale without providing personalised asthma advice.
Funding	Academic or government funding (Study funded by a grant from Asthma UK)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER INTERVENTION THAT MANIPULATES BREATHING PATTERN versus ASTHMA EDUCATION ONLY (IF EDUCATION ALSO GIVEN TO INTERVENTION ARM) Protocol outcome 1: Quality of life at ≥6 months - Actual outcome for ≥16 years: Quality of life: AQLQ, between-group difference (change score) at 6 months; Mean 0.38 (95%CI 0.08 to 0.68) (p value 0.01) AQLQ 32-224 Top=High is good outcome; Risk of bias: very high; Indirectness of outcome: No indirectness Protocol outcome 2: Asthma control (validated questionnaire for example ACT, ACQ, SGRQ) at ≥6 months - Actual outcome for ≥16 years: Asthma control: ACQ, between-group difference (change score) at 6 months; Mean -0.17 (95%CI 0.38 to 0.04) (p value 0.12) ACT 0-42 Top=High is poor outcome; Risk of bias: very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Severe asthma exacerbation (requiring OCS, hospital admission and/or ED visit) at ≥6 months; Mortality at ≥6 months; Hospitalisation at ≥6 months; SABA use at ≥6 months; Lung function (change in FEV_1; PEF variability) at ≥6 months; Adverse events at ≥6 months

H.10 Managing patients in relation to risk of poor outcomes

Study	Smith 2012[973]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=911)
Countries and setting	Conducted in United Kingdom; Setting: Primary care practices in Norfolk, UK.
Line of therapy	Mixed line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	≥16 years
Subgroup analysis within study	Not applicable
Inclusion criteria	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; or asthma admission in the last 5 years or A&E visit in last year or Brittle asthma.
Exclusion criteria	Not reported
Recruitment/selection of patients	Survey sent to GP practices. Clinicians at practices identified at-risk patients.
Age, gender and ethnicity	Age - Mean (SD): 45.5 (21.9). Gender (M:F): 353/558. Ethnicity: NA
Indirectness of population	Serious indirectness: lack of objective measurement in asthma diagnosis.
Interventions	(n=457) Intervention 1: Risk stratified care. 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 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 using case examples to highlight potential actions for receptionists, clinicians and dispensary teams. Alerts were activated once dissemination was complete. Duration 1 year. Concurrent medication/care: NA (n=454) Intervention 2: Standard care. 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. Duration 1 year. Concurrent medication/care: NA

Funding	Study funded by industry (Asthma UK)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISK STRATIFIED CARE versus STANDARD CARE Protocol outcome 1: Severe asthma exacerbations (requiring OCS) at ≥6 months - Actual outcome for ≥16 years: Oral prednisolone course for asthma exacerbation at 1 year; OR 1.28 (95%CI 0.95 to 1.73) (p value 0.112); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Hospitalisation at ≥6 months - Actual outcome for ≥16 years: Hospitalisation for asthma exacerbation at 1 year; OR 0.51 (95%CI 0.26 to 1) (p value 0.051); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: SABA use at ≥3 months - Actual outcome for ≥16 years: Rate of SABA inhalers prescribed at 1 year; OR 1.03 (95%CI 0.91 to 1.17) (p value 0.6); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at ≥6 months; Quality of life at ≥3 months; Asthma control (validated questionnaire: ACT, ACQ, SGRQ) at ≥3 months; SABA use at ≥3 months; Lung function (FEV_1 %predicted or morning PEF) at ≥3 months; Adverse events: linear growth at ≥1 year; Adverse events: infection at ≥3 months; Adverse events: adrenal insufficiency at ≥3 months; Adverse events: infection (serious infections) at ≥3 months

Appendix I: Health economic evidence tables

I.1 Treatment in patients not on regular preventers

None.

I.2 Choice of first-line preventer in patients with poor asthma control

Study	**Price 2011** [861]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Analysis of individual level EQ-5D and resource use, with unit costs applied **Perspective:** UK NHS **Time horizon:** 2 years **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	**Population:** Patient with diagnosed asthma not receiving steroids in the previous 12 weeks **Cohort settings:** Start age: 44.74 Male: 49.7% **Intervention 1 (n=158) (% of patients):** ICS beclometasone dipropionate (93%), budesonide (5%) or fluticasone propionate (2%) **Intervention 2 (n=148) (% of**	**Total NHS costs (mean per patient):** Intervention 1: £332 Intervention 2: £573 Incremental (2−1): £242 (95% CI: £100 to £384; p=NR) **Total NHS and societal costs** (mean per patient): Intervention 1: £372 Intervention 2: £666 Incremental (2−1): £294 (95% CI: £107 to £481; p=NR) **Currency & cost year:** 2005 UK pounds **Cost components**	**QALYs (mean per patient):** Intervention 1: 1.722 Intervention 2: 1.569 Incremental (2−1): -0.153 (95% CI: -0.274 to -0.032; p=NR) Adjusted incremental[(a)]: -0.05 (95% CI: -0.126 to 0.026; p=NR) **MiniAQLQ (mean per patient):** Intervention 1: 5.63 Intervention 2: 5.52 Incremental (2−1): -0.1 (95% CI: -0.35 to 0.17; p=NR) Adjusted incremental[(a)]: -0.11	**ICER (Intervention 2 versus Intervention 1):** ICS dominates leukotriene receptor antagonist

	patients): Leukotriene receptor antagonist montelukast 10 mg, once daily (89%) or zafirlukast 20 mg, twice daily (11%)	**incorporated:** Prescribed medication and devices, primary and secondary care activity, over the counter medications, lost productivity	(95% CI: -0.35 to 0.13; p=NR)	
Data sources				
Health outcomes: Within study participant completed questionnaires at baseline and each study visit over 2 years. **Quality-of-life weights:** Within-RCT analysis: EQ-5D UK tariff. **Cost sources:** Resource use from primary care practice databases using MIQUEST (www.connectingforhealth.nhs.uk/miquest), APOLLO SQL SUITE (www.apollo-medical.com/products/sql.htm) and manual extraction from practices. Unit costs from NHS reference costs, PSSRU and ePACT.				
Comments				
Source of funding: NIHR Health Technology Assessment programme. **Limitations:** No sensitivity analysis in the current publication. Montelukast patent ended in 2012 allowing generics and reducing the market prices since the date of analysis **Other:** Sensitivity analysis planned within secondary analysis.				
Overall applicability: directly applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; ePACT: Electronic Prescribing Analysis and CosT; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

a) Adjusted for baseline values

b) 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 of which the evaluation is based on may not reflect the true treatment effect sizes.

I.3 Escalating pharmacological treatment in patients poorly controlled on first-line preventer treatment

I.3.1 Second-line preventer

Study	**Jönsson 2004 [545]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA (health outcome: Severe exacerbations, symptom	**Population:** Group B from OPTIMA. Taking up to 400µg per day	**Total costs (mean per patient):**	**Severe exacerbations (mean per patient):**	**ICER (Intervention 2 versus Intervention 1):** £196.50 per severe exacerbation avoided

free days) **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Application of unit costs to resource use data collected within the trial **Perspective:** Swedish healthcare system **Time horizon:** 1 year **Discounting:** Costs: n/a ; Outcomes: n/a	of inhaled budesonide or equivalent for 3 months and a FEV_1 of ≥70% predicted normal **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Low dose ICS budesonide 400µg per day **Intervention 2:** Low dose ICS plus LABA budesonide 400µg per day plus formoterol 9µg per day	Intervention 1: £250 Intervention 2: £362 Incremental (2−1): £112 (95% CI: NR; p=NR) **Currency & cost year:** 1999 Swedish krona (SEK) (presented here as 1999 UK pounds[(a)]) **Cost components incorporated:** Study medication, Reliever medication, Other medication, Healthcare resource costs	Intervention 1: 0.92 Intervention 2: 0.35 Incremental (2−1): -0.57 (95% CI: NR; p=NR) **Symptom free days (mean per patient):** Intervention 1: 265 (72.54%) Intervention 2: 275 (75.19%) Incremental (2−1): 10 (95% CI: NR; p=NR)	£11.20 per symptom free day **Analysis of uncertainty:** The study applied unit costs from the UK and Spain to the entire population. This did not significantly change the overall results.
Data sources				
Health outcomes: OPTIMA clinical study. [776] **Quality-of-life weights:** NA **Cost sources:** Resource use from OPTIMA clinical study. [776] Swedish unit costs taken from published literature.				
Comments				
Source of funding: NR **Limitations:** Swedish healthcare system may not be reflective of UK NHS. Time horizon only 1 year not capturing full effect. Quality of life not included as an outcome. Costs from published Swedish literature rather than national statistics/data. Sensitivity analysis only conducted around country of unit costs and not effectiveness parameters.				
Overall applicability: partially applicable[(b)] **Overall quality:** potentially serious limitations[(c)]				

Abbreviations: CCA: cost-consequence analysis; 95% CI: 95% confidence interval; FEV_1: forced expiratory volume in 1 second; ICER: incremental cost-effectiveness ratio; ICS: inhaled corticosteroids; LABA; long-acting beta-adrenoceptor agonist; NR: not reported

(a) Converted using 1999 purchasing power parities[795]

(b) Swedish healthcare system may not be reflective of UK NHS. Quality of life not included as an outcome.

(c) Sensitivity analysis only conducted around country of unit costs and not effectiveness parameters. Costs from published Swedish literature rather than national statistics/data

Study	Price 2011 [861] Price 2010			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Analysis of individual level EQ-5D and resource use, with unit costs applied **Perspective:** UK NHS **Time horizon:** 2 years **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	**Population:** Patient with diagnosed asthma and symptomatic on low dose ICS for at least 12 weeks **Cohort settings:** Start age: 50.3 Male: 37.5% **Intervention 1 (n=182):** ICS + LABA (ICS = beclometasone dipropionate, budesonide or fluticasone propionate, LABA = salmeterol) **Intervention 2 (n=170:** ICS + LTRA (ICS = beclometasone dipropionate, budesonide or fluticasone propionate, LTRA = montelukast 10 mg, once daily or zafirlukast 20 mg, twice daily	**Total NHS costs (mean per patient):** Intervention 1: £869 Intervention 2: £956 Incremental (2−1): £88 (95% CI:NR; p=NR) Adjusted incremental[(a)]: £113 **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** Prescribed medication and devices, primary and secondary care activity, lost productivity	**QALYs (mean per patient):** Intervention 1: 1.548 Intervention 2: 1.601 Incremental (2−1): 0.053 (95% CI:NR; p=NR) Adjusted incremental[(a)]: 0.009 (95% CI:NR; p=NR) **MiniAQLQ (mean per patient):** Intervention 1: 5.416 Intervention 2: 5.452 Incremental (2−1): 0.037 (95% CI:NR; p=NR) Adjusted incremental[(a)]: 0.034 (95% CI:NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** ICS + LTRA costs £11,919 per QALY gained compared to ICS + LABA.
Data sources				

Health outcomes: Within study participant completed questionnaires at baseline and each study visit over 2 years. **Quality-of-life weights:** Within-RCT analysis: EQ-5D UK tariff. **Cost sources:** Resource use from primary care practice databases using MIQUEST (www.connectingforhealth.nhs.uk/miquest), APOLLO SQL SUITE (www.apollo-medical.com/products/sql.htm) and manual extraction from practices. Unit costs from NHS reference costs, PSSRU and ePACT.	
Comments	
Source of funding: NIHR Health Technology Assessment programme. **Limitations:** No sensitivity analysis in the current publication. Montelukast patent ended in 2012 allowing generics and reducing the market prices since the date of analysis **Other:** Sensitivity analysis planned within secondary analysis.	
Overall applicability[(b)]: directly applicable	**Overall quality[(c)]:** potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; ePACT: Electronic Prescribing Analysis and CosT; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Including imputed data and adjusted for baseline values

(b) Directly applicable

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

Study	**Lenney 2013 [622]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Analysis of individual QALYs using PAQLQ as a proxy and resource use, with unit costs applied **Perspective:** UK NHS **Time horizon:** 48 weeks	**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 **Cohort settings:** Start age: 10.4 Male: 63.5% **Intervention 1 (n=19):** ICS low dose Fluticasone propionate 100µg + placebo tablet once	**Total NHS costs (mean per patient):** Intervention 1: £144.75 Intervention 2: £458.80 Incremental 3: £447.99 **Currency & cost year:** 2011 UK pounds **Cost components incorporated:** Prescribed medication and devices,	**QALYs (mean per patient):** Intervention 1: 0.09 Intervention 2: 0.12 Incremental 3: 0.13	**Incremental cost-effectiveness ratios (£/QALY):** ICS + LABA versus ICS: £12,054 ICS + LTRA versus ICS: £6,827 ICS + LTRA versus ICS + LABA: –£588 (ICS + LTRA dominates) **Uncertainty:** ICS + LTRA has an 80% probability of being cost-effective compared to ICS at £30,000 threshold. ICS + LABA has an 60% probability of being cost-effective compared to ICS at £30,000

Discounting: Costs: n/a; Outcomes: n/a	daily **Intervention 2 (n=23:** ICS + LABA Fluticasone propionate 100µg + salmeterol 50µg twice daily + placebo tablet once daily **Intervention 3(n=21:** ICS + LTRA Fluticasone propionate 100µg twice daily + Montelukast 5mg tablet once daily	primary and secondary care activity		threshold. The study reports that the CEAC for ICS + LTRA versus ICS + LABA declines after the threshold ICER because of increasing uncertainty and that there is little evidence supporting either intervention over the other.
Data sources				
Health outcomes: MASCOT study. Within study participant completed questionnaires and economic diary at baseline and end of study. **Quality-of-life weights:** Within-RCT analysis: PAQLQ used as a proxy by converting to a 0-1 scale to match EQ-5D. **Cost sources:** Resource use recorded directly from patients using economic diary. Unit costs from NHS reference costs, PSSRU and BNF.				
Comments				
Source of funding: NIHR Health Technology Assessment programme. **Limitations:** QALYs estimated using PAQLQ as a proxy and converting onto a 0-1 scale rather than using a validated mapping algorithm. Number of study participants is too small to hold statistical power. Montelukast patent ended in 2012 allowing generics and reducing the market prices since the date of analysis				
Overall applicability[(a)]: partially applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; ePACT: Electronic Prescribing Analysis and CosT; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(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.

I.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

Study	Stallberg 2008			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CEA (health outcome: exacerbation) **Study design:** within trial analysis (RCT) **Approach to analysis:** **Perspective:** Swedish healthcare service **Time horizon/Follow-up** 1 year **Treatment effect duration:** 1 year **Discounting:** N/A	**Population:** Adults over 12 years of age with persistent asthma **Cohort settings:** Start age: 45 Male: 42% **Intervention 1:** Fixed dose budesonide/formoterol (160/4.5 mcg) **Intervention 2:** Budesonide/formoterol (160/4.5mcg) for maintenance and reliever	**Total costs (mean per patient):** Intervention 1: £486 Intervention 2: £387 Incremental (2−1): -£99 (95% CI: NR; p=<0.001) **Currency & cost year:** SEK presented here as 2008 UK GBP[(a)] **Cost components incorporated:** Asthma medication Hospitalisation Unplanned emergency visit Visit to GP Visit to nurse Telephone contact With GP Telephone contact with nurse	**No. exacerbations (per 100 patients per year):** Intervention 1: 15.2 Intervention 2: 12.4 Incremental (2−1): 2.8 (95% CI: NR; p=0.57)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. **Analysis of uncertainty: NR**
Data sources				
Health outcomes: number of exacerbations experienced in trial. **Quality-of-life weights:** N/A **Cost sources:** calculated within the trial				
Comments				
Source of funding: Astra Zeneca. **Limitations:** Swedish healthcare system may not be reflective of UK NHS. 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 be capturing full effect.				
Overall applicability: partially applicable[(b)] **Overall quality:** potentially serious limitations[(c)]				

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Converted using 2008 purchasing power parities[795]

(b) Swedish healthcare system may not be reflective of UK NHS.

(c) 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 be capturing full effect.

Study	**Johansson 2006**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CEA (health outcome: exacerbation) **Study design:** within trial analysis (RCT) **Approach to analysis:** **Perspective:** Swedish healthcare service **Time horizon/Follow-up** 1 year **Treatment effect duration:** 1 year **Discounting:** N/A	**Population:** Adults over 12 years of age with persistent asthma **Cohort settings:** Start age: 45 Male: 44% **Intervention 1:** Fixed dose salmeterol/fluticasone (moderate dose) + salbutamol for reliever **Intervention 2:** Budesonide/formoterol (moderate dose) for maintenance and reliever	**Total costs (mean per patient):** Intervention 1: £592 Intervention 2: £554 Incremental (2−1): £38 (95% CI: NR; p=0.002) **Currency & cost year:** Euros presented here as 2003 UK GBP(a) **Cost components incorporated:** Asthma medication Hospitalisation Unplanned emergency visit Visit to GP Visit to pulmonologist	**No. exacerbations (events per patient per year):** Intervention 1: 0.31 Intervention 2: 0.24 Rate ratio: 0.78 (95% CI: 0.66 – 0.91 NR; p=0.0025)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. **Analysis of uncertainty: NR**
Data sources				
Health outcomes: number of exacerbations experienced in trial. **Quality-of-life weights:** N/A **Cost sources:** calculated within the trial				
Comments				

Source of funding: Astra Zeneca. **Limitations:** 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. 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 be capturing full effect.

Overall applicability: partially applicable[(b)] **Overall quality:** potentially serious limitations[(c)]

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Converted using 2008 purchasing power parities[795]

(b) 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.

(c) 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 be capturing full effect.

Study	**Wickstrom 2009**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CEA (health outcome: exacerbation) **Study design:** systematic review of clinical trials and attaching Danish unit costs to resource use parameters **Approach to analysis:** **Perspective:** Swedish healthcare service **Time horizon/Follow-up** 1 year **Treatment effect**	**Population:** Adults over 12 years of age with persistent asthma 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. **Interventions** Kuna 2007 1) MART (ICS (mod dose) + LABA), n = 1144 2) ICS (high dose) +	**Total costs (mean per patient):** Kuna 2007 1) £569 2) £403 Incremental (2−1): -£166 Bousquet 2007 1) £536 2) £586 Incremental (2−1): £50 O'Byrne 2005 1) £333 2) £316 Incremental (2−1): -£17 Rabe 2006 1) £402	**No. exacerbations (events per patient per year):** Kuna 2007 1) 0.38 2) 0.24 Incremental (2−1): 0.14 (p<0.001) Bousquet 2007 1) 0.31 2) 0.25 Incremental (2−1): 0.06 (p=0.039) O'Byrne 2005 1) 0.35 2) 0.19 Incremental (2−1): 0.06 (p<0.001)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. Kuna 2007 Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. Bousquet 2007 Intervention 2 costs an additional £783 per exacerbation avoided O'Byrne 2005 Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. Rabe 2006

duration: 1 year **Discounting:** N/A	LABA, n = 1145 Bousquet 2007 1) MART (ICS (mod dose) + LABA), n = 1107 2) ICS (mod 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 + PRN SABA, n = 1141	2) £346 Incremental (2−1): -£55 **Currency & cost year:** DDK presented here as 2007 UK GBP[(a)] **Cost components incorporated:** Asthma medication Hospitalisation Unplanned emergency visit Visit to GP Visit to pulmonologist	Rabe 2006 3) 0.29 4) 0.19 Incremental (2−1): 0.1 (p<0.001)	Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. **Analysis of uncertainty: NR**
Data sources				
Health outcomes: number of exacerbations experienced in trial. **Quality-of-life weights:** N/A **Cost sources:** calculated within the trial				
Comments				
Source of funding: Astra Zeneca. **Limitations:** Danish unit costs were applied to each RCT. 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 be capturing full effect.				
Overall applicability: partially applicable[(b)] **Overall quality:** potentially serious limitations[(c)]				

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Converted using 2008 purchasing power parities[795]

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

(c) 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 be capturing full effect.

I.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

Study	**Wilson 2014**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Markov model **Approach to analysis:** Markov model with seven states. Controlled, partly controlled, uncontrolled, non-severe exacerbation, severe exacerbation, hospitalised and death . **Perspective:** UK NHS **Time horizon/Follow-up** lifetime **Treatment effect duration:** lifetime **Discounting:** 3.5% for both costs and QALYs	**Population:** Adults with uncontrolled asthma despite treatment with moderate dose ICS and LABAs **Cohort settings:** Start age: 53 Male: NR **Intervention 1:** Moderate dose ICS + LABA **Intervention 2:** Moderate dose ICS + LABA + tiotropium	**Total costs (mean per patient):** Intervention 1: £38,611 Intervention 2: £44,000 Incremental (2−1): £5,389 (95% CI: NR; p=0.002) **Currency & cost year:** 2014 UK GBP **Cost components incorporated:** Asthma medication Hospitalisation Unplanned emergency visit Visit to GP Visit to respiratory specialist Visit to nurse Lab tests	**QALYs:** Intervention 1: 14.33 Intervention 2: 14.52 Rate ratio: 0.19 (95% CI: NR; NR; p=0.0025)	**ICER (Intervention 2 versus Intervention 1):** £28,838 per QALY gained when the older, higher cost of respimat is used (£33.50) £16,288 per QALY gained when the current, lower cost of respimat is used (£23.00) **Analysis of uncertainty:** **Probabilistic** 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) 52.9% when the current, lower cost of respimat is used (£23.00) **Sensitivity analyses** These were all conducted with the higher price of Changed costs for uncontrolled asthma

				Changed costs for partly controlled asthma Changed utility for partly controlled asthma Changed costs of non-severe exacerbation Changed utility for non-severe exacerbation Changed utility for uncontrolled asthma Changed costs for controlled asthma Changed utility for severe exacerbation Changed utility for hospitalisation In all but one of these analyses the ICER remained above £20,000 per QALY. Increasing the costs of uncontrolled asthma reduced the ICER to £19,764 per QALY gained
Data sources				
Health outcomes: Within study participant completed questionnaires at baseline and each study visit over 1 year. **Quality-of-life weights:** Within-RCT analysis: EQ-5D UK tariff. **Cost sources:** Resource use gathered from clinical trial (PrimoTinA-asthma)				
Comments				
Source of funding: Boehringer Ingelheim. **Limitations:** Although EQ-5D was gathered in the clinical study the model was based on it did not use this data and instead attempted to calculate quality of life based on control applicable. The cost of a branded version of montelukast was used as opposed to the generic cost.				
Overall applicability: directly applicable[(a)] **Overall quality:** potentially serious limitations[(b)]				

(a) Directly applicable

(b) Although EQ-5D was gathered in the clinical study the model was based on, it 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 which significantly overestimates the cost of being uncontrolled.

I.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

None.

I.5 Improving adherence to treatment

None.

I.6 Self-management plans

Study	Schermer 2002 [937]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Within-trial analysis (cluster RCT) **Approach to analysis:** Analysis of individual level resource use, with unit costs applied. **Perspective:** Netherlands healthcare perspective **Follow-up:** 2 years **Discounting:** Costs: none; Outcomes: none	**Population:** People with asthma aged 16-60 years old who were being treated with inhaled steroids. **Cohort settings:** Start age: 39 Male: 38% **Intervention 1:** Usual care (no self-management) **Intervention 2:** Education and training on skills on an individual basis from family physician consisting of four visits within a 3-month period. Control visits for the remaining 21 months of the study. Package included checklists, booklets, diaries and peak flow meters to	**Total costs (mean per patient):** Intervention 1: £585 Intervention 2: £731 Incremental (2−1): £146 (95% CI: £51 to £240; p=NR) **Currency & cost year:** 2000 Euros (presented here as 2000 UK pounds[(a)]) **Cost components incorporated:** Program implementation cost, asthma medication, GP visits, ED visits	**QALYs (mean per patient):** Intervention 1: 0.024 Intervention 2: 0.039 Incremental (2−1): 0.015 (95% CI: 0.014 to 0.044; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £9,733 per QALY gained 95% CI: NR **Analysis of uncertainty:** 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.

	guide self-treatment.			
Data sources				
Health outcomes: n/a **Quality-of-life weights:** Patient reported from an interval rating scale ranging from 0-1 **Cost sources:** Guidebook for Cost Investigation (Dutch College of Health Insurance)				
Comments				
Source of funding: Netherlands Organization for Scientific Research (NWO) and Astra Zeneca BV (Zoetermeer, The Netherlands) **Limitations:** 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. 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.				
Overall applicability: partially applicable[(b)] **Overall quality:** potentially serious limitations[(c)]				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years

(d) Converted using 2000 purchasing power parities[795]

(e) Costs and effects were not discounted. Rating scale, not using standard gamble or time-trade off approach, used to capture QALYs. Netherlands healthcare perspective.

(f) 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.

I.7 Dose variation within self-management plans

None.

I.8 Decreasing regular maintenance treatment

None.

I.9 Breathing exercises in addition to pharmacological treatment

None.

I.10 Managing patients in relation to risk of poor outcomes

Study	**Smith 2012** [973]

Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: CC **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Analysis of individual resource use, with unit costs applied **Perspective:** UK NHS **Time horizon:** 1 year **Discounting:** Costs: n/a; Outcomes: n/a	**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; or asthma admission in the last 5 years or A&E visit in last year or Brittle asthma. **Cohort settings:** Start age: 45.5 Male: 38.7% **Intervention 1:** Standard care (n=454). 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. **Intervention 2:** Risk stratified care (n=457). Addition of electronic alerts visible to all staff to the	**Total cost change from baseline (mean per patient):** Intervention 1: £149.14 Intervention 2: £60.23 Incremental (2−1): -£88.91 (95% CI: NR; p=NR) **Currency & cost year:** 2007 – 2008 UK pounds **Cost components incorporated:** Intervention cost, primary care contact, secondary care contact, out of hours contact, medication	None	In the base case the cost difference is -£88.91. Incorporating only the respiratory related resource use, risk stratified care was no longer cost saving, costing an additional £62.03

	computerised records of identified at-risk patients to flag their at-risk status at each contact. A one hour practice-based 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.			
Data sources				
Health outcomes: ARRISA **Quality-of-life weights:** n/a **Cost sources:** PSSRU, NHS reference costs				
Comments				
Source of funding: Asthma UK **Limitations:** Clinical outcomes not reported as per patient totals. Cost analysis based on increase in costs from baseline rather than patient costs for the treatment year. No sensitivity analysis around cost parameters. Practice software created difficulties in extracting data leading to manual extraction of a sub-sample to inform primary care resource use and costs.				
Overall applicability: partially applicable[(a)] **Overall quality:** potentially serious limitations[(b)]				

Abbreviations: CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Quality of life and mortality were not assessed and therefore QALYs were not calculated.
(b) Potential inconsistencies with hospitalisations decreasing however asthma related secondary care costs increasing.

Appendix J: GRADE tables

J.1 Treatment in patients not on regular preventers

None.

J.2 Choice of first-line preventer in patients with poor asthma control

Table 15: Clinical evidence profile: ICS (low dose) compared to Placebo in people over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (low dose)	Placebo	Relative (95% CI)	Absolute		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
6	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[3]	none	996	700	-	MD 17.19 higher (11.15 to 23.24 higher)	VERY LOW	IMPORTANT
FEV_1 (% predicted) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	228	239	-	MD 2.25 higher (0.7 to 3.8 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 12 weeks; Better indicated by higher values)												
4	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	596	471	-	MD 0.16 higher (0.11 to 0.22 higher)	VERY LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 4.5 months; Better indicated by lower values)												
5	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[3]	none	824	710	-	MD 0.76 lower (1.23 to 0.29 lower)	VERY LOW	IMPORTANT
Reliever medication use - daytime (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	255	85	-	MD 0.55 lower (1.05 to 0.05 lower)	LOW	IMPORTANT
Reliever medication use - night-time (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	255	85	-	MD 0.41 lower (0.81 to 0.01 lower)	LOW	IMPORTANT
Exacerbations (follow-up mean 1 years)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	27/228 (11.8%)	23.4%	RR 0.51 (0.33 to 0.77)	115 fewer per 1000 (from 54 fewer to 157 fewer)	VERY LOW	CRITICAL
Infection (follow-up mean 12 weeks)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	35/437 (8%)	12.5%	RR 0.59 (0.37 to 0.97)	51 fewer per 1000 (from 4 fewer to 79 fewer)	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 or 2 increments because I^2 > 50%, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 or 2 increments because the confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis

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

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (moderate dose)**		**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 4 months; Better indicated by higher values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	152	68	-	MD 37.45 higher (19.34 to 55.55 higher)	LOW	IMPORTANT
FEV_1 (% predicted) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12	21	-	MD 5.2 higher (1.74 lower to 12.14 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 4 months; Better indicated by higher values)												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	246	157	-	MD 0.2 higher (0.08 to 0.32 higher)	VERY LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 4 months; Better indicated by lower values)												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	152	68	-	MD 2.16 lower (4.49 to 0.17 lower)	LOW	IMPORTANT

Reliever medication use - rescue-free days (%) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129	129	-	MD 12 higher (4.94 to 19.06 higher)	MODERATE	IMPORTANT
Reliever medication use - rescue-free nights (%) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129	129	-	MD 14 higher (4.54 lower to 32.54 higher)	MODERATE	IMPORTANT
Exacerbations (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/129 (10.1%)	13.2%	RR 0.76 (0.39 to 1.51)	32 fewer per 1000 (from 81 fewer to 67 more)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because I^2 > 50%, unexplained by subgroup analysis.
[3] 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 profile: ICS + LABA compared to Placebo in people over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LABA**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	564	581	-	MD 25.53 higher (18.08 to 32.97 higher)	LOW	IMPORTANT
FEV_1 (% predicted) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	231	239	-	MD 4.08 higher (2.04 to 6.12 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	564	356	-	MD 0.27 higher (0.21 to 0.33 higher)	LOW	IMPORTANT

Reliever medication use (puffs/day) (follow-up mean 7.5 months; Better indicated by lower values)												
2	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	651	451	-	MD 0.83 lower (2.02 to 0.35 lower)	VERY LOW	IMPORTANT
Reliever medication use (rescue free days%) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	none	no serious indirectness	none	none	-	-	OR 5.26 (3.12 to 8.85)	-	MODERATE	IMPORTANT
Exacerbations (follow-up mean 1 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	34/231 (14.7%)	23.4%	RR 0.63 (0.43 to 0.92)	87 fewer per 1000 (from 19 fewer to 133 fewer)	VERY LOW	CRITICAL
Infection (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	23/353 (6.5%)	4.9%	RR 1.33 (0.61 to 2.9)	16 more per 1000 (from 19 fewer to 93 more)	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 or 2 increments because $I^2 > 50\%$, unexplained by subgroup analysis.
[3] 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 profile: LTRA compared to Placebo in people over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12.5 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	445	200	-	MD 4.88 higher (12.36 lower to 22.13 higher)	VERY LOW	IMPORTANT
FEV_1 (L) (follow-up mean 12.5 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	445	200	-	MD 0.16 higher (0.03 lower to 0.34 higher)	VERY LOW	IMPORTANT

Reliever medication use (puffs/day) (follow-up mean 12.5 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	445	200	-	MD 0 higher (1.54 lower to 1.54 higher)	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 or 2 increments because I^2 > 50%, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (moderate dose)**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	140	67	-	MD 32.2 higher (14.33 lower to 50.07 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	140	67	-	MD 0.14 higher (0.01 lower to 0.29 higher)	LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	91	93	-	MD 0.44 higher (1.78 lower to 2.66 higher)	LOW	IMPORTANT

[1] 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
[2] 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 profile: ICS (high dose) compared to ICS (low dose) in people over 16

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (high dose)	ICS (low dose)	Relative (95% CI)	Absolute		
FEV_1 (% predicted) (follow-up mean 9 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 8 higher (18.77 lower to 34.77 higher)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS + LABA	ICS (low dose)	Relative (95% CI)	Absolute		
Morning PEF (follow-up mean 22 weeks; Better indicated by higher values)												
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	1885	1686	-	MD 4.58 higher (1.73 to 7.44 higher)	VERY LOW	IMPORTANT
FEV_1 (% predicted) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	231	228	-	MD 1.83 higher (0.26 to 3.4 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 6 months; Better indicated by higher values)												
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	1876	1679	-	MD 0.07 higher (0.04 to 0.1 higher)	LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 6 months; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	1007	799	-	MD 0.22 lower (0.32 to 0.11 lower)	LOW	IMPORTANT

Reliever medication use (rescue free days%) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	none	no serious indirectness	none	none	-	-	OR 1.79 (1.12 to 2.84)	-	MODERATE	IMPORTANT
Exacerbations (follow-up mean 1 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	34/231 (14.7%)	11.8%	RR 1.24 (0.78 to 1.99)	28 more per 1000 (from 26 fewer to 117 more)	VERY LOW	CRITICAL
Infection (follow-up mean 24 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23/353 (6.5%)	3.3%	RR 1.98 (0.82 to 4.77)	32 more per 1000 (from 6 fewer to 124 more)	VERY LOW	IMPORTANT
Mortality (follow-up mean 24 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/209 (0%)	0%	not pooled	not pooled	LOW	CRITICAL

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - no objective measure of asthma diagnosis.
[3] 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 profile: LTRA compared to ICS (low dose) in people over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 20 weeks; Better indicated by higher values)												
4	randomised trials	serious[1]	serious[2]	serious[3]	serious[4]	none	852	874	-	MD 19.41 lower (30.67 to 8.15 lower)	VERY LOW	IMPORTANT
FEV_1 (% predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	466	475	-	MD 3.09 lower (4.18 to 2 lower)	MODERATE	IMPORTANT

FEV_1 (L) (follow-up mean 24 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	384	392	-	MD 0.17 lower (0.23 to 0.1 lower)	LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 20 weeks; Better indicated by lower values)												
3	randomised trials	serious[1]	serious[2]	serious[3]	serious[4]	none	573	583	-	MD 0.58 higher (0.05 lower to 1.2 higher)	VERY LOW	IMPORTANT
Reliever medication use (rescue free days%) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	none	no serious indirectness	serious[4]	none	268	281	-	MD 1.32 higher (1.32 lower to 8.72 higher)	LOW	IMPORTANT
AQLQ (follow-up mean 18 weeks; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	386	389	-	MD 0.17 lower (0.33 to 0.01 lower)	LOW	CRITICAL
Exacerbations (follow-up mean 24 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	21/197 (10.7%)	9.6%	RR 1.11 (0.62 to 2)	11 more per 1000 (from 36 fewer to 96 more)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because $I^2 > 50\%$, unexplained by subgroup analysis.
[3] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Theophylline**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
FEV_1 (% predicted) (follow-up mean 9 months; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	62	53	-	MD 0 higher (10.3 lower to 10.3 higher)	LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.

Table 24: Clinical evidence profile: ICS + LABA compared to ICS (moderate dose) in people over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LABA**	**ICS (moderate dose)**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	180	182	-	MD 21 higher (11 to 31 higher)	VERY LOW	IMPORTANT
Reliever medication use - participants with 100% rescue free days (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40/180 (22.2%)	26/182 (14.3%)	RR 1.56 (0.99 to 2.44)	80 more per 1000 (from 1 fewer to 206 more)	LOW	IMPORTANT
								14.3%		80 more per 1000 (from 1 fewer to 206 more)		
Reliever medication use - participants with 100% rescue free nights (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	54/180 (30%)	31/182 (17%)	RR 1.76 (1.19 to 2.6)	129 more per 1000 (from 32 more to 273 more)	LOW	IMPORTANT
								17%		129 more per 1000 (from 32 more to 272 more)		

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.
[3] 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 profile: LTRA compared to ICS (moderate dose) in people over 16

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**ICS (moderate dose)**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 2 years; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	148	158	-	MD 6.8 lower (33.91 lower to 20.31 higher)	VERY LOW	IMPORTANT
Reliever medication use - daytime (follow-up mean 2 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	148	158	-	MD 0.43 higher (0.08 to 0.78 higher)	LOW	IMPORTANT
Reliever medication use - night-time (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	148	148	-	MD 0.04 higher (0.16 lower to 0.24 higher)	LOW	IMPORTANT
ACQ (follow-up mean 2 years; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	145	155	-	MD 0.08 higher (0.13 lower to 0.29 higher)	LOW	IMPORTANT
Hospitalisations (follow-up mean 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	4/151 (2.6%)	2/151 (1.3%)	RR 2.00 (0.37 to 10.76)	13 more per 1000 (from 8 fewer to 129 more)	VERY LOW	IMPORTANT
AQLQ (follow-up mean 2 years; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	145	155	-	MD 0.11 lower (0.36 lower to 0.14 higher)	LOW	CRITICAL
EQ-5D (follow-up mean 2 years; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	132	143	-	MD 0.06 lower (0.11 lower to 0 higher)	VERY LOW	IMPORTANT
Exacerbations (follow-up mean 2 years)												
1	randomised	serious[1]	no serious	serious[3]	serious[3]	none	36/148	17.1%	RR 1.42 (0.91	72 more per 1000 (from	VERY	CRITICAL

	trials		inconsistency				(24.3%)		to 2.22)	15 fewer to 209 more)	LOW	
Infection (follow-up mean 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[3]	none	70/148 (47.3%)	53.4%	RR 0.89 (0.71 to 1.11)	59 fewer per 1000 (from 155 fewer to 59 more)	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] 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 profile: Theophylline compared to ICS (high dose) in people over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Theophylline**	**ICS (high dose)**	**Relative (95% CI)**	**Absolute**		
FEV_1 (% predicted) (follow-up mean 9 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27	29	-	MD 7 lower (36.86 lower to 22.86 higher)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Clinical evidence profile: LTRA compared to ICS+LABA in people over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**ICS + LABA**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	395	382	-	MD 47.85 lower (59.35 to 36.34 lower)	LOW	IMPORTANT

FEV_1 (L) (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	396	384	-	MD 0.28 lower (0.34 to 0.22 lower)	VERY LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	396	384	-	MD 1.4 higher (0.99 to 1.81 higher)	LOW	IMPORTANT
AQLQ (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	183	171	-	MD 0.5 lower (0.74 to 0.26 lower)	MODERATE	CRITICAL

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.
[3] 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 profile: ICS (low dose) compared to Placebo in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (low dose)**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	225	220	-	MD 18.97 higher (9.96 to 27.97 higher)	LOW	IMPORTANT
FEV_1 (% predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	210	201	-	MD 5.26 higher (2.94 to 7.58 higher)	LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	97	-	MD 0.37 lower (0.73 to 0.01 lower)	MODERATE	IMPORTANT

Infection (follow-up mean 12 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	54/213 (25.4%)	25.6%	RR 0.99 (0.71 to 1.37)	3 fewer per 1000 (from 74 fewer to 95 more)	VERY LOW	IMPORTANT
Adrenal Insufficiency (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/105 (0%)	3.1%	OR 0.12 (0.01 to 1.19)	27 fewer per 1000 (from 31 fewer to 6 more)	LOW	IMPORTANT

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

Table 29: Clinical evidence profile: ICS (moderate dose) compared to Placebo in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (moderate)**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	100	104	-	MD 10.6 higher (0.34 lower to 21.54 higher)	LOW	IMPORTANT
FEV_1 (% predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	208	201	-	MD 3.39 higher (2.09 lower to 8.88 higher)	LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	108	97	-	MD 0.62 lower (0.98 to 0.26 lower)	LOW	IMPORTANT
Infection (follow-up mean 12 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46/212 (21.7%)	25.6%	RR 0.85 (0.6 to 1.2)	38 fewer per 1000 (from 102 fewer to 51 more)	LOW	IMPORTANT

Adrenal Insufficiency (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/108 (0.93%)	3.1%	OR 0.32 (0.04 to 2.34)	21 fewer per 1000 (from 30 fewer to 39 more)	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because $I^2 > 50\%$, unexplained by subgroup analysis.

Table 30: Clinical evidence profile: ICS (moderate dose) compared to ICS (low dose) in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (moderate)**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Morning PEF (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	100	-	MD 7.2 lower (18.13 lower to 3.73 higher)	MODERATE	IMPORTANT
FEV_1 (% predicted) (follow-up mean 12 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	208	210	-	MD 1.85 lower (7.24 lower to 3.54 higher)	LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	108	105	-	MD 0.25 lower (0.6 lower to 0.1 higher)	MODERATE	IMPORTANT
Infection (follow-up mean 12 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	46/212 (21.7%)	25.5%	RR 0.85 (0.6 to 1.2)	38 fewer per 1000 (from 102 fewer to 51 more)	LOW	IMPORTANT
Adrenal Insufficiency (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/108 (0.93%)	0%	OR 6.67 (0.13 to 338.23)	-	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 or 2 increments because I^2 > 50%, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 31: Clinical evidence profile: LTRA compared to ICS (low dose) in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTRA	ICS (low dose)	Relative (95% CI)	Absolute		
Quality of life (AQLQ) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	263	278	-	MD 0.13 lower (0.33 lower to 0.07 higher)	HIGH	CRITICAL
FEV_1 (%) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	439	442	-	MD 2.1 lower (3.65 to 0.55 lower)	HIGH	IMPORTANT
Rescue use (% of days) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	439	442	-	MD 2.7 higher (0.58 to 4.82 higher)	HIGH	IMPORTANT

Table 32: Clinical evidence profile: Cromolyn compared to ICS (low dose) in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cromolyn	ICS (low dose)	Relative (95% CI)	Absolute		
Morning PEF (% predicted) (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	26	34	-	MD 7.3 lower (11.43 to 3.17 lower)	VERY LOW	IMPORTANT
Exacerbations (follow-up mean 12 months)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/70 (7.1%)	9.6%	RR 0.74 (0.23 to 2.43)	25 fewer per 1000 (from 74 fewer to 137 more)	VERY LOW	CRITICAL
Growth Velocity (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	26	34	-	MD 0.5 higher (0.3 to 0.7 higher)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) -lack of objective diagnostic assessment for asthma.
[3] 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 profile: ICS (high dose) compared to ICS (moderate dose) in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (high dose)**	**ICS (moderate dose)**	**Relative (95% CI)**	**Absolute**		
FEV_1 (% predicted) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	15	-	MD 0.4 lower (2.56 lower to 1.76 higher)	MODERATE	IMPORTANT

[1] 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 profile: LTRA compared to ICS (moderate dose) in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**ICS (moderate dose)**	**Relative (95% CI)**	**Absolute**		
FEV_1 (% predicted) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	15	-	MD 2.5 lower (4.59 to 0.41 lower)	LOW	IMPORTANT

[1] 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
[2] 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 profile: LTRA compared to ICS (high dose) in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTRA	ICS (high dose)	Relative (95% CI)	Absolute		
FEV_1 (% predicted) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	18	-	MD 2.1 lower (3.65 to 0.55 lower)	LOW	IMPORTANT

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

Table 36: Clinical evidence profile: LTRA compared to ICS + LABA in people aged 5-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTRA	ICS+LABA	Relative (95% CI)	Absolute		
Quality of life (PAQLQ) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	267	281	-	MD 0.09 lower (0.3 lower to 0.12 higher)	MODERATE	CRITICAL
Rescue use (rescue-free 24-hr periods) (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 3.24 (2.09 to 5.02)	-	MODERATE	IMPORTANT
								0%		-		

[1] 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 37: Clinical evidence profile: ICS (low dose) compared to Placebo in children aged 1-5

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (low dose)	Placebo	Relative (95% CI)	Absolute		
Reliever medication use - daytime (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	45	43	-	MD 0.06 higher (0.19 lower to 0.31 higher)	HIGH	IMPORTANT
Reliever medication use - night-time use (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	45	43	-	MD 0.05 higher (0.04 lower to 0.14 higher)	MODERATE	IMPORTANT
Infection (follow-up mean 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	6/21 (28.6%)	6.7%	RR 4.29 (0.57 to 32.01)	220 more per 1000 (from 29 fewer to 1000 more)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - lack of physicians diagnosis.
[3] 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 profile: ICS (high dose) compared to Placebo in children aged 1-5

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (high dose)	Placebo	Relative (95% CI)	Absolute		
Reliever medication use - daytime (follow-up mean 6 months; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17	19	-	MD 1.6 lower (1.99 to 1.21 lower)	MODERATE	IMPORTANT
Reliever medication use - night-time use (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17	19	-	MD 1.7 lower (2.09 to 1.31 lower)	MODERATE	IMPORTANT

[1] 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 39: Clinical evidence profile: LTRA compared to Placebo in children aged 1-5

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Infection (follow-up mean 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	6/17 (35.3%)	6.7%	RR 5.29 (0.72 to 39.11)	287 more per 1000 (from 19 fewer to 1000 more)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - lack of physicians diagnosis.
[3] 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 profile: LTRA compared to ICS (low dose) in children aged 1-5

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Infection (follow-up mean 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	6/17 (35.3%)	28.6%	RR 1.24 (0.49 to 3.14)	69 more per 1000 (from 146 fewer to 612 more)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments)- lack of physicians diagnosis.
[3] 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 profile: Cromolyn compared to ICS (moderate dose) in children aged 1-5

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cromolyn	ICS (moderate dose)	Relative (95% CI)	Absolute		
Reliever medication use - puffs/day (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	37	-	MD 0.13 higher (0.1 lower to 0.36 higher)	MODERATE	IMPORTANT

[1] 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 42: Clinical evidence profile: ICS (low dose) compared to Placebo in children aged <1

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (low dose)	Placebo	Relative (95% CI)	Absolute		
Reliever medication use - puffs/day (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	18	-	MD 0.34 lower (0.88 lower to 0.2 higher)	VERY LOW	IMPORTANT
Reliever medication use - number of days (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 17.8 lower (18.75 to 16.85 lower)	HIGH	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - lack of physicians diagnosis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 43: Clinical evidence profile: ICS (moderate dose) compared to Placebo in children aged <1

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (moderate dose)	Placebo	Relative (95% CI)	Absolute		
Reliever medication use - days (follow-up mean 6 months; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	24	22	-	SMD 7.01 lower (19.25 lower to 5.23 higher)	LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 or 2 increments because I^2 > 50%, unexplained by subgroup analysis.

Table 44: Clinical evidence profile: ICS (moderate dose) compared to ICS (low dose) in children aged <1

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (moderate dose)	ICS (low dose)	Relative (95% CI)	Absolute		
Reliever medication use - number of days (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 2.6 higher (1.9 to 3.3 higher)	HIGH	IMPORTANT

J.3 Escalating pharmacological treatment in patients poorly controlled on first-line preventer treatment

J.3.1 Second-line preventer

J.3.1.1 People aged over 16

Table 45: ICS high dose versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS (high dose)	ICS (low dose)	Relative (95% CI)	Absolute		
Severe exacerbations (requiring OCS) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/52 (15.4%)	11/54 (20.4%)	RR 0.76 (0.33 to 1.73)	49 fewer per 1000 (from 136 fewer to 149 more)	VERY LOW	CRITICAL
PEF (L/min) (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	45	-	MD 15.1 higher (2.66 lower to 32.86 higher)	VERY LOW	IMPORTANT
Infections (all respiratory) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/52 (11.5%)	8/54 (14.8%)	RR 0.78 (0.29 to 2.09)	33 fewer per 1000 (from 105 fewer to 161 more)	VERY LOW	IMPORTANT

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

Table 46: ICS low dose + LABA versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ICS +	ICS (low	Relative	Absolute		

studies						considerations	LABA	dose)	(95% CI)			
Severe exacerbations (requiring OCS) (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/638 (0%)	0%	RR 0.57 (0.46 to 0.72)	-	LOW	CRITICAL
Hospitalisations (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/618 (0.81%)	9/615 (1.5%)	RR 0.57 (0.46 to 0.72)	7 fewer per 1000 (from 12 fewer to 9 more)	VERY LOW	IMPORTANT
Reliever medication use (reliever free days) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	409	207	-	MD 8.6 higher (4.21 to 12.99 higher)	HIGH	IMPORTANT
Reliever medication use (puffs/day) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	231	449	-	MD 0.80 lower (1.28 to 0.32 lower)	LOW	IMPORTANT
FEV_1 (L) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	231	449	-	MD 0.17 higher (0.10 to 0.24 higher)	LOW	IMPORTANT
PEF (L/min) (follow-up 12 weeks; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	640	656	-	MD 19.48 higher (13.74 to 25.21 higher)	MODERATE	IMPORTANT
Infections (all respiratory) (follow-up 12 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	55/409 (13.4%)	25/207 (12.1%)	RR 1.11 (0.72 to 1.73)	-	LOW	IMPORTANT

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

[4] Actual event numbers not reported

Table 47: LTRA + ICS low dose versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTRA + ICS	ICS (low dose)	Relative (95% CI)	Absolute		
Reliever medication use (puffs/day, % change from baseline) (follow-up 16 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	193	200	-	MD 11.55 lower (25.59 lower to 2.49 higher)	HIGH	IMPORTANT
FEV_1 (L) (follow-up 16 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	193	200	-	MD 0.12 higher (0.06 to 0.18 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up 16 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	193	200	-	MD 7.76 higher (2.06 to 13.46 higher)	HIGH	IMPORTANT
Infections (all respiratory) (follow-up 16 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	70/193 (36.3%)	79/200 (39.5%)	RR 0.92 (0.71 to 1.18)	32 fewer per 1000 (from 115 fewer to 71 more)	MODERATE	IMPORTANT

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

Table 48: Theophylline + ICS low dose versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Theophylline	ICS (low dose)	Relative (95% CI)	Absolute		

Severe exacerbations (requiring OCS) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/49 (6.1%)	11/54 (20.4%)	RR 0.3 (0.09 to 1.01)	143 fewer per 1000 (from 185 fewer to 2 more)	LOW	CRITICAL
PEF (L/min) (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38	45	-	MD 17.4 higher (1.47 lower to 36.27 higher)	VERY LOW	IMPORTANT
Infections (all respiratory) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/49 (10.2%)	8/54 (14.8%)	RR 0.69 (0.24 to 1.96)	46 fewer per 1000 (from 113 fewer to 142 more)	VERY LOW	IMPORTANT

[1] 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

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

Table 49: ICS low dose + LAMA versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (low dose) + LAMA**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Asthma control (ACQ, 0-6, lower is better)) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	152	154	-	MD 0.06 higher (0.07 lower to 0.19 higher)	HIGH	CRITICAL
FEV1 (% predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	152	154	-	MD 4.7 higher (2.54 to 6.86 higher)	MODERATE	IMPORTANT
PEF (L/min) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	152	152	-	MD 25.6 higher (15.21 to 35.99 higher)	MODERATE	IMPORTANT

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

Table 50: ICS low dose + LABA versus ICS moderate dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS + LABA	ICS (moderate dose)	Relative (95% CI)	Absolute		
Severe exacerbations (requiring OCS) (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/220 (8.2%)	19/206 (9.2%)	RR 0.89 (0.48 to 1.64)	10 fewer per 1000 (from 48 fewer to 59 more)	VERY LOW	CRITICAL
Hospitalisations (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/220 (0.45%)	0/206 (0%)	OR 6.96 (0.14 to 350.17)	-	VERY LOW	IMPORTANT
PEF (L/min) (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	69	65	-	MD 20.36 higher (3.16 higher to 37.56 higher)	VERY LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Unable to calculate absolute effects as control group event rate is 0
[4] 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
[5] Control group data not presented separately

Table 51: LTRA alone versus ICS high dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTRA	ICS (high dose)	Relative (95% CI)	Absolute		
Reliever medication use (puffs/day) (follow-up 3 months; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 0 higher (0.11 lower to 0.11 higher)	LOW	IMPORTANT
FEV_1 (%predicted) (follow-up 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 3.9 lower (6.8 to 1 lower)	VERY LOW	IMPORTANT

[1] 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

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

Table 52: ICS low dose + LABA versus ICS high dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LABA**	**ICS (high dose)**	**Relative (95% CI)**	**Absolute**		
FEV_1 (%predicted) (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 3.7 higher (1.35 to 6.05 higher)	VERY LOW	IMPORTANT

[1] 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

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

[3] 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 53: LTRA alone versus theophylline alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LTRA**	**Theophylline**	**Relative (95% CI)**	**Absolute**		
Reliever medication use (puffs/day) (follow-up 3 months; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	25	-	MD 0 higher (0.09 lower to 0.09 higher)	LOW	IMPORTANT
FEV_1 (%predicted) (follow-up 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25	24	-	MD 0.4 higher (1.66 lower to 2.46 higher)	VERY LOW	IMPORTANT

[1] 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

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

Table 54: ICS high dose versus theophylline + ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (high dose)**	**Theophylline**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/52 (15.4%)	3/49 (6.1%)	RR 2.51 (0.71 to 8.93)	92 more per 1000 (from 18 fewer to 486 more)	VERY LOW	CRITICAL
PEF (L/min) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	38	-	MD 2.3 lower (22.92 lower to 18.32 higher)	VERY LOW	IMPORTANT
Infections (all respiratory) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/52 (11.5%)	5/49 (10.2%)	RR 1.13 (0.37 to 3.47)	13 more per 1000 (from 64 fewer to 252 more)	VERY LOW	IMPORTANT

[1] 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

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

Table 55: ICS high dose versus theophylline alone

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS (high dose)**	**Theophylline**	**Relative (95% CI)**	**Absolute**		
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 0 higher (0.09 lower to 0.09 higher)	LOW	IMPORTANT
FEV_1 (%predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25	24	-	MD 0.4 higher (1.66 lower to 2.46 higher)	VERY LOW	IMPORTANT

[1] 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

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

Table 56: ICS low dose + LTRA versus ICS low dose + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LTRA**	**ICS + LABA**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up 48-104 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	299/1651 (18.1%)	275/1643 (16.7%)	RR 1.09 (0.94 to 1.26)	15 more per 1000 (from 10 fewer to 44 more)	LOW	CRITICAL
Quality of life (AQLQ/miniAQLQ, 1-7, higher is better outcome) (follow-up 48-104 weeks; Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1611	1649	-	MD 0.08 lower (0.15 lower to 0.01 higher)	MODERATE	CRITICAL
Quality of life (EQ-5D, 0-1, higher is better outcome) (follow-up 104 weeks; range of scores: 0-1; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	160	170	-	MD 0.01 higher (0.05 lower to 0.07 higher)	VERY LOW	CRITICAL
Asthma control (ACQ, 0-6, lower is better outcome) (Copy) (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	121	175	-	MD 0.06 lower (0.24 lower to 0.12 higher)	LOW	IMPORTANT
Hospitalisations (follow-up 104 weeks)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/1650 (0.67%)	17/1637 (1.03%)	OR 0.65 (0.31 to 1.37)	4 fewer per 1000 (from 7 fewer to 4 more)	LOW	IMPORTANT
Reliever medication use (puffs/day) (follow-up 12-104 weeks; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1052	1047	-	MD 0.41 higher (0.39 to 0.44 higher)	MODERATE	IMPORTANT
Reliever medication use (puffs/night) (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	75	87	-	MD 0.06 higher (0.24 lower to 0.36 higher)	VERY LOW	IMPORTANT
Reliever medication use (% reliever free nights) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	33	-	MD 16.5 lower (33.87 lower to 0.87 higher)	MODERATE	IMPORTANT
Reliever medication use (reliever free during study period) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[4]	none	369	356	OR 0.77 (0.61 to 0.97)	-	VERY LOW	IMPORTANT
FEV_1 (L) (follow-up 12-48 weeks; Better indicated by higher values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1374	1354	-	MD 0.14 lower (0.14 to 0.13 lower)	MODERATE	IMPORTANT

FEV_1 (% predicted) (follow-up 48 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	743	730	-	MD 1.98 lower (2.95 to 1.01 lower)	HIGH	IMPORTANT
PEF (L/min) (follow-up 12-104 weeks; Better indicated by higher values)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2167	2149	-	MD 11.97 lower (12.36 to 11.59 lower)	MODERATE	IMPORTANT
Infections (all respiratory) (follow-up 104 weeks)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[4]	serious[2]	none	124/571 (22%)	147/586 (25%)	RR 0.89 (0.74 to 1.07)	28 fewer per 1000 (from 65 fewer to 18 more)	VERY LOW	IMPORTANT

[1] 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
[2] 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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Adjusted control group event rates/final values/change scores not reported

J.3.1.2 People aged 5 to 16

Table 57: ICS moderate dose versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LABA**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Reliever medication use (puffs/day) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	100	-	MD 0.15 higher (0.31 lower to 0.61 higher)	HIGH	IMPORTANT
FEV_1 (% predicted) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised	no serious	no serious	no serious	no serious	none	97	100	-	MD 0.74 lower (5.35	HIGH	IMPORTANT

	trials	risk of bias	inconsistency	indirectness	imprecision					lower to 3.87 higher)		
PEF (L/min) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97	100	-	MD 10.0 lower (26.69 lower to 6.69 higher)	LOW	IMPORTANT
Infections (all respiratory) (follow-up 12 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/97 (1%)	2/100 (2%)	RR 0.52 (0.05 to 5.59)	10 fewer per 1000 (from 19 fewer to 92 more)	LOW	IMPORTANT

[1] 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

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

Table 58: ICS low dose + LABA versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LABA**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/15 (33.3%)	1/11 (9.1%)	RR 3.67 (0.5 to 27.12)	243 more per 1000 (from 45 fewer to 1000 more)	VERY LOW	CRITICAL
Quality of life (PAQLQ) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	15	10	-	MD 0.73 lower (1.75 lower to 0.29 higher)	VERY LOW	CRITICAL
Hospitalisations (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/15 (13.3%)	0/11 (0%)	OR 6.08 (0.35 to 106.55)	-	VERY LOW	IMPORTANT
FEV_1 (%predicted) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	13	8	-	MD 8.58 higher (3.56 lower to 20.72 higher)	VERY LOW	IMPORTANT

Infections (all respiratory) (follow-up 48 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29/124 (23.4%)	33/121 (27.3%)	RR 0.84 (0.55 to 1.29)	44 fewer per 1000 (from 123 fewer to 79 more)	VERY LOW	IMPORTANT

[1] 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
[2] 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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Adjusted final values/change scores not available
[5] Could not be calculated as no events in control group

Table 59: ICS low dose + LTRA versus ICS low dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LTRA**	**ICS (low dose)**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/12 (8.3%)	1/11 (9.1%)	RR 0.92 (0.06 to 12.95)	7 fewer per 1000 (from 85 fewer to 1000 more)	VERY LOW	CRITICAL
Quality of life (PAQLQ) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12	10	-	MD 0.12 higher (0.94 lower to 1.18 higher)	VERY LOW	CRITICAL
Hospitalisations (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/12 (0%)	0/11 (0%)	Not estimable	-	LOW	IMPORTANT
FEV_1 (%predicted) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15	8	-	MD 3.51 higher (9.22 lower to 16.24 higher)	VERY LOW	IMPORTANT
Infections (all respiratory) (follow-up 48 weeks)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[2]	none	7/21 (33.3%)	7/19 (36.8%)	RR 0.9 (0.39 to 2.1)	37 fewer per 1000 (from 225 fewer to 405 more)	VERY LOW	IMPORTANT

[1] 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
[2] 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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Adjusted final values/change scores not available
[5] No events in either arm

Table 60: ICS low dose + LTRA versus ICS low dose + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS + LTRA**	**ICS + LABA**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/12 (8.3%)	5/15 (33.3%)	RR 0.25 (0.03 to 1.86)	250 fewer per 1000 (from 323 fewer to 287 more)	VERY LOW	CRITICAL
Quality of life (PAQLQ) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	15	-	MD 0.84 higher (0.1 lower to 1.78 higher)	VERY LOW	CRITICAL
Hospitalisations (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/12 (0%)	2/15 (13.3%)	OR 0.15 (0.01 to 2.64)	111 fewer per 1000 (from 132 fewer to 156 more)	VERY LOW	IMPORTANT
FEV_1 (%predicted) (follow-up 48 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	15	13	-	MD 5.07 lower (16.7 lower to 6.56 higher)	VERY LOW	IMPORTANT
Infections (all respiratory) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	7/21 (33.3%)	9/23 (39.1%)	RR 0.85 (0.39 to 1.88)	59 fewer per 1000 (from 239 fewer to 344 more)	VERY LOW	IMPORTANT

[1] 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
[2] 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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Adjusted final values/change scores not available

Table 61: ICS low dose + LABA versus ICS moderate dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS + LABA	ICS (moderate dose)	Relative (95% CI)	Absolute		
Severe exacerbations (requiring OCS) (follow-up 26 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/72 (11.1%)	4/79 (5.1%)	RR 2.19 (0.69 to 6.98)	60 more per 1000 (from 16 fewer to 303 more)	VERY LOW	CRITICAL
FEV_1 (%predicted) (follow-up 26 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78	80	-	MD 1.00 higher (2.2 lower to 4.2 higher)	MODERATE	IMPORTANT
PEF (l/min, change score) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129	136	-	MD 9.3 higher (3.28 to 15.32 higher)	MODERATE	IMPORTANT
Adherence (participants with ≥75% compliance)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	138/150 (92%)	144/153 (94.1%)	RR 0.98 (0.92 to 1.04)	19 fewer per 1000 (from 75 fewer to 38 more)	MODERATE	IMPORTANT

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Adjusted control group values not provided

J.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

Table 62: Clinical evidence profile: MART versus Non-MART in people over the age of 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MART	Non-MART, >16	Relative (95% CI)	Absolute		
Severe exacerbations (follow-up 6-12 months)												
7	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	692/6035 (11.5%)	1009/5618 (18%)	RR 0.66 (0.6 to 0.72)	61 fewer per 1000 (from 50 fewer to 72 fewer)	MODERATE	CRITICAL
Mortality (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/1049 (0.1%)	1/1042 (0.1%)	RR 0.99 (0.06 to 15.86)	0 fewer per 1000 (from 1 fewer to 14 more)	LOW	CRITICAL
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1067	1076	-	MD 0.03 higher (0.07 lower to 0.13 higher)	MODERATE	CRITICAL
Control (ACQ, 0-6, higher is worse outcome) (follow-up 6-12 months; Better indicated by lower values)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4217	4253	-	MD 0.11 lower (0.14 to 0.08 lower)	HIGH	IMPORTANT
Hospitalisations (follow-up 6-12 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/2052 (0.88%)	52/2043 (2.5%)	RR 0.34 (0.2 to 0.59)	17 fewer per 1000 (from 10 fewer to 20 fewer)	HIGH	IMPORTANT
Reliever medication use (puffs/day) (follow-up 11-12 months; Better indicated by lower values)												
5	randomised	no serious	no serious	no serious	no serious	none	4985	4998	-	MD 0.15 lower (0.19	HIGH	IMPORTANT

	trials	risk of bias	inconsistency	indirectness	imprecision					to 0.11 lower)		
FEV_1 (%predicted) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	no serious imprecision	none	151	152	-	MD 2.5 higher (2 lower to 7 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up 6-12 months; Better indicated by lower values)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5136	5150	-	MD 0.05 higher (0.03 to 0.06 higher)	HIGH	IMPORTANT
PEF (L/minute) (follow-up 11-12 months; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3918	3922	-	MD 6.84 higher (4.71 to 8.98 higher)	HIGH	IMPORTANT
Infection (all respiratory) (follow-up 12 months)												
3	randomised trials	serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	240/3078 (7.8%)	226/3086 (7.3%)	RR 1.05 (0.89 to 1.24)	4 more per 1000 (from 8 fewer to 18 more)	LOW	IMPORTANT
Total steroid dose (predicted equiv, mg/year) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	no serious imprecision	none	151	152	-	MD 21.6 higher (199.38 lower to 242.58 higher)	LOW	IMPORTANT

[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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] 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
[4] Downgraded by 1 or 2 increments because the point estimate and/or the confidence intervals varied widely across studies, unexplained by subgroup analysis
[5] Adjusted baseline values for control group not available

Table 63: Clinical evidence profile: MART versus Non-MART in young people and children aged 5 to 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MART**	**Non-MART, 5 to 16**	**Relative (95% CI)**	**Absolute**		

Severe exacerbations (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/118 (8.5%)	36/117 (30.8%)	RR 0.28 (0.14 to 0.53)	222 fewer per 1000 (from 145 fewer to 265 fewer)	HIGH	CRITICAL
Reliever medication use (puffs/day) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	117	-	MD 0.18 lower (0.34 to 0.02 lower)	HIGH	IMPORTANT
FEV_1 (L) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	118	117	-	MD 0.16 higher (0.04 lower to 0.36 higher)	MODERATE	IMPORTANT
PEF (L/minute) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	118	117	-	MD 13 higher (10.52 lower to 36.52 higher)	LOW	IMPORTANT

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

J.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

Table 64: Clinical evidence profile: population uncontrolled on ICS + LABA at baseline, >16

MART (ICS moderate + LABA) vs ICS high + LABA + PRN SABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MART (ICS mod + LABA)**	**ICS high + LABA + PRN SABA**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (follow-up mean 6 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	108/1151 (9.4%)	130/1153 (11.3%)	RR 0.83 (0.65 to 1.06)	19 fewer per 1000 (from 39 fewer to 7 more)	LOW	CRITICAL
Asthma control (ACQ, 0-6, higher is worse outcome) (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1144	1145	-	MD 0.02 lower (0.07 lower to 0.03 higher)	HIGH	IMPORTANT
Rescue medication use (puffs/day) (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1144	1145	-	MD 0.04 lower (0.12 lower to 0.04 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1144	1145	-	MD 0.8 lower (4.4 lower to 2.8 higher)	HIGH	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

MART (ICS low + LABA) vs ICS low + LABA + PRN SABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MART (ICS low + LABA)**	**ICS low + LABA + PRN SABA**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/1107 (12.9%)	245/1138 (21.5%)	RR 0.6 (0.5 to 0.72)	86 fewer per 1000 (from 60 fewer to 108 fewer)	HIGH	CRITICAL
Asthma control (ACQ-5, 0-6, higher is worse outcome) (follow-up mean 1 years; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1107	1137	-	MD 0.15 lower (0.21 to 0.09 lower)	HIGH	
Reliever medication use (puffs/day) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1107	1137	-	MD 0.2 lower (0.28 to 0.12 lower)	HIGH	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1107	1138	-	MD 0.08 higher (0.05 to 0.11 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1107	1138	-	MD 7.5 higher (4.2 to 10.8 higher)	HIGH	IMPORTANT
Infections (all respiratory) (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	22/1107 (2%)	10/1138 (0.88%)	RR 2.26 (1.08 to 4.75)	11 more per 1000 (from 1 more to 33 more)	MODERATE	IMPORTANT

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

MART (ICS low + LABA) vs ICS high + LABA + PRN SABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MART (ICS low + LABA)**	**ICS high + LABA + PRN SABA**	**Relative (95% CI)**	**Absolute**		
Rescue medication use (puffs/day) (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	63	-	MD 0.04 lower (0.47 lower to 0.55 higher)	HIGH	IMPORTANT

ICS moderate/high + LABA + LAMA vs ICS moderate/high + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS mod/high + LABA + LAMA	ICS mod/high + LABA	Relative (95% CI)	Absolute		
Severe exacerbations (requiring OCS) (follow-up mean 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122/453 (26.9%)	149/454 (32.8%)	RR 0.82 (0.67 to 1)	59 fewer per 1000 (from 108 fewer to 0 more)	LOW	CRITICAL
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 24 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	456	456	-	MD 0.11 higher (0 to 0.21 higher)	MODERATE	CRITICAL
Control (ACQ, 0-6, higher is worse outcome) (follow-up mean 24 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	456	456	-	MD 0.17 lower (0.25 to 0.09 lower)	MODERATE	IMPORTANT
Reliever medication use (puffs/day) (follow-up mean 24 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	456	456	-	MD 0.17 lower (0.42 lower to 0.09 higher)	MODERATE	IMPORTANT
FEV_1 (L) (follow-up 24-52 weeks; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	523	467	-	MD 0.08 higher (0.04 to 0.12 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up 24-52 weeks; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	487	431	-	MD 18.2 higher (12.08 to 24.32	MODERATE	IMPORTANT

										higher)		
Infections (all respiratory) (follow-up 24-48 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	118/570 (20.7%)	50/513 (9.7%)	RR 1.4 (1.11 to 1.76)	39 more per 1000 (from 11 more to 74 more)	LOW	IMPORTANT
Infections (serious respiratory) (follow-up mean 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/456 (2.6%)	7/456 (1.5%)	RR 1.71 (0.68 to 4.31)	11 more per 1000 (from 5 fewer to 51 more)	VERY LOW	IMPORTANT

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

ICS high + LABA vs ICS moderate + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS high + LABA**	**ICS mod + LABA**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	54/443 (12.2%)	19/132 (14.4%)	RR 0.85 (0.52 to 1.38)	22 fewer per 1000 (from 69 fewer to 55 more)	VERY LOW	CRITICAL
Hospitalisations (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/443 (0.45%)	2/132 (1.5%)	OR 0.22 (0.02 to 2.22)	12 fewer per 1000 (from 15 fewer to 18 more)	VERY LOW	CRITICAL
Reliever medication use (puffs/day) (follow-up mean 1 years; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	438	130	-	MD 0.16 lower (0.37 lower to 0.05 higher)	MODERATE	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	436	129	-	MD 0.02 higher (0.02 lower to 0.06 higher)	MODERATE	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	441	130	-	MD 6.67 higher (0.99 lower to 14.33 higher)	MODERATE	IMPORTANT
Infections (all respiratory) (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	327/433 (75.5%)	101/132 (76.5%)	RR 0.99 (0.89 to 1.1)	8 fewer per 1000 (from 84 fewer to 77 more)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

ICS high + LABA vs ICS high

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS high + LABA**	**ICS high**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	54/443 (12.2%)	29/133 (21.8%)	RR 0.56 (0.37 to 0.84)	96 fewer per 1000 (from 35 fewer to 137 fewer)	LOW	CRITICAL
Hospitalisations (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/443 (0.45%)	0/133 (0%)	OR 3.68 (0.14 to 98.9)	-	VERY LOW	CRITICAL

Reliever medication use (puffs/day) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	438	130	-	MD 0.87 lower (1.08 to 0.66 lower)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	436	132	-	MD 0.11 higher (0.06 to 0.16 higher)	MODERATE	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	441	132	-	MD 34.7 higher (27.1 to 42.3 higher)	MODERATE	IMPORTANT
Infections (all respiratory) (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	327/443 (73.8%)	105/133 (78.9%)	RR 0.93 (0.84 to 1.04)	55 fewer per 1000 (from 126 fewer to 32 more)	MODERATE	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

ICS high vs ICS moderate + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS high**	**ICS mod + LABA**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (requiring OCS) (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	29/133 (21.8%)	19/132 (14.4%)	RR 1.51 (0.9 to 2.56)	73 more per 1000 (from 14 fewer to 225 more)	LOW	CRITICAL
Hospitalisations (follow-up mean 1 years)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/133 (0%)	2/132 (1.5%)	OR 0.13 (0.01 to 2.14)	13 fewer per 1000 (from 15 fewer to 17 more)	VERY LOW	CRITICAL
Reliever medication use (puffs/day) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	130	130	-	MD 0.72 higher (0.45 to 0.99 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	132	129	-	MD 0.09 lower (0.15 to 0.03 lower)	MODERATE	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	132	130	-	MD 28.04 lower (37.51 to 18.57 lower)	LOW	IMPORTANT
Infections (all respiratory) (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105/133 (78.9%)	101/132 (76.5%)	RR 1.03 (0.91 to 1.17)	23 more per 1000 (from 69 fewer to 130 more)	MODERATE	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

>16, ICS low + LAMA vs ICS low + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ICS low + LAMA**	**ICS low + LABA**	**Relative (95% CI)**	**Absolute**		
Number of participants experiencing at least one severe exacerbations (requiring OCS) (follow-up mean 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	111/532 (20.9%)	122/538 (22.7%)	RR 0.92 (0.73 to 1.16)	18 fewer per 1000 (from 61 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL

Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 18 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	349	371	-	MD 0.07 higher (0.21 lower to 0.35 higher)	⊕OOO VERY LOW	CRITICAL
Asthma control (ACQ, 0-6, higher is worse outcome) (follow-up mean 18 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	349	371	-	MD 0.04 lower (0.27 lower to 0.19 higher)	⊕OOO VERY LOW	IMPORTANT
FEV_1 (L) (follow-up mean 18 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	349	371	-	MD 0.03 lower (0.09 lower to 0.04 higher)	⊕OOO VERY LOW	IMPORTANT
Rescue medication use (puffs/day) (follow-up mean 18 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	349	371	-	MD 0.05 lower (0.84 lower to 0.74 higher)	⊕OOO VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 65: Clinical evidence profile: population uncontrolled on ICS moderate at baseline

>16, ICS high vs ICS moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, ICS high**	**ICS mod**	**Relative (95% CI)**	**Absolute**		

Severe Exacerbations (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	51/165 (30.9%)	56/160 (35%)	RR 0.88 (0.65 to 1.21)	42 fewer per 1000 (from 123 fewer to 74 more)	VERY LOW	CRITICAL

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Population + outcome indirectness.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

>16, ICS low + LABA vs ICS moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, ICS low + LABA**	**ICS mod**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	191/909 (21%)	176/926 (19%)	RR 1.11 (0.92 to 1.33)	21 more per 1000 (from 15 fewer to 63 more)	LOW	CRITICAL
								19%		21 more per 1000 (from 15 fewer to 63 more)		
Reliever medication (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	170	177	-	MD 0.6 lower (1.03 to 0.17 lower)	MODERATE	IMPORTANT
Reliever medication use (puffs/daytime) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	909	926	-	MD 0.19 lower (0.3 to 0.08 lower)	HIGH	IMPORTANT
Reliever medication use (puffs/night-time) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	909	926	-	MD 0.06 lower (0.1 to 0.02 lower)	HIGH	IMPORTANT

FEV_1 (L) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	909	926	-	MD 0.02 higher (0 to 0.04 higher)	HIGH	IMPORTANT
FEV_1 (%predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	170	177	-	MD 3 higher (2.17 lower to 8.17 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up 12-52 weeks; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1079	1103	-	MD 7.65 higher (3.65 to 11.65 higher)	HIGH	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

>16, ICS moderate + LABA vs ICS moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, ICS mod + LABA**	**ICS mod**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (follow-up mean 6 months)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision[3]	none	69/712 (9.7%)	99/683 (14.5%)	RR 0.66 (0.5 to 0.87)	49 fewer per 1000 (from 19 fewer to 72 fewer)	LOW	CRITICAL
Quality of life (pooled AQLQ, SGRQ) (follow-up mean 12-24 weeks; Better indicated by higher values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1040	1008	-	SMD 0.26 higher (0.17 to 0.35 higher)	MODERATE	CRITICAL
Asthma control (ACQ, 0-6, high is poor outcome) (follow-up mean 24 weeks; Better indicated by lower values)												
1	randomised	no serious	no serious	no serious	no serious	none	541	523	-	MD 0.2 lower (0.28 to	HIGH	IMPORTANT

	trials	risk of bias	inconsistency	indirectness	imprecision					0.12 lower)		
Reliever medication (puffs/day) (follow-up 12-24 weeks; Better indicated by lower values)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	688	675	-	MD 1.03 lower (1.21 to 0.85 lower)	MODERATE	IMPORTANT
Reliever medication use (puffs/daytime) (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	89	91	-	MD 0.54 lower (1.07 to 0.01 lower)	LOW	IMPORTANT
Reliever medication use (puffs/night-time) (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	89	91	-	MD 0.41 lower (0.82 lower to 0 higher)	LOW	IMPORTANT
PEF (L/min) (follow-up 12-24 weeks; Better indicated by higher values)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1827	1803	-	MD 21.72 higher (18.03 to 25.42 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up 12-24 weeks; Better indicated by higher values)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1071	1059	-	MD 0.19 higher (0.16 to 0.23 higher)	MODERATE	IMPORTANT
Infection (URTI) (follow-up 12-24 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	44/651 (6.8%)	45/636 (7.1%)	RR 0.95 (0.64 to 1.42)	4 fewer per 1000 (from 25 fewer to 30 more)	VERY LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Population and outcome indirectness.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

>16, MART (ICS low + LABA) vs ICS moderate

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, MART (ICS low + LABA)	ICS mod	Relative (95% CI)	Absolute		
Severe Exacerbations (follow-up mean 1 years)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	272/1872 (14.5%)	435/1869 (23.3%)	RR 0.62 (0.54 to 0.72)	88 fewer per 1000 (from 65 fewer to 107 fewer)	LOW	CRITICAL
Reliever medication use (puffs/daytime) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	925	926	-	MD 0.3 lower (0.48 to 0.12 lower)	HIGH	IMPORTANT
Reliever medication use (puffs/night-time) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	925	926	-	MD 0.15 lower (0.24 to 0.06 lower)	HIGH	IMPORTANT
Reliever medication use (rescue-free days %) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	947	943	-	MD 11 higher (8.2 to 13.8 higher)	MODERATE	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	925	926	-	MD 0.1 higher (0.04 to 0.16 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1872	1869	-	MD 19.71 higher (16.18 to 23.24 higher)	LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

>16, ICS moderate + LTRA vs ICS moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, ICS mod + LTRA	ICS mod	Relative (95% CI)	Absolute		
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 16 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	317	308	-	MD 0.08 higher (0.06 lower to 0.22 higher)	HIGH	CRITICAL
Reliever medication use (% change from baseline) (follow-up mean 16 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1786	1660	-	MD 12.34 lower (33.21 lower to 8.53 higher)	HIGH	IMPORTANT
FEV_1 (L, % change from baseline) (follow-up mean 16 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	317	308	-	MD 0.14 higher (4.36 lower to 4.64 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 16 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	317	308	-	MD 5.56 higher (3.95 lower to 15.07 higher)	HIGH	IMPORTANT

>16, ICS moderate + LAMA vs ICS moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, ICS mod + LAMA	ICS mod	Relative (95% CI)	Absolute		
Severe exacerbations (follow-up 6 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	31/519 (6%)	43/523 (8.2%)	RR 0.74 (0.47 to 1.13)	21 fewer per 1000 (from 44 fewer to 11 more)	LOW	
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	541	523	-	MD 0.04 higher (0.05 lower to 0.14 higher)	HIGH	CRITICAL
Asthma control (ACQ, 0-6, high is poor outcome) (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	541	523	-	MD 0.12 lower (0.2 to 0.04 lower)	HIGH	IMPORTANT
FEV_1 (L) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	541	523	-	MD 0.19 higher (0.15 to 0.22 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	541	523	-	MD 24.3 higher (17.9 to 30.7 higher)	MODERATE	IMPORTANT
Infection (URTI) (follow-up mean 6 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	19/517 (3.7%)	41/523 (7.8%)	RR 0.47 (0.28 to 0.8)	42 fewer per 1000 (from 16 fewer to 56 fewer)	LOW	IMPORTANT

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

>16, ICS low + LABA vs ICS high

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, ICS low + LABA**	**ICS high**	**Relative (95% CI)**	**Absolute**		

Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	197	194	-	MD 0.03 higher (0.15 lower to 0.21 higher)	MODERATE	CRITICAL
Asthma control (ACT, 5-25, high is good outcome) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	197	194	-	MD 0.8 higher (0.01 to 1.59 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	187	190	-	MD 0.21 higher (0.13 to 0.29 higher)	LOW	IMPORTANT
PEF (L/min) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	197	194	-	MD 33 higher (24.84 to 41.16 higher)	MODERATE	IMPORTANT

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

>16, ICS moderate + LABA vs ICS high

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, ICS mod + LABA**	**ICS high**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (follow-up mean 6 months)												
2	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	48/351 (13.7%)	53/338 (15.7%)	RR 0.87 (0.63 to 1.22)	20 fewer per 1000 (from 58 fewer to 34 more)	VERY LOW	CRITICAL
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	55	58	-	MD 0.45 higher (0.16 to 0.74 higher)	MODERATE	CRITICAL

Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	89	-	MD 1.5 lower (2.08 to 0.92 lower)	MODERATE	IMPORTANT
Reliever medication use (rescue-free days %) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	180	173	-	MD 32 higher (13.11 to 50.89 higher)	LOW	IMPORTANT
FEV_1 (%predicted) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	487	251	-	MD 5 higher (4.45 to 5.55 higher)	HIGH	IMPORTANT
FEV_1 (L) (follow-up median 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	180	173	-	MD 0.09 higher (0 to 0.18 higher)	MODERATE	IMPORTANT
PEF (L/min) (follow-up 12-24 weeks; Better indicated by higher values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	572	554	-	MD 21.74 higher (16.07 to 27.4 higher)	MODERATE	IMPORTANT
PEF (% predicted) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	487	251	-	MD 7 higher (5.51 to 8.49 higher)	HIGH	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Population and outcome.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

>16, ICS moderate + LTRA vs ICS high

Quality assessment							No of patients		Effect		Quality	Importance
No of	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**>16, ICS**	**ICS**	**Relative**	**Absolute**		

studies						considerations	mod + LTRA	high	(95% CI)			
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	485	479	-	MD 0.08 higher (0.05 lower to 0.21 higher)	MODERATE	CRITICAL
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	448	441	-	MD 0.03 lower (0.11 lower to 0.05 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 12 weeks; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	485	479	-	MD 3.21 higher (4.7 lower to 11.12 higher)	MODERATE	IMPORTANT

[1] 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

>16, ICS moderate + theophylline vs ICS high

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, ICS mod + theo	ICS high	Relative (95% CI)	Absolute		
FEV_1 (L) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	31	31	-	MD 0.08 higher (0.35 lower to 0.51 higher)	LOW	IMPORTANT
PEF (L/min) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	31	31	-	MD 6 higher (43.97 lower to 55.97 higher)	LOW	IMPORTANT

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

>16, MART (ICS low + LABA) vs ICS low + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, MART (ICS low + LABA)	ICS low + LABA	Relative (95% CI)	Absolute		
Severe Exacerbations (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	102/925 (11%)	191/909 (21%)	RR 0.52 (0.42 to 0.66)	101 fewer per 1000 (from 71 fewer to 122 fewer)	MODERATE	CRITICAL
Reliever medication use (puffs/daytime) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	925	909	-	MD 0.11 lower (0.17 to 0.05 lower)	HIGH	IMPORTANT
Reliever medication use (puffs/night-time) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	925	909	-	MD 0.09 lower (0.14 to 0.04 lower)	HIGH	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	925	909	-	MD 0.08 higher (0.03 to 0.13 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	925	909	-	MD 9 higher (3.65 to 14.35 higher)	HIGH	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.

>16, ICS moderate + LTRA vs ICS moderate + LABA

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, ICS mod + LTRA**	**ICS mod + LABA**	**Relative (95% CI)**	**Absolute**		
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	467	477	-	MD 0.2 higher (0.14 to 0.25 higher)	LOW	IMPORTANT
FEV_1 (%predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	25	-	MD 2.2 lower (5.6 lower to 1.2 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	472	476	-	MD 8.3 lower (22.16 lower to 5.56 higher)	LOW	IMPORTANT

[1] 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
[2] Downgraded by 1 or 2 increments because the point estimate and or the confidence intervals varied widely across studies, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

>16, ICS moderate + LAMA vs ICS moderate + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, ICS mod + LAMA**	**ICS mod + LABA**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	31/519 (6%)	22/541 (4.1%)	RR 1.47 (0.86 to 2.5)	19 more per 1000 (from 6 fewer to 61 more)	LOW	CRITICAL
Infection (URTI) (follow-up mean 6 months)												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	19/517 (3.7%)	41/541 (7.6%)	RR 0.48 (0.29 to 0.82)	39 fewer per 1000 (from 14 fewer to 54 fewer)	LOW	IMPORTANT

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

>16, MART (ICS moderate + LABA) vs ICS moderate + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, MART (ICS mod + LABA)**	**ICS mod + LABA**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	94/1107 (8.5%)	126/1105 (11.4%)	RR 0.74 (0.58 to 0.96)	30 fewer per 1000 (from 5 fewer to 48 fewer)	MODERATE	CRITICAL
Reliever medication use (puffs/day) (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1106	1105	-	MD 0.03 lower (0.12 lower to 0.06 higher)	HIGH	IMPORTANT
PEF (L/min) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1106	1105	-	MD 0.7 lower (4.5 lower to 3.1 higher)	HIGH	IMPORTANT
FEV_1 (L) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1106	1105	-	MD 0.01 higher (0.03 lower to 0.04 higher)	HIGH	IMPORTANT

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

>16, ICS moderate + LTRA vs ICS moderate + theophylline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, ICS mod + LTRA	ICS mod + theo	Relative (95% CI)	Absolute		
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	20	-	MD 0.1 higher (0.04 to 0.16 higher)	HIGH	IMPORTANT
FEV_1 (%predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19	20	-	MD 0.7 higher (2.91 lower to 4.31 higher)	MODERATE	IMPORTANT

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

>16, ICS moderate + LABA vs ICS moderate + theophylline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, ICS mod + LABA	ICS mod + theo	Relative (95% CI)	Absolute		
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	20	-	MD 0 higher (0.06 lower to 0.06 higher)	HIGH	IMPORTANT
FEV_1 (%predicted) (follow-up mean 12 weeks; Better indicated by higher values)												
1	randomised	no serious	no serious	no serious	serious[1]	none	25	20	-	MD 2.9 higher (0.48	MODERATE	IMPORTANT

	trials	risk of bias	inconsistency	indirectness						lower to 6.28 higher)		

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

5-16, MART (ICS low + LABA) vs ICS low + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**5-16, MART (ICS low + LABA)**	**ICS low + LABA**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	10/118 (8.5%)	36/117 (30.8%)	RR 0.28 (0.14 to 0.53)	222 fewer per 1000 (from 145 fewer to 265 fewer)	MODERATE	CRITICAL
Reliever medication use (puffs/day) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	118	117	-	MD 0.18 lower (1.24 lower to 0.88 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	118	117	-	MD 0.16 higher (0.03 lower to 0.35 higher)	MODERATE	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	118	117	-	MD 13 higher (7.72 lower to 33.72 higher)	MODERATE	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

5-16, MART (ICS low + LABA) vs ICS moderate

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**5-16, MART (ICS low + LABA)**	**ICS mod**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	10/118 (8.5%)	21/106 (19.8%)	RR 0.43 (0.21 to 0.87)	113 fewer per 1000 (from 26 fewer to 157 fewer)	MODERATE	CRITICAL
Reliever medication use (puffs/day) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	106	-	MD 0.16 lower (0.35 lower to 0.03 higher)	HIGH	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	118	106	-	MD 0.1 higher (0.14 lower to 0.34 higher)	MODERATE	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	118	106	-	MD 17 higher (6.4 to 27.6 higher)	MODERATE	IMPORTANT
Growth (cm) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	118	106	-	MD 1 higher (0.3 to 1.7 higher)	MODERATE	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

5-16, ICS low + LABA vs ICS moderate

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**5-16, ICS low + LABA**	**ICS mod**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	36/117 (30.8%)	21/106 (19.8%)	RR 1.55 (0.97 to 2.48)	109 more per 1000 (from 6 fewer to 293 more)	LOW	IMPORTANT
								19.8%		109 more per 1000 (from 6 fewer to 293 more)		
Reliever medication use (puffs/day) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	117	106	-	MD 0.02 higher (1.08 lower to 1.12 higher)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	117	106	-	MD 0.6 lower (2.09 lower to 0.89 higher)	LOW	IMPORTANT
PEF (L/min) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	117	106	-	MD 4 higher (0.04 lower to 8.04 higher)	HIGH	IMPORTANT
Growth (cm) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	117	106	-	MD 0.9 higher (0.2 to 1.6 higher)	MODERATE	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - time period for which population are preventer naïve prior to study is unclear. Outcome indirectness.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

ICS moderate + LAMA vs ICS moderate

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-16, ICS mod + LAMA	ICS mod	Relative (95% CI)	Absolute		
Severe Exacerbations (follow-up mean 48 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/134 (1.5%)	9/138 (6.5%)	RR 0.23 (0.05 to 1.04)	50 fewer per 1000 (from 62 fewer to 3 more)	MODERATE	CRITICAL
Quality of life (AQLQ, 1-7, higher is better outcome) - New Subgroup (follow-up mean 48 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	129	132	-	MD 0.03 higher (0.14 lower to 0.2 higher)	HIGH	CRITICAL
Reliever medication (puffs/day) (follow-up mean 48 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	123	126	-	MD 0.28 lower (0.55 lower to 0 higher)	HIGH	CRITICAL
FEV_1 (L) (follow-up mean 24 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	129	132	-	MD 1.17 higher (0.05 to 2.29 higher)	MODERATE	IMPORTANT

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

Table 66: Clinical evidence profile: population uncontrolled on ICS high at baseline

>16, Add LTRA vs placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, Add LTRA	Placebo	Relative (95% CI)	Absolute		
Reliever medication use (puffs/day) (follow-up mean 12 weeks; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	8	-	MD 0.8 lower (1.53 to 0.07 lower)	LOW	IMPORTANT
FEV_1 (L) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	8	-	MD 0.17 higher (0.08 to 0.25 higher)	LOW	IMPORTANT
PEF (L/min) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	8	-	MD 14.8 lower (26.62 to 2.98 lower)	LOW	IMPORTANT

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

>16, Add LABA vs placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, Add LABA**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Reliever medication use (puffs/day) (follow-up mean 12 months; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	279	177	-	MD 0.74 lower (1.1 to 0.38 lower)	MODERATE	IMPORTANT
FEV_1 (L) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	49	-	MD 0.03 higher (0.13 lower to 0.19 higher)	HIGH	IMPORTANT

PEF (L/min) (follow-up 12 weeks; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	612	332	-	MD 24.12 higher (18.65 to 29.59 higher)	MODERATE	IMPORTANT
Infection (all respiratory)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	27/341 (7.9%)	6/115 (5.2%)	RR 1.52 (0.64 to 3.58)	27 more per 1000 (from 19 fewer to 135 more)	VERY LOW	IMPORTANT

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

>16, Add LABA vs Add LABA, reduce ICS to moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>16, Add LABA**	**Add LABA, reduce ICS to moderate**	**Relative (95% CI)**	**Absolute**		
PEF (L/min) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	167	157	-	MD 3.2 higher (8.6 lower to 15 higher)	HIGH	IMPORTANT
Infection (all respiratory) (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/216 (8.3%)	26/212 (12.3%)	RR 0.68 (0.38 to 1.2)	39 fewer per 1000 (from 76 fewer to 25 more)	LOW	IMPORTANT
Infection (serious respiratory) (follow-up mean 12 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/216 (0.46%)	0/212 (0%)	OR 7.25 (0.14 to 365.61)	-	LOW	IMPORTANT

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

>16, MART (ICS moderate) vs ICS moderate + LABA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>16, MART (ICS mod)	ICS mod + LABA	Relative (95% CI)	Absolute		
Severe exacerbations (requiring OCS) (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	132/1067 (12.4%)	167/1076 (15.5%)	RR 0.8 (0.64 to 0.99)	31 fewer per 1000 (from 2 fewer to 56 fewer)	LOW	CRITICAL
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1067	1076	-	MD 0.03 higher (0.07 lower to 0.13 higher)	MODERATE	CRITICAL
Control (ACQ, 0-6, higher is worse outcome) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1067	1076	-	MD 0.08 lower (0.16 lower to 0 higher)	MODERATE	IMPORTANT
Reliever medication use (puffs/day, average over whole treatment) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1067	1076	-	MD 0.35 lower (0.55 to 0.15 lower)	MODERATE	IMPORTANT
FEV_1 (L) (follow-up mean 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1067	1076	-	MD 0.03 higher (0.01 lower to 0.07 higher)	MODERATE	IMPORTANT

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

5 to 16, Add LABA vs placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5 to 16, Add LABA	Placebo	Relative (95% CI)	Absolute		
FEV_1 (% predicted) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88	97	-	MD 3.63 higher (0.72 to 6.54 higher)	MODERATE	IMPORTANT
PEF (L/min) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	97	-	MD 10.8 higher (3.4 to 18.2 higher)	MODERATE	IMPORTANT
Infection (all respiratory) (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	31/95 (32.6%)	36/101 (35.6%)	RR 0.92 (0.62 to 1.35)	29 fewer per 1000 (from 135 fewer to 125 more)	VERY LOW	IMPORTANT

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

J.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

Table 67: Clinical evidence profile: intermittent ICS vs regular ICS in patients over 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent ICS	Regular ICS (>16)	Relative (95% CI)	Absolute		
Severe asthma exacerbations (follow-up 1 years; assessed with: Requirement for OCS, either self-administered or from ED)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/70 (11.4%)	10/67 (14.9%)	RR 0.77 (0.32 to 1.82)	34 fewer per 1000 (from 101 fewer to 122 more)	LOW	CRITICAL
AQLQ (change score) (follow-up 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	67	Mean control group change score 0.5	MD 0.2 lower (0.48 lower to 0.08 higher)	HIGH	CRITICAL
ACQ (change score) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	73	70	Mean control group change score -0.4	MD 0.1 higher (0.12 lower to 0.32 higher)	HIGH	IMPORTANT
Exacerbations requiring hospitalisation (follow-up 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/73 (0%)	0/76 (0%)	-	-	HIGH	IMPORTANT
Rescue medication use (puffs/day) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	124	110	Mean control group puffs/day 0.44	MD 0.06 higher (0.13 lower to 0.25 higher)	HIGH	IMPORTANT
Lung function (Morning PEF, change score, %) (follow-up 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	66	Mean control group change (%) 8.3	MD 1.2 lower (6.61 lower to 4.21 higher)	HIGH	IMPORTANT
Lung function (Morning PEF, final value, l/min) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	124	110	Mean control group final value 433.08 l/min	MD 9.67 higher (18.8 lower to 38.14 higher)	MODERATE	IMPORTANT
Lung function (FEV_1, change score, %) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	67	Mean control group change (%) 4.0	MD 3.3 lower (3.69 to 2.91 lower)	HIGH	IMPORTANT

Lung function (FEV_1, final value, %predicted) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	124	110	Mean control group final value 90.32 %predicted	MD 1.91 higher (1.29 lower to 5.11 higher)	HIGH	IMPORTANT

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

2 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 68: Clinical evidence profile: intermittent ICS vs regular ICS in patients 5 to 16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intermittent ICS**	**Regular ICS (5 to 16)**	**Relative (95% CI)**	**Absolute**		
Severe asthma exacerbations (follow-up 44 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	25/58 (43.1%)	42/126 (33.3%)	RR 1.29 (0.88 to 1.9)	97 more per 1000 (from 40 fewer to 300 more)	VERY LOW	CRITICAL
Linear growth (cm) (follow-up 44 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	58	126	Mean control group growth 3.5cm	MD 0.8 higher (0.05 to 1.55 higher)	LOW	IMPORTANT
Linear growth (velocity, cm) (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	46	52	Mean control group growth velocity 5.6cm	MD 0.6 higher (0.13 to 1.07 higher)	VERY LOW	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments)

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

[3] 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 69: Clinical evidence profile: intermittent ICS vs regular ICS in children under 5

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent ICS	Regular ICS (0 to 5)	Relative (95% CI)	Absolute		
Severe asthma exacerbations (time to event) (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	139	139	HR 1.03 (0.82 to 1.29)	-	VERY LOW	CRITICAL
Mortality (follow-up 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	0/139 (0%)	0/139 (0%)	-	-	MODERATE	CRITICAL
Exacerbations requiring hospitalisation (follow-up 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	5/139 (3.6%)	4/139 (2.9%)	RR 1.25 (0.34 to 4.56)	7 more per 1000 (from 19 fewer to 102 more)	VERY LOW	IMPORTANT
Rescue medication use (daytime, puffs/day) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	110	110	Mean control group 0.09 puffs/day	MD 0 higher (0.08 lower to 0.08 higher)	MODERATE	IMPORTANT
Rescue medication use (night-time, puffs/day) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	110	110	Mean control group 0.04 puffs/day	MD 0 higher (0.04 lower to 0.04 higher)	MODERATE	IMPORTANT
Rescue medication use (% of days with SABA use) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	139	139	Mean control group 5% of days with SABA use	MD 0.4 higher (1 lower to 1.8 higher)	LOW	IMPORTANT

Linear growth (cm) (follow-up 1 years; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	139	139	Mean control group 7.76cm growth	MD 0.26 higher (0.17 lower to 0.69 higher)	LOW	IMPORTANT

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

J.5 Improving adherence to treatment

Table 70: Clinical evidence profile: Education compared to usual care for adults with asthma (>16).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education	Usual care	Relative (95% CI)	Absolute		
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up 6-9 months; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	92	45	-	MD 0.22 higher (0.15 lower to 0.6 higher)	VERY LOW	CRITICAL
Asthma control (ACQ, 0-6, higher is worse outcome) (follow-up mean 9 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	33	13	-	MD 0.1 higher (0.56 lower to 0.76 higher)	VERY LOW	IMPORTANT
Adherence (%) (follow-up mean 9 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	33	13	-	MD 28.21 higher (1.93 to 54.49 higher)	LOW	CRITICAL
Adherence (self-reported, 1-10) (follow-up mean 2 years; range of scores: 1-10; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	33	34	-	MD 1 higher (0.03 lower to 2.03 higher)	LOW	CRITICAL

Adherence (self-reported, 4-16) (follow-up mean 6 months; range of scores: 4-16; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	none	serious[2]	none	59	32	-	MD 0.91 higher (0.19 lower to 2.01 higher)	LOW	CRITICAL
Adherence (pooled) (follow-up 6-24 months; Better indicated by higher values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[2]	none	125	79	-	SMD 0.48 higher (0.19 to 0.77 higher)	LOW	CRITICAL
Adherence (checklist - % with 100%) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	132	135	-	MD 39 higher (28 to 50 higher)	VERY LOW	CRITICAL

[1] 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.
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 71: Clinical evidence profile: Behavioural change intervention compared to usual care for adults with asthma (>16).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Behavioural change**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Quality of life (AQLQ, 1-7, higher is better outcome) (follow-up mean 1 years; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	33	39	-	MD 0.33 higher (0.23 lower to 0.89 higher)	LOW	CRITICAL
Adherence (%) (follow-up mean 1 years; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	serious[3]	serious[1]	serious[2]	none	35	39	-	MD 14.55 higher (0.98 to 28.12 higher)	VERY LOW	CRITICAL
Asthma control (ACQ, 0-6, higher is worse outcome) (follow-up mean 1 years; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	33	39	-	MD 0.37 lower (0.88 lower to 0.13 higher)	LOW	IMPORTANT

Asthma control (ACT, 5-25, higher is better outcome) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	26	28	-	MD 0 higher (2.7 lower to 2.7 higher)	LOW	IMPORTANT
Lung function - FEV_1 (% predicted) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	7	11	-	MD 5.2 higher (18.96 lower to 29.36 higher)	VERY LOW	IMPORTANT

[1] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 or 2 increments because of heterogeneity, I^2=76%, p=0.04, unexplained by subgroup analysis.

Table 72: Clinical evidence profile: Alerts/behavioural change compared to usual care for adults with asthma (>16).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Alerts**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Adherence (%) (follow-up mean 9 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	41	52	-	MD 14.6 higher (1.69 to 27.51 higher)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 73: Clinical evidence profile: Education compared to usual care for young people with asthma (5-16).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Education**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Adherence (self-reported, 1-10) (follow-up mean 2 years; range of scores: 1-10; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[1]	serious[2]	none	33	34	-	MD 1 higher (0.03 lower to 2.03 higher)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 74: Clinical evidence profile: Education + Behavioural change compared to usual care for young people with asthma (5-16).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Education + Behaviour**	**Education**	**Relative (95% CI)**	**Absolute**		
Quality of life (PedQL, 0-100, higher is better outcome) (follow-up mean 1 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	2	3	-	MD 14.32 higher (17.35 lower to 45.99 higher)	VERY LOW	CRITICAL

[1] 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.
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

J.6 Self-management plans

Table 75: Clinical evidence profile: Self-management package versus usual care in patients aged 16 and over

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Self-Management package**	**Usual care (>16)**	**Relative (95% CI)**	**Absolute**		
Quality of life (follow-up mean 9 months; Better indicated by lower values)												

2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	128	87	-	MD 0.38 higher (0.32 to 0.45 higher)	LOW	CRITICAL
Serious exacerbations (follow-up mean 15 months)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	46/182 (25.3%)	33/142 (23.2%)	RR 1.05 (0.72 to 1.52)	12 more per 1000 (from 65 fewer to 121 more)	VERY LOW	CRITICAL
Serious exacerbations per patient (follow-up mean 12 months; Better indicated by lower values)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	132	91	-	MD 0.53 lower (0.84 to 0.22 lower)	VERY LOW	CRITICAL
Total no. of hospital admissions (follow-up mean 9 months)												
4	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	25/200 (12.5%)	48/151 (31.8%)	OR 0.27 (0.15 to 0.49)	206 fewer per 1000 (from 132 fewer to 253 fewer)	MODERATE	IMPORTANT
Total no. of hospital admissions per patient (follow-up mean 12 months; Better indicated by lower values)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	145	100	-	MD 0.01 higher (0.09 lower to 0.1 higher)	VERY LOW	IMPORTANT
% predicted FEV_1 (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	37	37	-	MD 6.1 higher (2.67 lower to 14.87 higher)	VERY LOW	IMPORTANT

[1] 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.
[2] Downgraded by 1 increment if the measure if I^2 50-75%, downgraded by 2 increments if I^2 greater than 75%.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both

Table 76: Clinical evidence profile: Self-management package versus usual care in patients aged between 5 and 16 years

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-Management package	Usual care (5 to 16)	Relative (95% CI)	Absolute		
Quality of life (follow-up mean 10.3 months; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	302	286	-	MD 0.18 higher (0.03 to 0.34 higher)	LOW	CRITICAL
Total no. of hospital admissions (follow-up mean 6.5 months)												
2	randomised trials	serious[1]	serious[3]	serious[2]	very serious[4]	none	8/109 (7.3%)	6/100 (6%)	RR 1.21 (0.44 to 3.13)	13 more per 1000 (from 34 fewer to 128 more)	VERY LOW	IMPORTANT
Total no. of hospital admissions per patient (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	175	170	-	MD 0.19 lower (0.37 to 0.01 lower)	MODERATE	IMPORTANT
Serious exacerbations (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4]	none	6/46 (13%)	7/44 (15.9%)	RR 0.82 (0.3 to 2.25)	29 fewer per 1000 (from 111 fewer to 199 more)	VERY LOW	CRITICAL
Serious exacerbations per patient (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[4]	none	32	28	-	MD 0.5 lower (0.83 to 0.17 lower)	VERY LOW	CRITICAL
Asthma control (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	46	44	-	MD 0.04 higher (0.26 lower to 0.34 higher)	MODERATE	IMPORTANT
Peak expiratory flow rate (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4]	none	45	46	-	MD 1.97 higher (3.04 lower to 6.98 higher)	VERY LOW	IMPORTANT

[1] 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.
[2] Downgraded by1 increment due to indirectness in the population or by 2 increments if further indirectness in the outcome.
[3] Downgraded by 1 increment if the measure if I^2 50-75%, downgraded by 2 increments if I^2 greater than 75%.
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 77: Clinical evidence profile: Self-management package versus usual care in children aged under 5

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-Management package	Usual care (<5)	Relative (95% CI)	Absolute		
Total no. of hospital admissions (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/97 (26.8%)	19/90 (21.1%)	RR 1.4 (0.83 to 2.35)	84 more per 1000 (from 36 fewer to 285 more)	LOW	IMPORTANT

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

J.7 Dose variation within self-management plans

Table 78: Clinical evidence profile: Doubling compared to fixed dose for adults (>16) with asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doubling	Fixed dose	Relative (95% CI)	Absolute		
Severe exacerbations (requiring OCS) (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	19/110 (17.3%)	22/97 (22.7%)	RR 0.76 (0.44 to 1.32)	54 fewer per 1000 (from 127 fewer to 73 more)	VERY LOW	CRITICAL
Exacerbation (at 3 months following treatment success) (follow-up mean 12 months)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/34 (14.7%)	6/35 (17.1%)	RR 0.86 (0.29 to 2.55)	24 fewer per 1000 (from 122 fewer to 266 more)	VERY LOW	CRITICAL
Treatment failure (OCS within 14 days) (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	12/46 (26.1%)	9/52 (17.3%)	RR 1.51 (0.70 to 3.25)	88 more per 1000 (from 52 fewer to 389 more)	LOW	CRITICAL

Treatment failure (unscheduled visit/persistent PEF or symptom changes) (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	7/46 (15.2%)	12/52 (23.1%)	RR 0.66 (0.28 to 1.53)	78 fewer per 1000 (from 166 fewer to 122 more)	LOW	CRITICAL
Treatment failure (symptoms fail to improve/PEF remains low/withdrawal due to adverse events at 14 days) (follow-up unclear)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/18 (61.1%)	11/18 (61.1%)	RR 1 (0.59 to 1.68)	0 fewer per 1000 (from 251 fewer to 416 more)	LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] 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 79: Clinical evidence profile: Quadrupling compared to fixed dose for adults (>16) with asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quadrupling**	**Fixed dose**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (OCS) (follow-up 12 months)												
1	randomised trials	none	none	serious[2]	none	none	12/56 (21.4%)	19/38 (50%)	RR 0.43 (0.24 to 0.78)	285 fewer per 1000 (from 110 fewer to 380 fewer)	MODERATE	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
[3] 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 profile: Quintupling compared to fixed dose for adults (>16) with asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quadrupling**	**Fixed dose**	**Relative (95% CI)**	**Absolute**		
Exacerbations (risk of second exacerbation) (follow-up 6 months)												

1	randomised trials	serious[1]	none	none	very serious[3]	none	5/12 (41.7%)	7/24 (29.2%)	RR 1.43 (0.57 to 3.57)	125 more per 1000 (from 125 fewer to 750 fewer)	VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
[3] 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 profile: Quadrupling compared to doubling dose for young people (5-16) with asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quadrupling**	**Doubling**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (OCS) (follow-up mean unclear)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/30 (6.7%)	2/24 (8.3%)	RR 0.8 (0.12 to 5.27)	17 fewer per 1000 (from 73 fewer to 356 more)	VERY LOW	CRITICAL

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

Table 82: Clinical evidence profile: Octupling compared to doubling dose for young people (5-16) with asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Octupling**	**Doubling**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (OCS) (follow-up mean unclear)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	2/24 (8.3%)	OR 0.11 (0.01 to 1.69)	73 fewer per 1000 (from 82 fewer to 59 more)	VERY LOW	CRITICAL

[1] 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
[2] 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 profile: Octupling compared to quadrupling dose for young people (5-16) with asthma

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Octupling**	**Quadrupling**	**Relative (95% CI)**	**Absolute**		
Severe exacerbations (OCS) (follow-up mean unclear)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	2/30 (6.7%)	OR 0.14 (0.01 to 2.29)	57 fewer per 1000 (from 66 fewer to 74 more)	VERY LOW	CRITICAL

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

J.8 Decreasing regular maintenance treatment

Quality assessment							**Quality**
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations, including publication bias where possible	
ACQ							
1	Cohort study	Very high [a]	NA	None	serious imprecision	None	VERY LOW
FeNO							
2	Cohort study	Very high [a]	NA	serious indirectness[b]	serious imprecision	None	LOW
Duration of asthma control							
1	Cohort study	High[a]	NA	very serious indirectness[b]	no serious imprecision	None	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity/specificity as this was the primary measure discussed in decision-making
(a) Risk of bias was assessed based on consideration of the areas covered by the NICE, CASP and SIGN checklists.

(b) Indirectness was assessed referring to applicability of the study.

(c) Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. As a rule of thumb a range of 0–20% of differences in point estimates of sensitivity was considered not imprecise, 20–40% serious imprecisions, and >40% very serious imprecision. Imprecision was assessed on the primary measure for decision-making.

J.9 Breathing exercises in addition to pharmacological treatment

Table 84: Clinical evidence profile: breathing exercise versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Breathing exercise	Usual care	Relative (95% CI)	Absolute		
Quality of life: AQLQ at 6 months, scale 1 to 7, better indicated by higher values (follow-up mean 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	94	89	-	MD 0.38 higher (0.08 higher to 0.68 higher)	VERY LOW	CRITICAL
Quality of life: SGRQ at 12 months, final score (follow-up mean 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	32	40	-	MD 1.5 lower (6.71 lower to 3.71 higher)	VERY LOW	CRITICAL
Quality of life: SF-36 physical at 6 months, final score (follow-up mean 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	20	20	-	MD 3.51 higher (0.13 lower to 7.15 higher)	VERY LOW	CRITICAL
Quality of life: SF-36 mental at 6 months, final score (follow-up mean 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	20	20	-	MD 1.52 lower (7.54 lower to 4.5 higher)	VERY LOW	CRITICAL
Asthma control: ACQ, between-group difference at 6 months, change score, scale 1 to 6, better indicated by lower values (follow-up mean 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	63	66	-	MD -0.17 lower (-0.38 lower to 0.04 higher)	VERY LOW	IMPORTANT

Asthma control: ACT at 6 months, final score (follow-up mean 6 months; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	20	20	-	MD 1.7 higher (0.27 lower to 3.67 higher)	VERY LOW	IMPORTANT
Lung function: FEV_1 (l) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	39	46	-	MD 0.10 higher (0.26 lower to 0.46 higher)	VERY LOW	IMPORTANT
Lung function: FEV_1 % predicted at 6 months (follow-up median 6 months; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	141	140	-	MD 12.86 higher (11.83 to 13.88 higher)	VERY LOW	IMPORTANT
Lung function: PEF % predicted at 6 months (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	121	120	-	MD 10.54 higher (9.48 to 11.6 higher)	LOW	IMPORTANT

[1] Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one/two increments because: Heterogeneity, I^2=50%
[3] Downgraded by one/two increments because the majority of the evidence included an indirect population (downgraded by one increment) or by a very indirect population (downgraded by two increments)
[4] Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDS

J.10 Managing patients in relation to risk of poor outcomes

Table 85: Clinical evidence profile: Care by risk stratification compared to usual care for people with asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Care by risk stratification**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Severe Exacerbations (requiring OCS) (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	247/457 (54%)	213/454 (46.9%)	OR 1.28 (0.95 to 1.72)	62 more per 1000 (from 13 fewer to 134 more)	LOW	CRITICAL

Hospitalisations (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	15/457 (3.3%)	29/454 (6.4%)	OR 0.51 (0.26 to 1)	30 fewer per 1000 (from 46 fewer to 0 more)	LOW	CRITICAL
SABA use (rate of prescriptions) (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	6/457 (1.3%)	7/454 (1.5%)	1.03 (0.91 to 1.17)	0 more per 1000 (from 1 fewer to 3 more)	MODERATE	IMPORTANT

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments) - lack of physicians diagnosis.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix K: Forest plots

K.1 Treatment in patients not on regular preventers

None.

K.2 Choice of first-line preventer in patients with poor asthma control

K.2.1 ICS (low dose) versus Placebo in patients over 16

Figure 14: Severe exacerbations (requiring OCS)

Figure 15: Lung function (morning PEF)

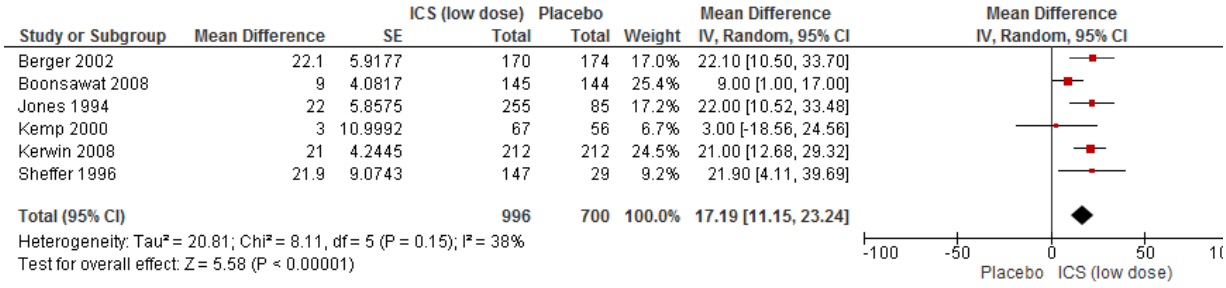


Figure 16: Lung function (FEV_1 %)

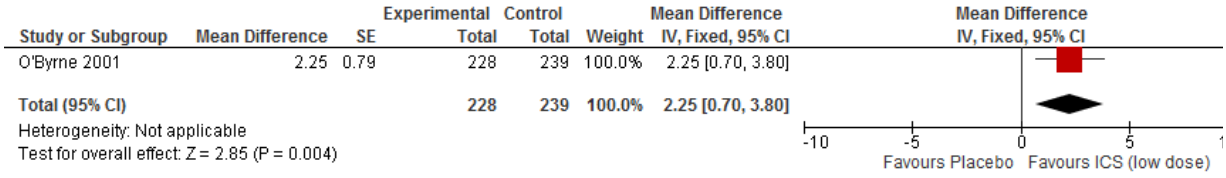


Figure 17: Lung function (FEV_1 [L])

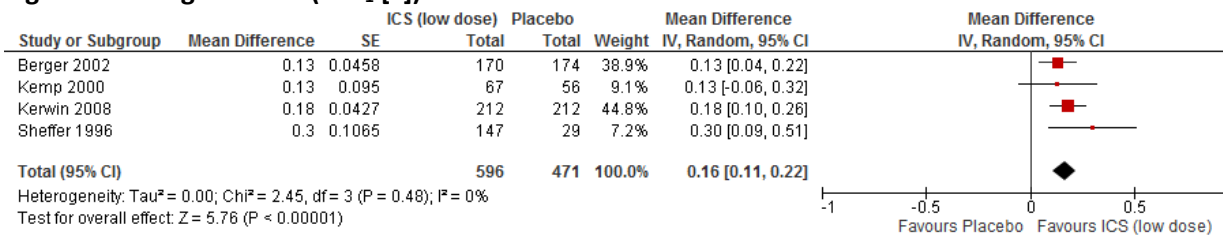


Figure 18: Reliever medication use (puffs/day)

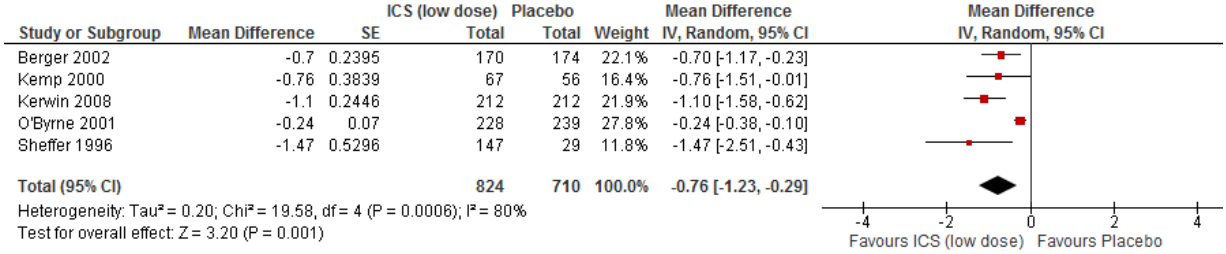


Figure 19: Reliever medication use (daytime puffs)

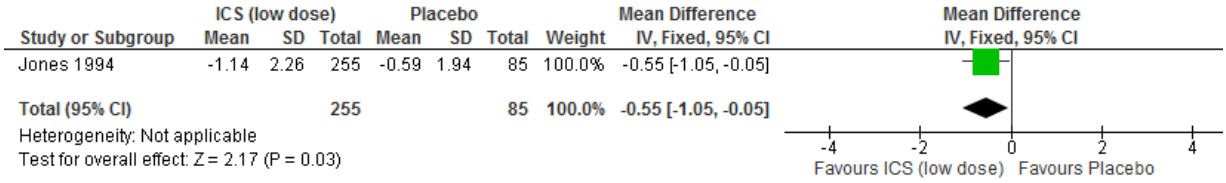


Figure 20: Reliever medication use (night-time puffs)

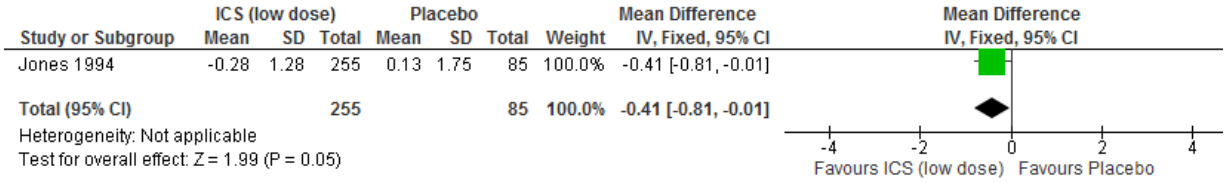


Figure 21: Infection (URTI)

K.2.2 ICS (moderate dose) versus Placebo in patients over 16

Figure 22: Severe exacerbations (requiring OCS)

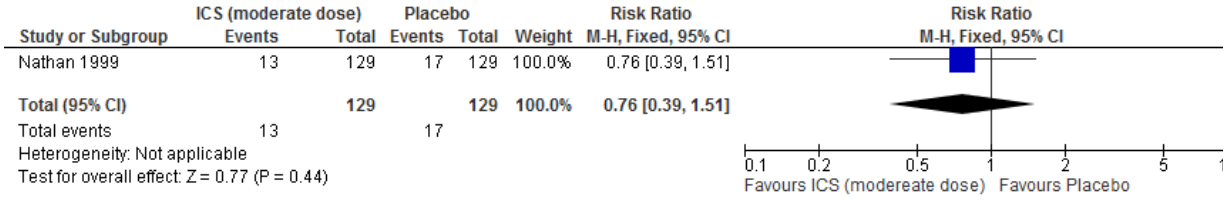


Figure 23: Lung function (morning PEF)

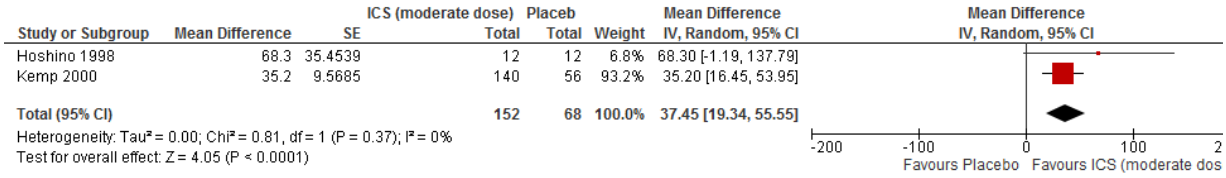


Figure 24: Lung function (FEV_1 %)

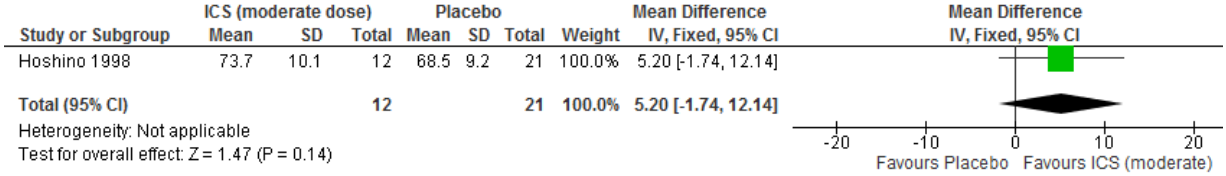


Figure 25: Lung function (FEV_1 [L])

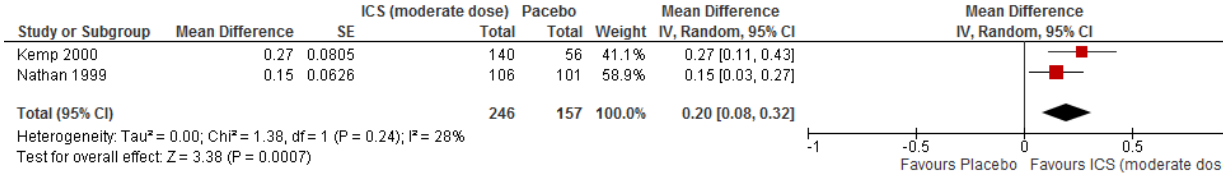


Figure 26: Reliever medication use (puffs/day)

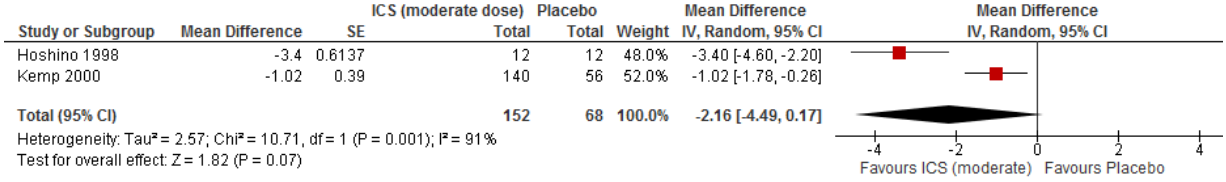


Figure 27: Reliever medication use (daytime puffs)

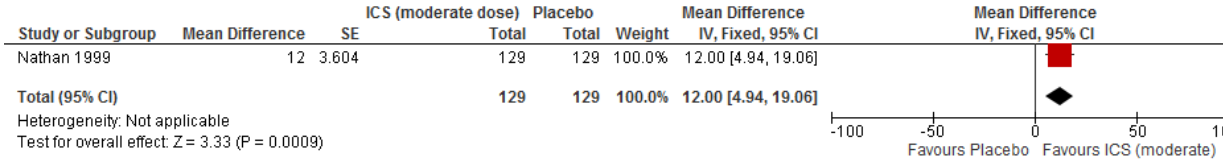
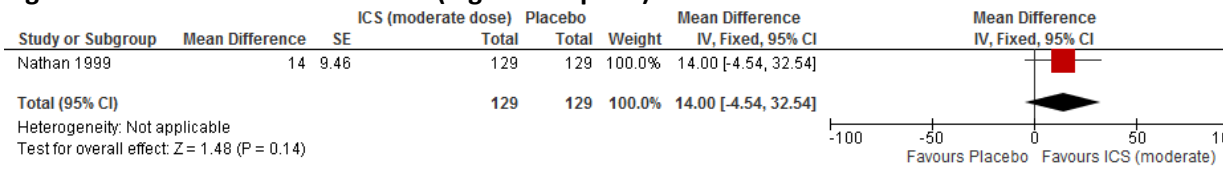


Figure 28: Reliever medication use (night-time puffs)



K.2.3 ICS + LABA versus Placebo in patients over 16

Figure 29: Severe exacerbations (requiring OCS)

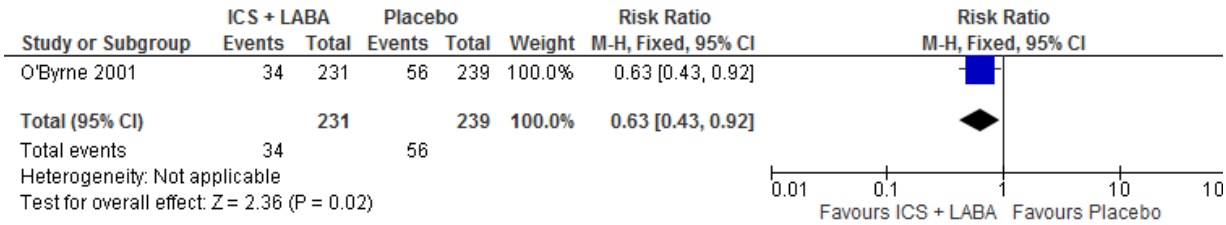


Figure 30: Lung function (morning PEF)

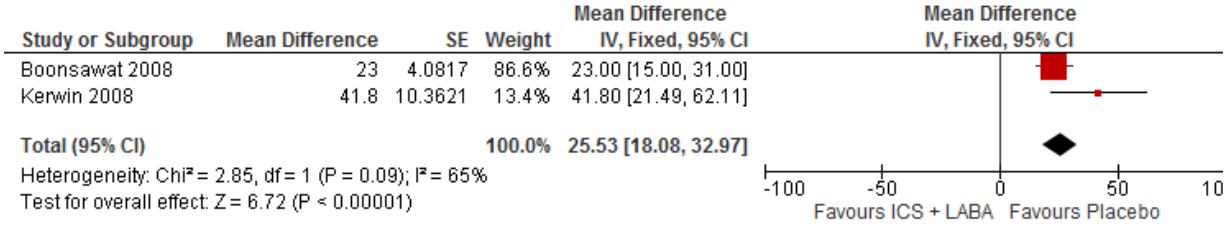


Figure 31: Lung function (FEV_1 %)

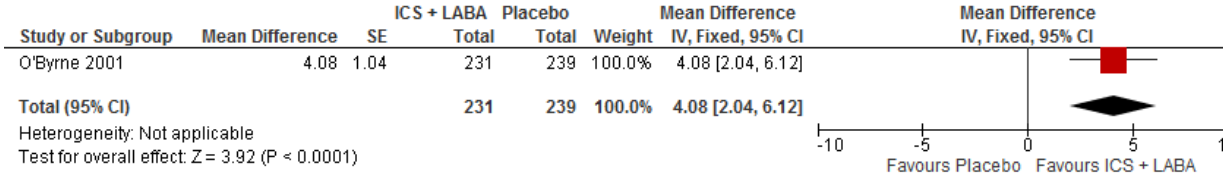


Figure 32: Lung function (FEV_1 [L])

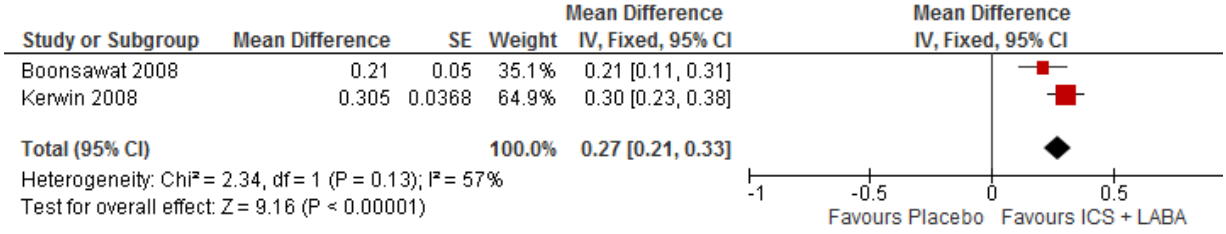


Figure 33: Reliever medication use (puffs/day)

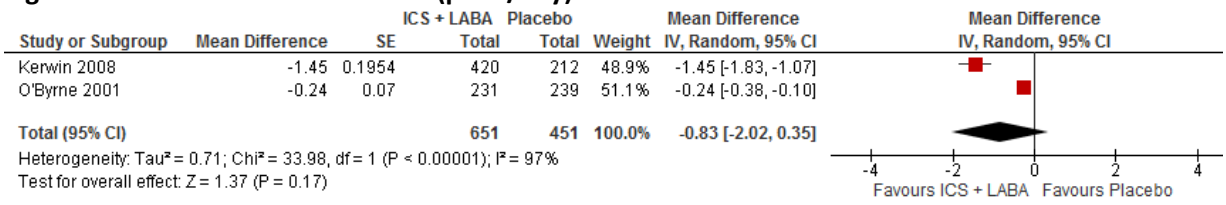
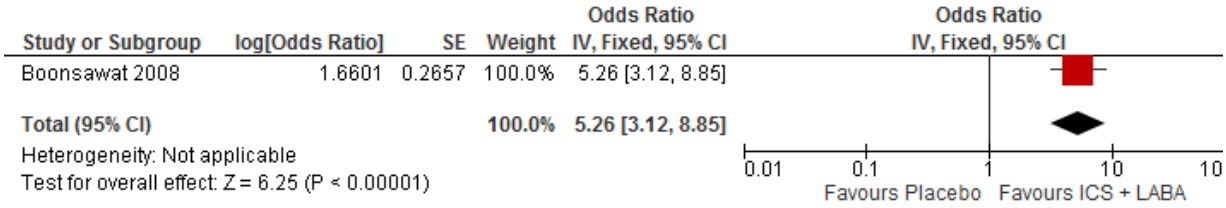


Figure 34: Reliever medication use (rescue free days (%))



K.2.4 LTRA versus Placebo in patients over 16

Figure 35: Lung function (morning PEF)

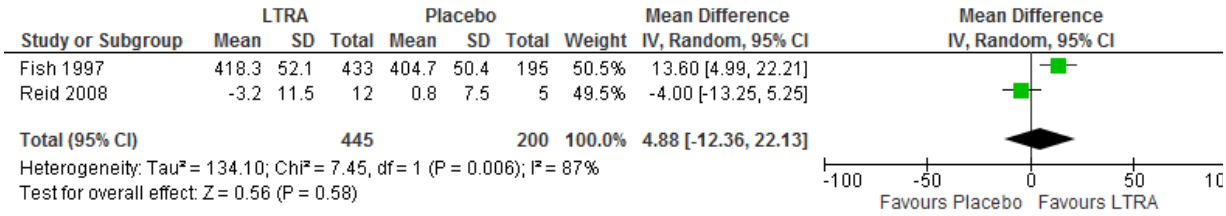


Figure 36: Lung function (FEV_1 [L])

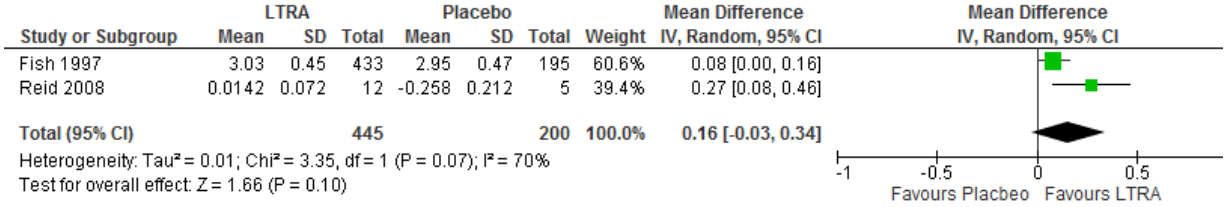
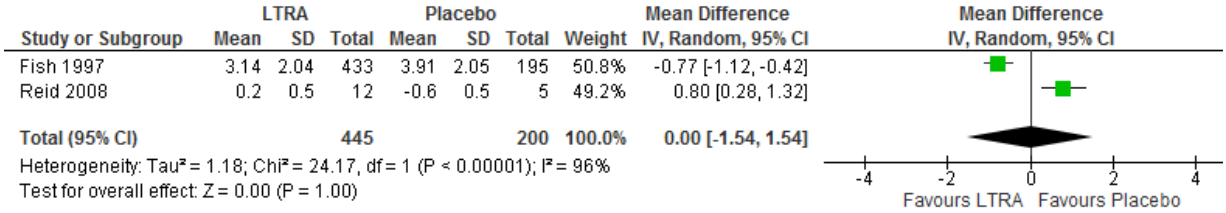


Figure 37: Reliever medication use (puffs/day)



K.2.5 ICS (moderate dose) versus ICS (low dose) in patients over 16

Figure 38: Lung function (morning PEF)

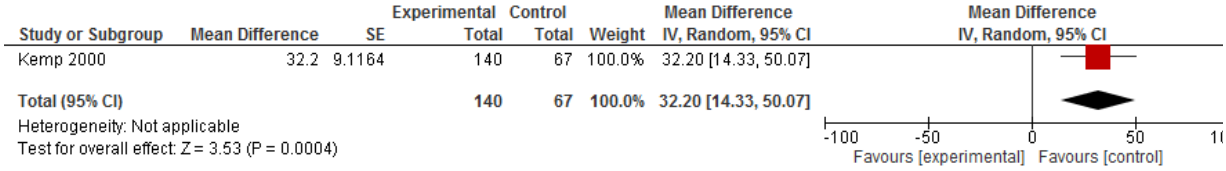
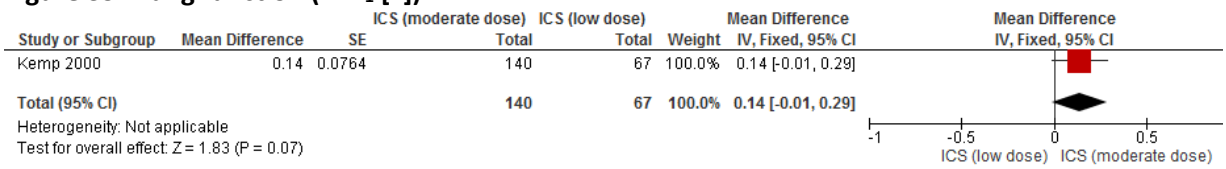
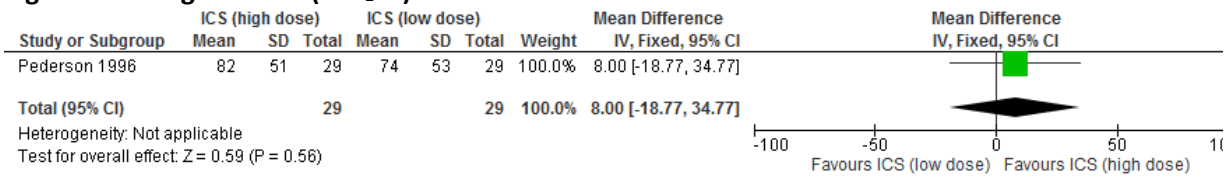


Figure 39: Lung function (FEV_1 [L])



K.2.6 ICS (high dose) versus ICS (low dose) in patients over 16

Figure 40: Lung function (FEV_1 %)



K.2.7 ICS + LABA versus ICS (low dose) in patients over 16

Figure 41: Severe exacerbations (requiring OCS)

Study or Subgroup	ICS + LABA Events	ICS + LABA Total	ICS (low dose) Events	ICS (low dose) Total	Weight	Risk Ratio M-H, Fixed, 95% CI
O'Byrne 2001	34	231	27	228	100.0%	1.24 [0.78, 1.99]
Total (95% CI)		**231**		**228**	**100.0%**	**1.24 [0.78, 1.99]**
Total events	34		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)

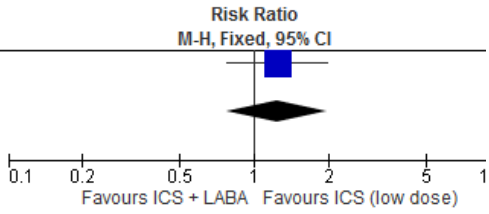


Figure 42: Mortality

Study or Subgroup	ICS + LABA Events	ICS + LABA Total	ICS (low dose) Events	ICS (low dose) Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Renzi 2010	0	209	0	224		Not estimable
Total (95% CI)		**209**		**224**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

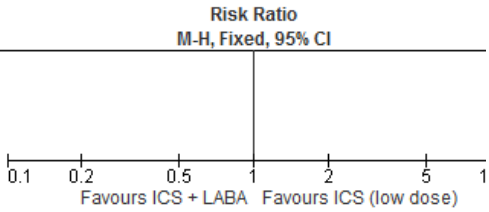


Figure 43: Lung function (morning PEF)

Study or Subgroup	Mean Difference	SE	ICS + LABA Total	ICS (low dose) Total	Weight	Mean Difference IV, Fixed, 95% CI
Boonsawat 2008	14	3.9286	144	145	13.8%	14.00 [6.30, 21.70]
Chuchalin 2008	-5.3	1.9388	973	970	56.5%	-5.30 [-9.10, -1.50]
Kerwin 2008	20.8	3.6789	420	212	15.7%	20.80 [13.59, 28.01]
Nelson 2003	23.5	8.0343	86	89	3.3%	23.50 [7.75, 39.25]
Renzi 2010	15	4.4389	262	270	10.8%	15.00 [6.30, 23.70]
Total (95% CI)			**1885**	**1686**	**100.0%**	**4.58 [1.73, 7.44]**

Heterogeneity: Chi² = 62.21, df = 4 (P < 0.00001); I² = 94%
Test for overall effect: Z = 3.15 (P = 0.002)

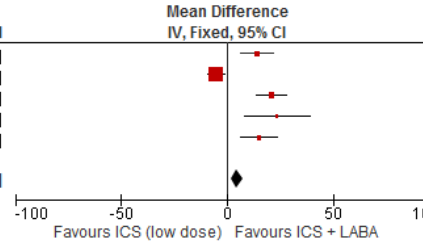


Figure 44: Lung function (FEV_1 %)

Study or Subgroup	Mean Difference	SE	ICS + LABA Total	ICS (low dose) Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Byrne 2001	1.83	0.8	231	228	100.0%	1.83 [0.26, 3.40]
Total (95% CI)			**231**	**228**	**100.0%**	**1.83 [0.26, 3.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)

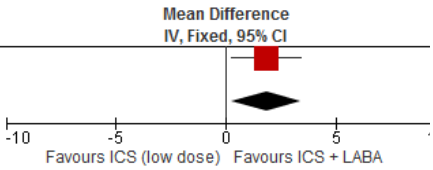


Figure 45: Lung function (FEV_1 [L])

Study or Subgroup	Mean Difference	SE	ICS + LABA Total	ICS (low dose) Total	Weight	Mean Difference IV, Fixed, 95% CI
Boonsawat 2008	0.18	0.0444	144	145	9.9%	0.18 [0.09, 0.27]
Chuchalin 2008	0.027	0.0194	973	970	52.1%	0.03 [-0.01, 0.07]
Kerwin 2008	0.125	0.0368	420	212	14.5%	0.13 [0.05, 0.20]
Nelson 2003	0.18	0.0741	86	89	3.6%	0.18 [0.03, 0.33]
Renzi 2010	0.06	0.0314	253	263	19.9%	0.06 [-0.00, 0.12]
Total (95% CI)			**1876**	**1679**	**100.0%**	**0.07 [0.04, 0.10]**

Heterogeneity: Chi² = 15.58, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 4.89 (P < 0.00001)

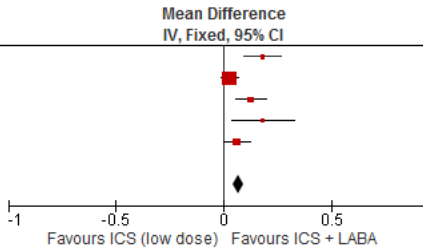


Figure 46: Reliever medication use (puffs/day)

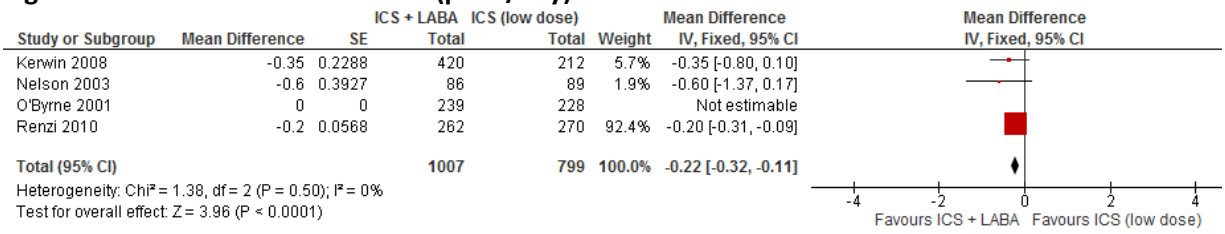


Figure 47: Reliever medication use (rescue free days (%))

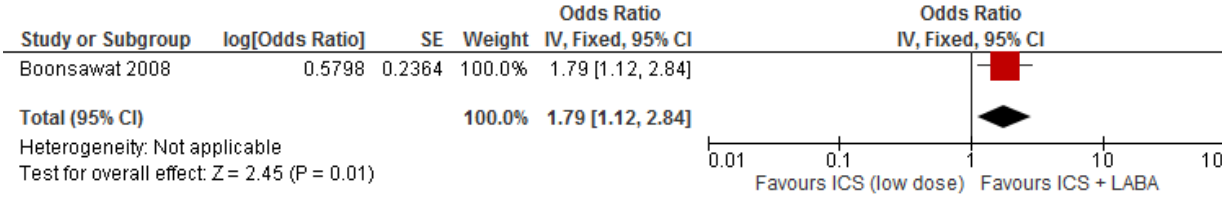
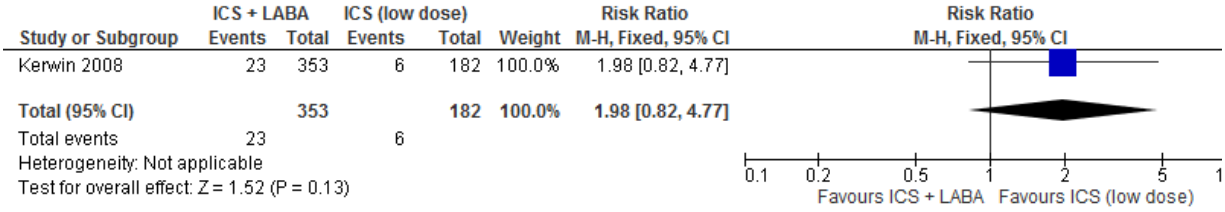


Figure 48: Infection (URTI)



K.2.8 LTRA versus ICS (low dose) in patients over 16

Figure 49: Severe exacerbations (requiring OCS)

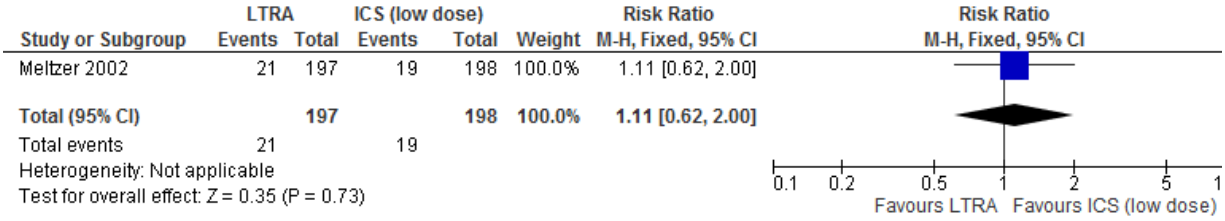


Figure 50: Quality of life (AQLQ)

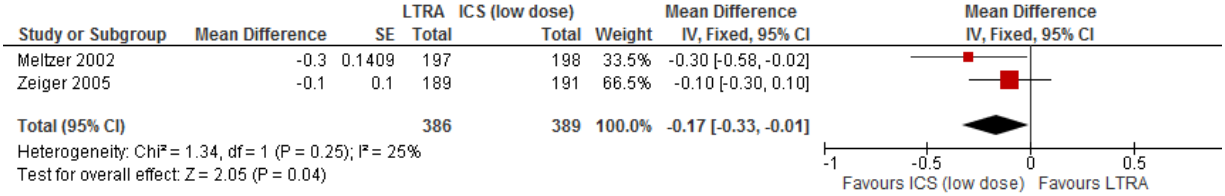


Figure 51: Lung function (morning PEF)

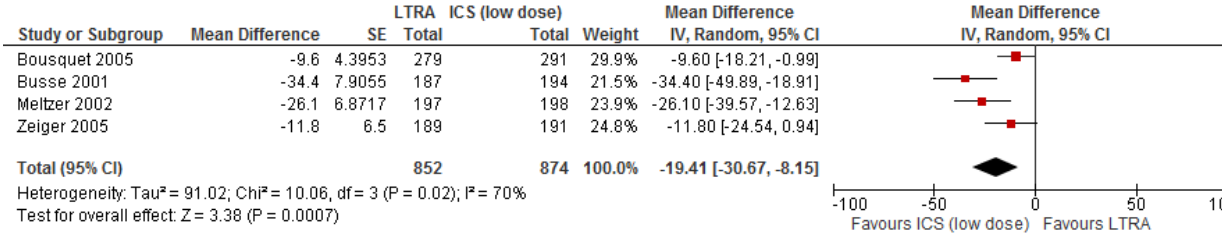


Figure 52: Lung function (FEV_1 %)

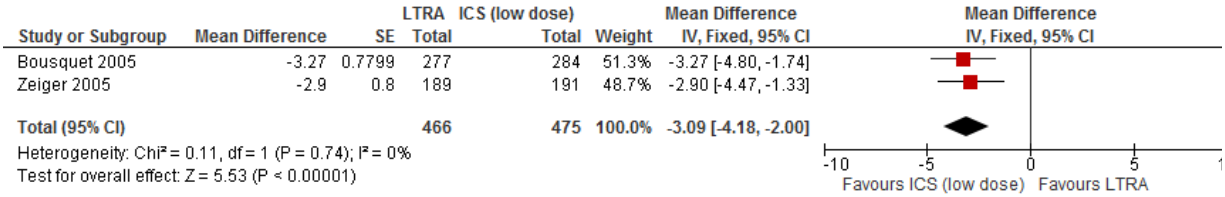


Figure 53: Lung function (FEV_1 [L])

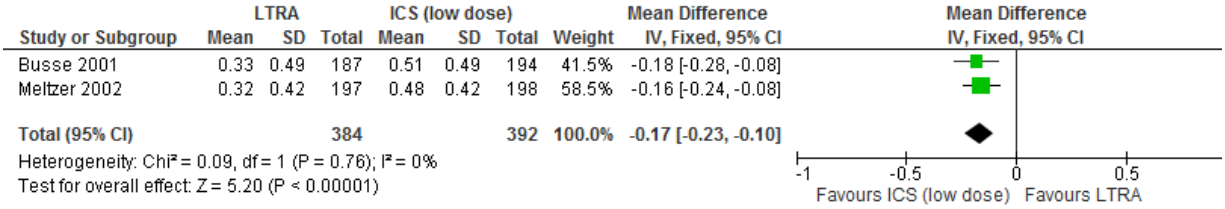


Figure 54: Reliever medication use (puffs/day)

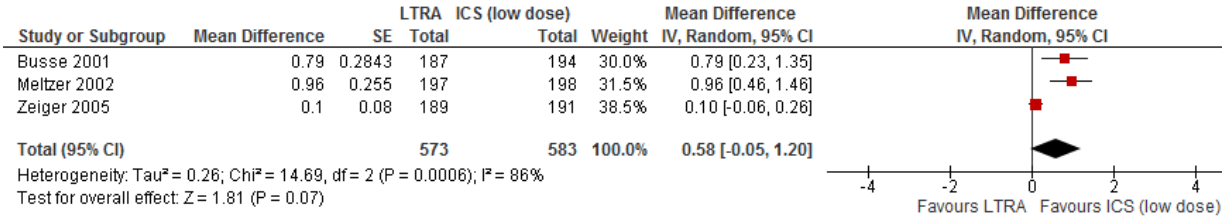
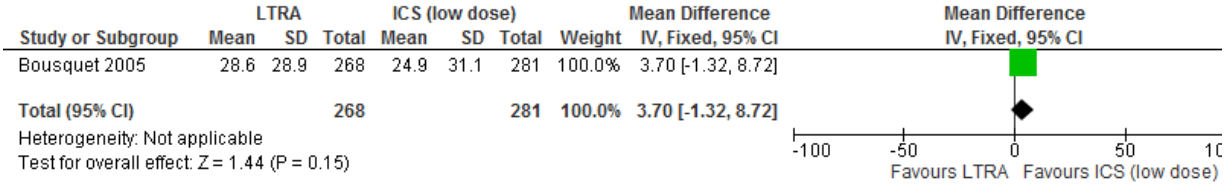
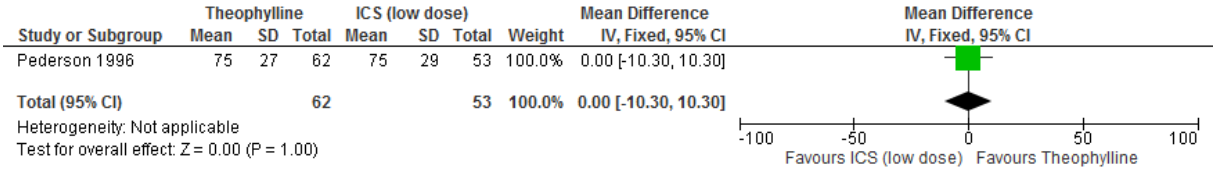


Figure 55: Reliever medication use (puffs/day)



K.2.9 Theophylline versus ICS (low dose) in patients over 16

Figure 56: Lung function (FEV_1 %)



K.2.10 ICS + LABA versus ICS (moderate dose) in patients over 16

Figure 57: Lung function (morning PEF)

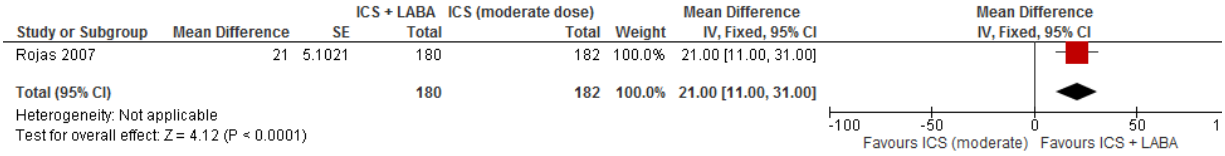


Figure 58: Reliever medication use (participants with 100% rescue free days)

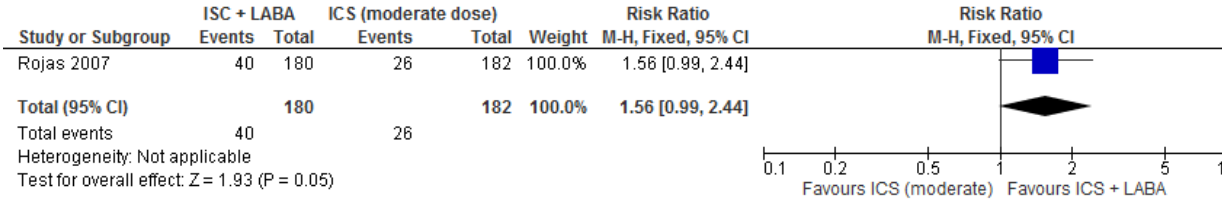
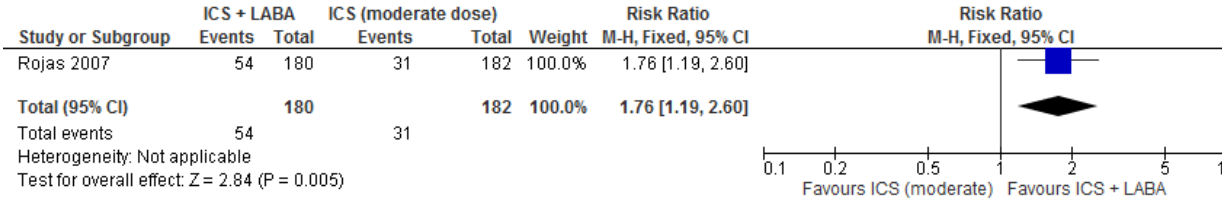


Figure 59: Reliever medication use (participants with 100% rescue free nights)



K.2.11 LTRA versus ICS (moderate dose) in patients over 16

Figure 60: Severe exacerbations (requiring OCS)

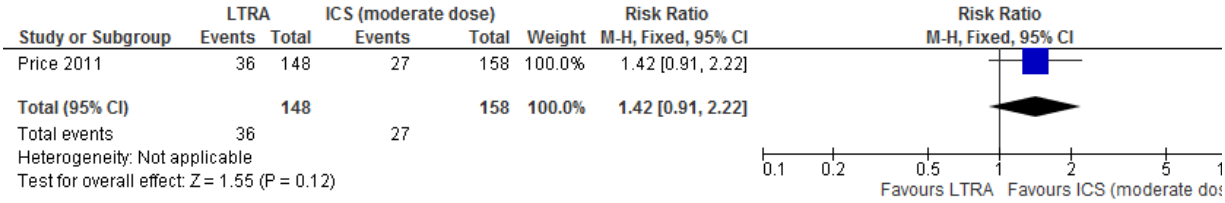


Figure 61: Quality of life (AQLQ)

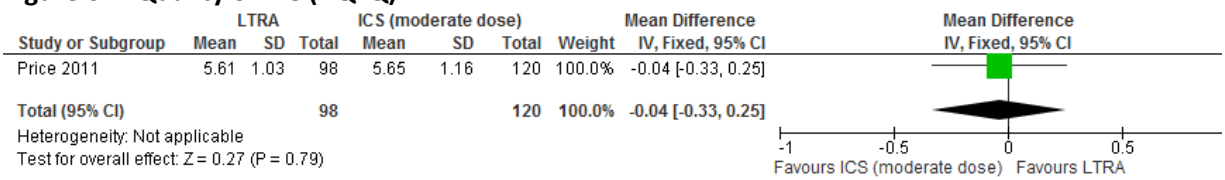


Figure 62: Quality of life (EQ-5D)

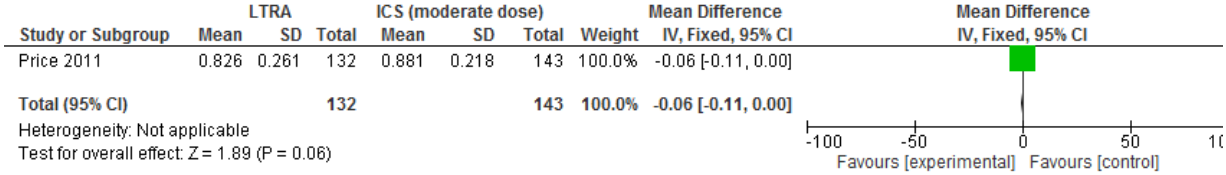


Figure 63: Asthma control (ACQ, 0-6, lower is better outcome)

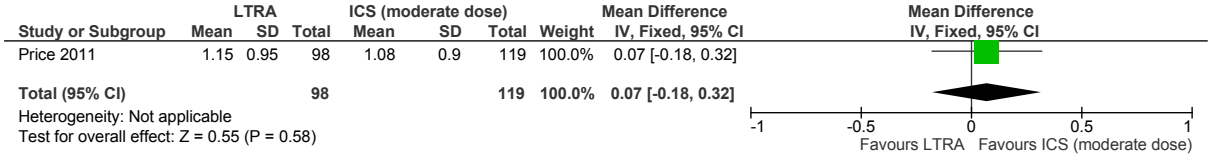


Figure 64: Hospitalisations

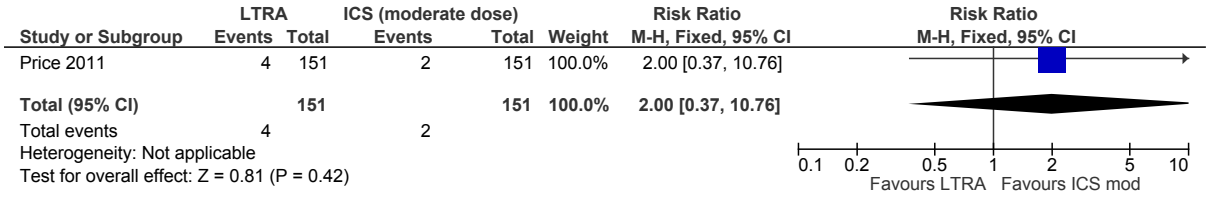


Figure 65: Lung function (morning PEF)

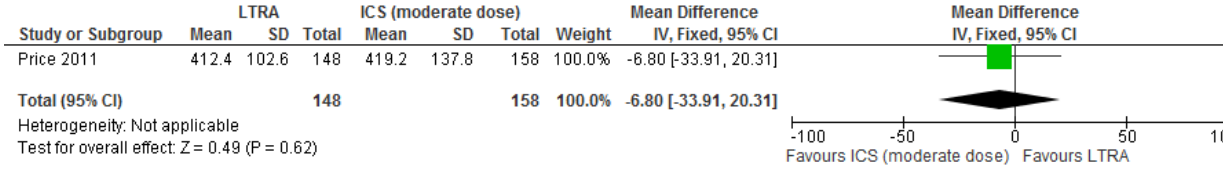


Figure 66: Reliever medication use (puffs/daytime)

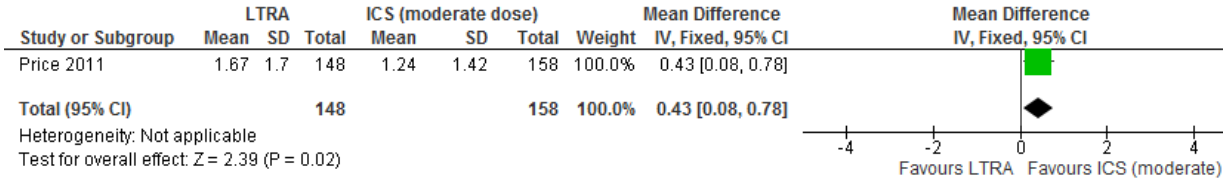


Figure 67: Reliever medication use (puffs/night-time)

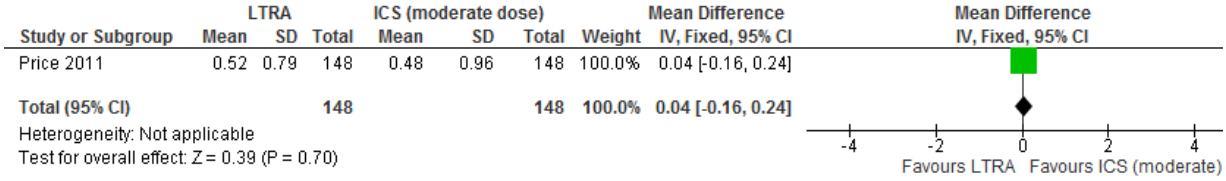
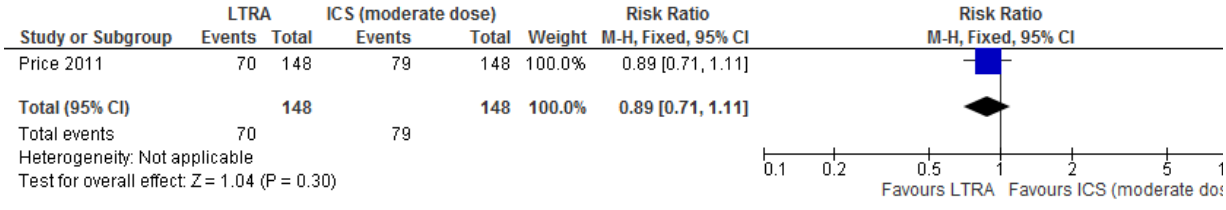
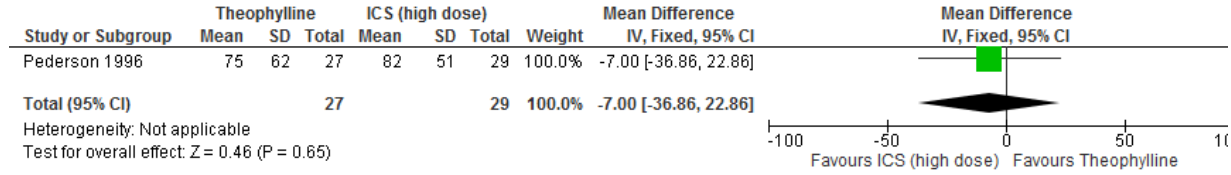


Figure 68: Infection (URTI)



K.2.12 Theophylline versus ICS (high dose) in patients over 16

Figure 69: Lung function (FEV_1 %)



K.2.13 LTRA versus ICS + LABA in patients over 16

Figure 70: Quality of life (AQLQ)

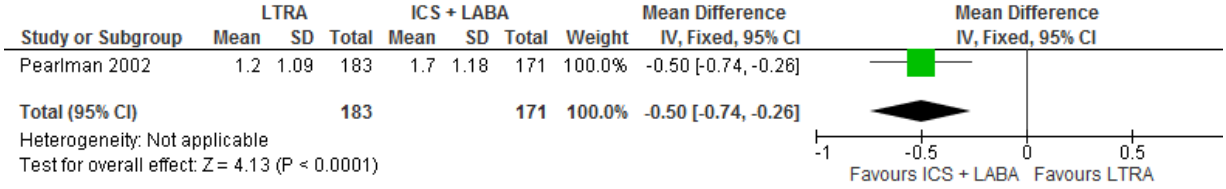


Figure 71: Lung function (morning PEF)

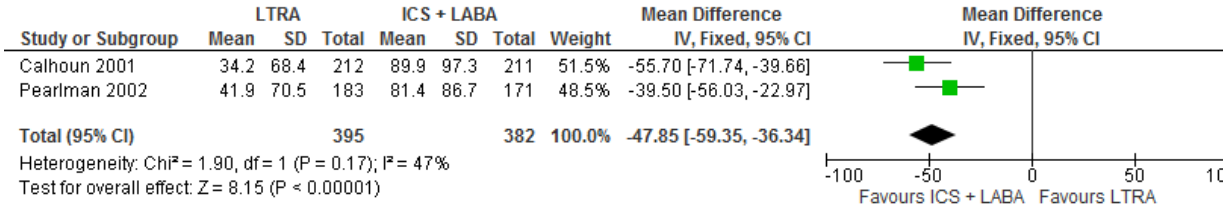


Figure 72: Lung function (FEV_1 [L])

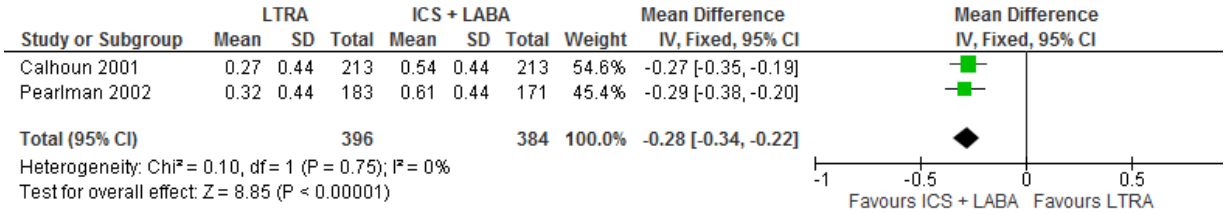
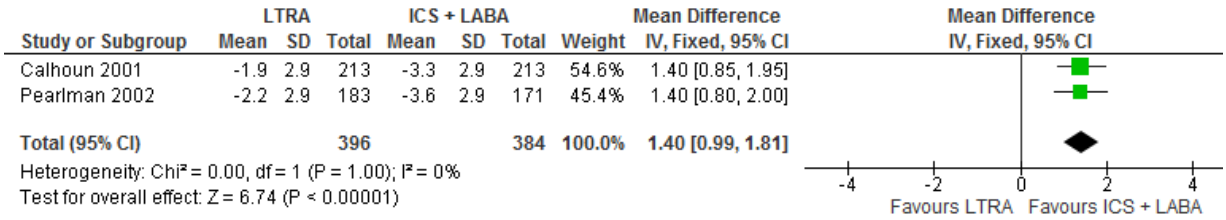


Figure 73: Reliever medication use (puffs/day)



K.2.14 ICS (low dose) versus placebo in patients aged 5-16

Figure 74: Lung function (morning PEF)

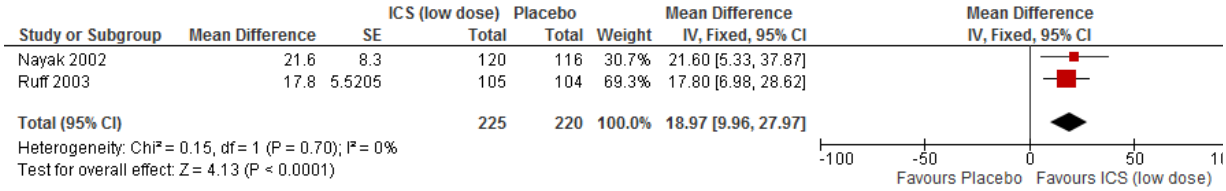


Figure 75: Lung function (FEV_1 %)

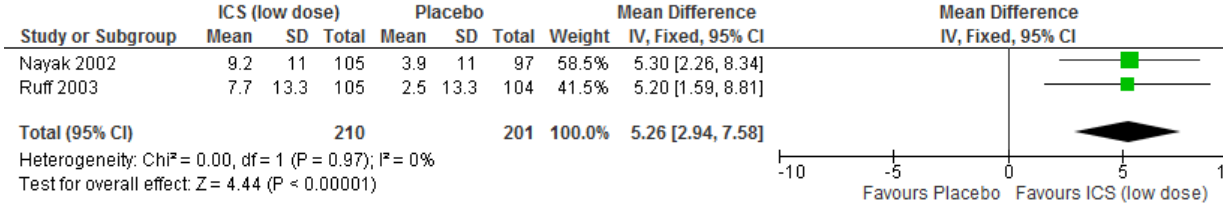


Figure 76: Reliever medication use (puffs/day)

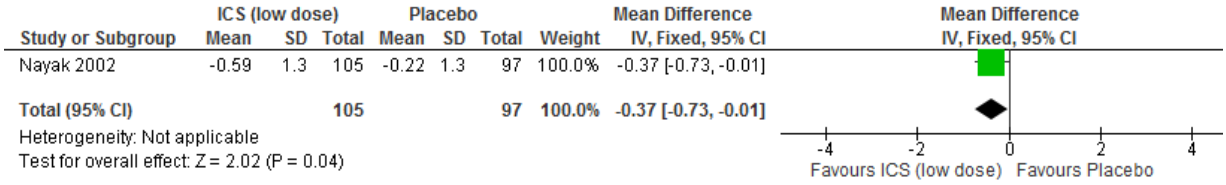


Figure 77: Infection (URTI)

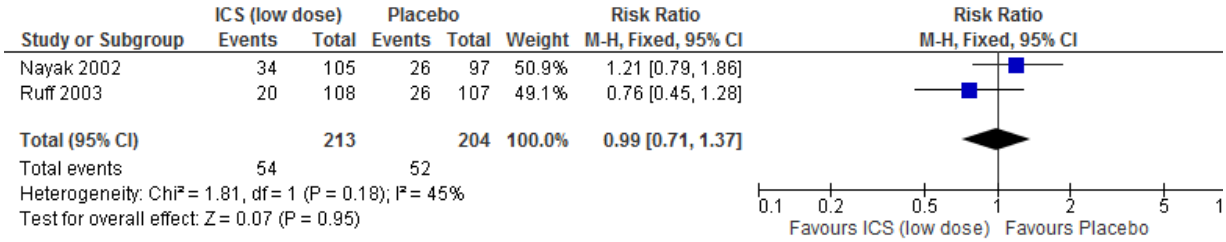
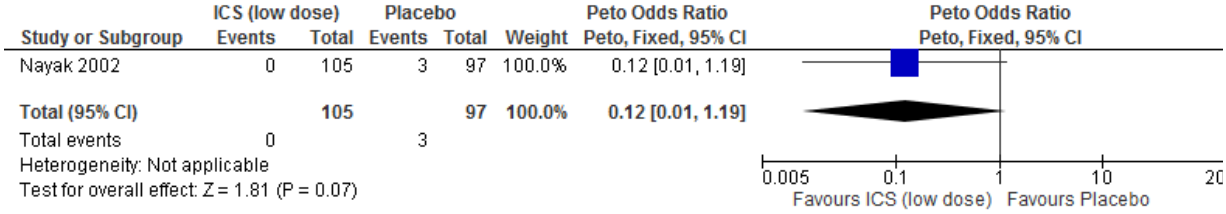


Figure 78: Adrenal insufficiency



K.2.15 ICS (moderate dose) versus placebo in patients aged 5-16

Figure 79: Lung function (morning PEF)

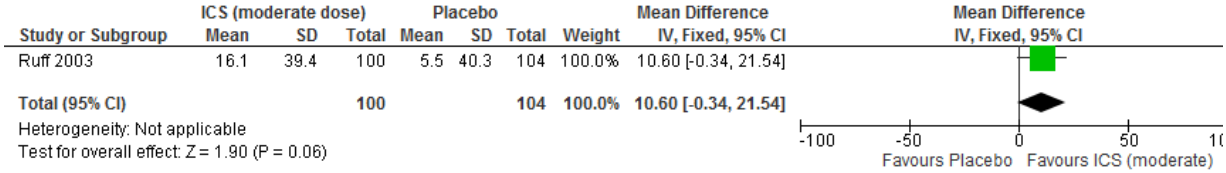


Figure 80: Lung function (FEV_1 %)

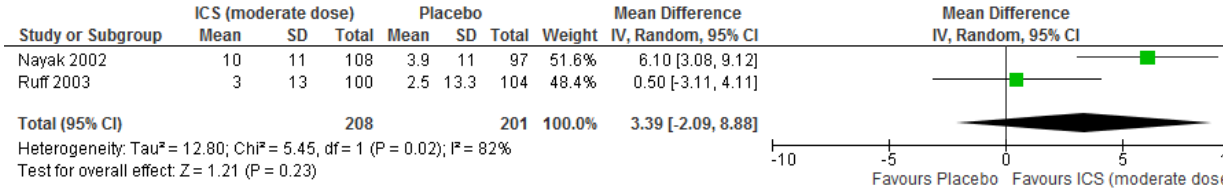


Figure 81: Reliever medication use (puffs/day)

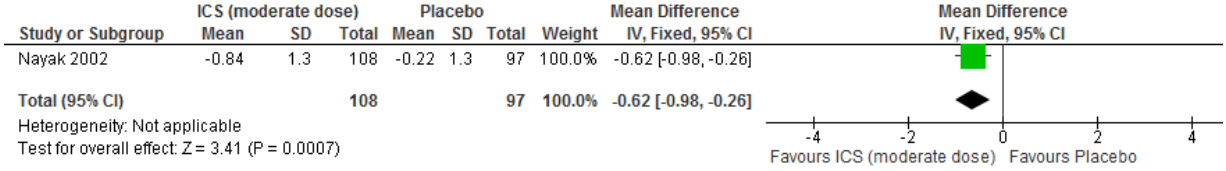
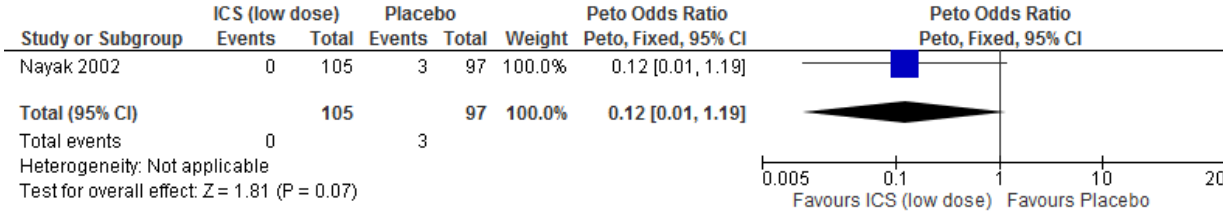


Figure 82: Infection (URTI)

Figure 83: Adrenal insufficiency



K.2.16 ICS (moderate dose) versus ICS (low dose) in patients aged 5-16

Figure 84: Lung function (morning PEF)

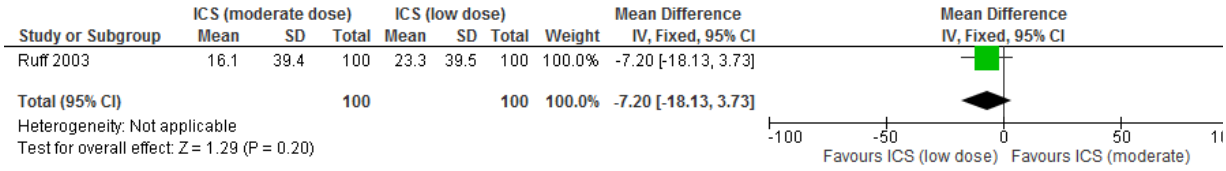


Figure 85: Lung function (FEV_1 %)

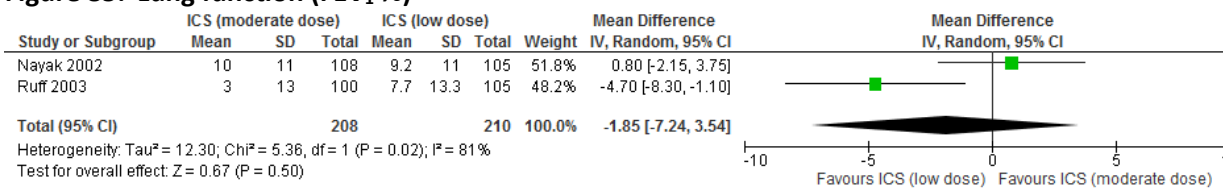


Figure 86: Reliever medication use (puffs/day)

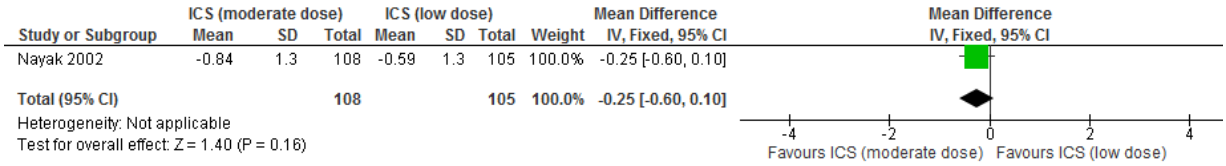


Figure 87: Infection (URTI)

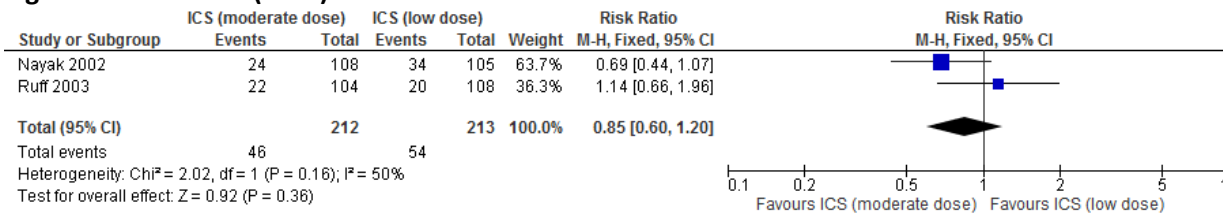
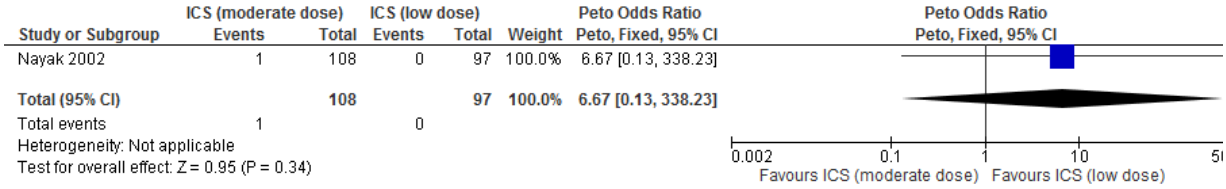


Figure 88: Adrenal insufficiency



K.2.17 LTRA versus ICS (low dose) in patients aged 5-16

Figure 89: Quality of life (AQLQ)

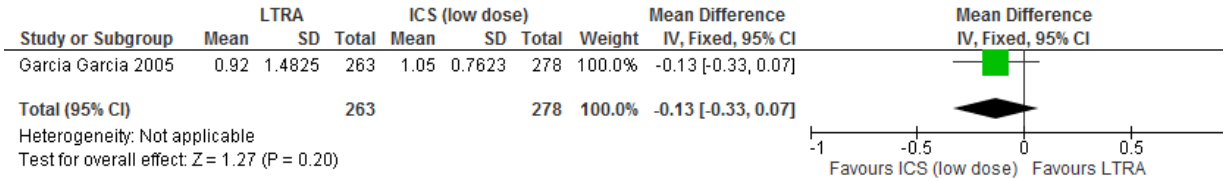


Figure 90: Lung function (FEV_1 [%])

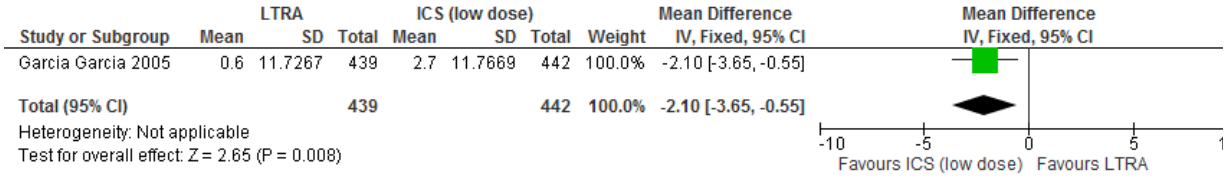
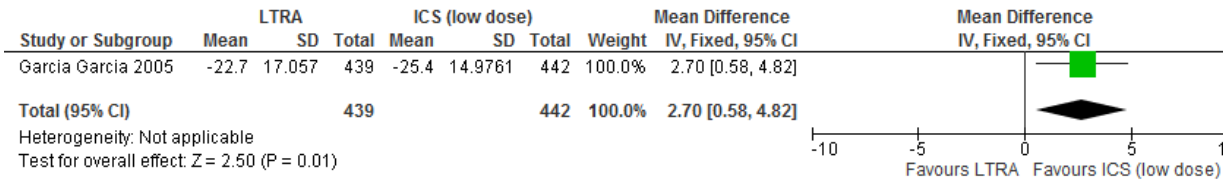


Figure 91: Reliever medication use (days of use [change %])



K.2.18 Cromolyn versus ICS (low dose) in patients aged 5-16

Figure 92: Severe exacerbations (requiring OCS)

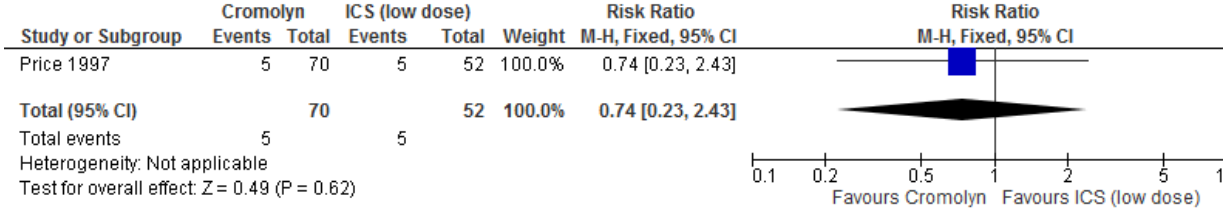


Figure 93: Lung function (morning PEF % of predicted)

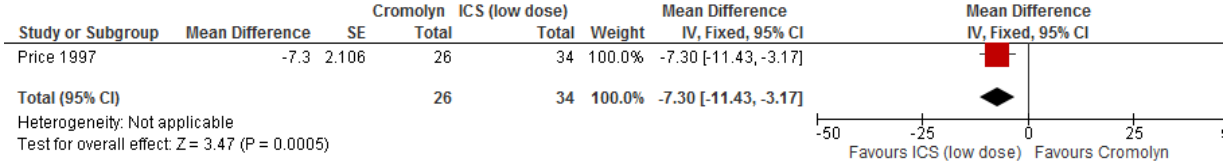
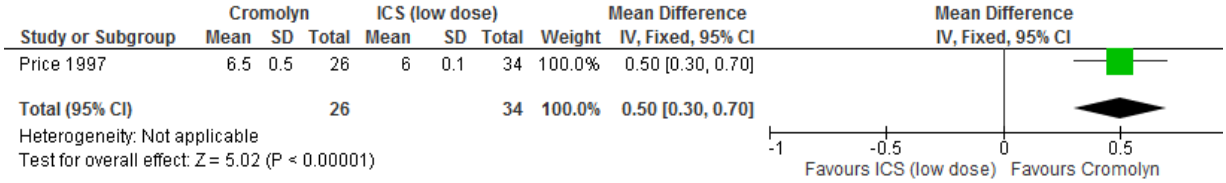
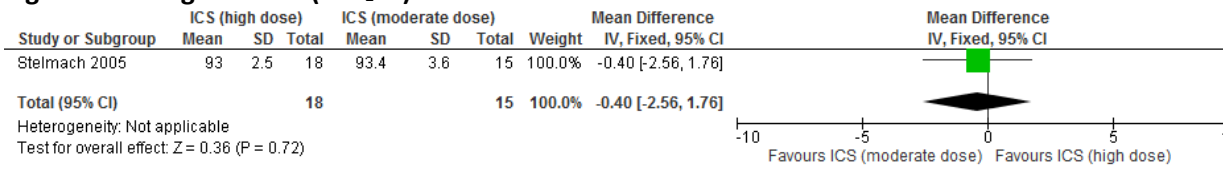


Figure 94: Linear growth (velocity – cm/year)



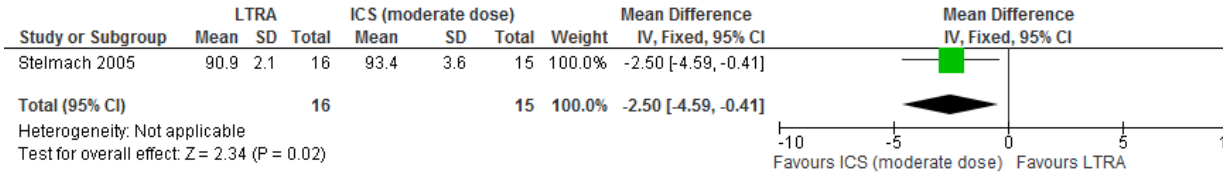
K.2.19 ICS (high dose) versus ICS (moderate dose) in patients aged 5-16

Figure 95: Lung function (FEV_1 %)



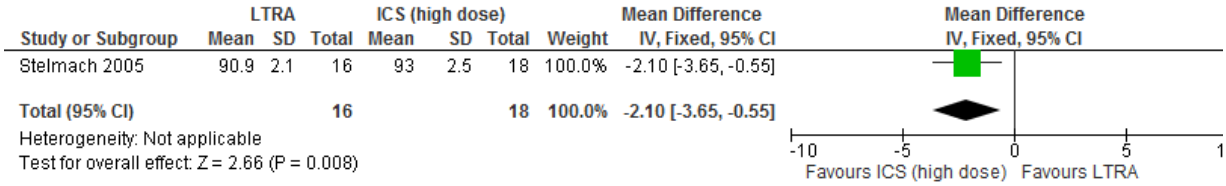
K.2.20 LTRA versus ICS (moderate dose) in patients aged 5-16

Figure 96: Lung function (FEV_1 %)



K.2.21 LTRA versus ICS (high dose) in patients aged 5-16

Figure 97: Lung function (FEV_1 %)



K.2.22 LTRA versus ICS + LABA in people aged 5-16

Figure 98: Quality of life (PAQLQ)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Maspero 2008	-0.09	0.1071	100.0%	-0.09 [-0.30, 0.12]
Total (95% CI)			**100.0%**	**-0.09 [-0.30, 0.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)

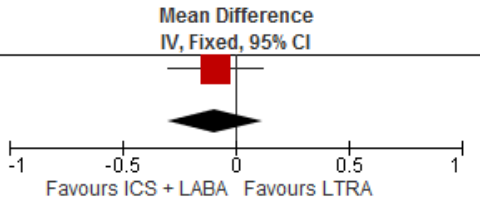
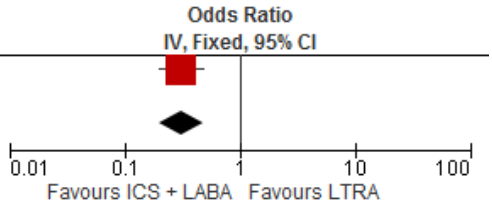


Figure 99: Rescue use (rescue free 24 hour periods)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Maspero 2008	-1.1777	0.2229	100.0%	0.31 [0.20, 0.48]
Total (95% CI)			**100.0%**	**0.31 [0.20, 0.48]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.28 (P < 0.00001)



K.2.23 ICS (low dose) versus placebo in children aged 1-5

Figure 100: Reliever medication use (daytime use)

Study or Subgroup	ICS (low dose) Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schokker 2008	0.37	0.7	45	0.31	0.49	43	100.0%	0.06 [-0.19, 0.31]
Total (95% CI)			**45**			**43**	**100.0%**	**0.06 [-0.19, 0.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

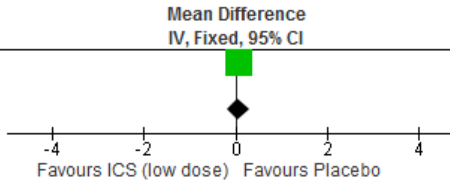


Figure 101: Reliever medication use (night-time use)

Study or Subgroup	ICS (low dose) Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schokker 2008	0.11	0.29	45	0.06	0.13	43	100.0%	0.05 [-0.04, 0.14]
Total (95% CI)			**45**			**43**	**100.0%**	**0.05 [-0.04, 0.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

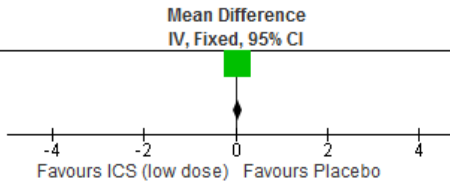
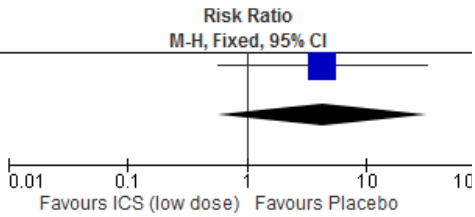


Figure 102: Infection (URTI)

Study or Subgroup	ICS (low dose) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kooi 2008	6	21	1	15	100.0%	4.29 [0.57, 32.01]
Total (95% CI)		**21**		**15**	**100.0%**	**4.29 [0.57, 32.01]**
Total events	6		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)



K.2.24 ICS (low dose) versus placebo in children aged 1-5

Figure 103: Reliever medication use (daytime)

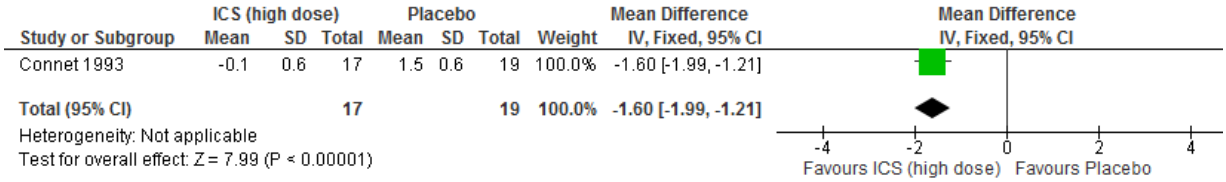
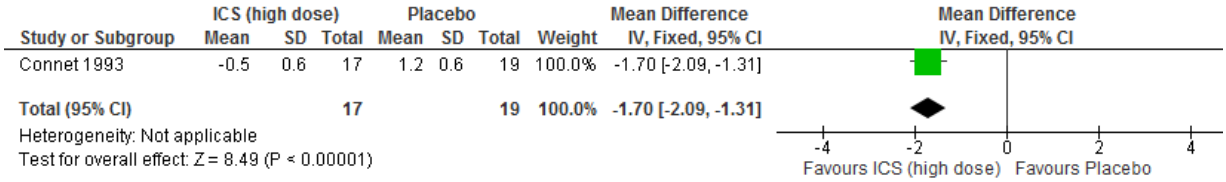
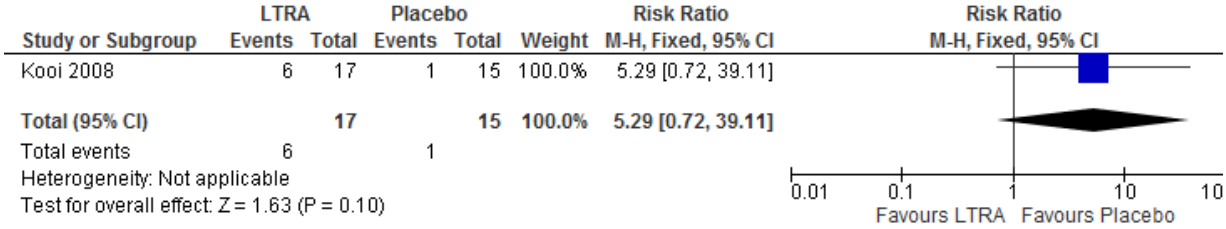


Figure 104: Reliever medication use (daytime)



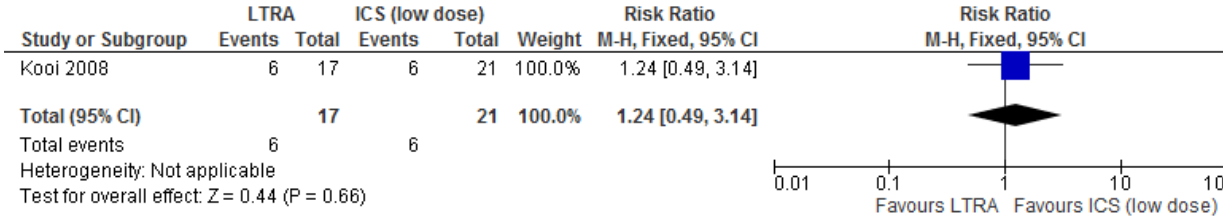
K.2.25 LTRA versus placebo in children aged 1-5

Figure 105: Infection (URTI)



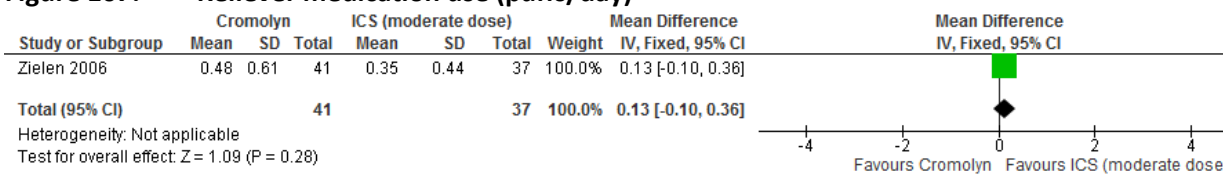
K.2.26 LTRA versus ICS (low dose) in children aged 1-5

Figure 106: Infection (URTI)



K.2.27 Cromolyn versus ICS (moderate dose) in children aged 1-5

Figure 107: Reliever medication use (puffs/day)



K.2.28 ICS (low dose) versus placebo in children aged <1

Figure 108: Reliever medication use (puffs/day)

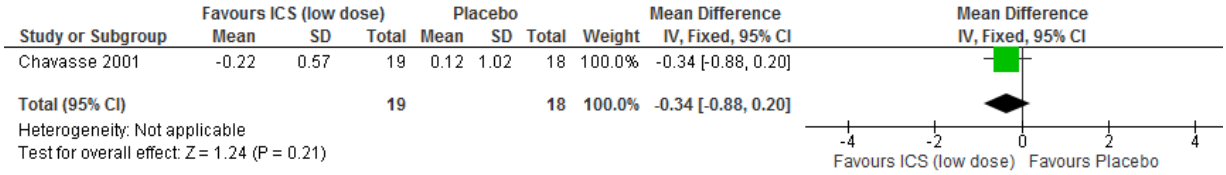
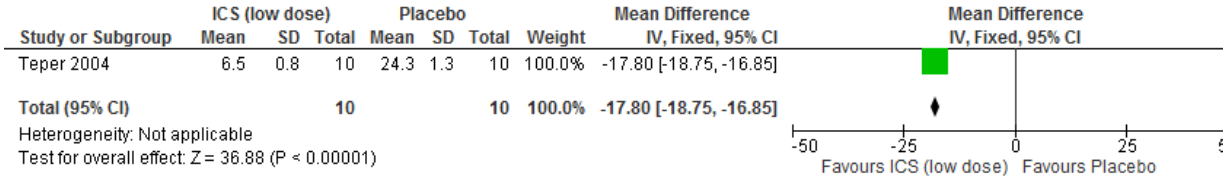
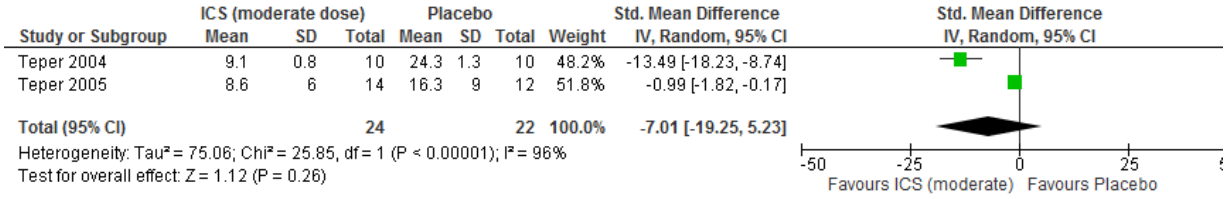


Figure 109: Reliever medication use (number of days)



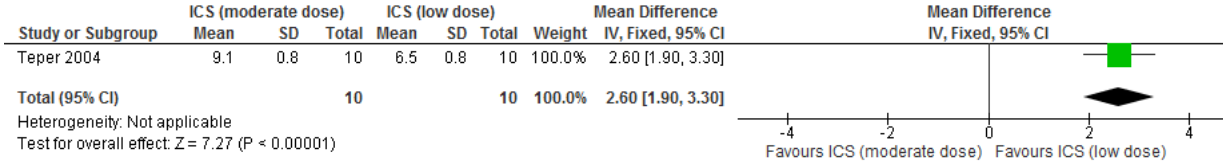
K.2.29 ICS (moderate dose) versus placebo in children aged <1

Figure 110: Reliever medication use (days)



K.2.30 ICS (moderate dose) versus ICS (low dose) in children aged <1

Figure 111: Reliever medication use (number of days)



K.3 Escalating pharmacological treatment in patients poorly controlled on first-line preventer treatment

K.3.1 Second-line preventer

K.3.1.1 ICS (high dose) versus ICS (low dose) in patients over 16

Figure 112: Severe exacerbations (requiring OCS)

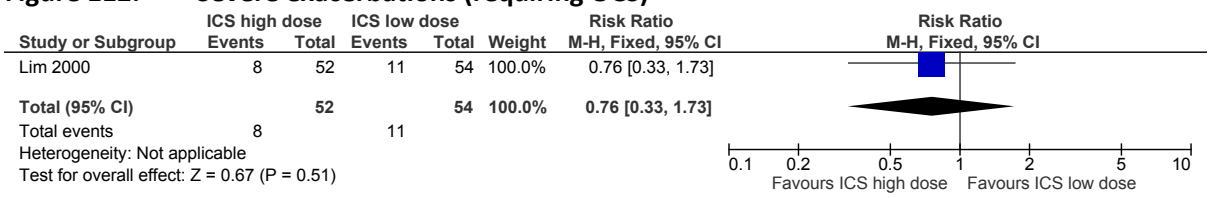


Figure 113: Lung function (PEF [L/min])

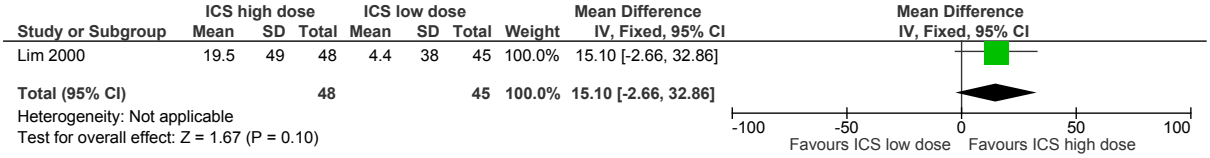


Figure 114: Infections (all respiratory)

K.3.1.2 ICS (low dose) + LABA versus ICS (low dose) in patients over 16

Figure 115: Severe exacerbations (requiring OCS)

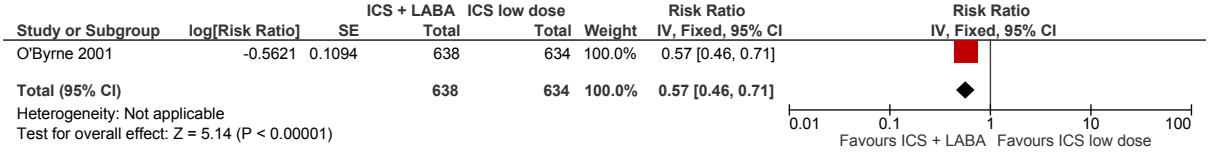


Figure 116: Hospitalisations

Figure 117: Reliever medication use (puffs/day)

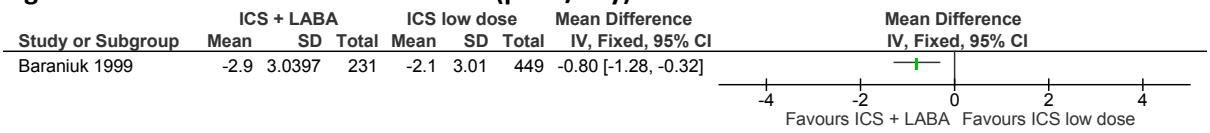


Figure 118: Lung function (FEV_1 [L])

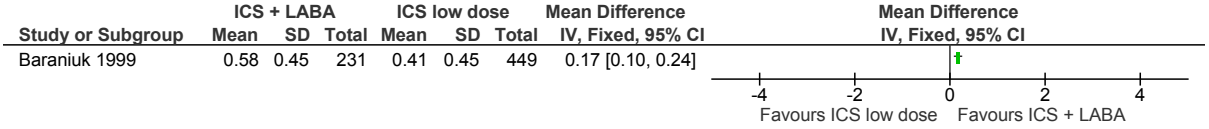


Figure 119: Lung function (PEF [L/min])

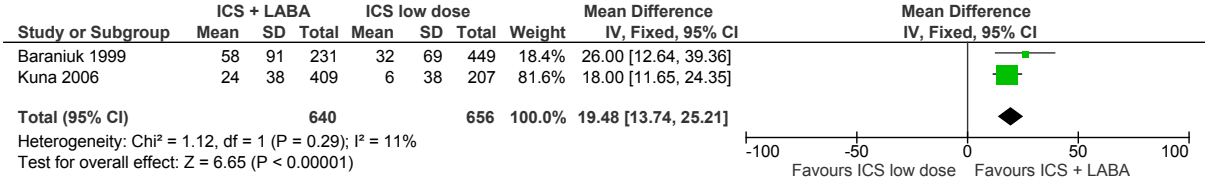
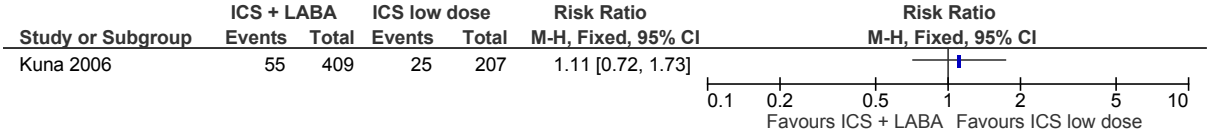


Figure 120: Infections (all respiratory)



K.3.1.3 LTRA + ICS versus ICS (low dose) in patients over 16

Figure 121: Reliever medication use (% change in puffs/day)

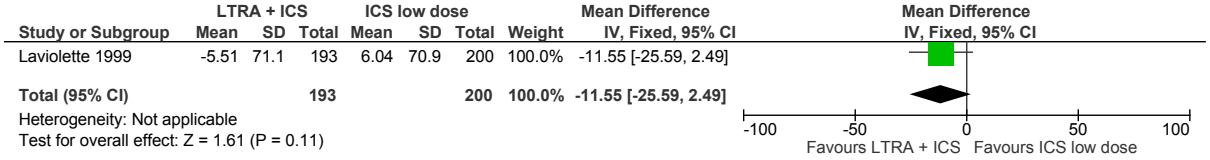


Figure 122: Lung function (FEV_1 [L])

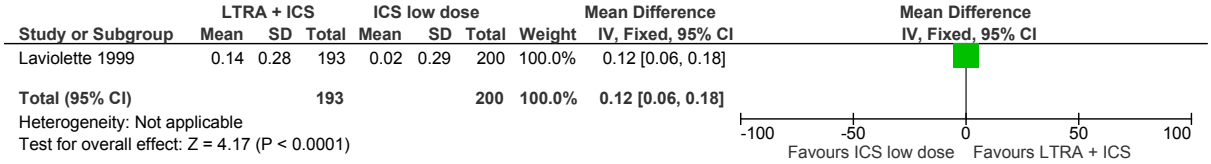


Figure 123: Lung function (PEF [L/min])

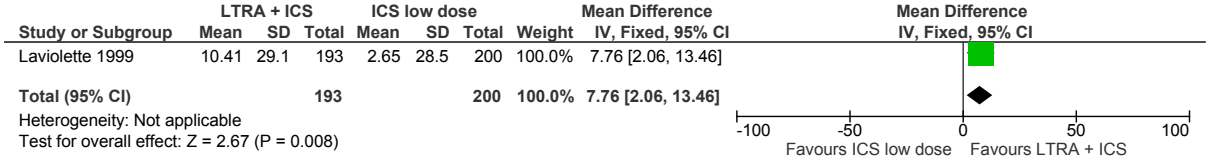


Figure 124: Infections (all respiratory)

K.3.1.4 Theophylline + ICS (low dose) versus ICS (low dose) in patients over 16

Figure 125: Severe exacerbations (requiring OCS)

Figure 126: Lung function (PEF [L/min])

Study or Subgroup	Theophylline Mean	SD	Total	ICS low dose Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lim 2000	21.8	48	38	4.4	38	45	100.0%	17.40 [-1.47, 36.27]
Total (95% CI)			**38**			**45**	**100.0%**	**17.40 [-1.47, 36.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)

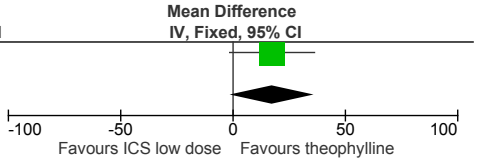
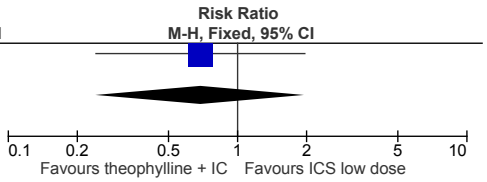


Figure 127: Infections (all respiratory)

Study or Subgroup	Theophylline + ICS Events	Total	ICS low dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lim 2000	5	49	8	54	100.0%	0.69 [0.24, 1.96]
Total (95% CI)		**49**		**54**	**100.0%**	**0.69 [0.24, 1.96]**
Total events	5		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)



K.3.1.5 ICS low dose + LAMA versus ICS low dose in patients over 16

Figure 128: Lung function (FEV_1 [%])

Study or Subgroup	Mean Difference	SE	ICS (low) + LAMA Total	ICS (low) Total	Weight	Mean Difference IV, Fixed, 95% CI
Paggiaro 2016	4.7	1.1	152	154	100.0%	4.70 [2.54, 6.86]
Total (95% CI)			**152**	**154**	**100.0%**	**4.70 [2.54, 6.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.27 (P < 0.0001)

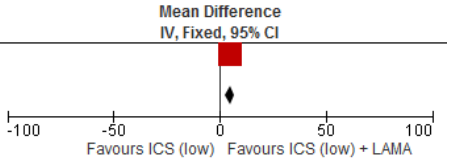


Figure 129: Lung function (PEF [L/min])

Study or Subgroup	Mean Difference	SE	ICS (low) + LAMA Total	ICS (low) Total	Weight	Mean Difference IV, Fixed, 95% CI
Paggiaro 2016	25.6	5.3	152	152	100.0%	25.60 [15.21, 35.99]
Total (95% CI)			**152**	**152**	**100.0%**	**25.60 [15.21, 35.99]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.83 (P < 0.00001)

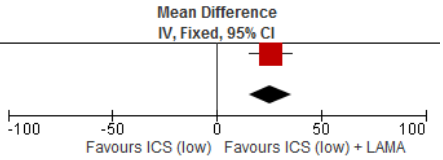
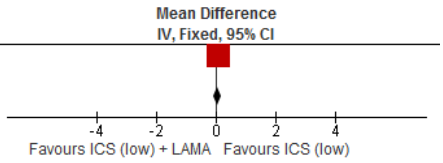


Figure 130: Asthma controle (ACQ-7)

Study or Subgroup	Mean Difference	SE	ICS (low) + LAMA Total	ICS (low) Total	Weight	Mean Difference IV, Fixed, 95% CI
Paggiaro 2016	0.061	0.067	152	154	100.0%	0.06 [-0.07, 0.19]
Total (95% CI)			**152**	**154**	**100.0%**	**0.06 [-0.07, 0.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)



K.3.1.6 ICS low dose + LABA versus ICS moderate dose in patients over 16

Figure 131: Severe exacerbations (requiring OCS)

Study or Subgroup	ICS + LABA Events	Total	ICS moderate dose Events	Total	Risk Ratio M-H, Fixed, 95% CI
Greening 1994	18	220	19	206	0.89 [0.48, 1.64]

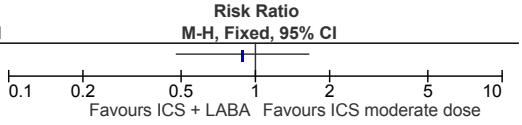


Figure 132: Hospitalisations

Study or Subgroup	ICS + LABA Events	Total	ICS moderate dose Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Greening 1994	1	220	0	206	6.93 [0.14, 350.17]

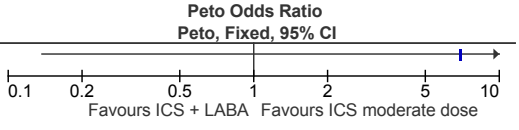
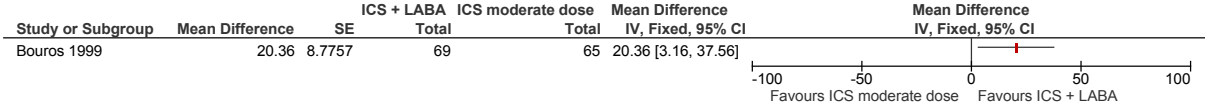


Figure 133: Lung function (PEF [L/min])



K.3.1.7 LTRA alone versus ICS high dose in patients over 16

Figure 134: Reliever medication use (puffs/day)

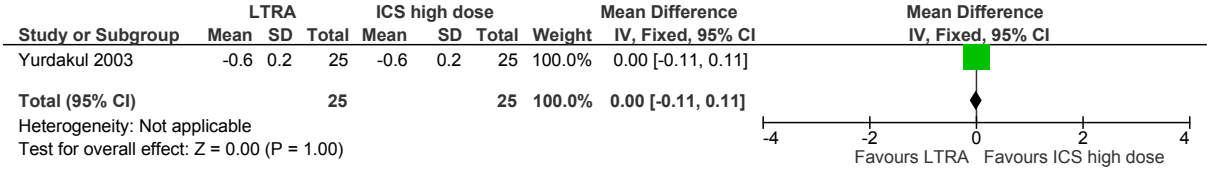
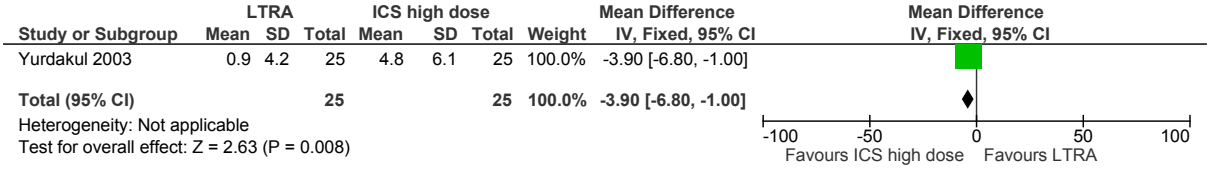
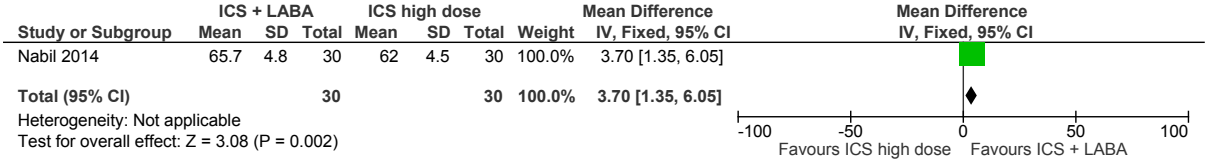


Figure 135: Lung function (FEV_1 [%predicted])



K.3.1.8 ICS low dose + LABA versus ICS high dose in patients aged over 16

Figure 136: Lung function (FEV_1 [%predicted])



K.3.1.9 LTRA alone versus theophylline alone in patients over 16

Figure 137: Reliever medication use (puffs/day)

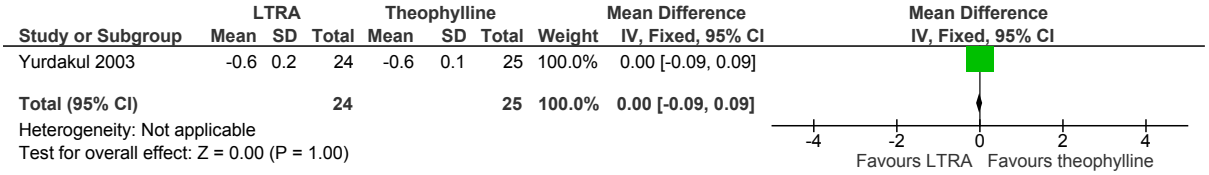
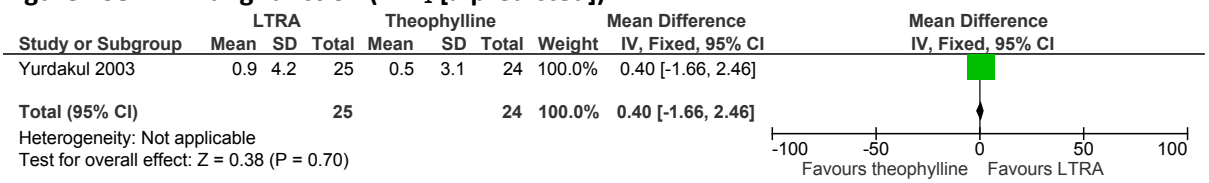


Figure 138: Lung function (FEV_1 [%predicted])



K.3.1.10 ICS high dose versus theophylline + ICS low dose in patients over 16

Figure 139: Severe exacerbations (requiring OCS)

Study or Subgroup	ICS high dose Events	Total	Theophylline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lim 2000	8	52	3	49	100.0%	2.51 [0.71, 8.93]
Total (95% CI)		**52**		**49**	**100.0%**	**2.51 [0.71, 8.93]**
Total events	8		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.15)

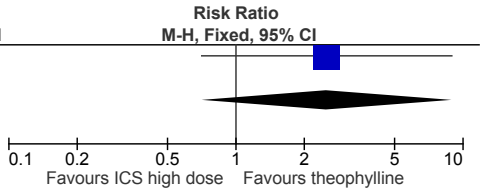


Figure 140: Lung function (PEF [L/min])

Study or Subgroup	ICS high dose Mean	SD	Total	Theophylline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lim 2000	19.5	49	48	21.8	48	38	100.0%	-2.30 [-22.92, 18.32]
Total (95% CI)			**48**			**38**	**100.0%**	**-2.30 [-22.92, 18.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

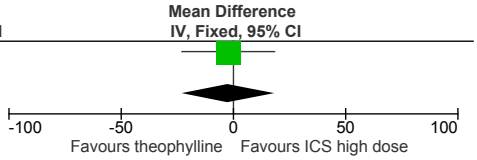
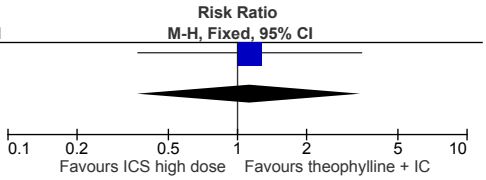


Figure 141: Infections (all respiratory)

Study or Subgroup	ICS high dose Events	Total	Theophylline + ICS Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lim 2000	6	52	5	49	100.0%	1.13 [0.37, 3.47]
Total (95% CI)		**52**		**49**	**100.0%**	**1.13 [0.37, 3.47]**
Total events	6		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)



K.3.1.11 ICS high dose versus theophylline alone in patients over 16

Figure 142: Reliever medication use (puffs/day)

Study or Subgroup	ICS high dose Mean	SD	Total	Theophylline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Yurdakul 2003	-0.6	0.2	25	-0.6	0.1	25	100.0%	0.00 [-0.09, 0.09]
Total (95% CI)			**25**			**25**	**100.0%**	**0.00 [-0.09, 0.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

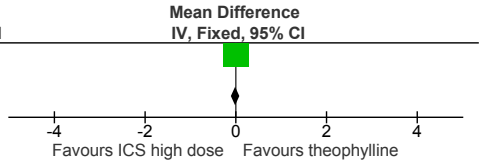
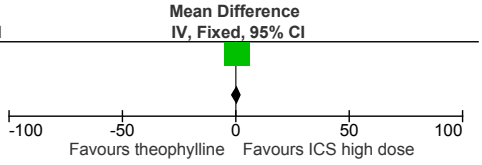


Figure 143: Lung function (FEV_1 [%predicted])

Study or Subgroup	ICS high dose Mean	SD	Total	Theophylline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Yurdakul 2003	0.9	4.2	25	0.5	3.1	24	100.0%	0.40 [-1.66, 2.46]
Total (95% CI)			**25**			**24**	**100.0%**	**0.40 [-1.66, 2.46]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)



K.3.1.12 ICS low dose + LTRA versus ICS low dose + LABA in patients over 16

Figure 144: Severe exacerbations (requiring OCS)

Study or Subgroup	ICS + LTRA Events	Total	ICS + LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bjermer 2003	118	747	107	743	39.1%	1.10 [0.86, 1.40]
Ilowite 2004	123	734	102	718	37.6%	1.18 [0.93, 1.50]
Price 2011	58	170	66	182	23.3%	0.94 [0.71, 1.25]
Total (95% CI)		**1651**		**1643**	**100.0%**	**1.09 [0.94, 1.26]**
Total events	299		275			

Heterogeneity: Chi² = 1.45, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)

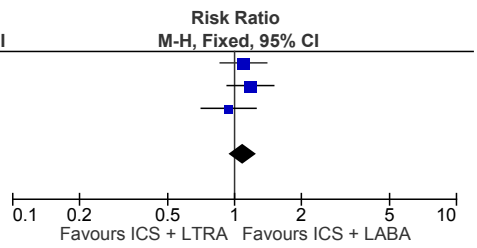


Figure 145: Quality of life (AQLQ/miniAQLQ, 1-7, higher is better outcome)

Study or Subgroup	Mean Difference	SE	ICS + LTRA Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Bjermer 2003	-0.05	0.0566	747	743	40.2%	-0.05 [-0.16, 0.06]
Ilowite 2004	-0.12	0.051	743	730	49.5%	-0.12 [-0.22, -0.02]
Price 2011	0.01	0.1122	121	176	10.2%	0.01 [-0.21, 0.23]
Total (95% CI)			**1611**	**1649**	**100.0%**	**-0.08 [-0.15, -0.01]**

Heterogeneity: Chi² = 1.54, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)

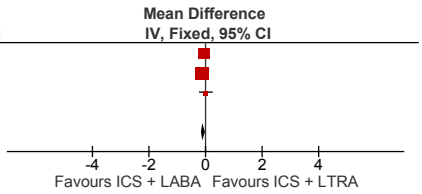


Figure 146: Quality of life (EQ-5D, 0-1, higher is better outcome)

Study or Subgroup	ICS + LTRA Mean	SD	Total	ICS + LABA Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Price 2011	0.807	0.255	160	0.798	0.268	170	0.01 [-0.05, 0.07]

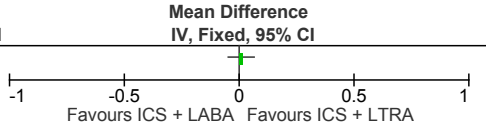


Figure 147: Asthma control (ACQ, 0-6, lower is better outcome)

Study or Subgroup	Mean Difference	SE	ICS + LTRA Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Price 2011	0.04	0.0969	169	181	100.0%	0.04 [-0.15, 0.23]
Total (95% CI)			**169**	**181**	**100.0%**	**0.04 [-0.15, 0.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

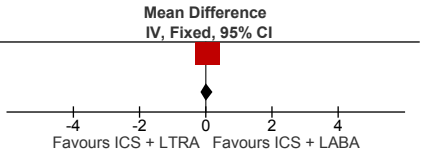


Figure 148: Hospitalisations

Study or Subgroup	ICS + LTRA Events	Total	ICS + LABA Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bjermer 2003	5	747	7	743	43.0%	0.71 [0.23, 2.21]
Ilowite 2004	3	734	5	718	28.7%	0.59 [0.15, 2.37]
Price 2011	3	169	5	176	28.3%	0.63 [0.15, 2.54]
Total (95% CI)		**1650**		**1637**	**100.0%**	**0.65 [0.31, 1.37]**
Total events	11		17			

Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

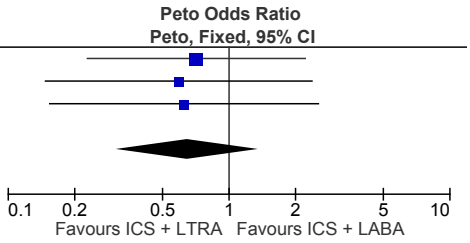


Figure 149: Reliever medication use (puffs/day)

Study or Subgroup	ICS + LTRA Mean	SD	Total	ICS + LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ilowite 2004	-1.15	1.6355	743	-1.66	1.6211	730	2.1%	0.51 [0.34, 0.68]
Nelson 2000	-1.14	0.12	225	-1.55	0.14	222	97.8%	0.41 [0.39, 0.43]
Price 2011	1.89	2.31	84	1.49	1.65	95	0.2%	0.40 [-0.20, 1.00]
Total (95% CI)			**1052**			**1047**	**100.0%**	**0.41 [0.39, 0.44]**

Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 33.77 (P < 0.00001)

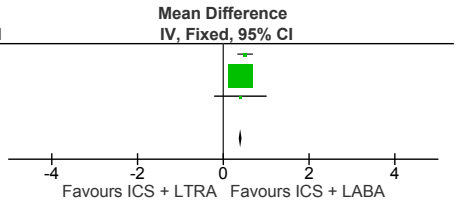


Figure 150: Reliever medication use (% reliever free days)

Study or Subgroup	Mean Difference	SE	ICS + LTRA Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Pavord 2007	-16.5	8.86	33	33	100.0%	-16.50 [-33.87, 0.87]
Total (95% CI)			**33**	**33**	**100.0%**	**-16.50 [-33.87, 0.87]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)

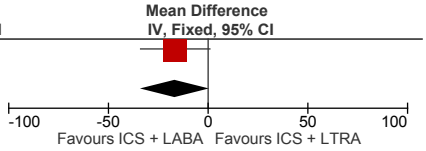


Figure 151: Reliever medication use (reliever free days during study)

Study or Subgroup	log[Odds Ratio]	SE	ICS + LTRA Total	ICS + LABA Total	Odds Ratio IV, Fixed, 95% CI
Ringdal 2003	-0.2614	0.1188	369	356	0.77 [0.61, 0.97]

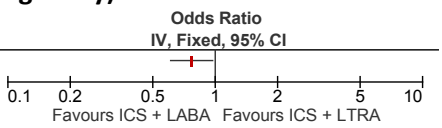


Figure 152: Reliever medication use (puffs/night)

Study or Subgroup	ICS + LTRA Mean	SD	Total	ICS + LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Price 2011	0.69	1.04	75	0.63	0.87	87	100.0%	0.06 [-0.24, 0.36]
Total (95% CI)			**75**			**87**	**100.0%**	**0.06 [-0.24, 0.36]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)

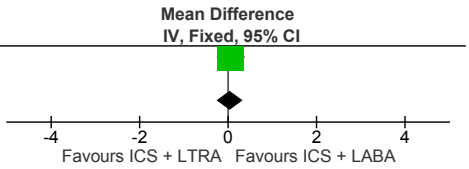


Figure 153: Lung function (PEF [L/min])

Study or Subgroup	Mean Difference	SE	ICS + LTRA Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Bjermer 2003	-16.96	2.4042	747	743	0.7%	-16.96 [-21.67, -12.25]
Ilowite 2004	-14.2	3.9598	743	730	0.2%	-14.20 [-21.96, -6.44]
Nelson 2000	-11.9	0.199	225	222	98.4%	-11.90 [-12.29, -11.51]
Price 2011	-13.7	6.0715	83	98	0.1%	-13.70 [-25.60, -1.80]
Ringdal 2003	-17	2.5511	369	356	0.6%	-17.00 [-22.00, -12.00]
Total (95% CI)			**2167**	**2149**	**100.0%**	**-11.97 [-12.36, -11.59]**

Heterogeneity: Chi² = 8.72, df = 4 (P = 0.07); I² = 54%
Test for overall effect: Z = 60.66 (P < 0.00001)

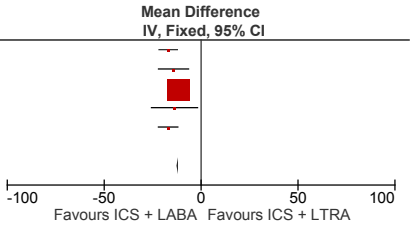


Figure 154: Lung function (FEV_1 [L])

Study or Subgroup	Mean Difference	SE	ICS + LTRA Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Bjermer 2003	-0.08	0.028	747	743	0.7%	-0.08 [-0.13, -0.03]
Nelson 2000	-0.14	0.0024	225	222	98.4%	-0.14 [-0.14, -0.14]
Pavord 2007	-0.11	0.1071	33	33	0.0%	-0.11 [-0.32, 0.10]
Ringdal 2003	-0.11	0.0255	369	356	0.9%	-0.11 [-0.16, -0.06]
Total (95% CI)			**1374**	**1354**	**100.0%**	**-0.14 [-0.14, -0.13]**

Heterogeneity: Chi² = 5.97, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 58.52 (P < 0.00001)

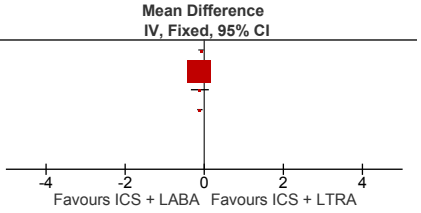


Figure 155: Lung function (FEV_1 [%predicted])

Study or Subgroup	ICS + LTRA Mean	SD	Total	ICS + LABA Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Ilowite 2004	3.14	9.5403	743	5.12	9.4565	730	-1.98 [-2.95, -1.01]

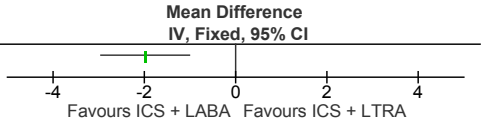
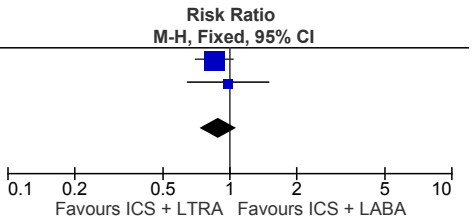


Figure 156: Infections (all respiratory)

Study or Subgroup	ICS + LTRA Events	Total	ICS + LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Price 2011	85	170	107	182	72.2%	0.85 [0.70, 1.03]
Ringdal 2003	39	401	40	404	27.8%	0.98 [0.65, 1.49]
Total (95% CI)		**571**		**586**	**100.0%**	**0.89 [0.74, 1.07]**
Total events	124		147			

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)



K.3.1.13 ICS moderate dose versus ICS low dose in patients aged 5 to 16

Figure 157: Reliever medication use (puffs/day)

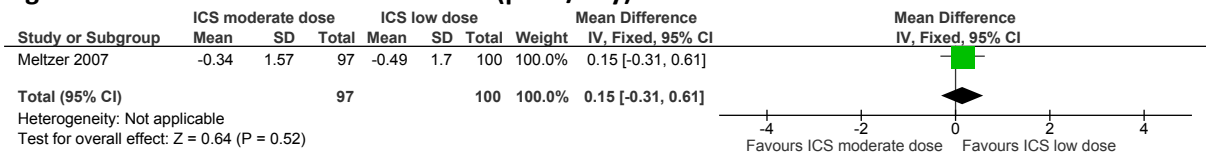


Figure 158: FEV_1 (% predicted)

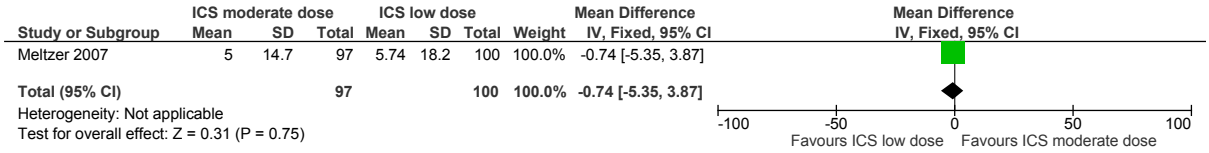


Figure 159: PEF (L/min)

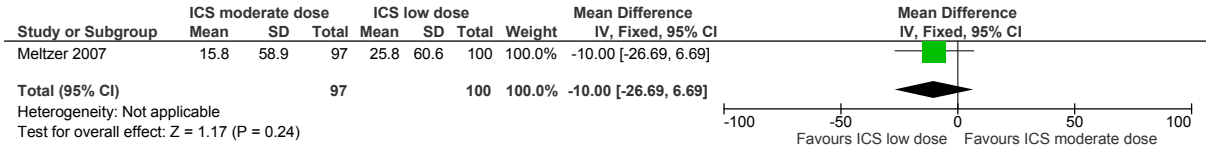
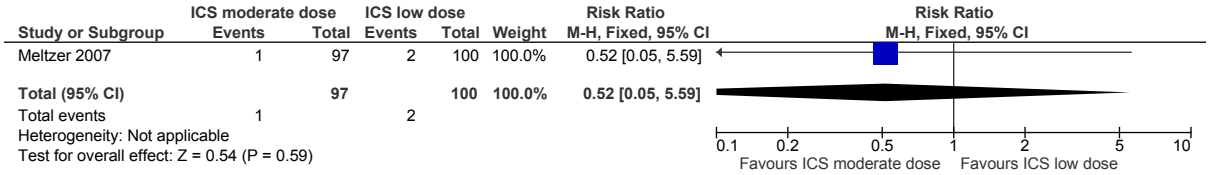


Figure 160: Infections (all respiratory)



K.3.1.14 ICS low dose + LABA versus ICS low dose in patients aged 5 to 16

Figure 161: Exacerbations (requiring OCS)

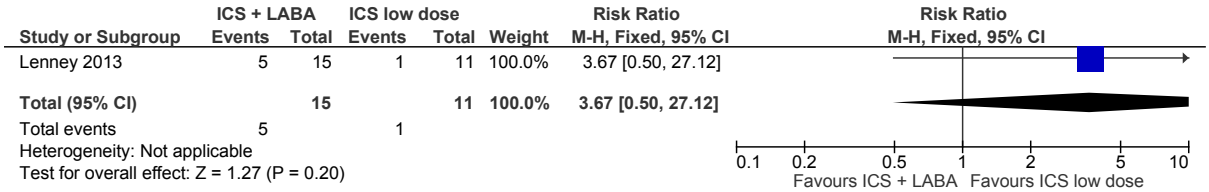


Figure 162: Quality of life (PAQLQ)

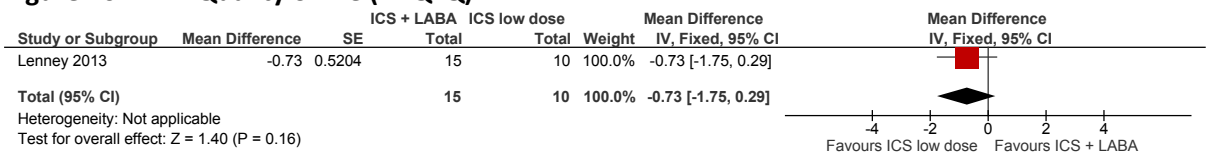


Figure 163: Hospitalisations

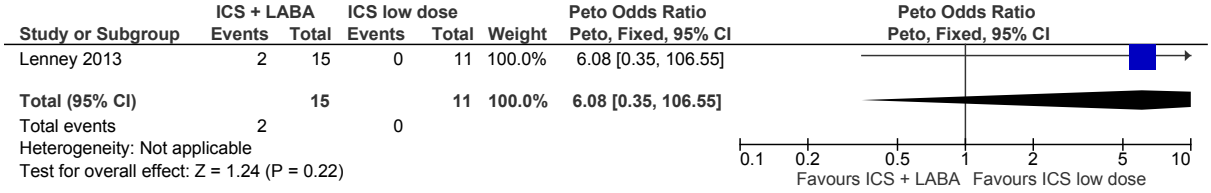


Figure 164: Lung function (FEV_1 [%predicted])

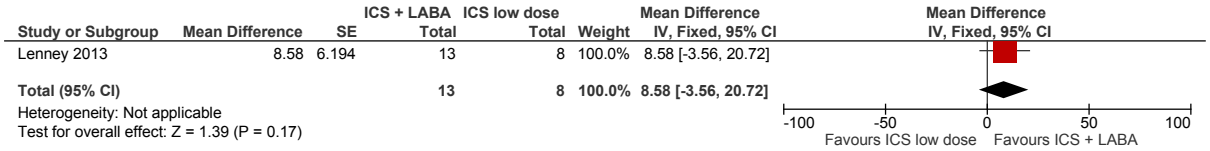
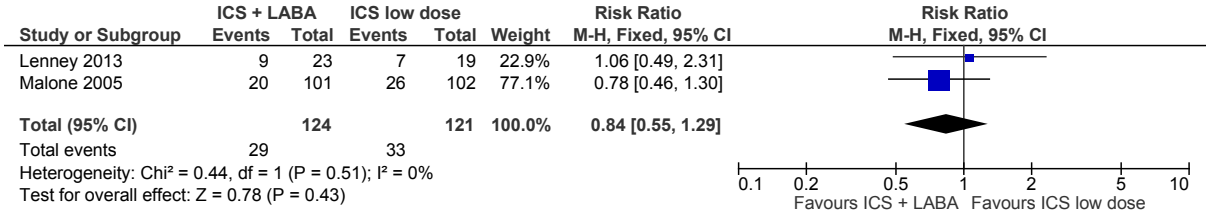


Figure 165: Infections (all respiratory)



K.3.1.15 ICS low dose + LTRA versus ICS low dose in patients aged 5 to 16

Figure 166: Exacerbations (requiring OCS)

Figure 167: Quality of life (PAQLQ)

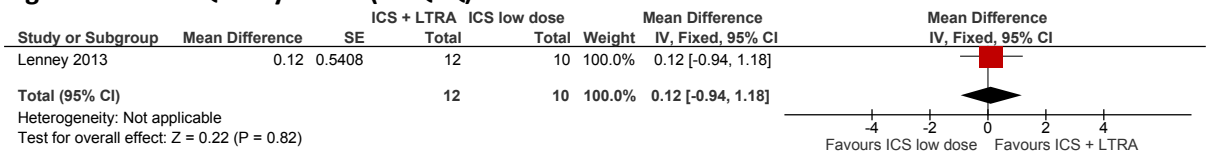


Figure 168: Hospitalisations

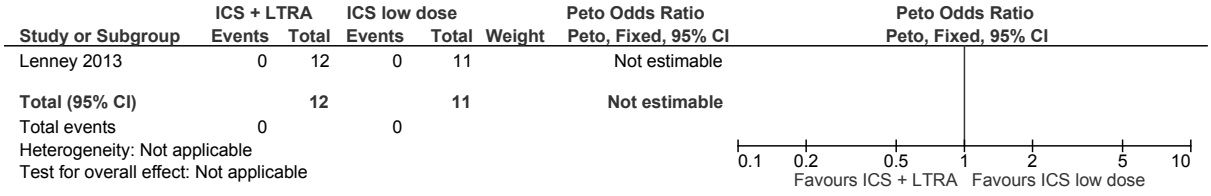


Figure 169: Lung function (FEV_1 [%predicted])

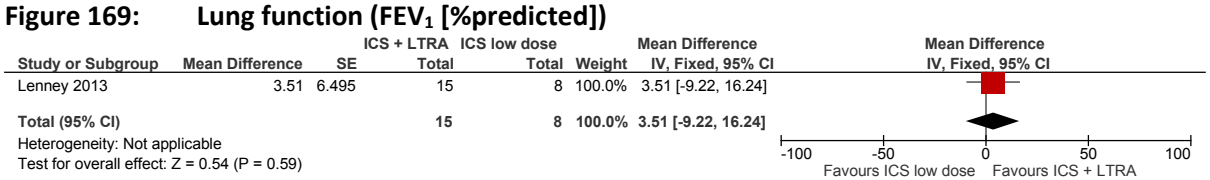
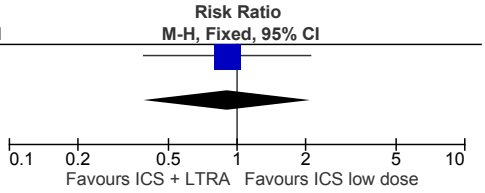


Figure 170: Infections (all respiratory)

Study or Subgroup	ICS + LTRA Events	ICS + LTRA Total	ICS low dose Events	ICS low dose Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lenney 2013	7	21	7	19	100.0%	0.90 [0.39, 2.10]
Total (95% CI)		**21**		**19**	**100.0%**	**0.90 [0.39, 2.10]**
Total events	7		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



K.3.1.16 ICS low dose + LTRA versus ICS low dose + LABA in patients aged 5 to 16

Figure 171: Exacerbations (requiring OCS)

Study or Subgroup	ICS + LTRA Events	ICS + LTRA Total	ICS + LABA Events	ICS + LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lenney 2013	1	12	5	15	100.0%	0.25 [0.03, 1.86]
Total (95% CI)		**12**		**15**	**100.0%**	**0.25 [0.03, 1.86]**
Total events	1		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)

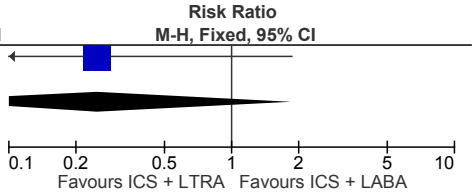


Figure 172: Quality of life (PAQLQ)

Study or Subgroup	Mean Difference	SE	ICS + LTRA Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Lenney 2013	0.84	0.4796	12	15	100.0%	0.84 [-0.10, 1.78]
Total (95% CI)			**12**	**15**	**100.0%**	**0.84 [-0.10, 1.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)

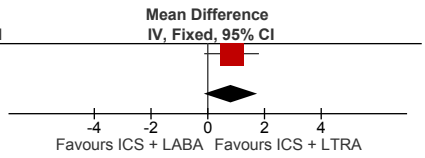


Figure 173: Hospitalisations

Study or Subgroup	ICS + LTRA Events	ICS + LTRA Total	ICS + LABA Events	ICS + LABA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lenney 2013	0	12	2	15	100.0%	0.15 [0.01, 2.64]
Total (95% CI)		**12**		**15**	**100.0%**	**0.15 [0.01, 2.64]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)

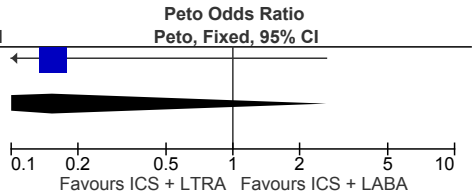


Figure 174: Lung function (FEV_1 (%predicted))

Study or Subgroup	Mean Difference	SE	ICS + LTRA Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Lenney 2013	-5.07	5.9338	15	13	100.0%	-5.07 [-16.70, 6.56]
Total (95% CI)			**15**	**13**	**100.0%**	**-5.07 [-16.70, 6.56]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)

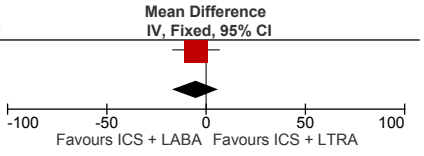
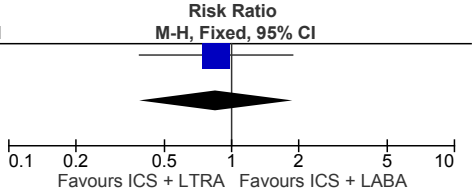


Figure 175: Infections (all respiratory)

Study or Subgroup	ICS + LTRA Events	ICS + LTRA Total	ICS + LABA Events	ICS + LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lenney 2013	7	21	9	23	100.0%	0.85 [0.39, 1.88]
Total (95% CI)		**21**		**23**	**100.0%**	**0.85 [0.39, 1.88]**
Total events	7		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



K.3.1.17 ICS low dose + LABA versus ICS moderate dose in patients aged 5 to 16

Figure 176: Exacerbations (requiring OCS)

Study or Subgroup	ICS + LABA Events	Total	ICS moderate dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vaesses-Verberne 2010	8	72	4	79	100.0%	2.19 [0.69, 6.98]
Total (95% CI)		**72**		**79**	**100.0%**	**2.19 [0.69, 6.98]**
Total events	8		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)

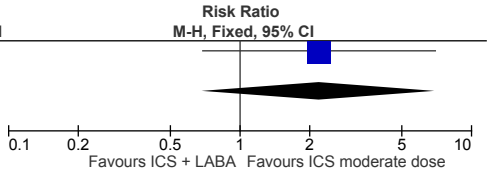


Figure 177: Lung function (FEV_1 [%predicted])

Study or Subgroup	Mean Difference	SE	ICS + LABA Total	ICS moderate dose Total	Weight	Mean Difference IV, Fixed, 95% CI
Vaesses-Verberne 2010	1	1.6327	78	80	100.0%	1.00 [-2.20, 4.20]
Total (95% CI)			**78**	**80**	**100.0%**	**1.00 [-2.20, 4.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

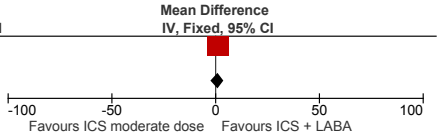


Figure 178: Lung function (PEF [L/min])

Study or Subgroup	ICS + LABA Mean	SD	Total	ICS moderate dose Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
de Blic 2009	27.7	25.1	129	18.4	24.9	136	100.0%	9.30 [3.28, 15.32]
Total (95% CI)			**129**			**136**	**100.0%**	**9.30 [3.28, 15.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.03 (P = 0.002)

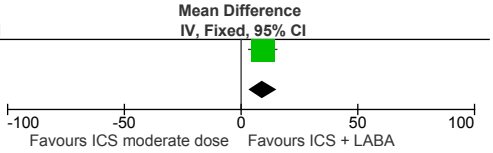
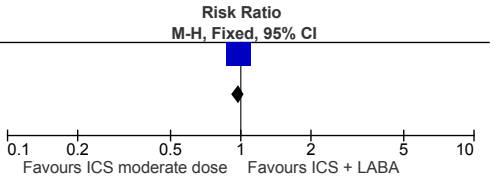


Figure 179: Adherence (≥75% compliance across treatment period)

Study or Subgroup	ICS + LABA Events	Total	ICS moderate dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Blic 2009	138	150	144	153	100.0%	0.98 [0.92, 1.04]
Total (95% CI)		**150**		**153**	**100.0%**	**0.98 [0.92, 1.04]**
Total events	138		144			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



K.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

K.3.2.1 MART with ICS + LABA versus preventer ICS + LABA with reliever SABA, people aged 16 or older

Figure 180: Severe exacerbations

Study or Subgroup	MART Events	Total	Non-MART Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Atienza 2009	130	1049	168	1042	16.5%	0.77 [0.62, 0.95]
O'Byrne 2005	102	925	191	909	18.9%	0.52 [0.42, 0.66]
Papi 2013	89	852	143	849	14.0%	0.62 [0.48, 0.79]
Patel 2013	28	151	50	152	4.9%	0.56 [0.38, 0.84]
Rabe 2006	143	1107	245	1138	23.6%	0.60 [0.50, 0.72]
Stallberg 2008	68	884	45	452	5.8%	0.77 [0.54, 1.11]
Vogelmeier 2005	132	1067	167	1076	16.3%	0.80 [0.64, 0.99]
Total (95% CI)		**6035**		**5618**	**100.0%**	**0.66 [0.60, 0.72]**
Total events	692		1009			

Heterogeneity: $Chi^2 = 11.65$, df = 6 (P = 0.07); $I^2 = 48\%$
Test for overall effect: Z = 9.16 (P < 0.00001)

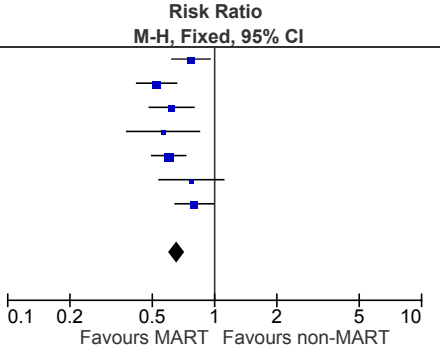


Figure 181: Mortality

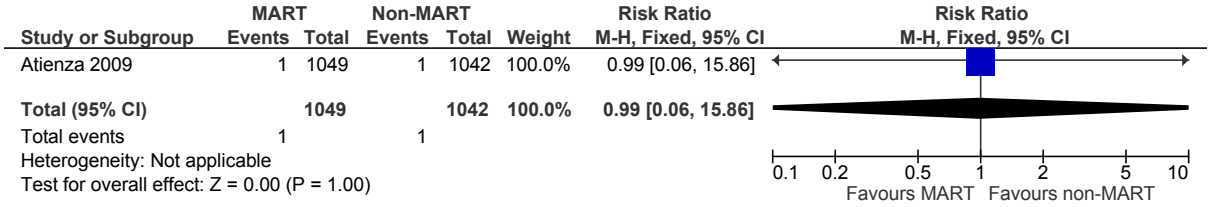


Figure 182: Quality of life (AQLQ, 1-7, higher is better outcome)

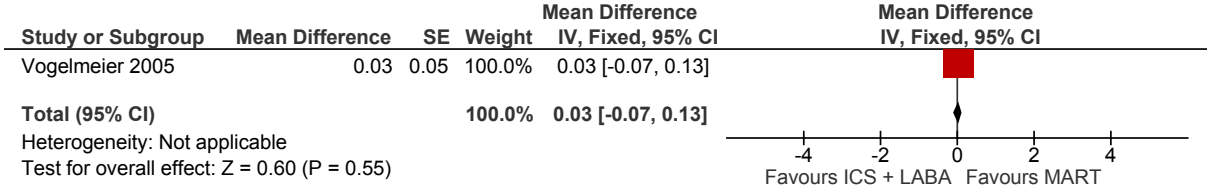


Figure 183: Control (ACQ, 0-6, higher is worse outcome)

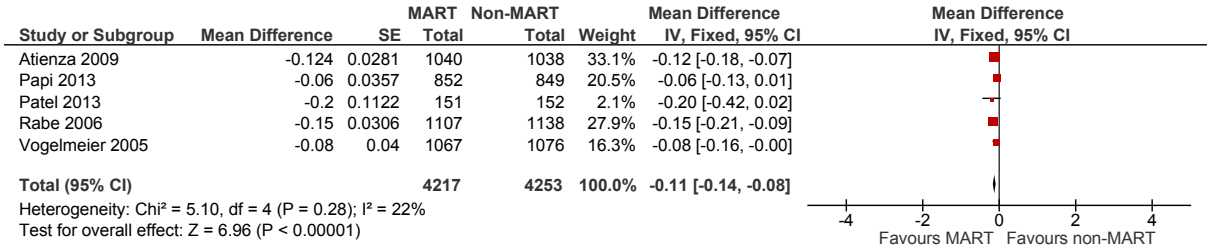


Figure 184: Hospitalisations

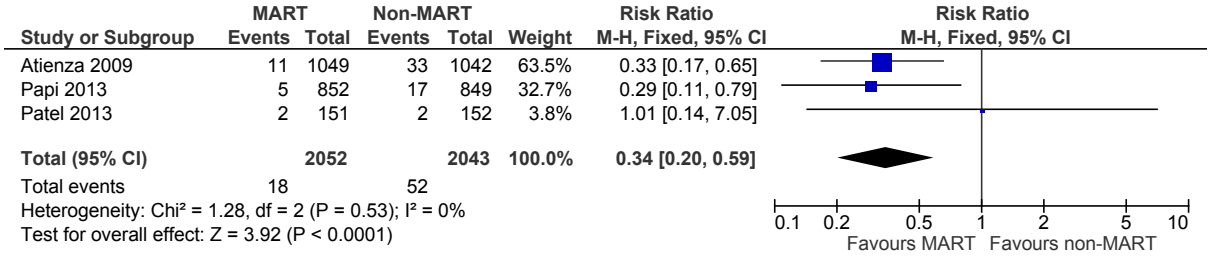


Figure 185: Reliever medication use (puffs/day)

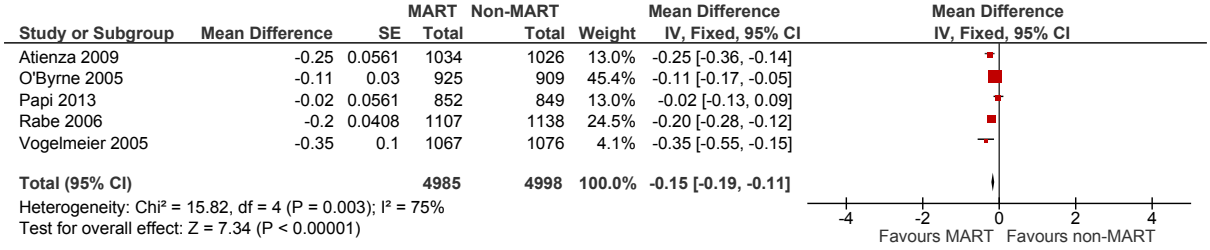


Figure 186: FEV_1 (%predicted)

Study or Subgroup	Mean Difference	SE	MART Total	Non-MART Total	Weight	Mean Difference IV, Fixed, 95% CI
Patel 2013	2.5	2.296	151	152	100.0%	2.50 [-2.00, 7.00]
Total (95% CI)			**151**	**152**	**100.0%**	**2.50 [-2.00, 7.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)

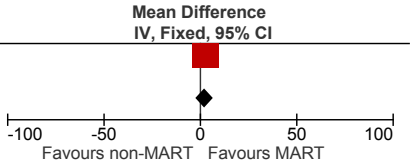


Figure 187: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	MART Total	Non-MART Total	Weight	Mean Difference IV, Fixed, 95% CI
Atienza 2009	0.04	0.0128	1034	1026	34.4%	0.04 [0.01, 0.07]
O'Byrne 2005	0.08	0.02	925	909	14.1%	0.08 [0.04, 0.12]
Papi 2013	0.001	0.0209	852	849	12.9%	0.00 [-0.04, 0.04]
Patel 2013	0.15	0.1071	151	152	0.5%	0.15 [-0.06, 0.36]
Rabe 2006	0.08	0.0153	1107	1138	24.1%	0.08 [0.05, 0.11]
Vogelmeier 2005	0.03	0.02	1067	1076	14.1%	0.03 [-0.01, 0.07]
Total (95% CI)			**5136**	**5150**	**100.0%**	**0.05 [0.03, 0.06]**

Heterogeneity: Chi² = 14.07, df = 5 (P = 0.02); I² = 64%
Test for overall effect: Z = 6.58 (P < 0.00001)

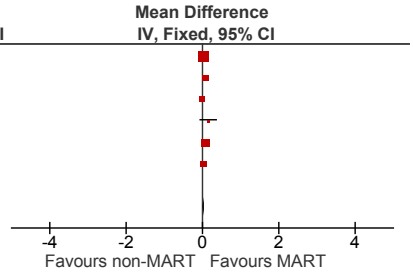


Figure 188: PEF (L/minute)

Study or Subgroup	Mean Difference	SE	MART Total	Non-MART Total	Weight	Mean Difference IV, Fixed, 95% CI
Atienza 2009	5.8	1.8878	1034	1026	33.2%	5.80 [2.10, 9.50]
O'Byrne 2005	9	2.7	925	909	16.2%	9.00 [3.71, 14.29]
Papi 2013	3.69	3.6735	852	849	8.8%	3.69 [-3.51, 10.89]
Rabe 2006	7.5	1.6837	1107	1138	41.8%	7.50 [4.20, 10.80]
Total (95% CI)			**3918**	**3922**	**100.0%**	**6.84 [4.71, 8.98]**

Heterogeneity: Chi² = 1.83, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 6.29 (P < 0.00001)

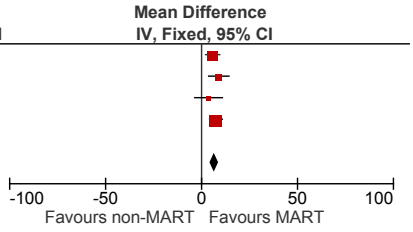


Figure 189: Infection (all respiratory)

Study or Subgroup	MART Events	MART Total	Non-MART Events	Non-MART Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Atienza 2009	60	1049	72	1042	31.8%	0.83 [0.59, 1.15]
O'Byrne 2005	158	922	144	906	63.9%	1.08 [0.88, 1.33]
Rabe 2006	22	1107	10	1138	4.3%	2.26 [1.08, 4.75]
Total (95% CI)		**3078**		**3086**	**100.0%**	**1.05 [0.89, 1.24]**
Total events	240		226			

Heterogeneity: Chi² = 6.14, df = 2 (P = 0.05); I² = 67%
Test for overall effect: Z = 0.56 (P = 0.57)

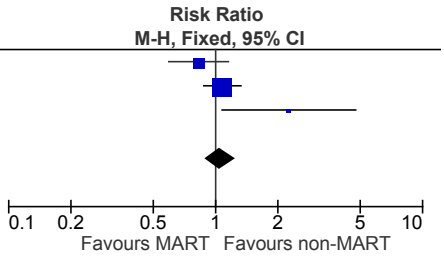
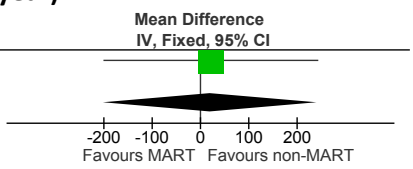


Figure 190: Total steroid dose (prednisolone equivalent, mg/year)

Study or Subgroup	MART Mean	MART SD	MART Total	Non-MART Mean	Non-MART SD	Non-MART Total	Weight	Mean Difference IV, Fixed, 95% CI
Patel 2013	793.7	893.1	151	772.1	1,062.7	152	100.0%	21.60 [-199.38, 242.58]
Total (95% CI)			**151**			**152**	**100.0%**	**21.60 [-199.38, 242.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)



K.3.2.2 MART with ICS + LABA versus preventer ICS + LABA with reliever SABA, children and young people aged 5 to 16

Figure 191: Severe exacerbations

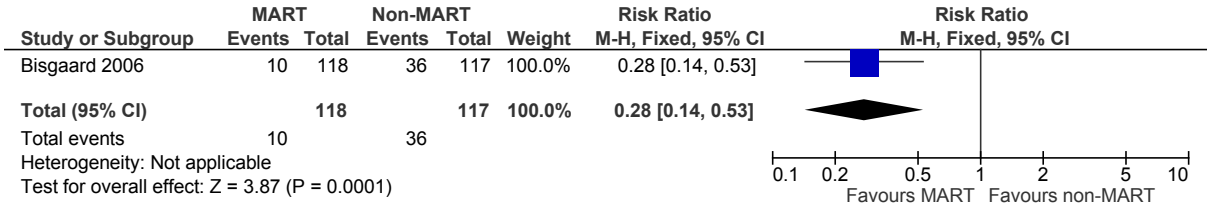


Figure 192: Reliever medication use (puffs/day)

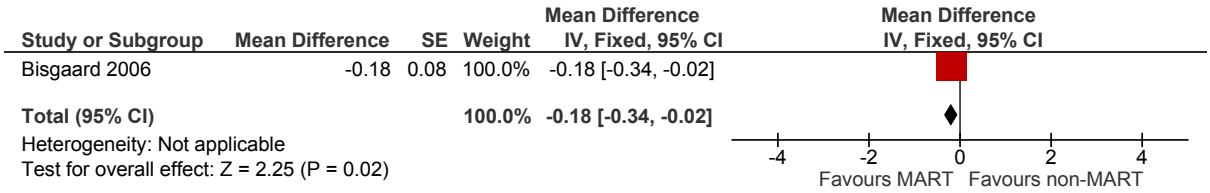


Figure 193: FEV_1 (L)

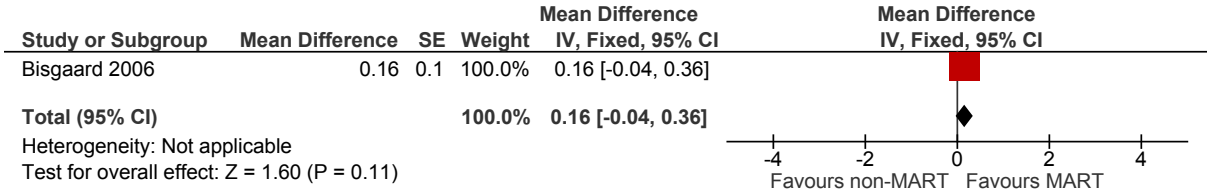
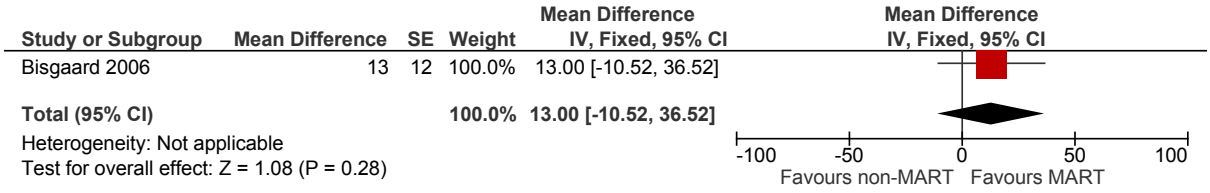


Figure 194: PEF (L/minute)



K.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

K.3.3.1 Population uncontrolled on ICS + LABA, over 16

MART (ICS moderate + LABA) vs ICS high + LABA + PRN SABA

Figure 195: Severe exacerbations

Figure 196: Asthma control (ACQ, 0-6, higher is worse outcome)

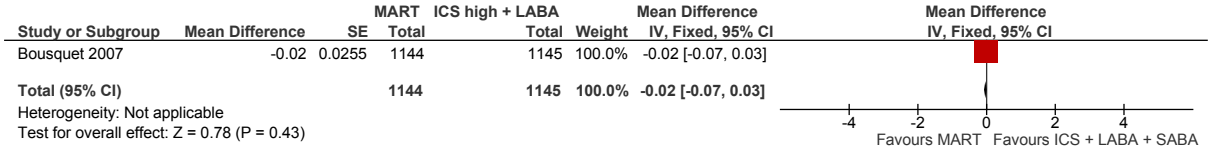


Figure 197: Rescue medication use (puffs/day)

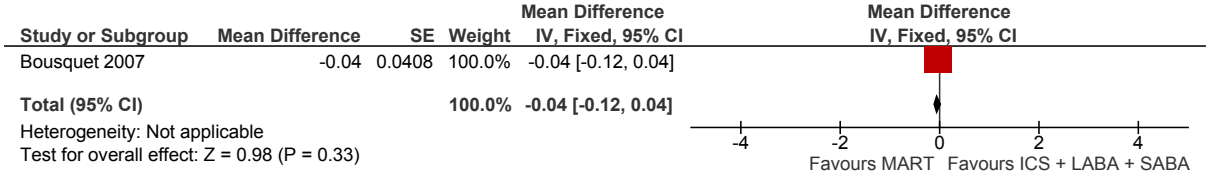
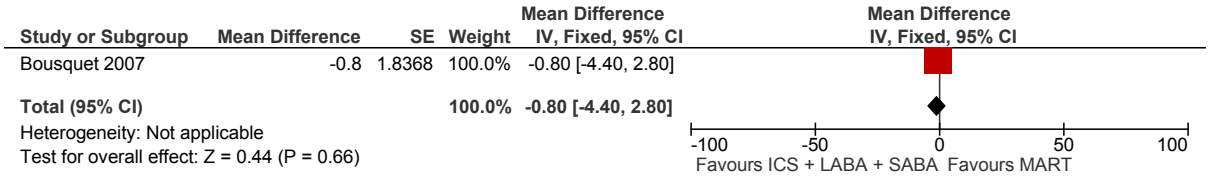


Figure 198: PEF (L/min)



MART (ICS low + LABA) vs ICS low + LABA + PRN SABA

Figure 199: Severe exacerbations

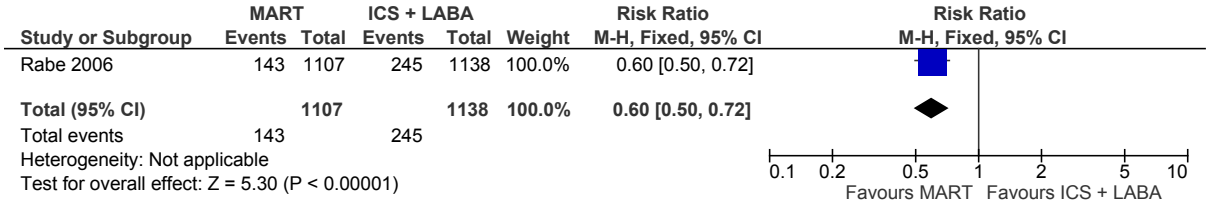


Figure 200: Asthma control (ACQ, 0-6, higher is worse outcome)

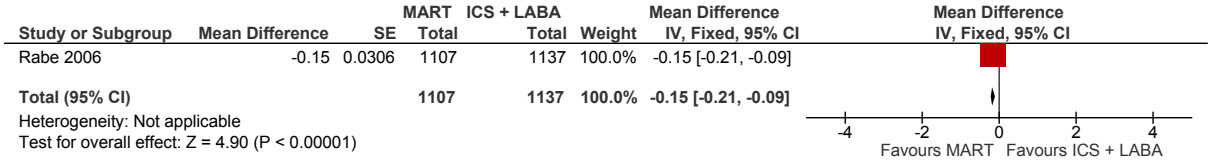


Figure 201: Reliever medication use (puffs/day)

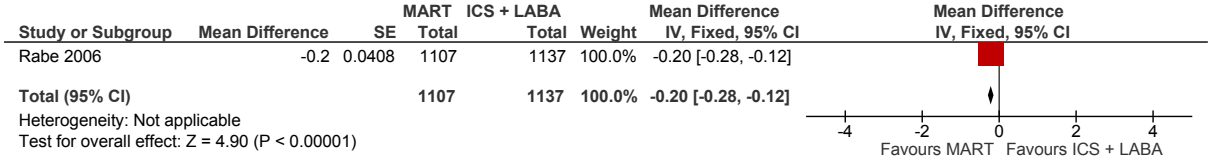


Figure 202: FEV_1 (L)

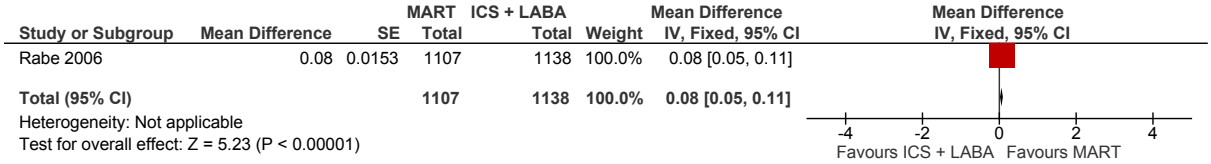


Figure 203: PEF (L/min)

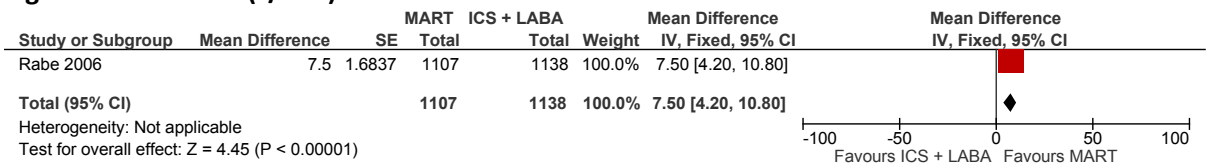
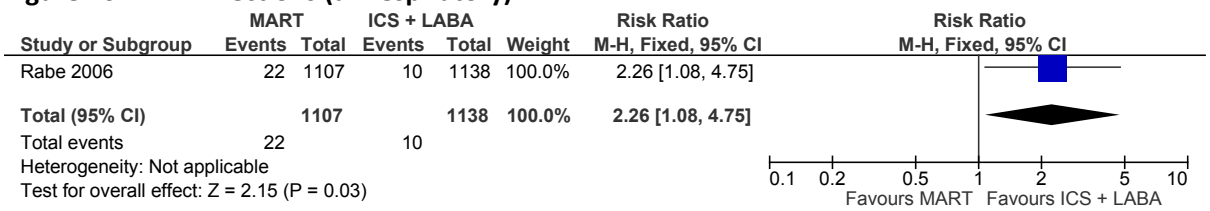


Figure 204: Infections (all respiratory)

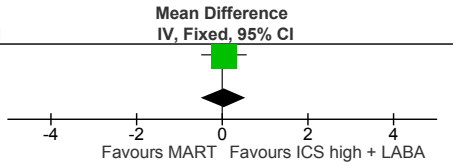


MART (ICS low + LABA) vs ICS high + LABA + PRN SABA

Figure 205: Reliever medication use (puffs/day)

Study or Subgroup	MART Mean	MART SD	MART Total	ICS high + LABA Mean	ICS high + LABA SD	ICS high + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Pavord 2009	-0.46	1.48	64	-0.5	1.48	63	100.0%	0.04 [-0.47, 0.55]
Total (95% CI)			**64**			**63**	**100.0%**	**0.04 [-0.47, 0.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)



ICS + LABA + LAMA vs ICS + LABA

Figure 206: Severe exacerbations

Study or Subgroup	+ LAMA Events	+ LAMA Total	+ placebo Events	+ placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kerstjens 2012 - Combined	122	453	149	454	100.0%	0.82 [0.67, 1.00]
Total (95% CI)		**453**		**454**	**100.0%**	**0.82 [0.67, 1.00]**
Total events	122		149			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)

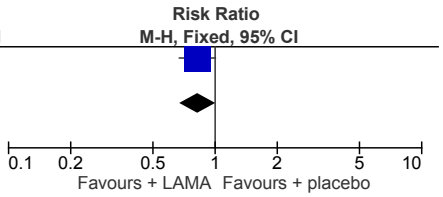


Figure 207: Quality of life (AQLQ, 1-7, higher is better outcome)

Study or Subgroup	Mean Difference	SE	+ LAMA Total	+ placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Kerstjens 2012 - Trial 1	0.04	0.0714	237	222	53.4%	0.04 [-0.10, 0.18]
Kerstjens 2012 - Trial 2	0.18	0.0765	219	234	46.6%	0.18 [0.03, 0.33]
Total (95% CI)			**456**	**456**	**100.0%**	**0.11 [0.00, 0.21]**

Heterogeneity: Chi² = 1.79, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 2.02 (P = 0.04)

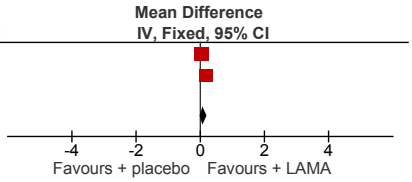


Figure 208: Control (ACQ, 0-6, higher is worse outcome)

Study or Subgroup	Mean Difference	SE	+ LAMA Total	+ placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Kerstjens 2012 - Trial 1	-0.13	0.0663	237	222	37.2%	-0.13 [-0.26, -0.00]
Kerstjens 2012 - Trial 2	-0.2	0.051	219	234	62.8%	-0.20 [-0.30, -0.10]
Total (95% CI)			**456**	**456**	**100.0%**	**-0.17 [-0.25, -0.09]**

Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 4.30 (P < 0.0001)

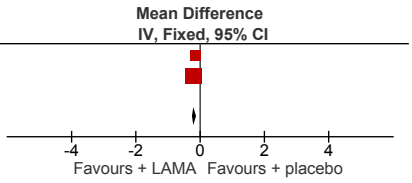


Figure 209: Reliever medication use (puffs/day)

Study or Subgroup	Mean Difference	SE	+ LAMA Total	+ placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Kerstjens 2012 - Trial 1	-0.09	0.1735	237	222	55.5%	-0.09 [-0.43, 0.25]
Kerstjens 2012 - Trial 2	-0.26	0.1939	219	234	44.5%	-0.26 [-0.64, 0.12]
Total (95% CI)			**456**	**456**	**100.0%**	**-0.17 [-0.42, 0.09]**

Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)

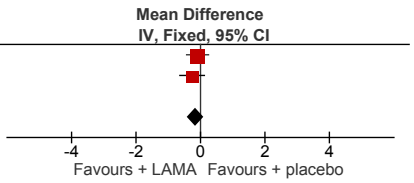


Figure 210: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	+ LAMA Total	+ placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Kerstjens 2012 - Trial 1	0.042	0.0321	208	209	39.3%	0.04 [-0.02, 0.10]
Kerstjens 2012 - Trial 2	0.092	0.0306	201	201	43.2%	0.09 [0.03, 0.15]
Ohta 2015	0.112	0.048	114	57	17.6%	0.11 [0.02, 0.21]
Total (95% CI)			**523**	**467**	**100.0%**	**0.08 [0.04, 0.12]**

Heterogeneity: Chi² = 1.96, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 3.77 (P = 0.0002)

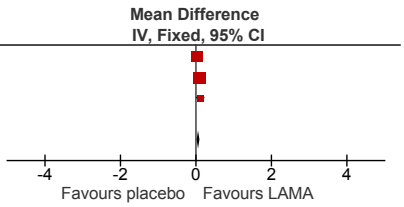


Figure 211: PEF (L/min)

Study or Subgroup	Mean Difference	SE	+ LAMA Total	+ placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Kerstjens 2012 - Trial 1	20.3	4.5919	184	185	46.3%	20.30 [11.30, 29.30]
Kerstjens 2012 - Trial 2	14	4.5409	189	189	47.3%	14.00 [5.10, 22.90]
Ohta 2015	34.2	12.3982	114	57	6.4%	34.20 [9.90, 58.50]
Total (95% CI)			**487**	**431**	**100.0%**	**18.20 [12.08, 24.32]**

Heterogeneity: Chi² = 2.73, df = 2 (P = 0.26); I² = 27%
Test for overall effect: Z = 5.82 (P < 0.00001)

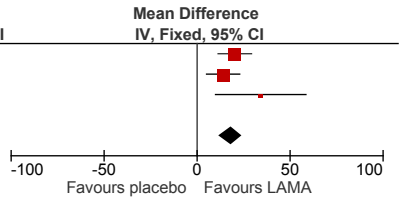


Figure 212: Infections (all respiratory)

Study or Subgroup	+ LAMA Events	+ LAMA Total	+ placebo Events	+ placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kerstjens 2012 - Combined	21	456	16	456	26.1%	1.31 [0.69, 2.48]
Ohta 2015	97	114	34	57	73.9%	1.43 [1.14, 1.79]
Total (95% CI)		**570**		**513**	**100.0%**	**1.40 [1.11, 1.76]**
Total events	118		50			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005)

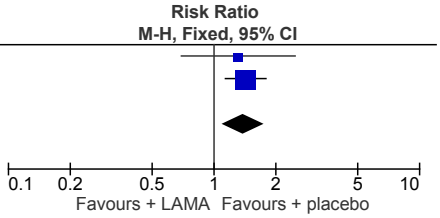
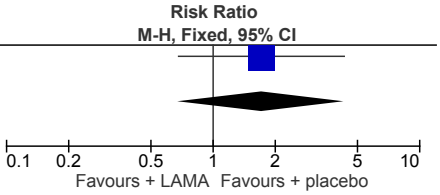


Figure 213: Infections (serious infections)

Study or Subgroup	+ LAMA Events	+ LAMA Total	+ placebo Events	+ placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kerstjens 2012 - Combined	12	456	7	456	100.0%	1.71 [0.68, 4.31]
Total (95% CI)		**456**		**456**	**100.0%**	**1.71 [0.68, 4.31]**
Total events	12		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)



ICS high + LABA vs ICS moderate + LABA

Figure 214: Severe exacerbations

Study or Subgroup	ICS high + LABA Events	ICS high + LABA Total	ICS mod + LABA Events	ICS mod + LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Peters 2008	54	443	19	132	100.0%	0.85 [0.52, 1.38]
Total (95% CI)		**443**		**132**	**100.0%**	**0.85 [0.52, 1.38]**
Total events	54		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

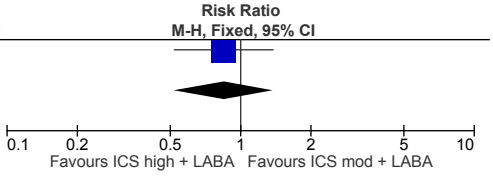


Figure 215: Hospitalisations

Study or Subgroup	ICS high + LABA Events	ICS high + LABA Total	ICS mod + LABA Events	ICS mod + LABA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Peters 2008	2	443	2	132	100.0%	0.22 [0.02, 2.22]
Total (95% CI)		**443**		**132**	**100.0%**	**0.22 [0.02, 2.22]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)

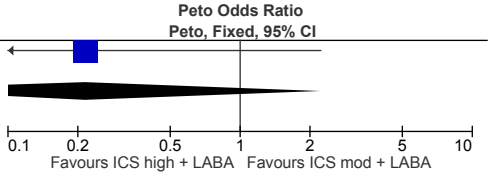


Figure 216: Reliever medication use (puffs/day)

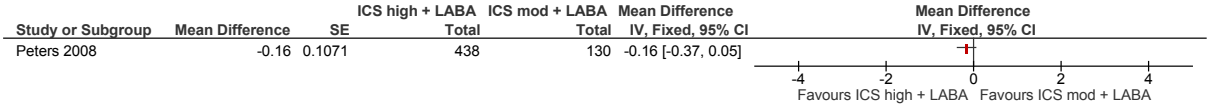


Figure 217: FEV_1 (L)

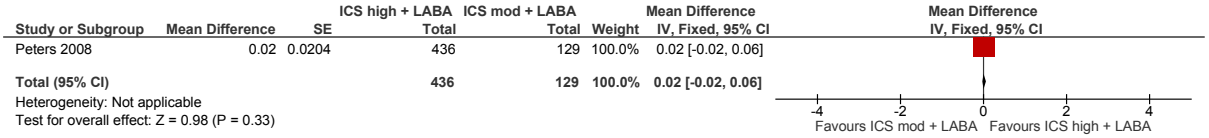


Figure 218: PEF (L/min)

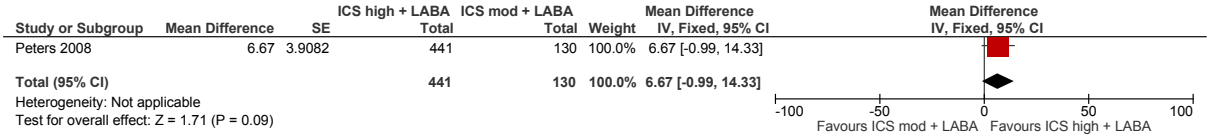


Figure 219: Infections (all respiratory)

ICS high + LABA vs ICS high

Figure 220: Severe exacerbations

Figure 221: Hospitalisations

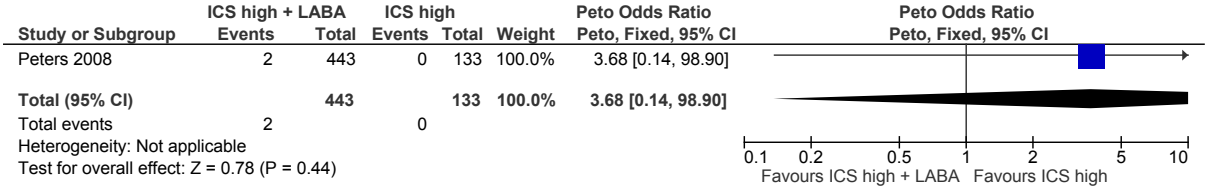


Figure 222: Reliever medication use (puffs/day)

Study or Subgroup	Mean Difference	SE	ICS high + LABA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Peters 2008	-0.87	0.1071	438	130	100.0%	-0.87 [-1.08, -0.66]
Total (95% CI)			**438**	**130**	**100.0%**	**-0.87 [-1.08, -0.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.12 (P < 0.00001)

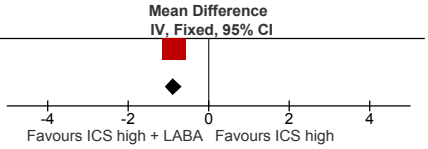


Figure 223: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	ICS high + LABA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Peters 2008	0.11	0.0255	436	132	100.0%	0.11 [0.06, 0.16]
Total (95% CI)			**436**	**132**	**100.0%**	**0.11 [0.06, 0.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.31 (P < 0.0001)

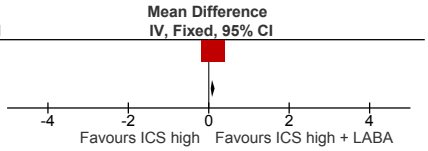


Figure 224: PEF (L/min)

Study or Subgroup	Mean Difference	SE	ICS high + LABA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Peters 2008	0.11	0.0255	436	132	100.0%	0.11 [0.06, 0.16]
Total (95% CI)			**436**	**132**	**100.0%**	**0.11 [0.06, 0.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.31 (P < 0.0001)

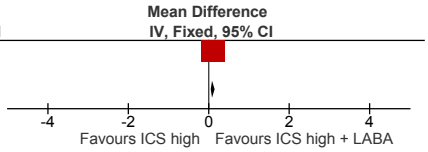
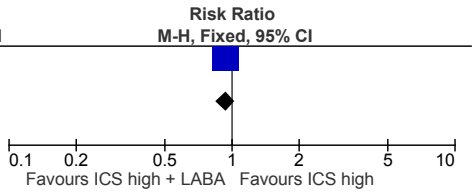


Figure 225: Infections (all respiratory)

Study or Subgroup	ICS high + LABA Events	Total	ICS high Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Peters 2008	327	443	105	133	100.0%	0.93 [0.84, 1.04]
Total (95% CI)		**443**		**133**	**100.0%**	**0.93 [0.84, 1.04]**
Total events	327		105			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)



ICS high vs ICS moderate + LABA

Figure 226: Severe exacerbations

Study or Subgroup	ICS high Events	Total	ICS mod + LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Peters 2008	29	133	19	132	100.0%	1.51 [0.90, 2.56]
Total (95% CI)		**133**		**132**	**100.0%**	**1.51 [0.90, 2.56]**
Total events	29		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

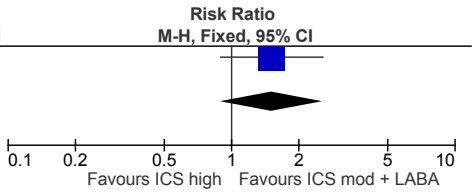


Figure 227: Hospitalisations

Study or Subgroup	ICS high Events	Total	ICS mod + LABA Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Peters 2008	0	133	2	132	100.0%	0.13 [0.01, 2.14]
Total (95% CI)		**133**		**132**	**100.0%**	**0.13 [0.01, 2.14]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.15)

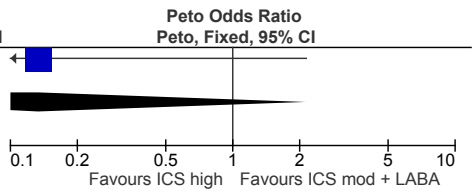


Figure 228: Reliever medication use (puffs/day)

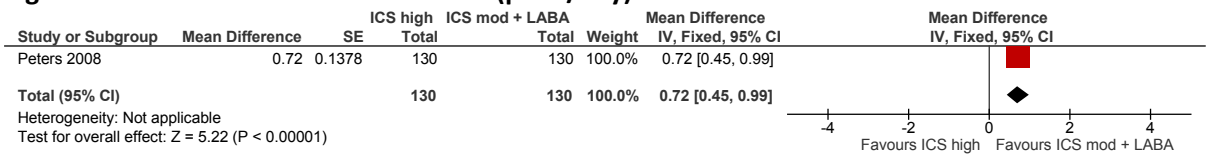


Figure 229: FEV_1 (L)

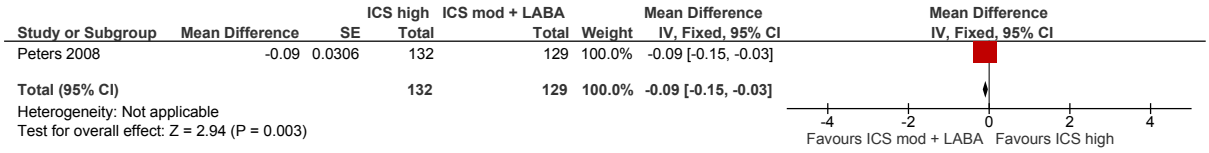


Figure 230: PEF (L/min)

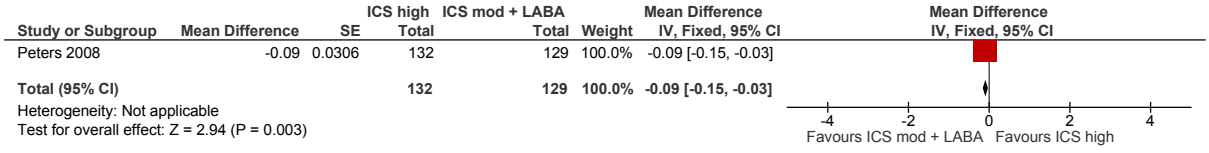
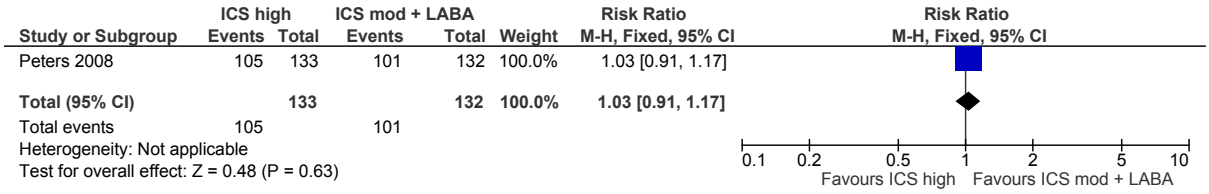


Figure 231: Infections (all respiratory)



ICS low + LAMA vs ICS low + LABA

Figure 232: Severe exacerbations

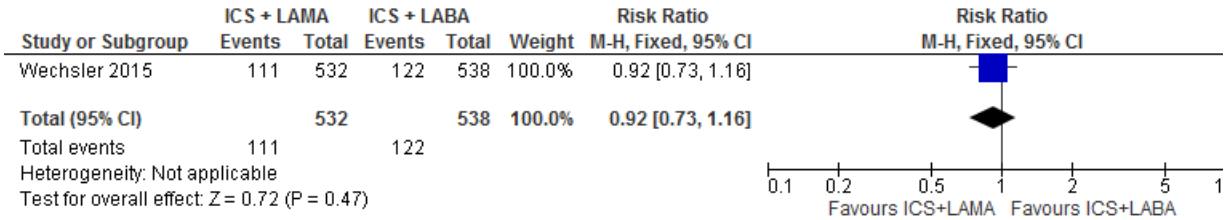


Figure 233: Quality of life (AQLQ, 1-7, higher is better outcome)

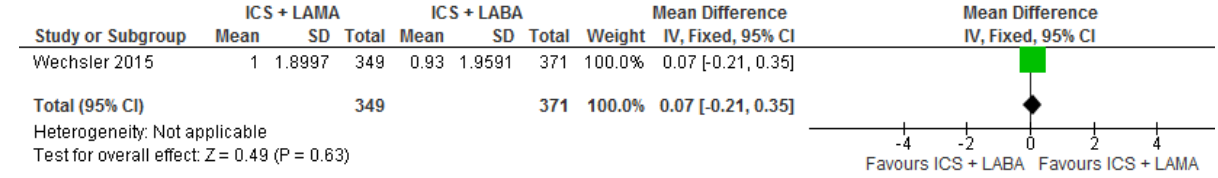


Figure 234: Asthma control (ACQ, 0-6, higher is worse outcome)

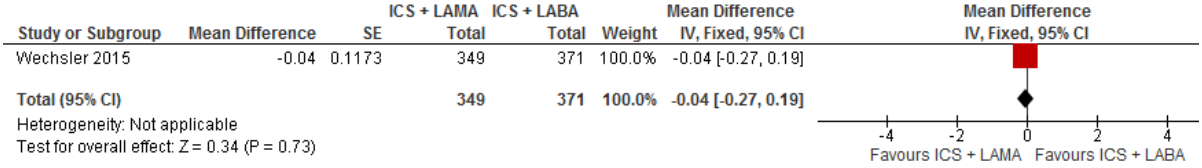


Figure 235: FEV_1 (L)

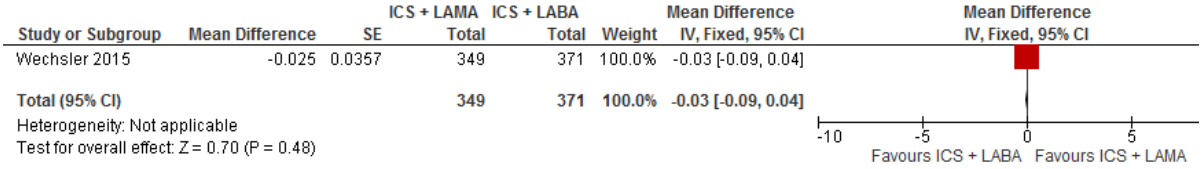
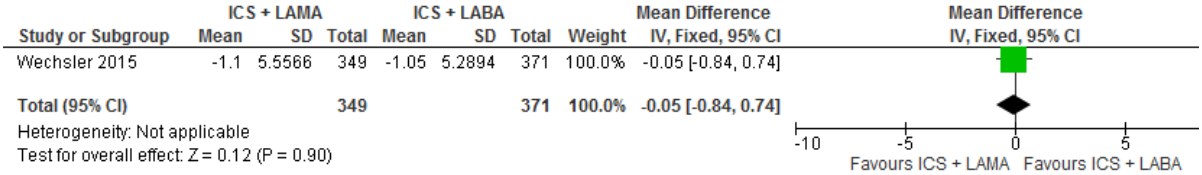


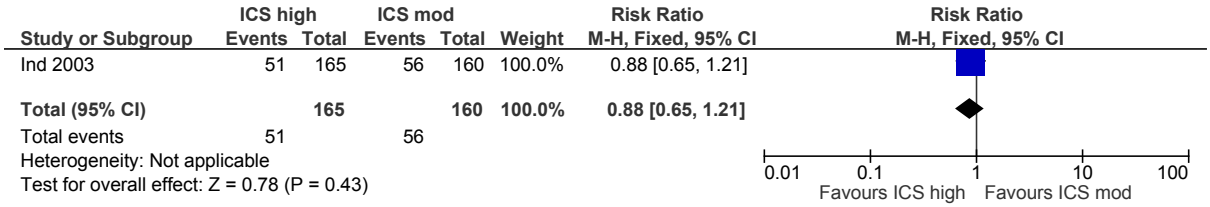
Figure 236: Rescue medication use (puffs/day)



K.3.3.2 Population uncontrolled on ICS moderate, over 16

ICS high vs ICS moderate

Figure 237: Severe exacerbations



ICS low + LABA vs ICS moderate

Figure 238: Severe exacerbations

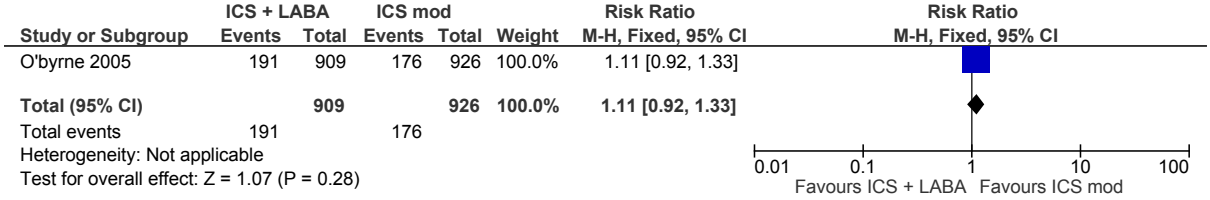


Figure 239: Reliever medication use (puffs/day)

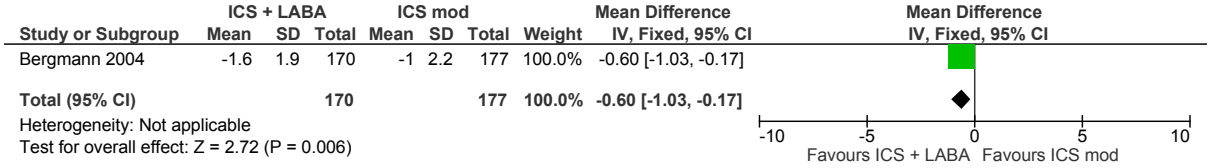


Figure 240: Reliever medication use (puffs/daytime)

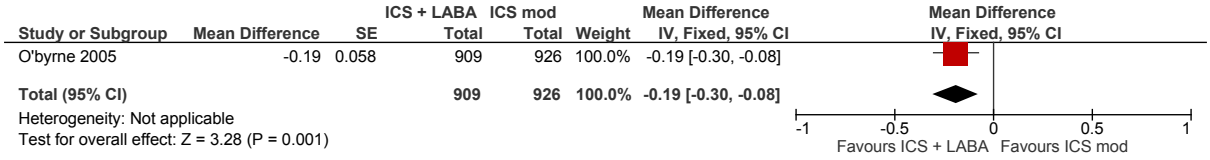


Figure 241: Reliever medication use (puffs/night)

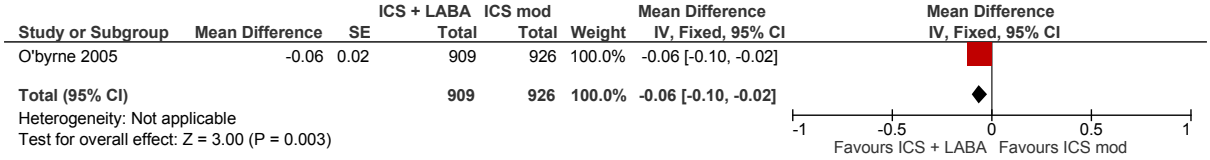


Figure 242: FEV_1 (L)

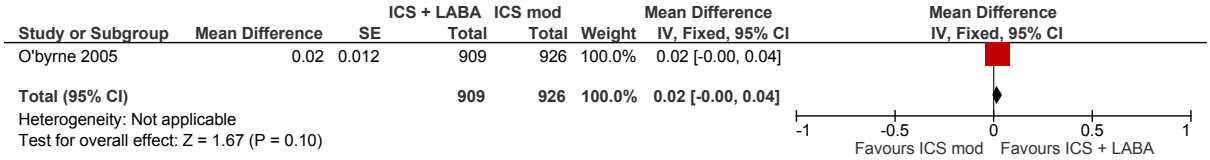


Figure 243: FEV_1 (%predicted)

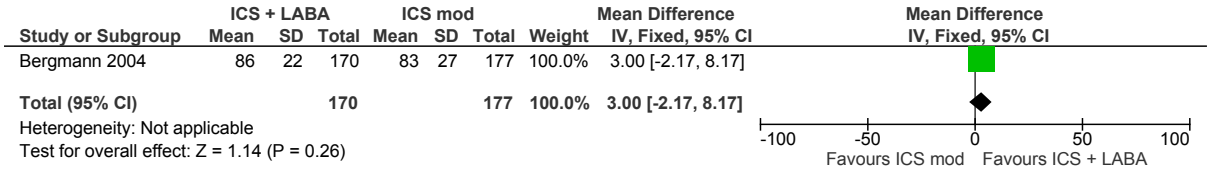
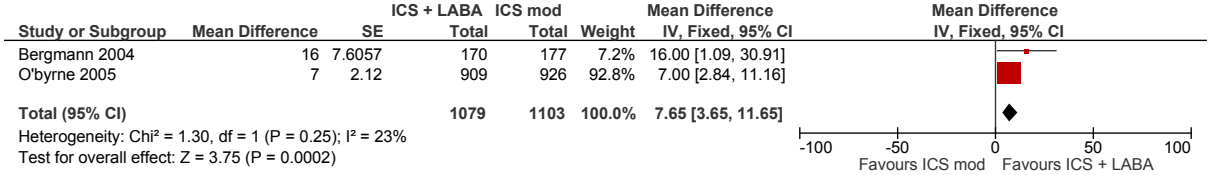


Figure 244: PEF (L/min)



ICS moderate + LABA vs ICS moderate

Figure 245: Severe exacerbations

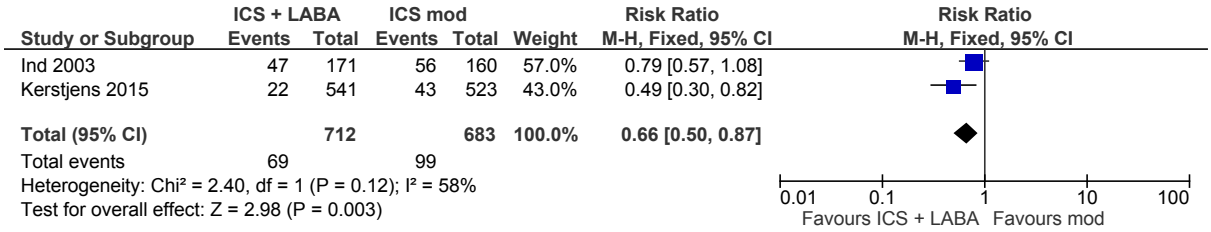


Figure 246: Quality of life (pooled AQLQ, SGRQ)

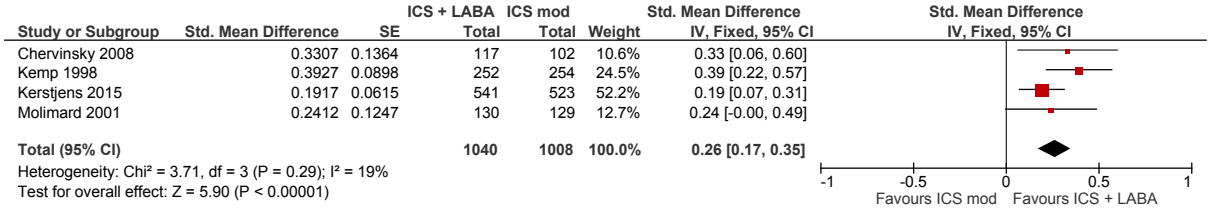


Figure 247: Asthma control (ACQ, 0-6, higher is worse outcome)

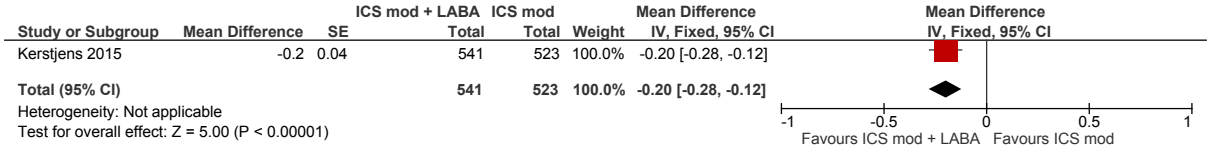


Figure 248: Reliever medication use (puffs/day)

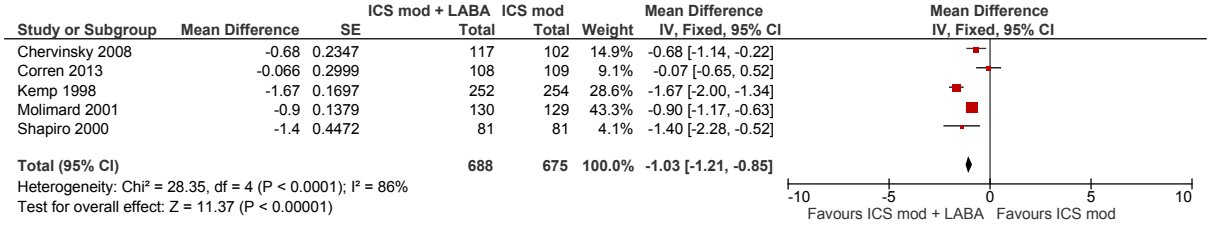


Figure 249: Reliever medication use (puffs/daytime)

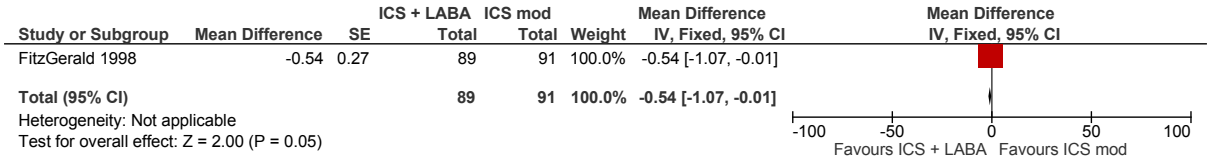


Figure 250: Reliever medication use (puffs/night time)

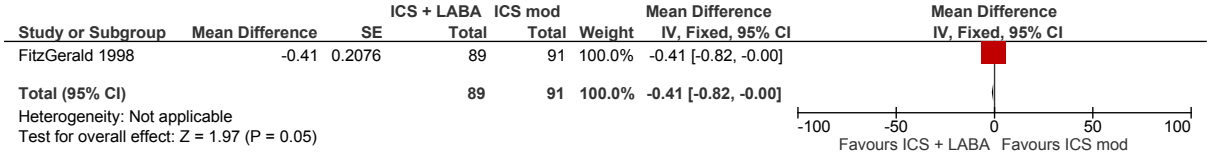


Figure 251: PEF (L/min)

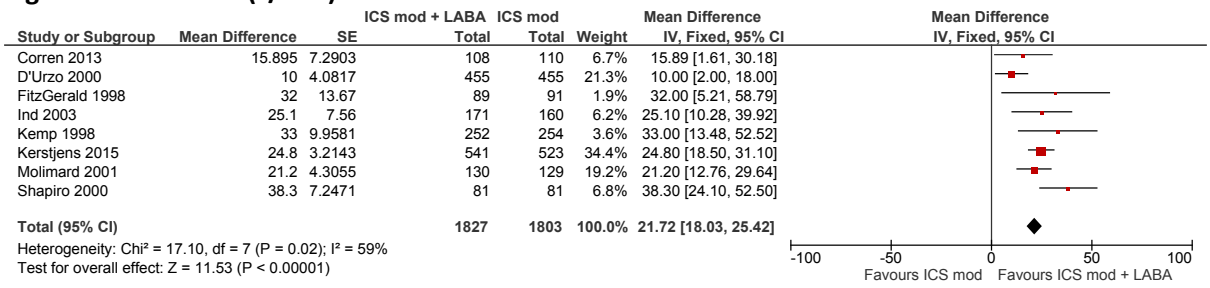


Figure 252: FEV_1 (L)

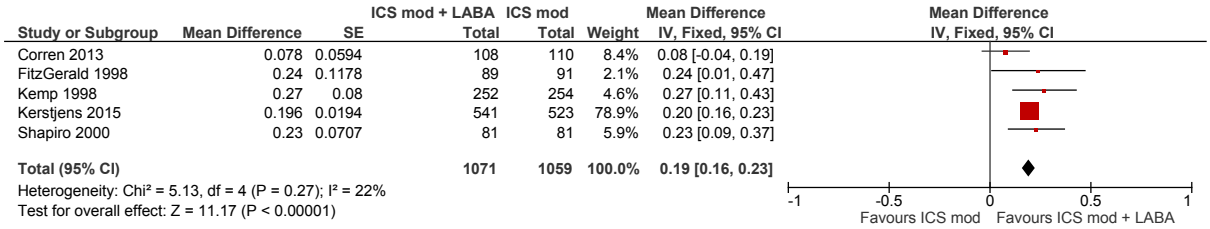
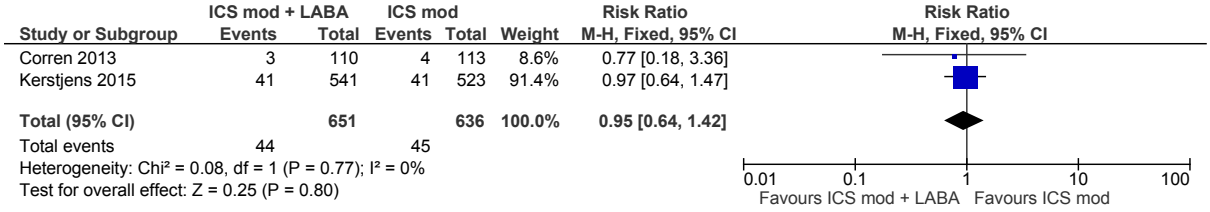


Figure 253: Infection (all respiratory)



MART (ICS low + LABA) vs ICS moderate

Figure 254: Severe exacerbations

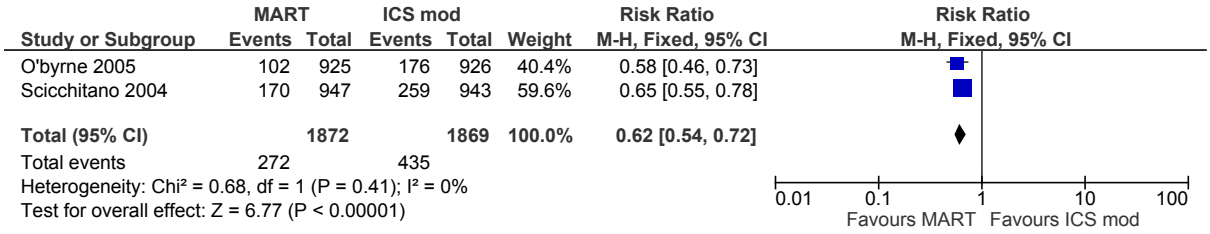


Figure 255: Reliever medication use (puffs/daytime)

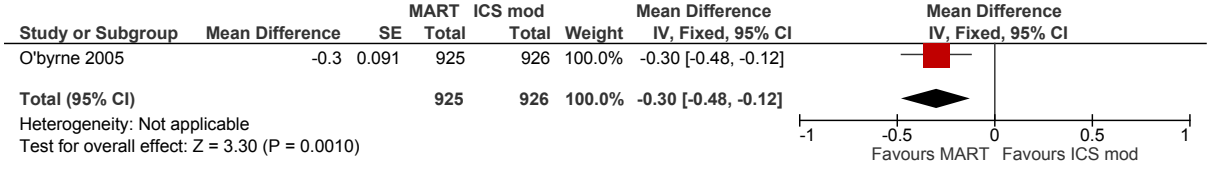


Figure 256: Reliever medication use (puffs/night time)

Study or Subgroup	Mean Difference	SE	MART Total	ICS mod Total	Weight	Mean Difference IV, Fixed, 95% CI
O'byrne 2005	-0.15	0.046	925	926	100.0%	-0.15 [-0.24, -0.06]
Total (95% CI)			**925**	**926**	**100.0%**	**-0.15 [-0.24, -0.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.26 (P = 0.001)

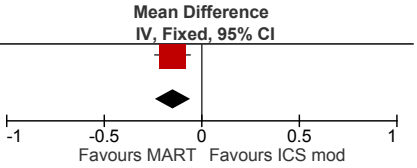


Figure 257: Reliever medication use (reliever-free days %)

Study or Subgroup	Mean Difference	SE	MART Total	ICS mod Total	Weight	Mean Difference IV, Fixed, 95% CI
Scicchitano 2004	11	1.4286	947	943	100.0%	11.00 [8.20, 13.80]
Total (95% CI)			**947**	**943**	**100.0%**	**11.00 [8.20, 13.80]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.70 (P < 0.00001)

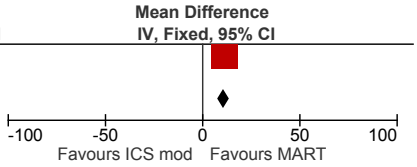


Figure 258: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	MART Total	ICS mod Total	Weight	Mean Difference IV, Fixed, 95% CI
O'byrne 2005	0.1	0.03	925	926	100.0%	0.10 [0.04, 0.16]
Total (95% CI)			**925**	**926**	**100.0%**	**0.10 [0.04, 0.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.33 (P = 0.0009)

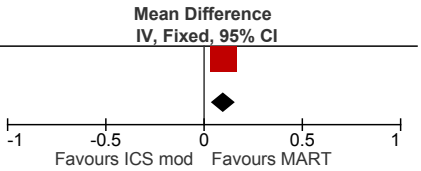
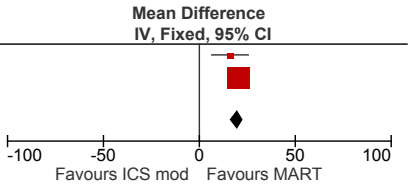


Figure 259: PEF (L/min)

Study or Subgroup	Mean Difference	SE	MART Total	ICS mod Total	Weight	Mean Difference IV, Fixed, 95% CI
O'byrne 2005	16	4.85	925	926	13.8%	16.00 [6.49, 25.51]
Scicchitano 2004	20.3	1.9388	947	943	86.2%	20.30 [16.50, 24.10]
Total (95% CI)			**1872**	**1869**	**100.0%**	**19.71 [16.18, 23.24]**

Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 10.95 (P < 0.00001)



ICS moderate + LTRA vs ICS moderate

Figure 260: Quality of life (AQLQ, 1-7, higher is better outcome)

Study or Subgroup	ICS mod + LTRA Mean	SD	Total	ICS mod + placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Vaquerizo 2003	0.6	0.8902	317	0.52	0.8775	308	100.0%	0.08 [-0.06, 0.22]
Total (95% CI)			**317**			**308**	**100.0%**	**0.08 [-0.06, 0.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)

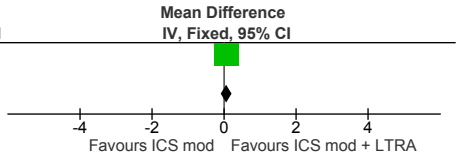


Figure 261: Reliever medication use (% change from baseline)

Study or Subgroup	ICS mod + LTRA Mean	SD	Total	ICS mod + placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Vaquerizo 2003	-17.26	317	1786	-4.92	308	1660	100.0%	-12.34 [-33.21, 8.53]
Total (95% CI)			**1786**			**1660**	**100.0%**	**-12.34 [-33.21, 8.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)

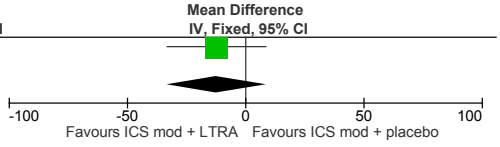


Figure 262: FEV_1 (L, % change from baseline)

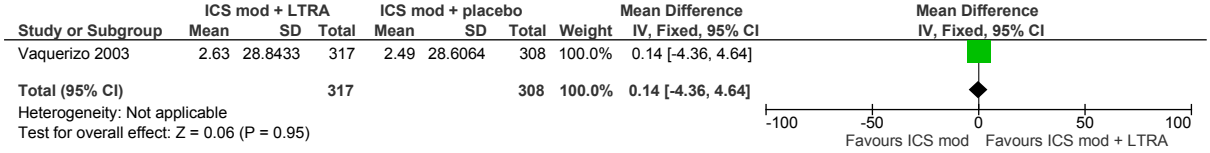
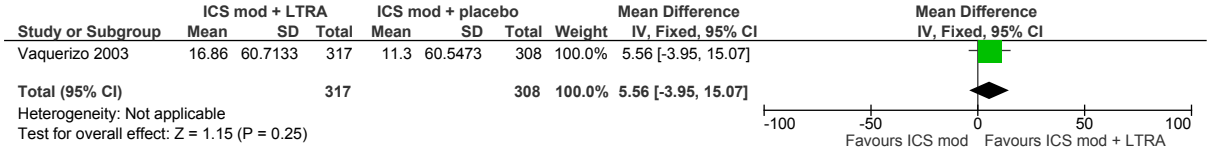


Figure 263: PEF (L/min)



ICS moderate + LAMA vs ICS moderate

Figure 264: Severe exacerbations

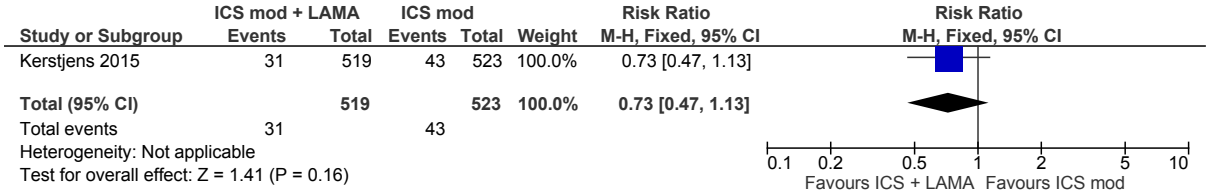


Figure 265: Quality of life (AQLQ, 1-7, higher is better outcome)

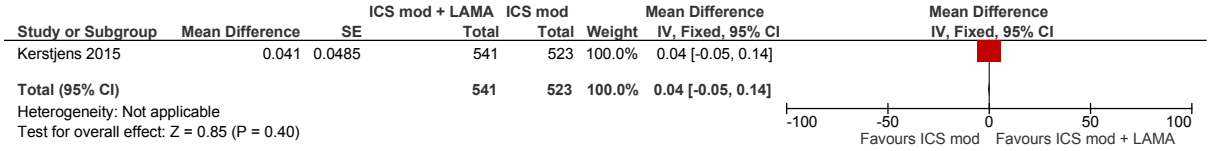


Figure 266: Asthma control (ACQ, 0-6, higher is worse outcome)

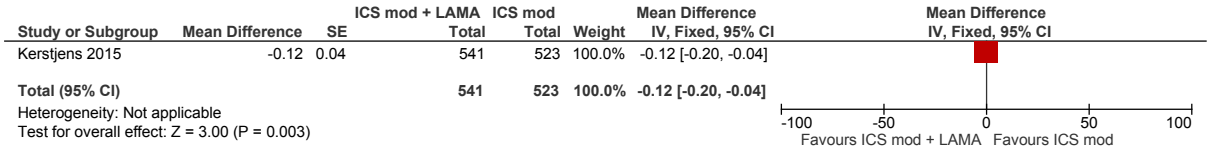


Figure 267: FEV_1 (L)

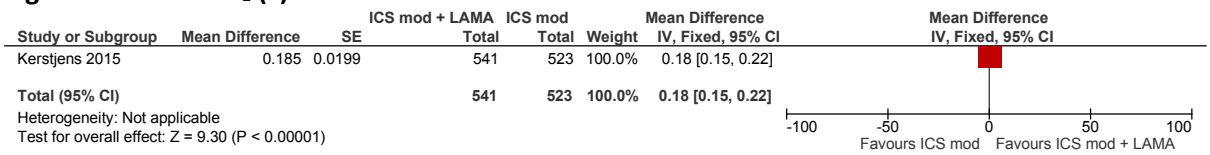


Figure 268: PEF (L/min)

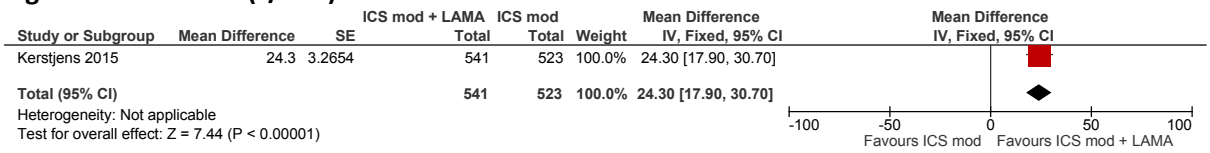
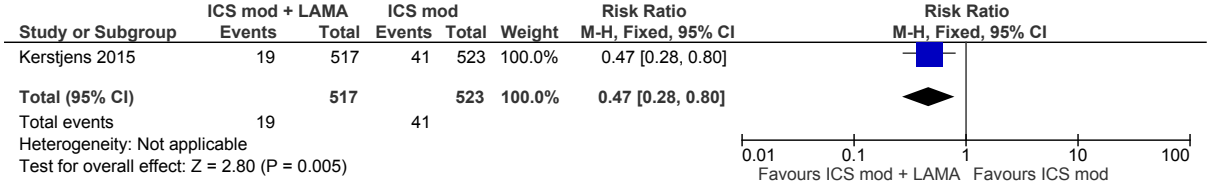


Figure 269: Infection (all respiratory)



ICS low + LABA vs ICS high

Figure 270: Quality of life (AQLQ, 1-7, higher is better outcome)

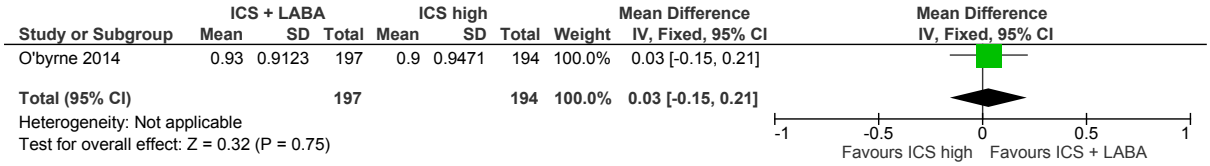


Figure 271: Asthma control (ACT, 5-25, higher is better outcome)

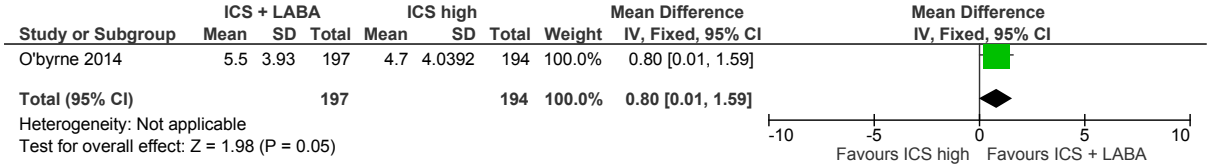


Figure 272: FEV_1 (L)

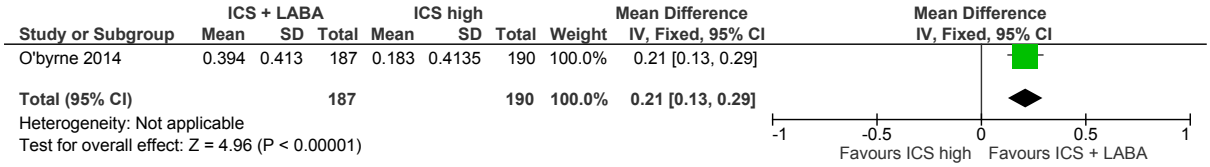
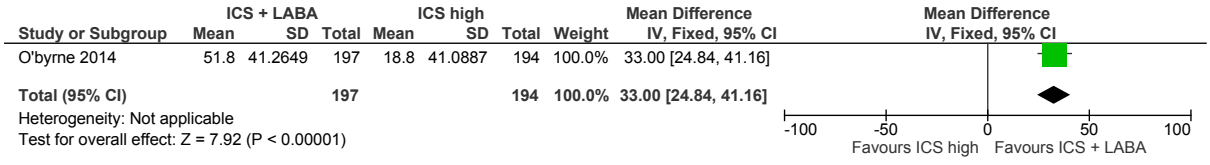


Figure 273: PEF (L/min)



ICS moderate + LABA vs ICS high

Figure 274: Severe exacerbations

Study or Subgroup	ICS mod + LABA Events	Total	ICS high Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ind 2003	47	171	51	165	96.2%	0.89 [0.64, 1.24]
Jenkins 2000	1	180	2	173	3.8%	0.48 [0.04, 5.25]
Total (95% CI)		**351**		**338**	**100.0%**	**0.87 [0.63, 1.22]**
Total events	48		53			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.42)

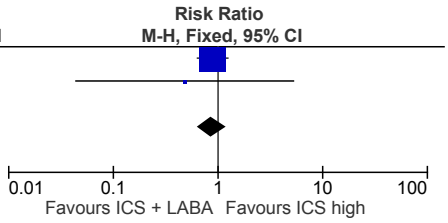


Figure 275: Quality of life (AQLQ, 1-7, higher is better outcome)

Study or Subgroup	ICS mod + LABA Mean	SD	Total	ICS high Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Juniper 2002	0.89	0.8158	55	0.44	0.7616	58	100.0%	0.45 [0.16, 0.74]
Total (95% CI)			**55**			**58**	**100.0%**	**0.45 [0.16, 0.74]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.03 (P = 0.002)

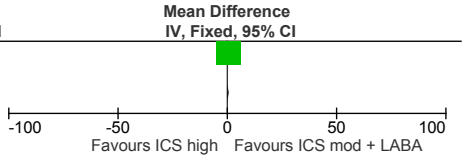


Figure 276: Reliever medication use (puffs/day)

Study or Subgroup	ICS mod + LABA Mean	SD	Total	ICS high Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mitchell 2003	0.93	1.38	89	2.43	2.43	89	100.0%	-1.50 [-2.08, -0.92]
Total (95% CI)			**89**			**89**	**100.0%**	**-1.50 [-2.08, -0.92]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.06 (P < 0.00001)

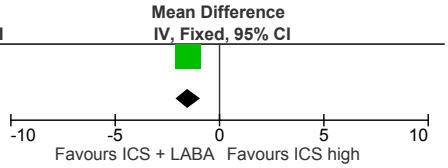


Figure 277: Reliever medication use (% reliever free days)

Study or Subgroup	Mean Difference	SE	ICS mod + LABA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Jenkins 2000	32	9.64	180	173	100.0%	32.00 [13.11, 50.89]
Total (95% CI)			**180**	**173**	**100.0%**	**32.00 [13.11, 50.89]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)

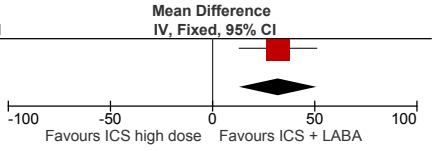


Figure 278: FEV_1 (%predicted)

Study or Subgroup	ICS mod + LABA Mean	SD	Total	ICS high Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Woolcock 1996	8	4.4136	487	3	3.1686	251	100.0%	5.00 [4.45, 5.55]
Total (95% CI)			**487**			**251**	**100.0%**	**5.00 [4.45, 5.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 17.68 (P < 0.00001)

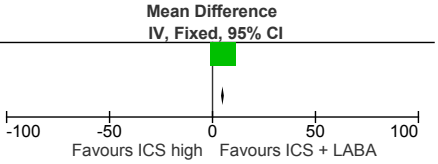


Figure 279: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	ICS mod + LABA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Jenkins 2000	0.09	0.0459	180	173	100.0%	0.09 [0.00, 0.18]
Total (95% CI)			**180**	**173**	**100.0%**	**0.09 [0.00, 0.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)

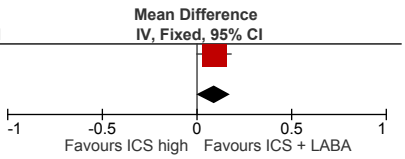


Figure 280: PEF (L/min)

Study or Subgroup	Mean Difference	SE	ICS mod + LABA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Ind 2003	25.5	7.68	171	165	14.2%	25.50 [10.45, 40.55]
Jenkins 2000	26	5.6123	173	165	26.5%	26.00 [15.00, 37.00]
Mitchell 2003	26.1	18.0306	89	89	2.6%	26.10 [-9.24, 61.44]
Van Noord 1999	18.6	3.84	139	135	56.7%	18.60 [11.07, 26.13]
Total (95% CI)			**572**	**554**	**100.0%**	**21.74 [16.07, 27.40]**

Heterogeneity: Chi² = 1.54, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 7.52 (P < 0.00001)

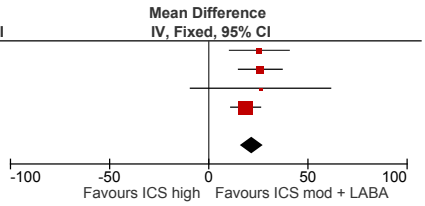
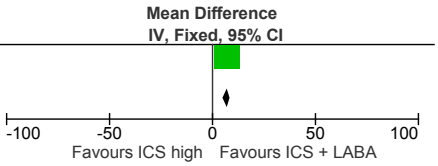


Figure 281: PEF (% predicted)

Study or Subgroup	ICS mod + LABA Mean	SD	Total	ICS high Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Woolcock 1996	92	11.034	487	85	9.0305	251	100.0%	7.00 [5.51, 8.49]
Total (95% CI)			**487**			**251**	**100.0%**	**7.00 [5.51, 8.49]**

Heterogeneity: Not applicable
Test for overall effect: Z = 9.23 (P < 0.00001)



ICS moderate + LTRA vs ICS high

Figure 282: Quality of life (AQLQ, 1-7, higher is better outcome)

Study or Subgroup	Mean Difference	SE	ICS mod + LTRA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Barnes 2007	-0.25	0.199	37	38	11.0%	-0.25 [-0.64, 0.14]
Price 2003	0.12	0.07	448	441	89.0%	0.12 [-0.02, 0.26]
Total (95% CI)			**485**	**479**	**100.0%**	**0.08 [-0.05, 0.21]**

Heterogeneity: Chi² = 3.08, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.20 (P = 0.23)

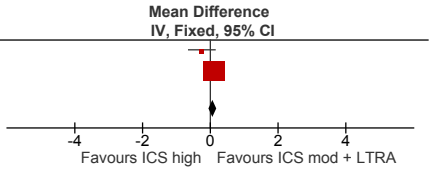


Figure 283: Reliever medication use (puffs/day)

Study or Subgroup	Mean Difference	SE	ICS mod + LTRA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Price 2003	-0.03	0.04	448	441	100.0%	-0.03 [-0.11, 0.05]
Total (95% CI)			**448**	**441**	**100.0%**	**-0.03 [-0.11, 0.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)

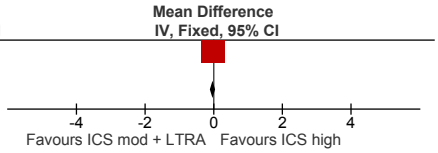
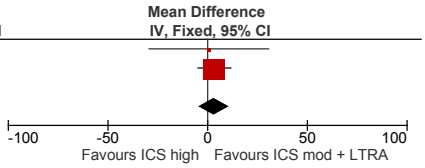


Figure 284: PEF (L/min)

Study or Subgroup	Mean Difference	SE	ICS mod + LTRA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Barnes 2007	0.6	15.3064	37	38	7.0%	0.60 [-29.40, 30.60]
Price 2003	3.4	4.1838	448	441	93.0%	3.40 [-4.80, 11.60]
Total (95% CI)			**485**	**479**	**100.0%**	**3.21 [-4.70, 11.12]**

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)



ICS moderate + theophylline vs ICS high

Figure 285: FEV_1 (L)

Study or Subgroup	ICS mod + Theophylline Mean	SD	Total	ICS high Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Evans 1997	2.69	0.8908	31	2.61	0.8352	31	100.0%	0.08 [-0.35, 0.51]
Total (95% CI)			**31**			**31**	**100.0%**	**0.08 [-0.35, 0.51]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

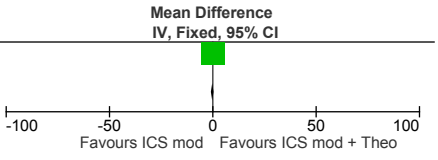
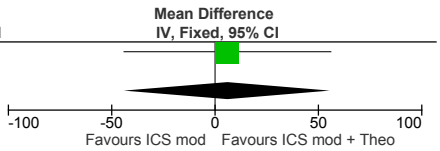


Figure 286: PEF (L/min)

Study or Subgroup	ICS mod + Theophylline Mean	SD	Total	ICS high Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Evans 1997	411	105.7875	31	405	94.652	31	100.0%	6.00 [-43.97, 55.97]
Total (95% CI)			**31**			**31**	**100.0%**	**6.00 [-43.97, 55.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



MART (ICS low + LABA) vs ICS low + LABA + PRN SABA

Figure 287: Severe exacerbations

Study or Subgroup	MART Events	Total	ICS + LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
O'byrne 2005	102	925	191	909	100.0%	0.52 [0.42, 0.66]
Total (95% CI)		**925**		**909**	**100.0%**	**0.52 [0.42, 0.66]**
Total events	102		191			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.69 (P < 0.00001)

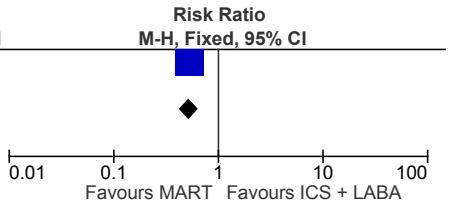


Figure 288: Reliever medication use (puffs/daytime)

Study or Subgroup	Mean Difference	SE	MART Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
O'byrne 2005	-0.11	0.033	925	909	100.0%	-0.11 [-0.17, -0.05]
Total (95% CI)			**925**	**909**	**100.0%**	**-0.11 [-0.17, -0.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.33 (P = 0.0009)

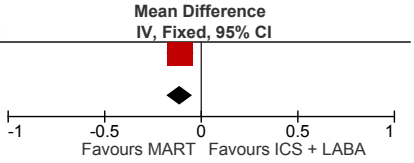


Figure 289: Reliever medication use (puffs/night time)

Study or Subgroup	Mean Difference	SE	MART Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
O'byrne 2005	-0.09	0.027	925	909	100.0%	-0.09 [-0.14, -0.04]
Total (95% CI)			**925**	**909**	**100.0%**	**-0.09 [-0.14, -0.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.33 (P = 0.0009)

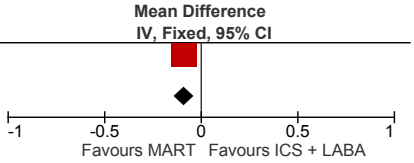


Figure 290: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	MART Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
O'byrne 2005	0.08	0.024	925	909	100.0%	0.08 [0.03, 0.13]
Total (95% CI)			**925**	**909**	**100.0%**	**0.08 [0.03, 0.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.33 (P = 0.0009)

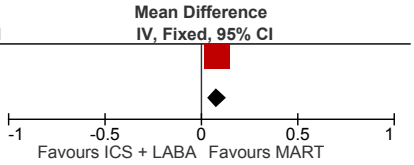
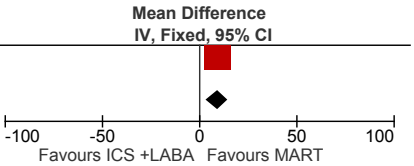


Figure 291: PEF (L/min)

Study or Subgroup	Mean Difference	SE	MART Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
O'byrne 2005	9	2.73	925	909	100.0%	9.00 [3.65, 14.35]
Total (95% CI)			**925**	**909**	**100.0%**	**9.00 [3.65, 14.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)



ICS moderate + LTRA vs ICS moderate + LABA

Figure 292: Reliever medication use (puffs/day)

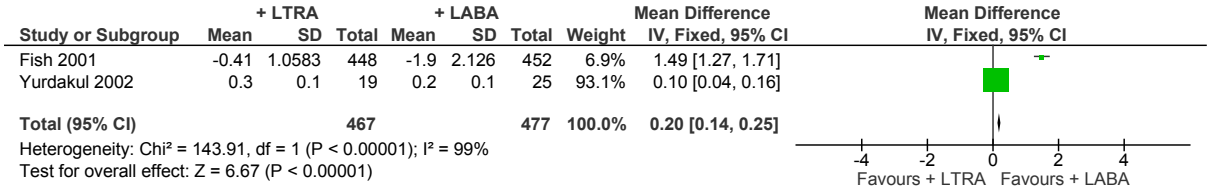


Figure 293: FEV_1 (%predicted)

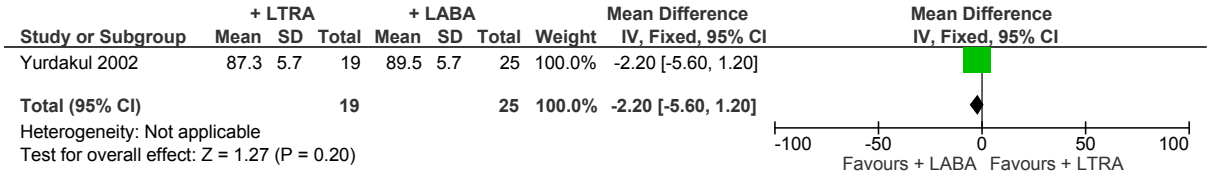
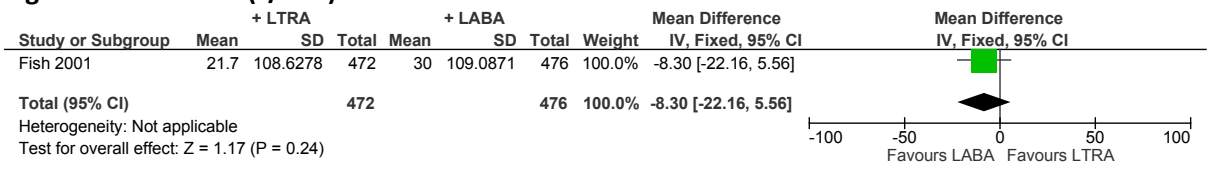


Figure 294: PEF (L/min)



ICS moderate + LAMA vs ICS moderate + LABA

Figure 295: Severe exacerbations

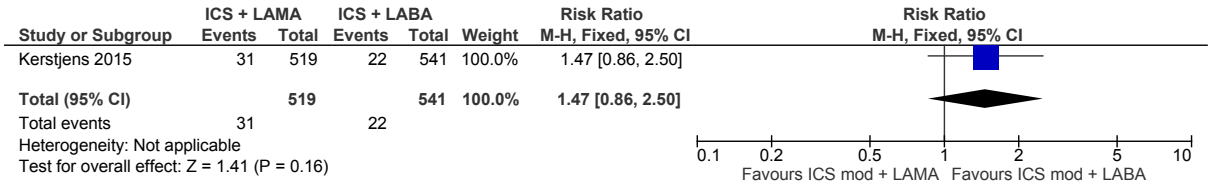
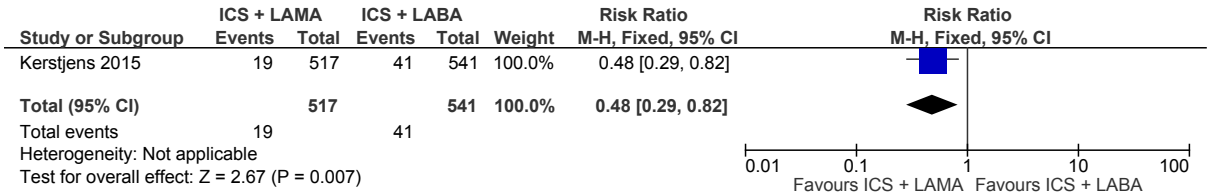


Figure 296: Infection (all respiratory infections)



MART (ICS moderate + LABA) vs ICS moderate + LABA

Figure 297: Severe exacerbations

Study or Subgroup	MART Events	MART Total	ICS + LABA Events	ICS + LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kuna 2007	94	1107	126	1105	100.0%	0.74 [0.58, 0.96]
Total (95% CI)		**1107**		**1105**	**100.0%**	**0.74 [0.58, 0.96]**
Total events	94		126			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)

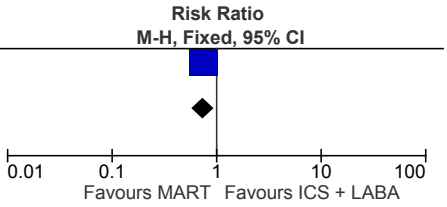


Figure 298: Reliever medication use (puffs/day)

Study or Subgroup	Mean Difference	SE	MART Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Kuna 2007	-0.03	0.0459	1106	1105	100.0%	-0.03 [-0.12, 0.06]
Total (95% CI)			**1106**	**1105**	**100.0%**	**-0.03 [-0.12, 0.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)

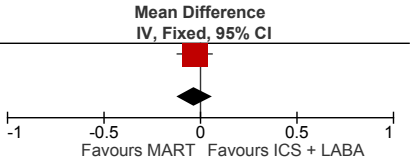


Figure 299: PEF (L/min)

Study or Subgroup	Mean Difference	SE	MART Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Kuna 2007	-0.7	1.9388	1106	1105	100.0%	-0.70 [-4.50, 3.10]
Total (95% CI)			**1106**	**1105**	**100.0%**	**-0.70 [-4.50, 3.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

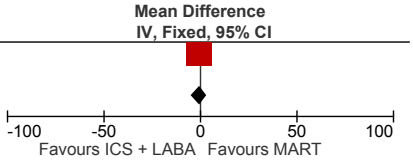
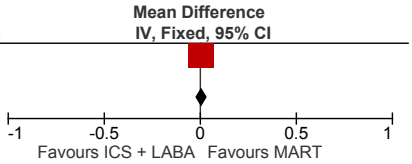


Figure 300: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	MART Total	ICS + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Kuna 2007	0.005	0.0158	1106	1105	100.0%	0.01 [-0.03, 0.04]
Total (95% CI)			**1106**	**1105**	**100.0%**	**0.01 [-0.03, 0.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)



ICS moderate + LTRA vs ICS moderate + theophylline

Figure 301: Reliever medication use (puffs/day)

Study or Subgroup	+ LTRA Mean	+ LTRA SD	+ LTRA Total	+ theo Mean	+ theo SD	+ theo Total	Weight	Mean Difference IV, Fixed, 95% CI
Yurdakul 2002	0.3	0.1	19	0.2	0.1	20	100.0%	0.10 [0.04, 0.16]
Total (95% CI)			**19**			**20**	**100.0%**	**0.10 [0.04, 0.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.12 (P = 0.002)

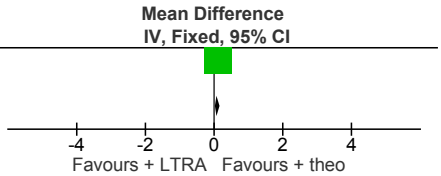
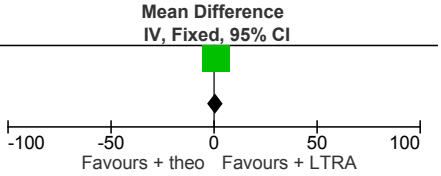


Figure 302: FEV_1 (%predicted)

Study or Subgroup	+ LTRA Mean	+ LTRA SD	+ LTRA Total	+ theo Mean	+ theo SD	+ theo Total	Weight	Mean Difference IV, Fixed, 95% CI
Yurdakul 2002	87.3	5.7	19	86.6	5.8	20	100.0%	0.70 [-2.91, 4.31]
Total (95% CI)			**19**			**20**	**100.0%**	**0.70 [-2.91, 4.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)



ICS moderate + LABA vs ICS moderate + theophylline

Figure 303: Reliever medication use (puffs/day)

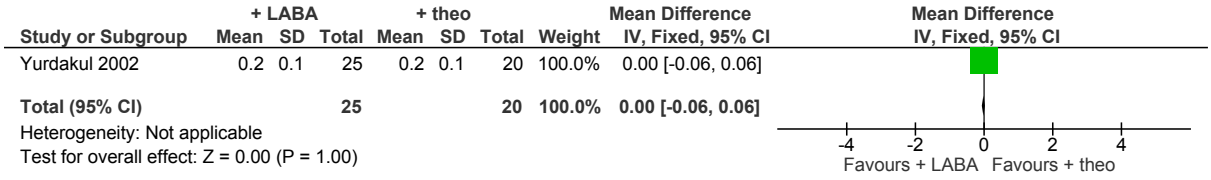
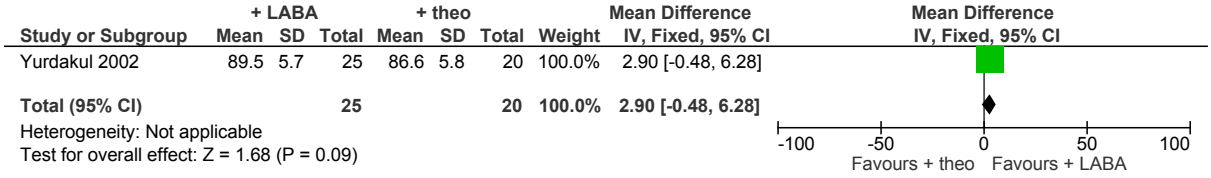


Figure 304: FEV_1 (%predicted)



K.3.3.3 Population uncontrolled on ICS moderate, 5 to 16

MART (ICS low + LABA) vs ICS low + LABA + PRN SABA

Figure 305: Severe exacerbations

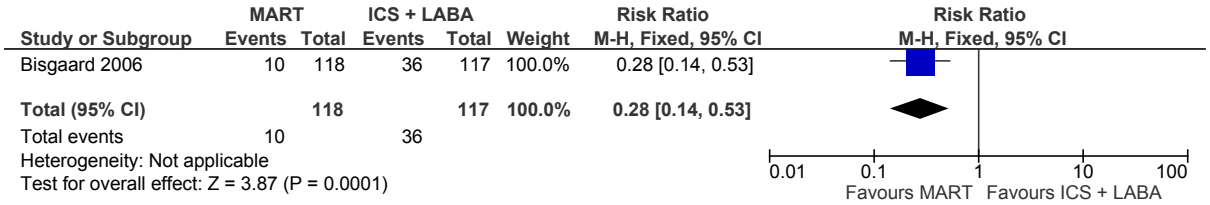


Figure 306: Reliever medication use (puffs/day)

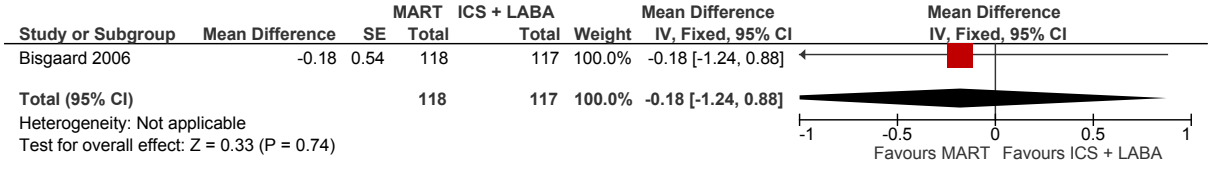


Figure 307: FEV_1 (L)

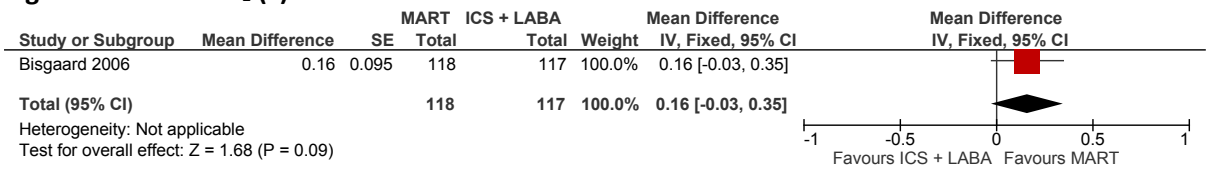
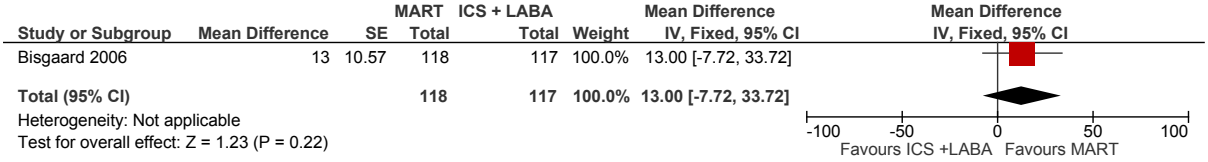


Figure 308: PEF (L/min)



MART (ICS low + LABA) vs ICS moderate + PRN SABA

Figure 309: Severe exacerbations

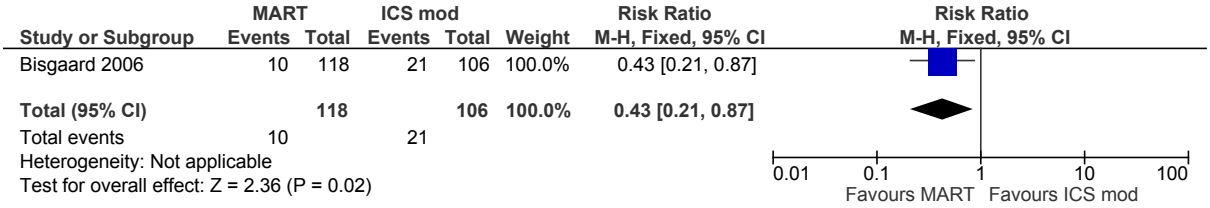


Figure 310: Reliever medication use (puffs/day)

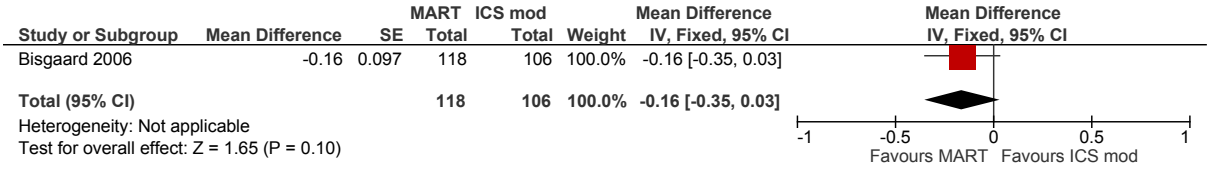


Figure 311: FEV_1 (L)

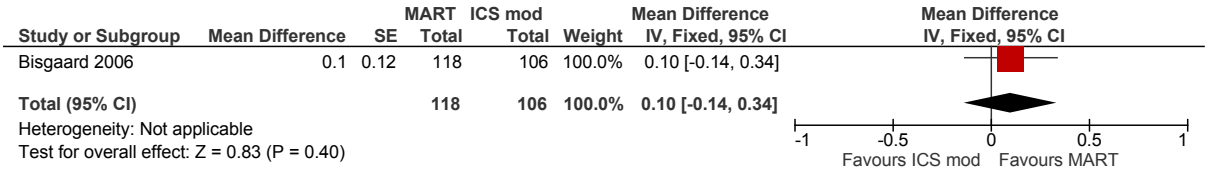


Figure 312: PEF (L/min)

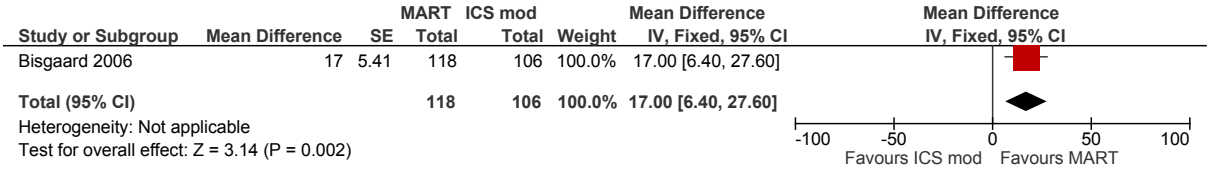
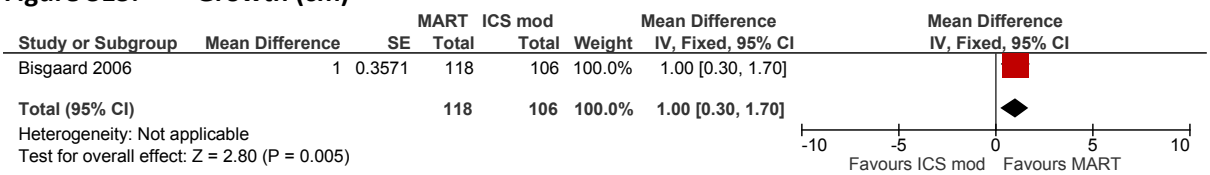


Figure 313: Growth (cm)



ICS low + LABA vs ICS moderate

Figure 314: Severe exacerbations

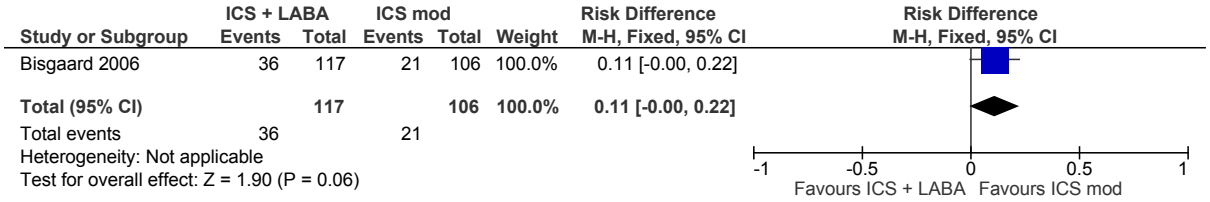


Figure 315: Reliever medication use (puffs/day)

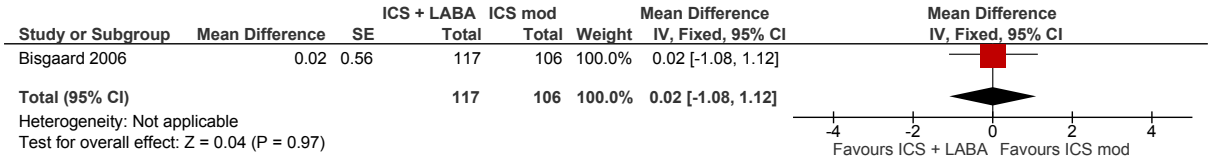


Figure 316: FEV_1 (L)

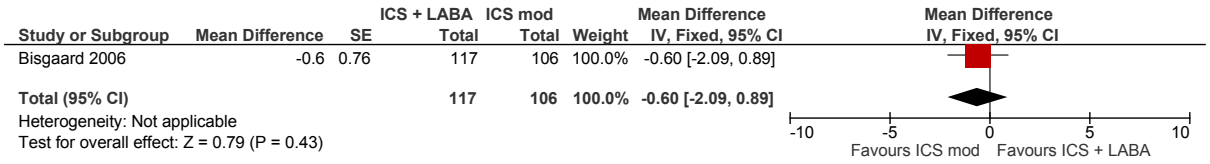


Figure 317: PEF (L/min)

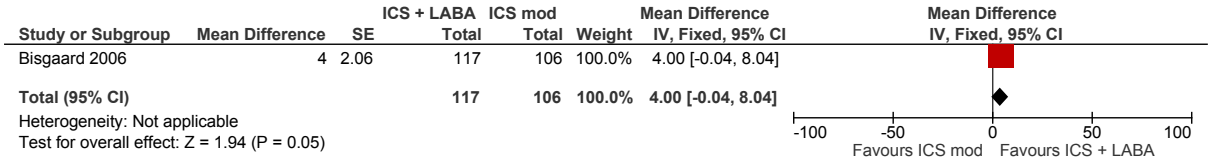
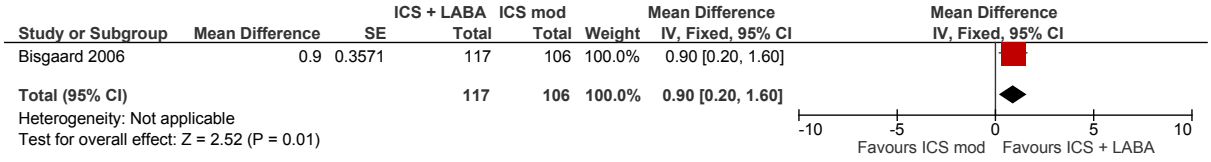


Figure 318: Growth (cm)



ICS moderate + LAMA vs ICS moderate

Figure 319: Severe exacerbations

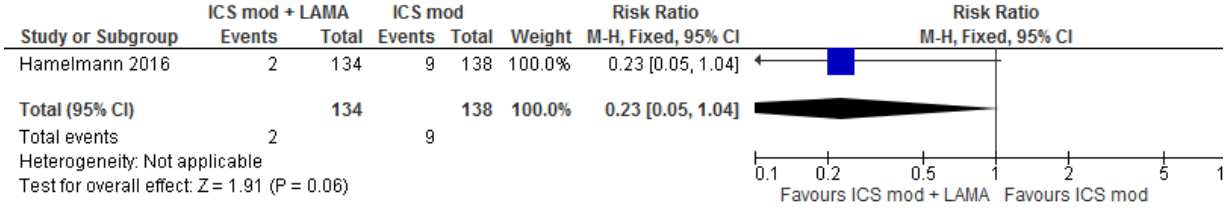


Figure 320: Quality of life (AQLQ, 1-7, higher is better outcome)

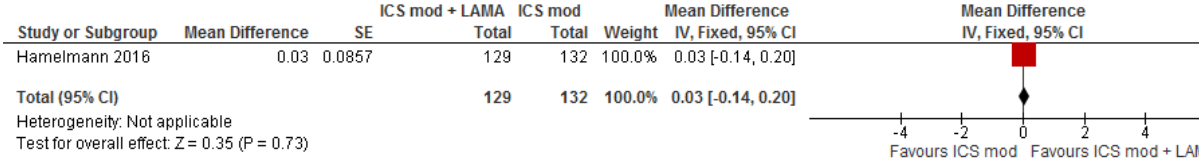


Figure 321: Reliever medication use (puffs/day)

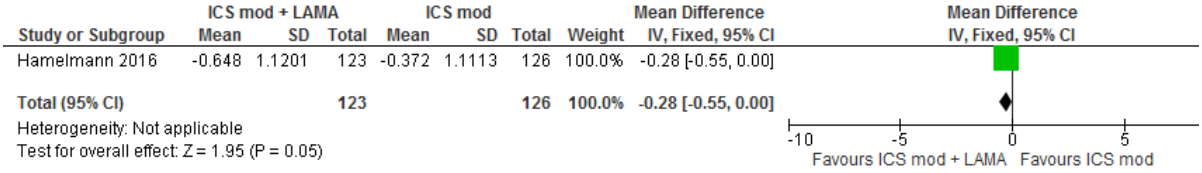
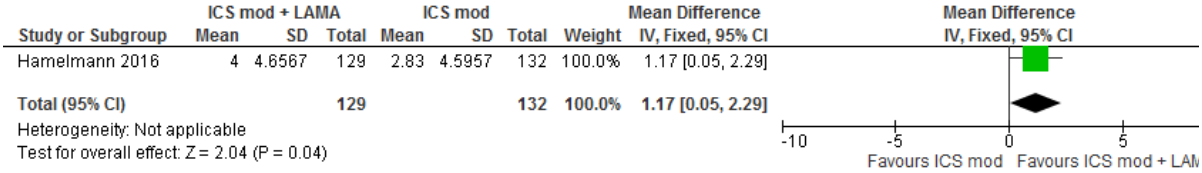


Figure 322: FEV_1 (L)



K.3.3.4 Population uncontrolled on ICS high, over 16

ICS high + LTRA vs ICS high

Figure 323: Reliever medication use (puffs/day)

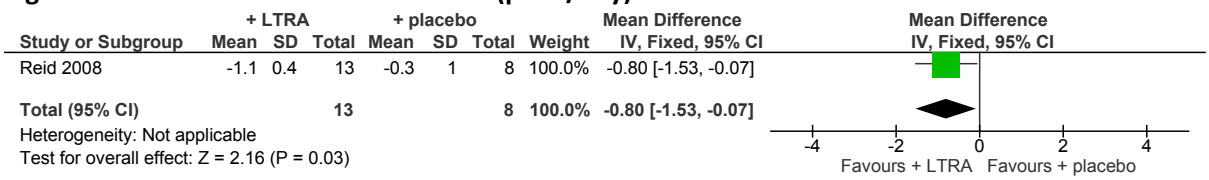


Figure 324: FEV_1 (L)

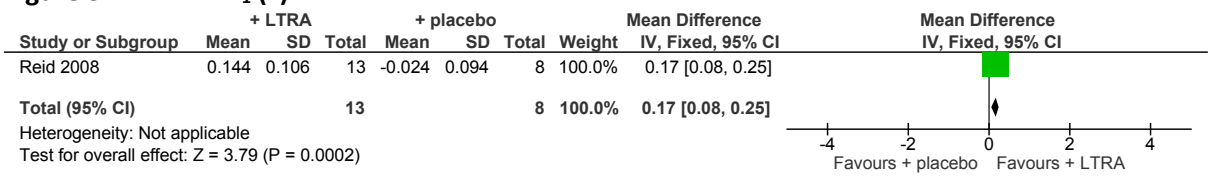
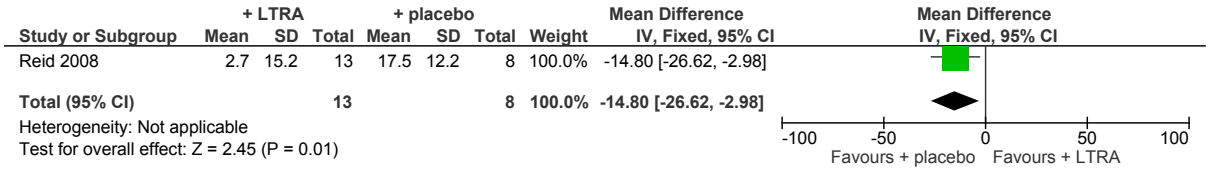


Figure 325: PEF (L/min)



ICS high + LABA vs ICS high

Figure 326: Reliever medication use (puffs/day)

Study or Subgroup	Mean Difference	SE	Add LABA Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyd 1995	-2.6	0.8215	53	62	5.1%	-2.60 [-4.21, -0.99]
Jenkins 2006	-0.64	0.19	226	115	94.9%	-0.64 [-1.01, -0.27]
Total (95% CI)			**279**	**177**	**100.0%**	**-0.74 [-1.10, -0.38]**

Heterogeneity: Chi² = 5.40, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 3.99 (P < 0.0001)

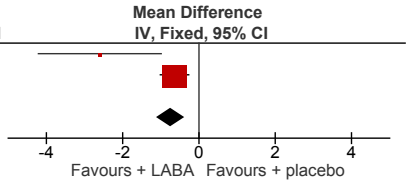


Figure 327: FEV_1 (L)

Study or Subgroup	Mean Difference	SE	ICS high + LABA Total	ICS high Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyd 1995	0.03	0.0816	47	49	100.0%	0.03 [-0.13, 0.19]
Total (95% CI)			**47**	**49**	**100.0%**	**0.03 [-0.13, 0.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

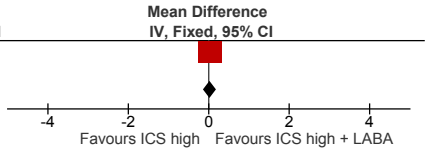


Figure 328: PEF (L/min)

Study or Subgroup	Mean Difference	SE	+ LABA Total	+ placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Aubier 1999	19	3.7988	338	165	54.0%	19.00 [11.55, 26.45]
Boyd 1995	22.4	8.0104	48	52	12.1%	22.40 [6.70, 38.10]
Jenkins 2006	32.9	4.796	226	115	33.9%	32.90 [23.50, 42.30]
Total (95% CI)			**612**	**332**	**100.0%**	**24.12 [18.65, 29.59]**

Heterogeneity: Chi² = 5.21, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 8.64 (P < 0.00001)

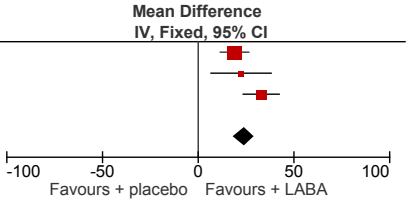
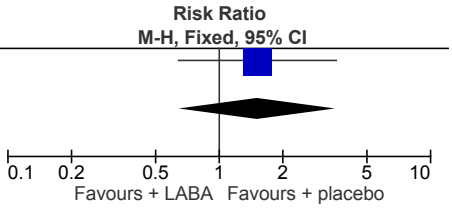


Figure 329: Infections (all respiratory)

Study or Subgroup	+ LABA Events	+ LABA Total	+ placebo Events	+ placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jenkins 2006	27	341	6	115	100.0%	1.52 [0.64, 3.58]
Total (95% CI)		**341**		**115**	**100.0%**	**1.52 [0.64, 3.58]**
Total events	27		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



ICS high + LABA vs ICS moderate + LABA

Figure 330: PEF (L/min)

Study or Subgroup	Mean Difference	SE	ICS high + LABA Total	ICS mod + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Ringdal 2002	3.2	6.0205	167	157	100.0%	3.20 [-8.60, 15.00]
Total (95% CI)			**167**	**157**	**100.0%**	**3.20 [-8.60, 15.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

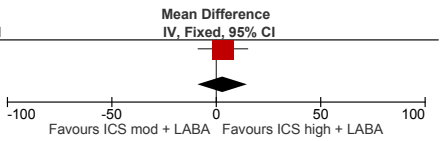


Figure 331: Infection (all respiratory)

Study or Subgroup	ICS high + LABA Events	Total	ICS mod + LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ringdal 2002	18	216	26	212	100.0%	0.68 [0.38, 1.20]
Total (95% CI)		**216**		**212**	**100.0%**	**0.68 [0.38, 1.20]**
Total events	18		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)

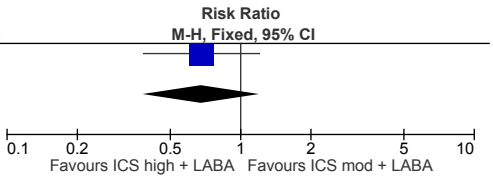
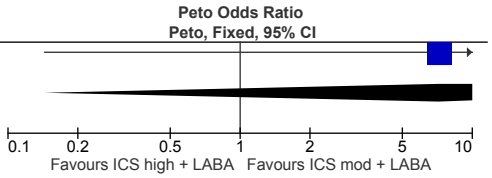


Figure 332: Infection (serious respiratory)

Study or Subgroup	ICS high + LABA Events	Total	ICS mod + LABA Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ringdal 2002	1	216	0	212	100.0%	7.25 [0.14, 365.61]
Total (95% CI)		**216**		**212**	**100.0%**	**7.25 [0.14, 365.61]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)



MART (ICS moderate + LABA) vs ICS moderate + LABA + PRN SABA

Figure 333: Severe exacerbations

Study or Subgroup	MART Events	Total	ICS mod + LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vogelmeier 2005	132	1067	167	1076	100.0%	0.80 [0.64, 0.99]
Total (95% CI)		**1067**		**1076**	**100.0%**	**0.80 [0.64, 0.99]**
Total events	132		167			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)

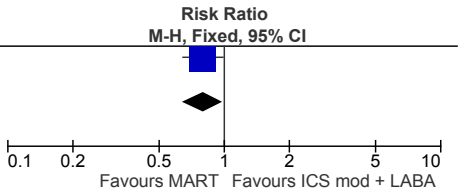


Figure 334: Quality of life (AQLQ, 1-7, higher is better outcome)

Study or Subgroup	Mean Difference	SE	MART Total	ICS mod + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Vogelmeier 2005	0.03	0.05	1067	1076	100.0%	0.03 [-0.07, 0.13]
Total (95% CI)			**1067**	**1076**	**100.0%**	**0.03 [-0.07, 0.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

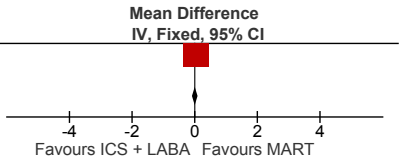


Figure 335: Control (ACQ, 0-6, higher is worse outcome)

Study or Subgroup	Mean Difference	SE	MART Total	ICS mod + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Vogelmeier 2005	-0.08	0.04	1067	1076	100.0%	-0.08 [-0.16, -0.00]
Total (95% CI)			**1067**	**1076**	**100.0%**	**-0.08 [-0.16, -0.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)

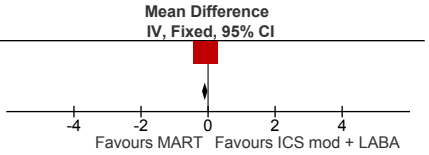


Figure 336: Reliever medication use (puffs/day, average over whole treatment period)

Study or Subgroup	Mean Difference	SE	MART Total	ICS mod + LABA Total	Weight	Mean Difference IV, Fixed, 95% CI
Vogelmeier 2005	-0.35	0.1	1067	1076	100.0%	-0.35 [-0.55, -0.15]
Total (95% CI)			**1067**	**1076**	**100.0%**	**-0.35 [-0.55, -0.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.50 (P = 0.0005)

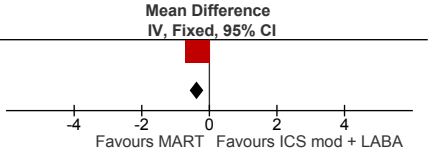
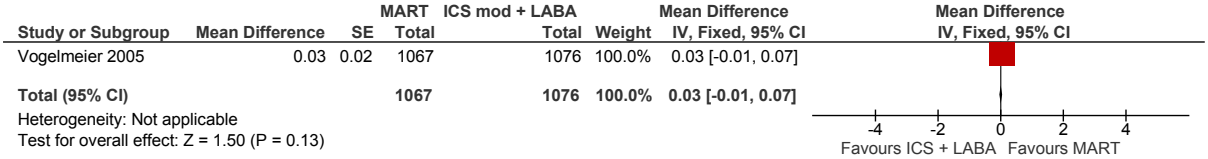


Figure 337: FEV_1 (L)



K.3.3.5 Population uncontrolled on ICS high, 5 to 16

ICS high + LABA vs ICS high

Figure 338: FEV_1 (% predicted)

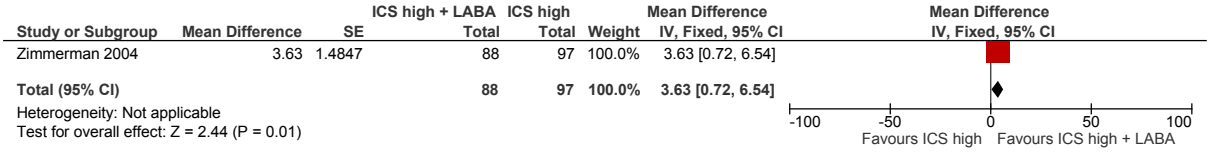


Figure 339: PEF (L/min)

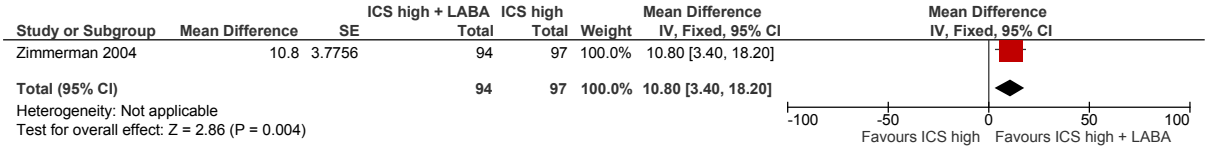
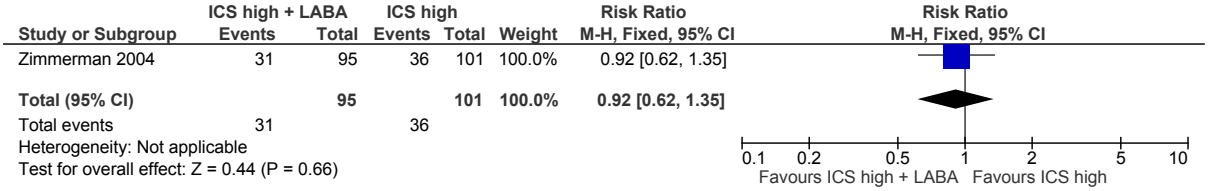


Figure 340: Infection (all respiratory)



K.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

K.4.1 Intermittent vs regular ICS in patients over 16

Figure 341: Severe asthma exacerbations (requiring OCS)

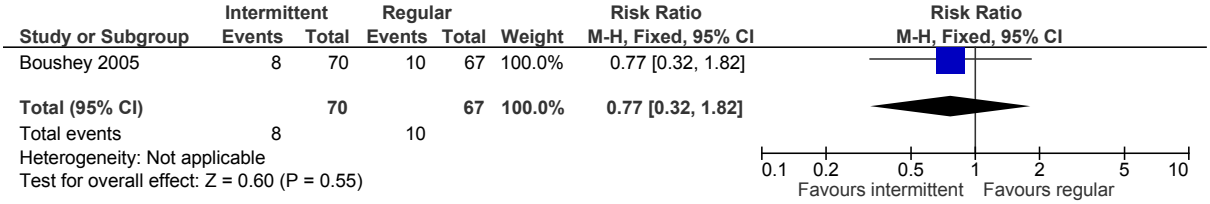


Figure 342: Quality of life (AQLQ, change score)

Study or Subgroup	Intermittent Mean	SD	Total	Regular Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Boushey 2005	0.3	0.84	70	0.5	0.82	67	100.0%	-0.20 [-0.48, 0.08]
Total (95% CI)			**70**			**67**	**100.0%**	**-0.20 [-0.48, 0.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)

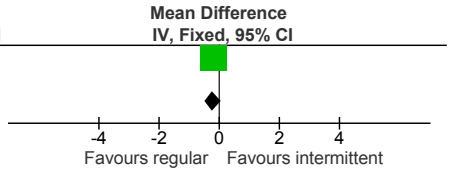


Figure 343: Control (ACQ, change score)

Study or Subgroup	Intermittent Mean	SD	Total	Regular Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Boushey 2005	-0.3	0.43	73	-0.4	0.84	70	100.0%	0.10 [-0.12, 0.32]
Total (95% CI)			**73**			**70**	**100.0%**	**0.10 [-0.12, 0.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

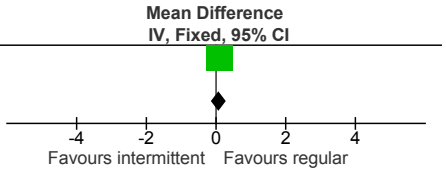


Figure 344: Hospitalisation (exacerbations requiring hospitalisation)

Study or Subgroup	Intermittent Events	Total	Regular Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Boushey 2005	0	73	0	76		Not estimable
Total (95% CI)		**73**		**76**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

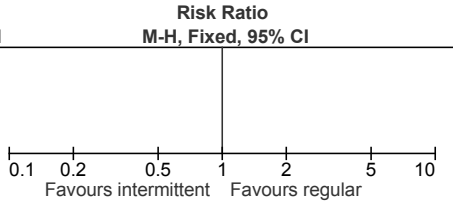


Figure 345: Rescue medication use (puffs per day)

Study or Subgroup	Intermittent Mean	SD	Total	Regular Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Papi 2007	0.5	0.78	124	0.44	0.73	110	100.0%	0.06 [-0.13, 0.25]
Total (95% CI)			**124**			**110**	**100.0%**	**0.06 [-0.13, 0.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

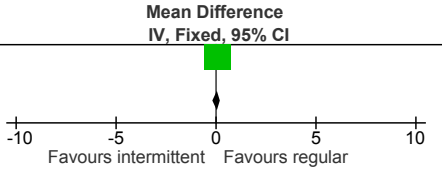


Figure 346: Lung function (PEFR, change score, %)

Study or Subgroup	Intermittent Mean	SD	Total	Regular Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Boushey 2005	7.1	16.8	70	8.3	15.4	66	100.0%	-1.20 [-6.61, 4.21]
Total (95% CI)			**70**			**66**	**100.0%**	**-1.20 [-6.61, 4.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.66)

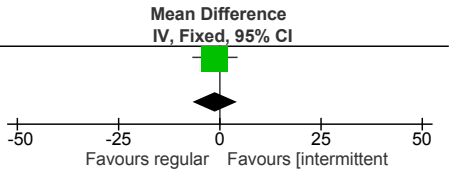


Figure 347: Lung function (PEFR, litres per minute)

Study or Subgroup	Intermittent Mean	SD	Total	Regular Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Papi 2007	442.75	107.8	124	433.08	113.59	110	100.0%	9.67 [-18.80, 38.14]
Total (95% CI)			**124**			**110**	**100.0%**	**9.67 [-18.80, 38.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.51)

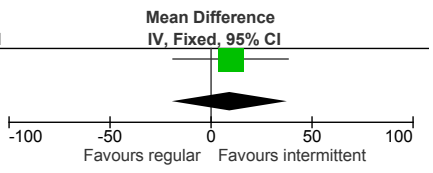


Figure 348: Lung function (FEV_1, change score, %)

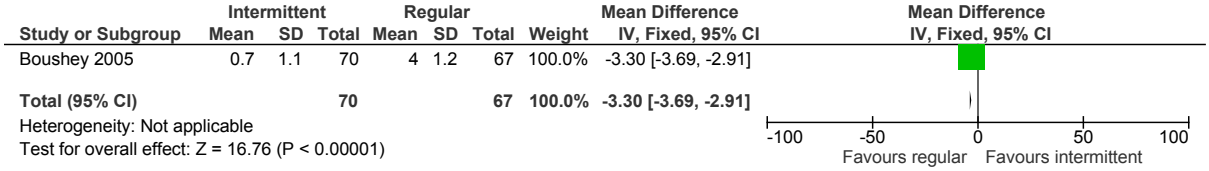
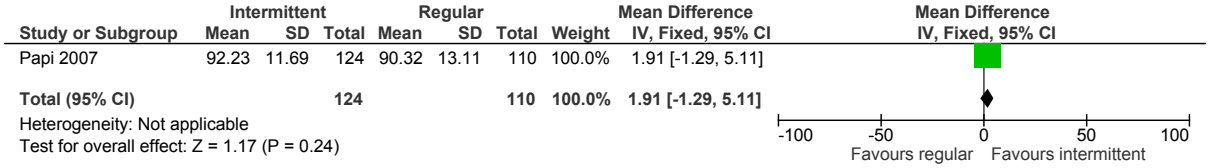


Figure 349: Lung function (FEV_1, % predicted)



K.4.2 Intermittent vs regular ICS in children 5 to 16

Figure 350: Severe asthma exacerbations (requiring OCS)

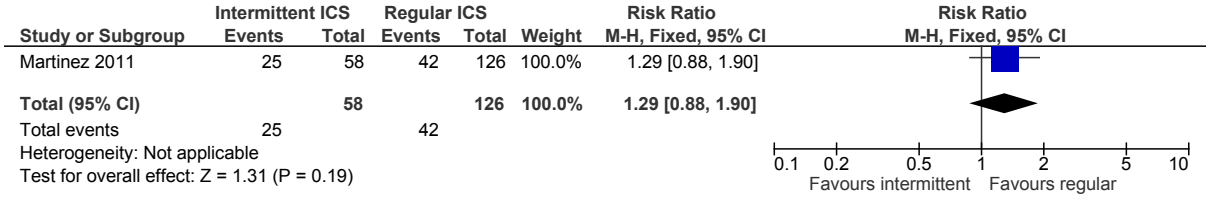


Figure 351: Linear growth (cm)

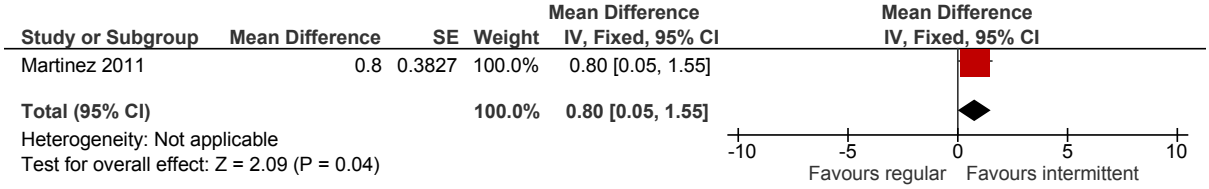
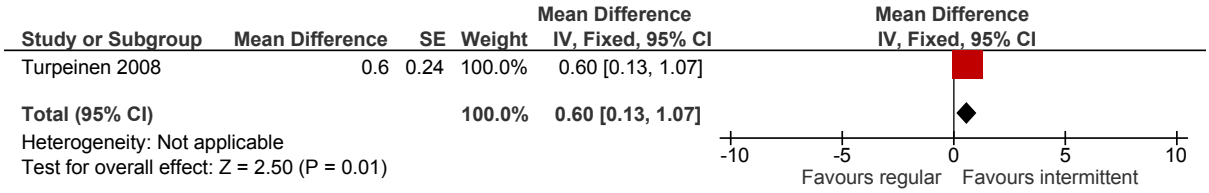


Figure 352: Linear growth (velocity, cm)



K.4.3 Intermittent vs regular ICS in children <5

Figure 353: Severe asthma exacerbations (time to event)

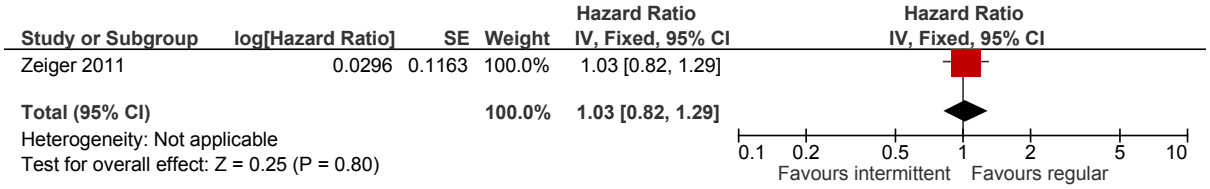


Figure 354: Mortality

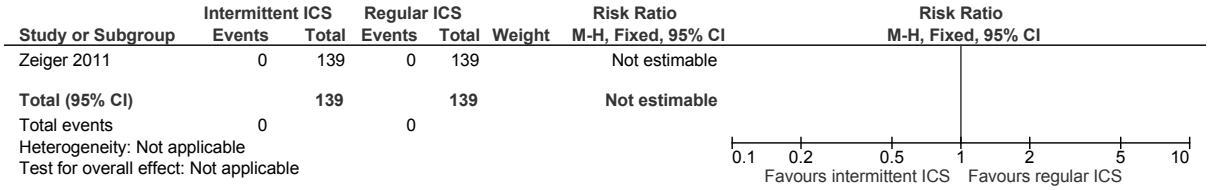


Figure 355: Exacerbations requiring hospitalisation

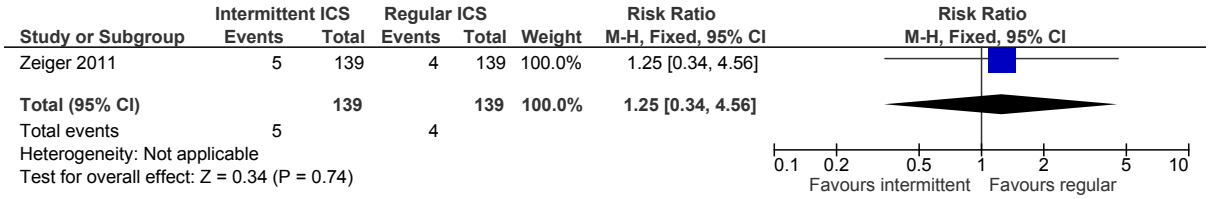


Figure 356: Rescue medication use (% of days with SABA use)

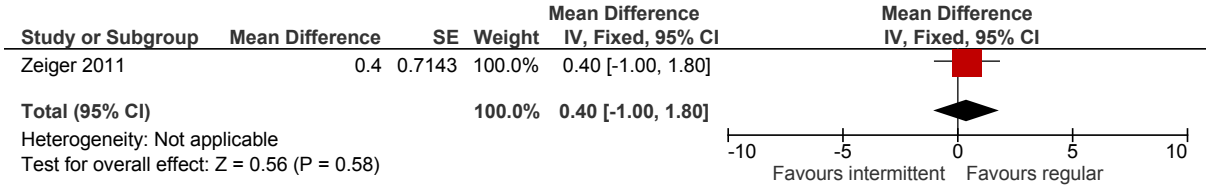


Figure 357: Rescue medication use (during day, puffs per day)

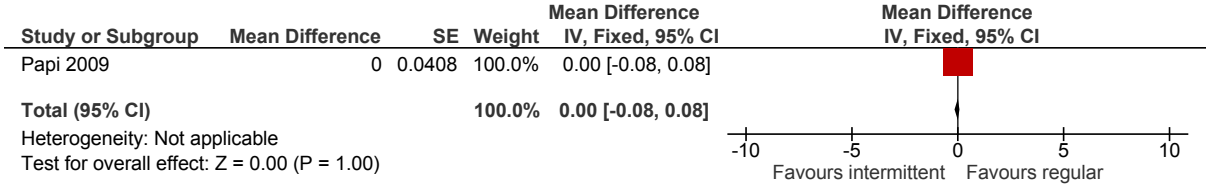


Figure 358: Rescue medication use (at night, puffs per day)

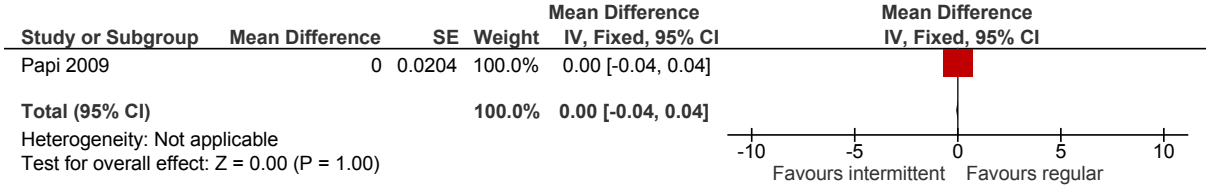
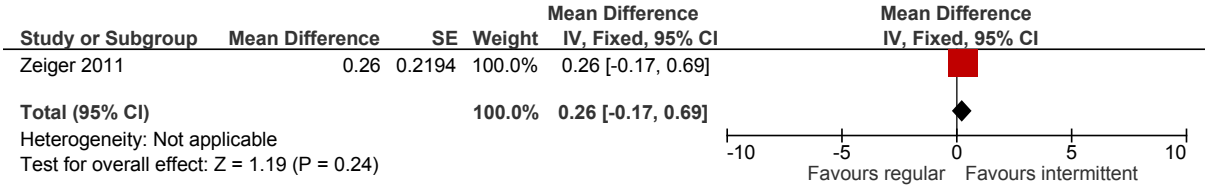


Figure 359: Linear growth (cm)



K.5 Improving adherence to treatment

K.5.1 Education vs Usual care in adults (>16)

Figure 360: Quality of life (AQLQ)

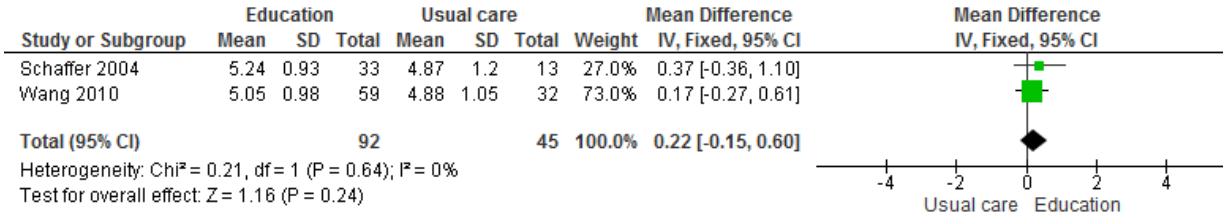


Figure 361: Adherence (%)

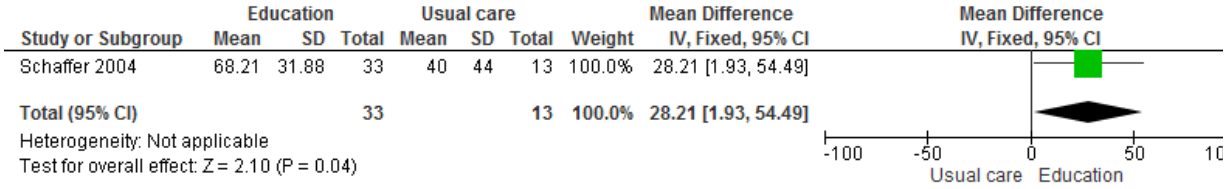


Figure 362: Adherence (self-reported 1-10)

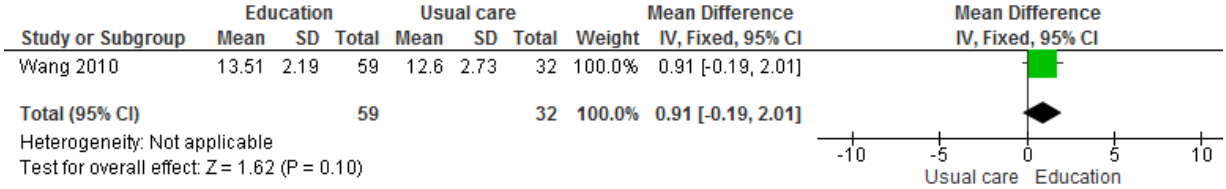
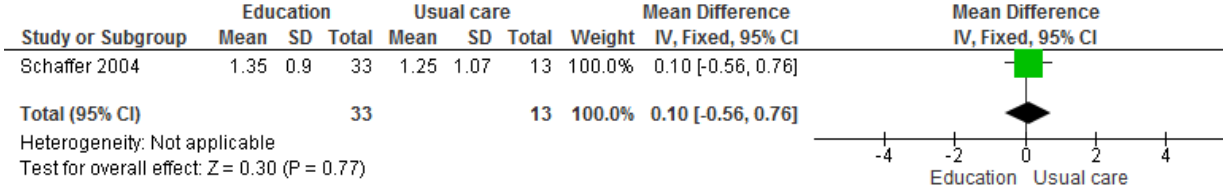


Figure 363: Asthma control (ACQ)



K.5.2 Behavioural change intervention vs Usual care in adults (>16)

Figure 364: Quality of life (AQLQ)

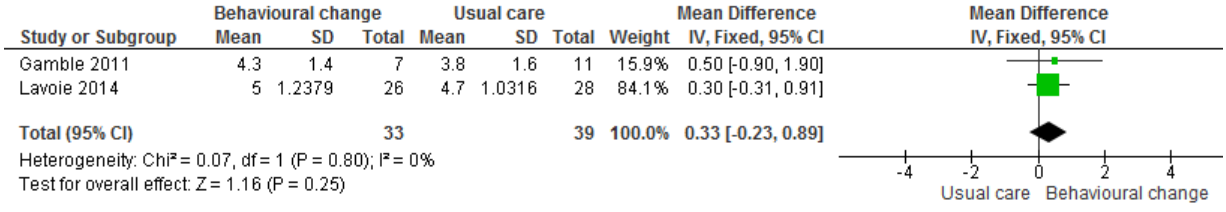


Figure 365: Adherence (%)

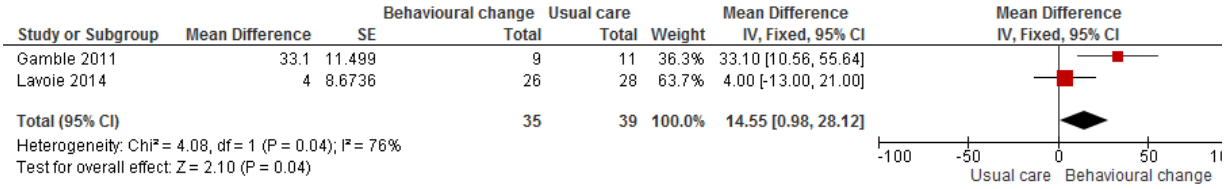


Figure 366: Asthma control (ACQ)

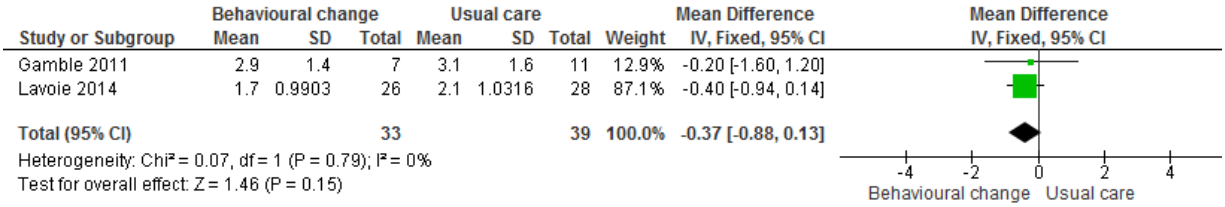


Figure 367: Asthma control (ACT)

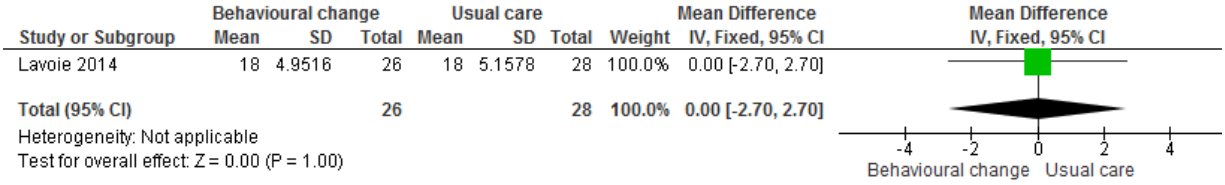
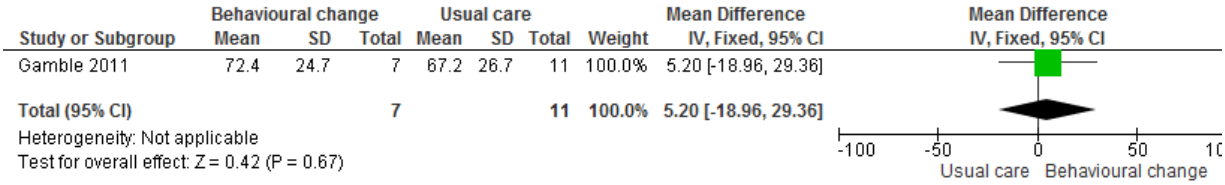
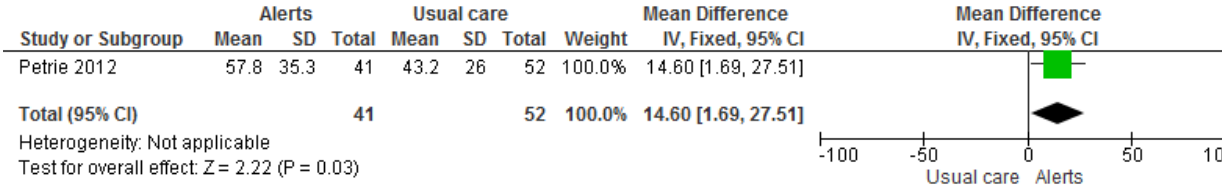


Figure 368: Lung function – FEV_1 (% predicted)



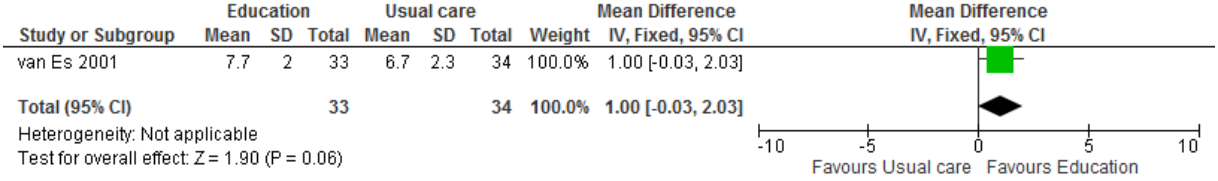
K.5.3 Alerts vs Usual Care in adults (>16)

Figure 369: Adherence (%)



K.5.4 Education and Behavioural change vs Usual care in young people (5-16)

Figure 370: Adherence (self-reported 1-10)



K.6 Self-management plans

K.6.1 Self-management versus usual care in people aged over 16 years

Figure 371: Quality of life

Study or Subgroup	Self-management package Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
CASTRO 2003	3.9	1.5	33	4	1.3	33	1.0%	-0.10 [-0.78, 0.58]
CÔTE 2000	5.689	0.256	95	5.3	0.16	54	99.0%	0.39 [0.32, 0.46]
Total (95% CI)			**128**			**87**	**100.0%**	**0.38 [0.32, 0.45]**

Heterogeneity: Chi² = 1.98, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 11.32 (P < 0.00001)

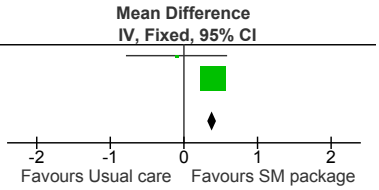


Figure 372: Serious exacerbations (requiring OCS)

Study or Subgroup	SM package Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COWIE 1997	19	91	19	48	64.4%	0.53 [0.31, 0.90]
THOONEN 2003	27	91	14	94	35.6%	1.99 [1.12, 3.55]
Total (95% CI)		**182**		**142**	**100.0%**	**1.05 [0.72, 1.52]**
Total events	46		33			

Heterogeneity: Chi² = 11.17, df = 1 (P = 0.0008); I² = 91%
Test for overall effect: Z = 0.25 (P = 0.80)

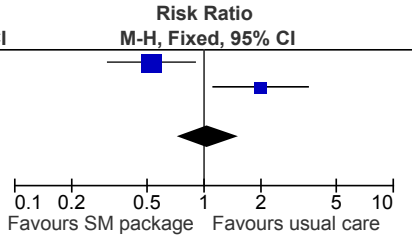


Figure 373: Serious exacerbations per patient (requiring OCS)

Study or Subgroup	Self management package Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
CÔTÉ 1997	0.795	1.357	95	0.5	1.5	54	41.0%	0.30 [-0.19, 0.78]
MILENKOVIĆ 2007	0.3	0.6	37	1.4	1.1	37	59.0%	-1.10 [-1.50, -0.70]
Total (95% CI)			**132**			**91**	**100.0%**	**-0.53 [-0.84, -0.22]**

Heterogeneity: Chi² = 18.81, df = 1 (P < 0.0001); I² = 95%
Test for overall effect: Z = 3.34 (P = 0.0008)

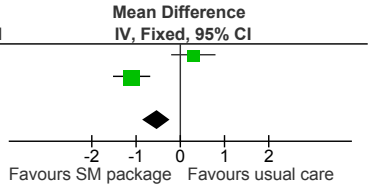


Figure 374: Total no. of hospital admissions

Study or Subgroup	Self-management package Events	Total	Usual care Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
CASTRO 2003	20	50	25	46	51.6%	0.57 [0.25, 1.26]
COWIE 1997	4	91	12	48	27.6%	0.13 [0.05, 0.40]
MILENKOVIĆ 2007	1	37	1	37	4.2%	1.00 [0.06, 16.30]
OLIVEIRA 1999	0	22	10	20	16.6%	0.07 [0.02, 0.28]
Total (95% CI)		**200**		**151**	**100.0%**	**0.27 [0.15, 0.49]**
Total events	25		48			

Heterogeneity: Chi² = 9.43, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 4.43 (P < 0.00001)

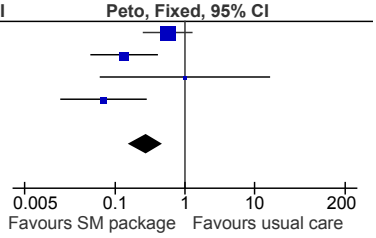


Figure 375: Total no. of hospital admissions per patient

Study or Subgroup	Self-management package Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
CASTRO 2003	0.4	0.9	50	0.9	1.5	46	3.5%	-0.50 [-1.00, 0.00]
CÔTÉ 1997	0.064	0.276	95	0.04	0.29	54	96.5%	0.02 [-0.07, 0.12]
Total (95% CI)			**145**			**100**	**100.0%**	**0.01 [-0.09, 0.10]**

Heterogeneity: Chi² = 4.07, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 0.12 (P = 0.91)

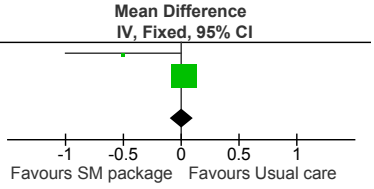
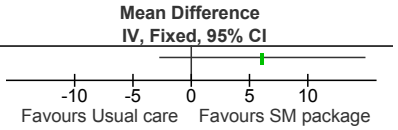


Figure 376: Lung function (% predicted FEV_1)

Study or Subgroup	Self-management package Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
MILENKOVIĆ 2007	85.1	17.2	37	79	21.1	37	6.10 [-2.67, 14.87]



K.6.2 Self-management versus usual care in people aged between 5 and 16 years

Figure 377: Quality of life

Study or Subgroup	Mean Difference	SE	Self-management package Total	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
BRUZZESE 2010	0.3	0.10490612	175	170	60.0%	0.30 [0.09, 0.51]
HORNER 2013	0.08291874	0.16204206	81	72	25.2%	0.08 [-0.23, 0.40]
RIKKERS-MUTSAERTS 2012	-0.10815851	0.21103168	46	44	14.8%	-0.11 [-0.52, 0.31]
Total (95% CI)			**302**	**286**	**100.0%**	**0.18 [0.03, 0.34]**

Heterogeneity: Chi² = 3.53, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 2.27 (P = 0.02)

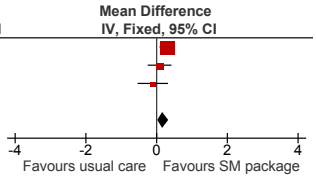


Figure 378: Total no. of hospital admissions

Study or Subgroup	Self-management package Events	Total	Usual care Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
FARBER 2004	3	28	0	28	22.0%	7.97 [0.79, 79.91]
HORNER 2013	5	81	6	72	78.0%	0.72 [0.21, 2.47]
Total (95% CI)		**109**		**100**	**100.0%**	**1.23 [0.42, 3.62]**
Total events	8		6			

Heterogeneity: Chi² = 3.24, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 0.37 (P = 0.71)

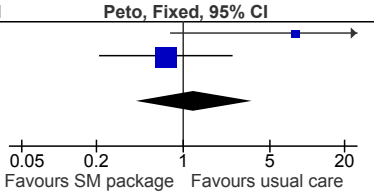


Figure 379: Total no. of hospital admissions per patient

Study or Subgroup	Self-management package Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
BRUZZESE 2010	0.05	0.3	175	0.24	1.18	170	-0.19 [-0.37, -0.01]

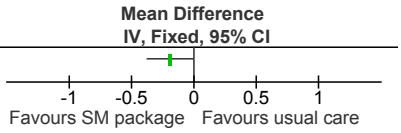


Figure 380: Serious exacerbations (requiring OCS)

Study or Subgroup	Self-management package Events	Total	Usual care Events	Total	Risk Ratio M-H, Fixed, 95% CI
RIKKERS-MUTSAERTS 2012	6	46	7	44	0.82 [0.30, 2.25]

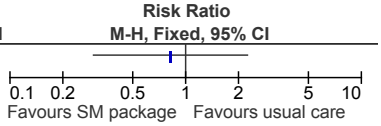


Figure 381: Serious exacerbations (requiring OCS) per patient

Study or Subgroup	Self management package Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
AGRAWAL 2005	0.5	0.71	32	1	0.61	28	-0.50 [-0.83, -0.17]

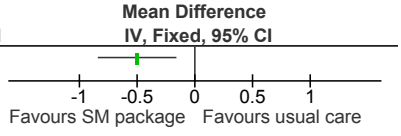


Figure 382: Asthma control

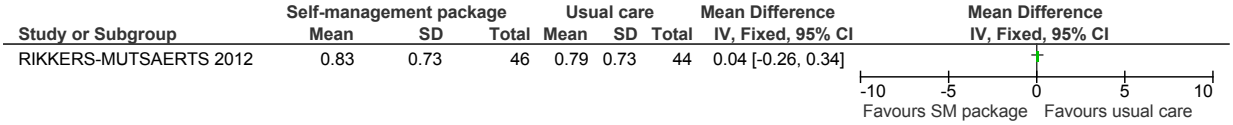
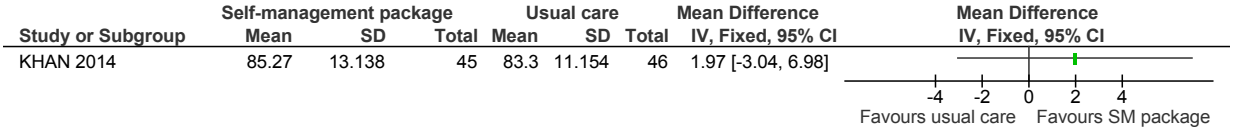
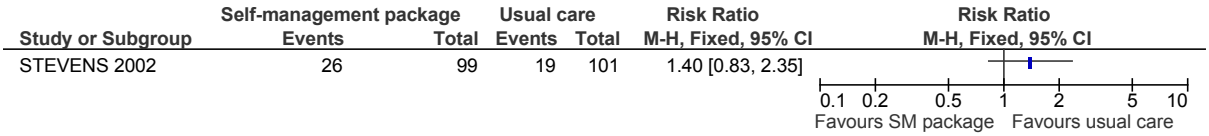


Figure 383: Peak expiratory flow rate



K.6.3 Self-management versus usual care in people aged between 1 and 5 years

Figure 384: Total no. of hospitalisations



K.7 Dose variation within self-management plans

K.7.1 Doubling compared to fixed dose for adults (>16) with asthma

Figure 385: Severe exacerbations (subsequent exacerbation after index)

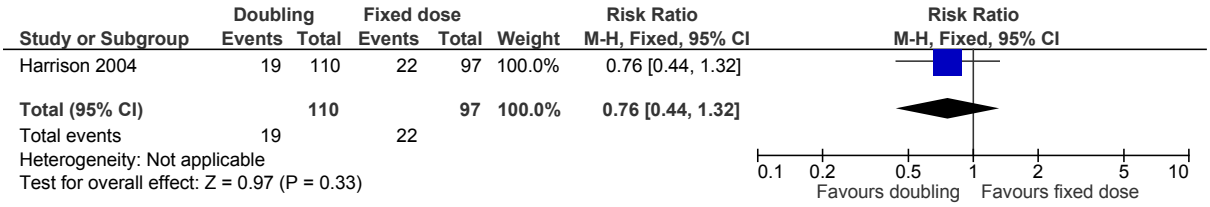


Figure 386: Exacerbations (at 3 months following treatment success)

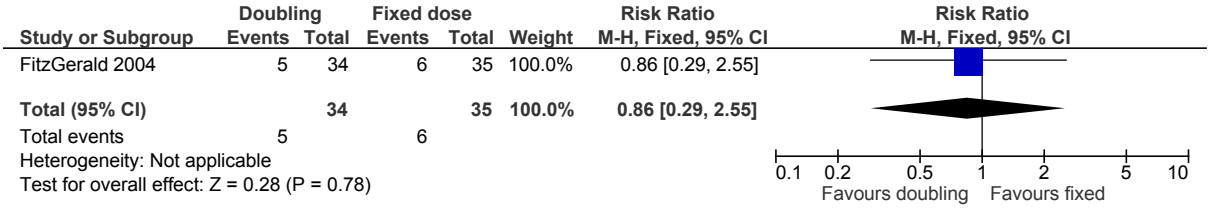


Figure 387: Treatment failure (requiring OCS within 14 days)

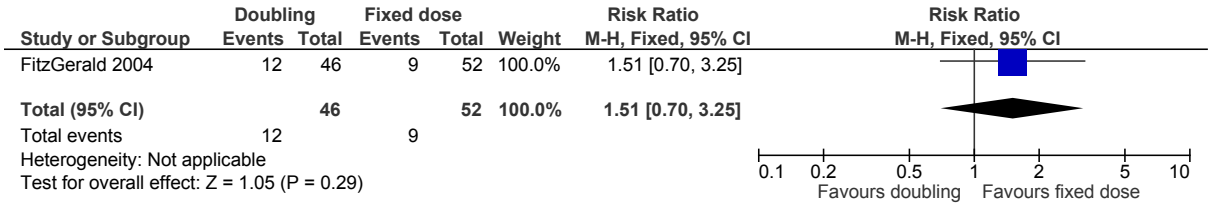


Figure 388: Treatment failure (unscheduled visit/persistent low PEF/symptoms at 14 days)

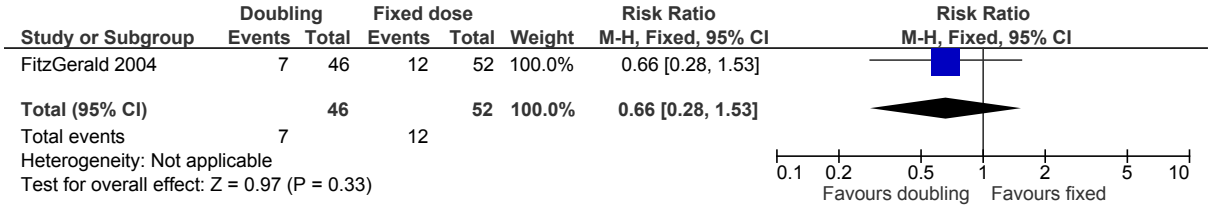
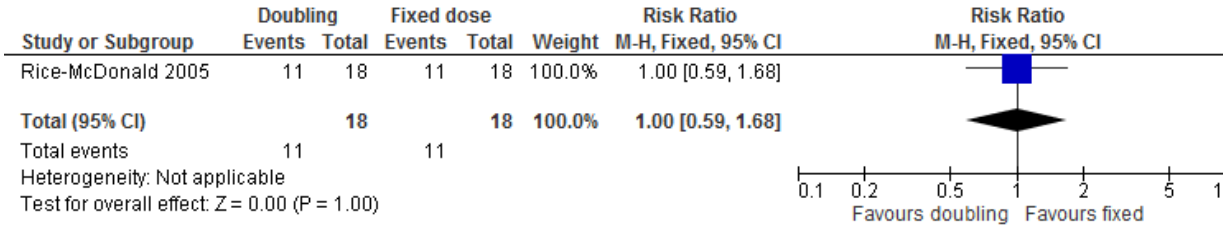
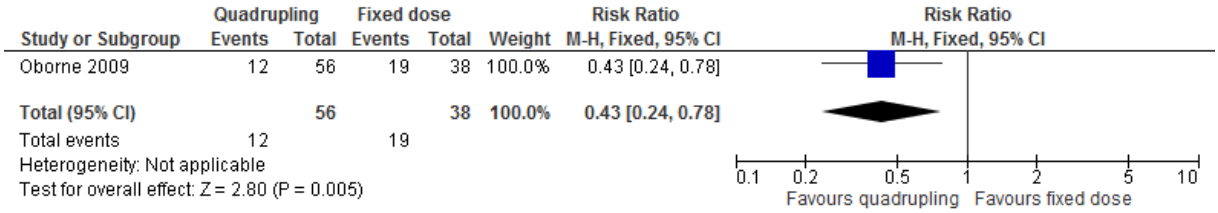


Figure 389: Treatment failure (symptoms fail to improve/PEF remains low/adverse events at 14 days)



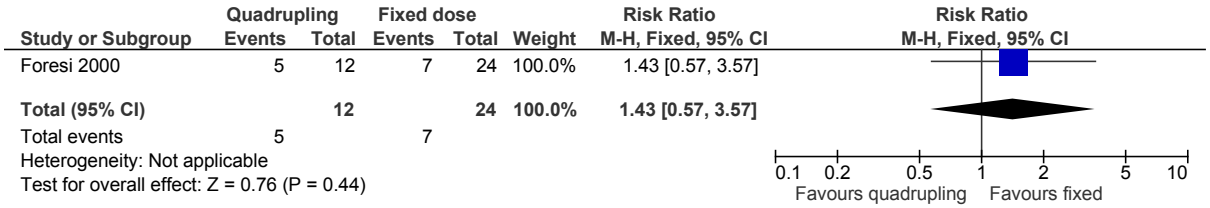
K.7.2 Quadrupling compared to fixed dose for adults (>16) with asthma

Figure 390: Severe exacerbations (subsequent to index, requiring OCS)



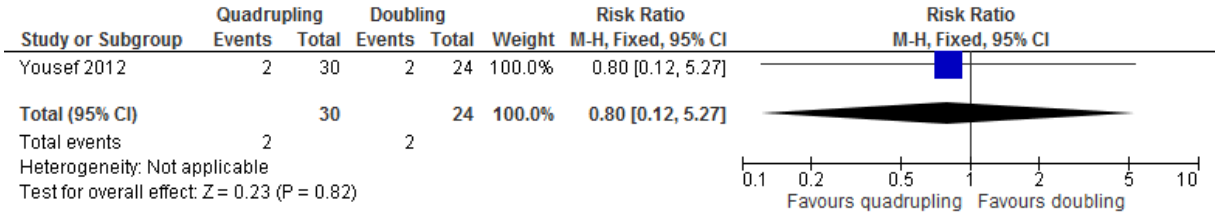
K.7.3 Quintupling compared to fixed dose for adults (>16) with asthma

Figure 391: Exacerbations (subsequent to index exacerbation)



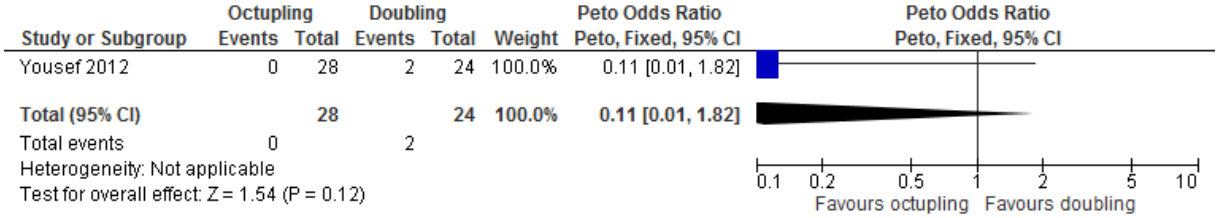
K.7.4 Quadrupling compared to doubling dose for young people (5-16) with asthma

Figure 392: Severe exacerbations (subsequent to index, requiring OCS)



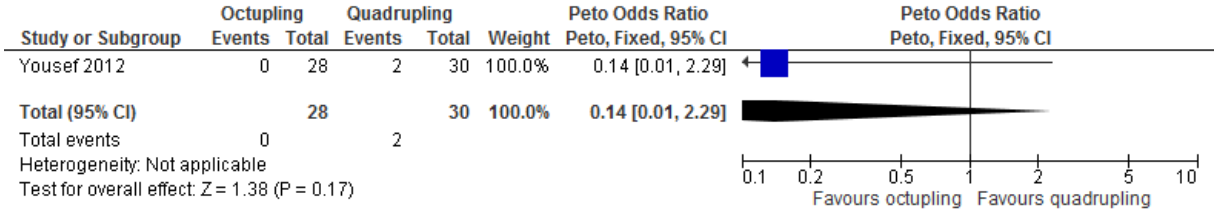
K.7.5 Octupling compared to doubling dose for young people (5-16) with asthma

Figure 393: Severe exacerbations (subsequent to index, requiring OCS)



K.7.6 Octupling compared to quadrupling dose for young people (5-16) with asthma

Figure 394: Severe exacerbations (subsequent to index, requiring OCS)



K.8 Decreasing regular maintenance treatment

Figure 395: **Asthma control for predicting step-down failure.**

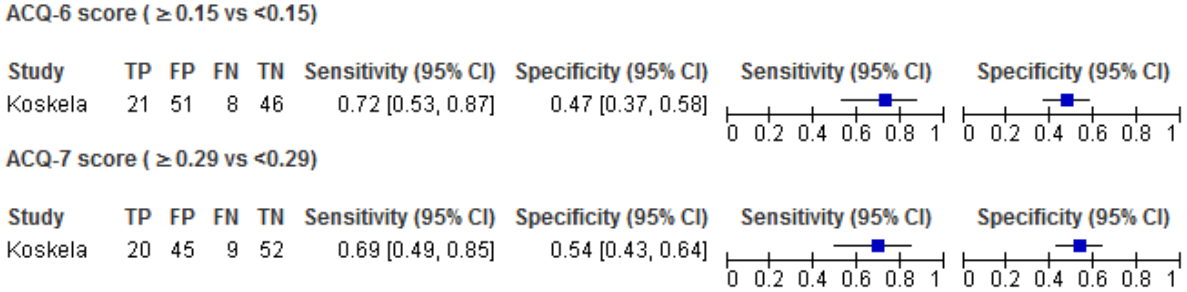
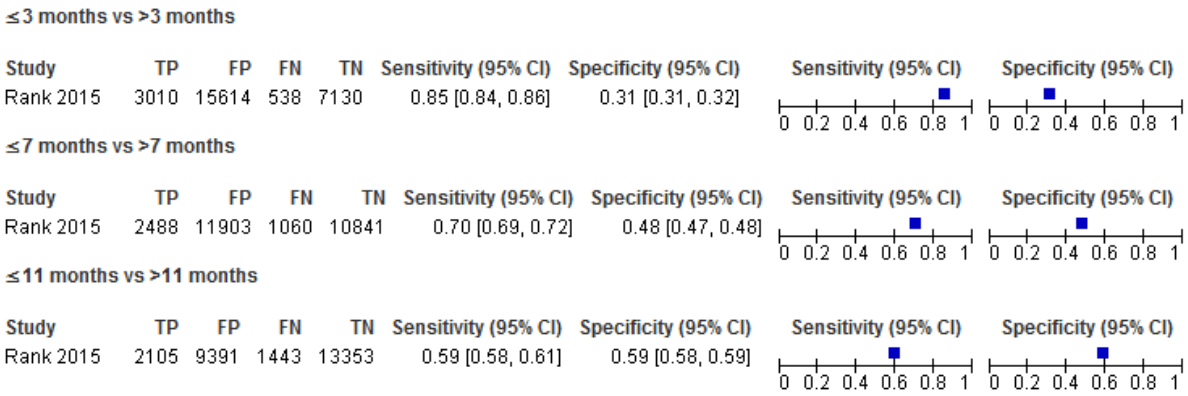


Figure 396: **Asthma control for predicting step-down failure.**



K.9 Breathing exercises in addition to pharmacological treatment

K.9.1 Breathing exercises versus usual care

Figure 397: Breathing exercise versus usual care – Quality of life: AQLQ at 6 months

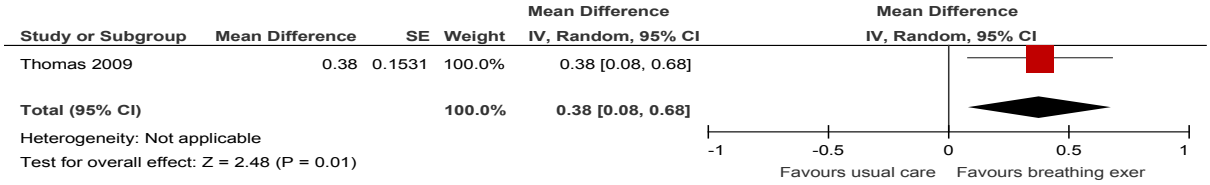


Figure 398: Breathing exercise versus usual care – Quality of life: SGRQ at 12 months

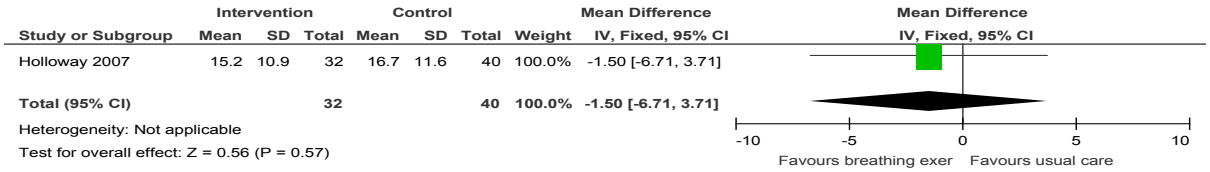


Figure 399: Breathing exercise versus usual care – Quality of life: SF-36 physical component

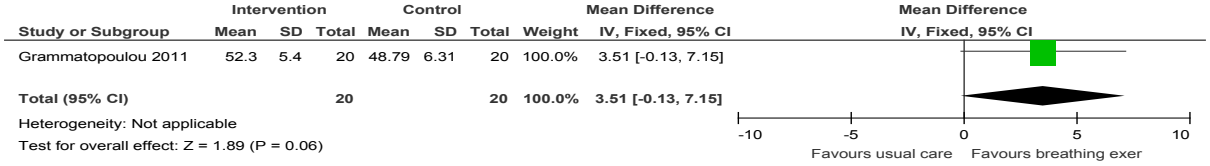


Figure 400: Breathing exercise versus usual care – Quality of life: SF-36 mental component

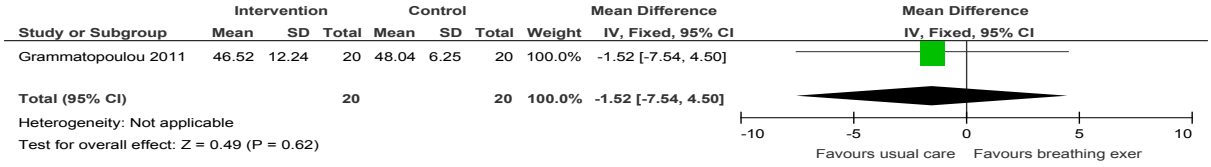


Figure 401: Breathing exercise versus usual care - Asthma control: ACQ at 6 months

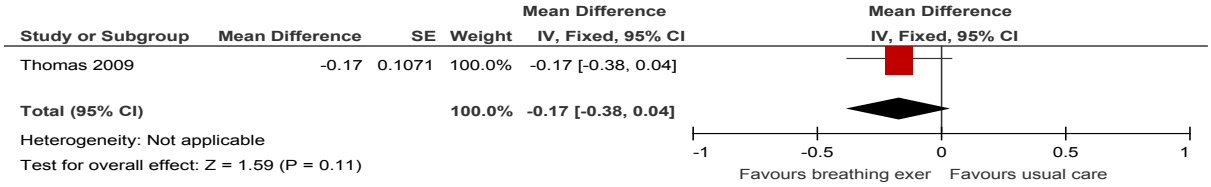


Figure 402: Breathing exercise versus usual care – Asthma control: ACT at 6 months

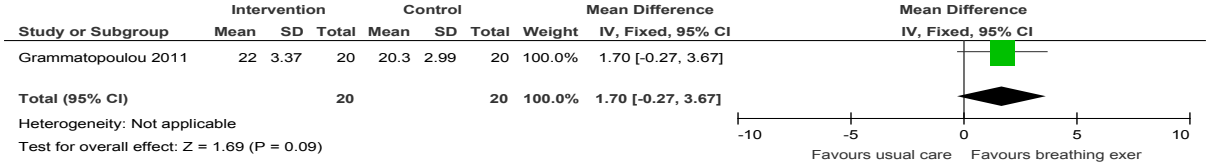


Figure 403: Breathing exercise versus usual care – Lung function: FEV_1 (L)

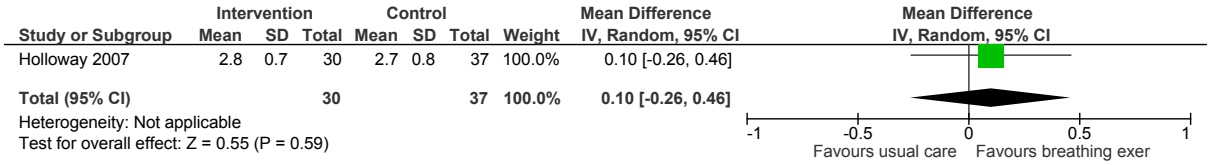


Figure 404: Breathing exercise versus usual care – Lung function: FEV_1 % predicted at 6 months

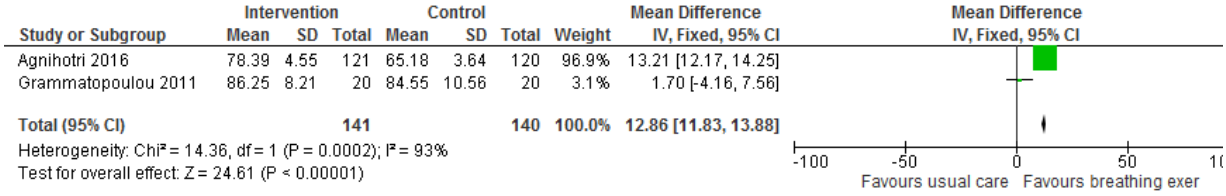
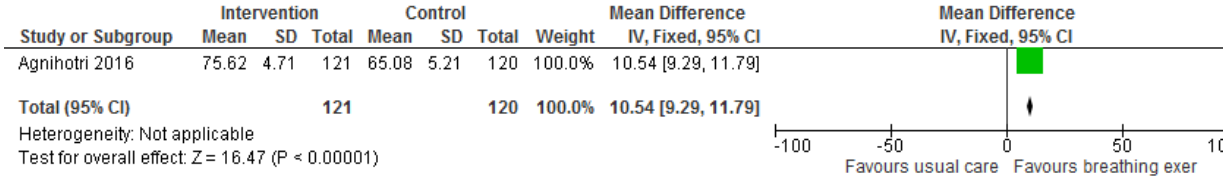


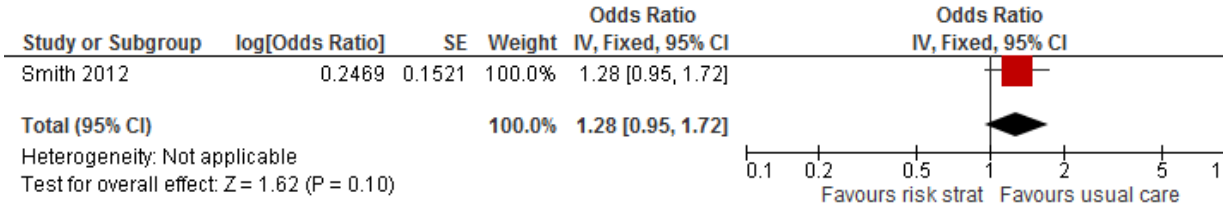
Figure 405: Breathing exercise versus usual care – Lung function: PEF% predicted at 6 months



K.10 Managing patients in relation to risk of poor outcomes

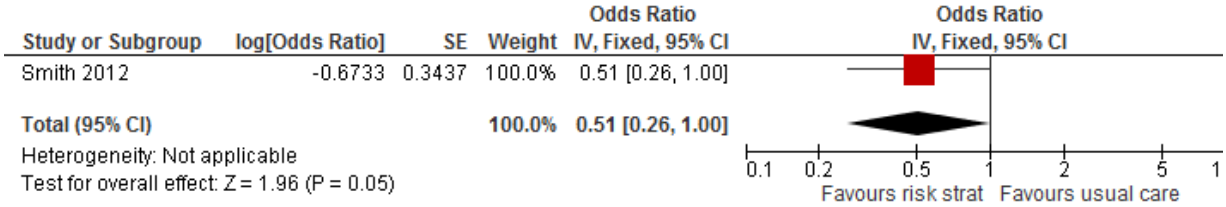
K.10.1 Severe exacerbations (requiring OCS)

Figure 406: Care by risk stratification versus usual care in people with asthma



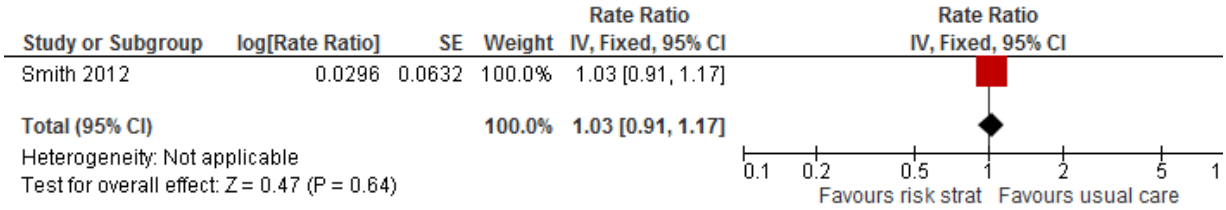
K.10.2 Hospitalisations

Figure 407: Care by risk stratification versus usual care in people with asthma



K.10.3 SABA use (rate of prescriptions)

Figure 408: Care by risk stratification versus usual care in people with asthma



Appendix L: Excluded clinical studies

L.1 Treatment in patients not on regular preventers

Table 86: Studies excluded from the clinical review

Reference	Reason for exclusion
Aldridge 2002[25]	Duration <3 months, crossover study
Al-Kazaz 2012[23]	Systematic review not consistent with review question PICO
Antoniu 2003[47]	Not review population
Arets 2002[54]	Not review population
Bacharier 2009[69]	Not review population
Baxter-Jones 2000[103]	Not review population
Den Otter 2007[323]	Not review population
Haahtela 2009[468]	Not review population
Hancox 1999[475]	Duration <3 months, crossover study
Kerstjens 1992[575]	Not review population
Laitinen 1992 [609]	Not review population
Macaluso 1986[650]	Not review population
Morice 1999[728]	Duration <3 months. Intervention arm received ICS without SABA PRN.
O'Byrne 2006[781]	Not review population
Osterman 1997[797]	Not review population
Rutten-van Molken 1993[925]	Not review population
Sheffer 2005[960]	Not review population
Silverman 2006[963]	Not review population
Sullivan 2003[1005]	Not review population
Tan 2006[1017]	Not review population
Tattersfield 2001[1023]	Not review population
Turpeinen 2000[1048]	Conference abstract only
Van Essen-Zandvliet 1992[1062]	Not review population
Weiss 2006[1101]	Not review population

L.2 Choice of first-line preventer in patients with poor asthma control

Table 87: Studies excluded from the clinical review

Study	Exclusion reason
Adams 2001 [6]	Systematic review is not relevant to review question or unclear PICO
Adams 2001 [7]	Systematic review is not relevant to review question or unclear PICO

Adams 2008 [8]	Systematic review is not relevant to review question or unclear PICO
Adinoff 1998 [9]	Not review population
Allen 1998 [28]	Not review population
Altman 1992 [35]	Crossover study. Not review population
Andersson 2001 [37]	Incorrect interventions
Ankerst 2001 [41]	Systematic review is not relevant to review question or unclear PICO
Anon 2005 [517]	Not review population
Anonymous 1990 [42]	Duplicate of other study
Anonymous 2000 [1028]	Duplicate of other study
Antilla 2014 [45]	Not review population
Arduino 2001 [53]	Abstract only
Arets 2002 [54]	Not review population
Asrilant 1975 [60]	Incorrect study design
Awad 2002 [67]	Unable to obtain full text
Bacharier 2009 [69]	Not review population
Baker 1999 [78]	Not review population
Banov 2001 [80]	Not review population
Banov 2003 [79]	Not review population
Bateman 2008 [97]	Incorrect line of therapy
Baxter-jones 2000 [102]	Not review population
Becker 2006 [104]	Not review population
Bel 1990 [108]	Not review population
Bensch 2006 [116]	Not review population
Bensch 2011 [115]	Not review population
Berg 2003 [117]	Not review population
Berger 2005 [124]	Not review population
Bergmann 1989 [126]	Not in English
Bisca 2000 [135]	Abstract only
Bisgaard 1999 [138]	Not review population
Bisgaard 2000 [137]	Abstract only
Bisgaard 2001 [141]	Not review population
Bisgaard 2005 [142]	Not review population
Bleecker 2000 [148]	Not review population
Bleecker 2006 [149]	Incorrect study design
Bleecker 2014 [147]	Unable to obtain full text
Blumenthal 1998 [152]	Not review population
Bodzenta-lukaszyk 2011 [153]	Not review population
Booms 1997 [156]	Not review population
Boonsawat 2010 [157]	Not review population
Borker 2005 [159]	Same data set as Pearlman 2002 - already extracted

Bose 1987 [160]	Not review population
Boskovska 2001 [161]	Abstract only
Boushey 2005 [164]	Not review population. Incorrect interventions
Bousquet 2007 [165]	Not review population
Brand 2011 [177]	Not review population
Briggs 2006 [178]	Incorrect interventions
Bukstein 2003 [196]	Not review population
Busse 1998 [210]	Not review population
Busse 1999 [214]	Abstract only
Busse 2001 [208]	Not review population
Busse 2008 [212]	Not review population
Busse 2014 [209]	Not review population
Carlsen 2005 [226]	No usable outcomes
Carrasco 1989 [227]	Not review population
Carter 2002 [228]	Letter
Cates 2013 [233]	Systematic review is not relevant to review question or unclear PICO
Chanez 2001 [244]	Not review population
Chapman 2002 [245]	Conference abstract
Chen 2001 [253]	Not in English
Chen 2006 [255]	Not review population
Cherniack 1990 [257]	Duplicate of other study
Chi 2006 [259]	Not in English
Chuchalin 2002[269]	Not review population
Chuchalin 2002[270]	Not review population
Chung 1977 [271]	Less than minimum duration
Cisneros 2010 [273]	Text in Spanish
Coleman 2011 [276]	Incorrect study design
Collins-williams 1971 [279]	Crossover study
Couch 1977 [288]	Not review population
Creticos 1999 [293]	Not review population
Crişan 2008 [294]	Not in English
Dahl 2002 [305]	Not review population
Dal negro 2003 [307]	Not review population
Damsbo 1994 [309]	Not in English
Danov 2009 [310]	Commentary only
Davies 2004 [311]	Not review population
Dawood 1977 [312]	Crossover study
De blic 1996 [314]	Incorrect interventions. Not review population
Di franco 1999 [329]	Not review population
Djukanovic 2010 [331]	Incorrect interventions

Dockhorn 1994 [332]	Abstract only
Dombrowski 2004 [335]	Not review population
Dorinsky 2001 [338]	No abstract
Doull 1995 [340]	Not review population
Dowling 2000 [341]	Unable to locate full text paper
Drollman 2001 [342]	No abstract
Ducharme 2000 [346]	Systematic review is not relevant to review question or unclear PICO
Ducharme 2002 [347]	Systematic review is not relevant to review question or unclear PICO
Dudley 2004 [353]	Systematic review is not relevant to review question or unclear PICO
Duplantier 2006 [355]	Commentary
Dykes 1974 [357]	Commentary
Ebden 1984 [358]	Letter
Edelman 2001 [359]	Abstract only
Edin 2009 [360]	Not review population
Edmunds 1980 [361]	Crossover study
Edwards 1995 [364]	Less than minimum duration
Egelstã¤tter 2002 [365]	Conference abstract
Ehrs 2010 [366]	Not review population
Eigen 1987 [368]	Not review population
Eliraz 2001 [369]	Abstract only
Emami 2014 [372]	Not review population
Ericsson 2001 [373]	No abstract
Ericsson 2001 [374]	Abstract only
Ericsson 2006 [375]	Not review population
Fairfax 1986 [381]	Not review population
Fairfax 1988 [382]	Not review population
Fernandes 2001 [384]	Not review population. Duration of follow-up only 8 weeks
Foresi 2001 [401]	Abstract only
Freezer 1995 [409]	Not review population
Furukawa 1984 [415]	Not review population
Furukawa 1998 [414]	Commentary
Galant 1996 [420]	Not review population
Galant 2001 [419]	Abstract only
Gelfand 2006 [431]	Not review population
Giorgi 1998 [440]	Not review population
Goodwin 1996 [445]	Unable to access full text paper
Gradman 2010 [448]	Not review population
Grifoni 1971 [453]	Crossover study
Grossman 1999 [455]	Incorrect interventions
Guilbert 2006 [459]	Not review population

Guilbert 2011 [458]	Not review population
Guo 2000 [461]	Text not in English
Guo 2002 [462]	Not in English
Haahtela 1991 [466]	Not review population
Haber 1989 [469]	Not review population
Hansel 2006 [476]	Not review population
Hermance 1973 [481]	Crossover study
Hiller 1977 [483]	Crossover study
Hofstra 1997 [486]	Abstract only
Hofstra 2000 [485]	Not review population
Hong 2011 [492]	Not in English
Horiguchi 2007 [494]	Not review population
Hoshino 1998 [496]	Not review population
Hoshino 2001 [499]	Not review population
Huang 2006 [505]	Not in English
Igde 2009 [511]	Letter
Ige 2010 [512]	Not review population
Irani 2001 [519]	Conference abstract
Jackson 2000 [522]	Abstract only
Jat 2006 [528]	Not review population
Jehan 2014 [530]	Not review population
Johansson 1999 [536]	Not review population
Johansson 2006 [534]	Not review population
Jonasson 1998 [540]	Not review population
Jonasson 2000 [541]	Not review population
Jonasson 2000 [542]	Not review population
Jonsson 2004 [545]	Results already reported in O'Byrne
Juniper 1990 [551]	Not review population
Kannisto 2002 [558]	Incorrect interventions
Katz 1998 [559]	Not review population
Kavuru 2000 [565]	Not review population
Kemp 1999 [571]	Not review population
Kemp 1999 [567]	Not review population
Kemp 2004 [570]	Not review population
Knorr 2001 [585]	Not review population
Konig 1995 [587]	Not review population
Krawiec 2015 [595]	Not clinician diagnosed asthma
Kudo 1995 [597]	Not in English
Kumar 2007 [600]	Not review population
Laforce 1994 [605]	Abstract only

Laforce 2000 [607]	Not review population
Lanier 2001 [612]	Abstract only
Lau 2002 [613]	Not in English
Lee 2014 [618]	Systematic review is not relevant to review question or unclear PICO
Leff 1998 [619]	Not review population
Li 1999 [629]	Not review population
Li 2000 [628]	Not in English
Li 2003 [630]	Not in English
Lin 2015 [634]	Not review population
Lindqvist 2003 [638]	Not review population
Lundback 2006 [647]	Not review population
Macharadze 1999 [651]	Not in English
Magnussen 2007 [653]	Not review population
Mahajan 1997 [654]	Not review population
Mahajan 1998 [655]	Not review population
Mallol 2009 [660]	Not review population
Malmstrom 1999 [661]	Not review population
Manolitsas 1995 [667]	Not review population
Mansur 2013 [668]	Not review population
Martin 1974 [673]	Crossover study
Maspero 2001 [679]	Not review population
Maspero 2013 [677]	Not review population
Massingham 2014 [681]	All studies individually ordered
Mastronarde 2008 [682]	Not review population
Mattishent 2014 [685]	Systematic review is not relevant to review question or unclear PICO
Mccarthy 2001 [688]	Abstract only
Mcfadden 1999 [690]	Not review population
Mckeage 2013 [693]	Systematic review is not relevant to review question or unclear PICO
Mckeage 2015 [694]	Systematic review is not relevant to review question or unclear PICO
Mclean 1973 [695]	Crossover study
Medina-rojas 2012 [697]	Commentary
Mellon 2000 [702]	Unable to locate full text paper
Meltzer 2001 [704]	Abstract only
Menendez 2001 [710]	Not review population
Meyer 1971 [713]	Not in English
Michael 1970 [714]	Crossover study
Micheletto 2000 [715]	Abstract only
Miller 2007 [720]	Not review population
Miller 2008 [719]	Not review population
Mitchell 1976 [722]	Crossover study

Mitsui 1977 [723]	Unable to obtain full text
Morice 2001 [727]	Letter
Moro 1980 [730]	Commentary
Moskovljevic 2009 [733]	Abstract only
Moy 2002 [737]	Conference abstract
Murphy 2003 [740]	Not review population
Murphy 2008 [739]	Not review population
Murray 2004 [742]	Not review population
Mzurek 2001 [744]	Abstract only
Nakazono 2004 [748]	Not in English
Nathan 1998 [750]	Not review population
Nathan 2012 [751]	Not review population
Nayak 2000 [757]	Not review population
Nelson 2009 [759]	Not review population
Ng 2004 [762]	Duplicate of other study
Ni chroinin 2009 [764]	Systematic review is not relevant to review question or unclear PICO
Nie 2013 [766]	Not review population
Nishima 2005 [768]	Not in English
Nutini 1998 [773]	Not review population. Incorrect interventions
O'byrne 1996 [775]	Not review population
O'byrne 2005 [777]	Not review population
O'byrne 2006 [781]	Not review population
O'byrne 2009 [779]	Not review population
O'byrne 2014 [778]	Not review population
O'byrne 2014 [782]	Not review population
O'connor 2010 [784]	Not review population
Olszowiec-chlebna 2010 [792]	Not review population
Orefice 1992 [794]	Not review population
Osterman 1997 [797]	Not review population
Ostrom 2005 [799]	Not review population
Overbeek 1996 [801]	Not review population
Papi 2013 [806]	Not review population
Papi 2015 [811]	Systematic review is not relevant to review question or unclear PICO
Patel 2013 [813]	Not review population
Pauli 1995 [816]	Less than minimum duration
Pauwels 2003 [818]	Not review population
Pearlman 2004 [823]	Not review population
Pearlman 2013 [822]	Not review population
Peden 1998 [825]	Not review population
Pedersen 2010 [827]	Not review population

Peters 2007 [833]	Not review population
Petty 1989 [839]	Not review population
Pinnas 2005 [847]	Not review population
Pohunek 2006 [849]	Not review population
Ponce castro 2009 [851]	Not in English
Ponticiello 1997 [852]	Not review population
Postma 2011 [853]	Not review population
Powell 2004 [856]	Systematic review is not relevant to review question or unclear PICO
Prasad 2004 [858]	Not review population
Price 2013 [863]	Not review population
Pruteanu 2014 [870]	Systematic review is not relevant to review question or unclear PICO
Qaqundah 2006 [872]	Not review population
Quirce 2011 [873]	Incorrect interventions
Radwan 2013 [877]	Not review population
Rand 2007 [883]	No usable outcome
Rangsithienchai 2008 [884]	Letter
Reddel 2008 [892]	Not review population
Reed 1998 [895]	Not review population
Reid 1988 [898]	Not review population
Riccioni 2002 [903]	Not in English
Riccioni 2002 [903]	Not review population
Riccioni 2003 [905]	Not review population
Richardson 1999 [907]	Commentary
Rickard 2001 [908]	Abstract only
Riemersma 2012 [911]	Not review population
Ringdal 2003 [914]	Not review population
Riordan 1974 [915]	Not review population
Roux 2003 [920]	Not review population
Ruff 2003 [923]	Erratum
Satre 2002 [933]	Abstract only
Schwartz 1998 [944]	Not review population
Shah 2014 [951]	Not review population
Sharek 1999 [956]	Systematic review is not relevant to review question or unclear PICO
Sheffer 2005 [960]	Not review population
Sheth 2002 [962]	Economic analysis of previously included study, no new clinical outcomes
Silverman 2006 [963]	Not review population
Skoner 2011 [967]	Not review population
Smith 1973 [971]	Not review population. Crossover study
Soes-petersen 2011 [979]	Not review population
Sorkness 2007 [982]	Not review population

Stafford 1983 [987]	Abstract only
Stafford 1984 [986]	Not review population
Stankovic 2007 [990]	Not review population
Stella 2001 [991]	Abstract only
Stelmach 2011 [993]	No outcomes that meet protocol
Stempel 2007 [995]	Incorrect study design
Strand 2004 [1000]	Not review population
Straub 2005 [1002]	Less than minimum duration
Sugar 2002 [1003]	Conference abstract
Suissa 1997 [1004]	Not review population
Szefler 2007 [1008]	Not review population
Szefler 2013 [1009]	Not review population
Tasche 1997 [1021]	Not review population
Tasche 1998 [1020]	Erratum
Tattersfield 2001 [1023]	Incorrect interventions
Tinkelman 1993 [1037]	Not review population
Trigg 1994 [1044]	Not review population
Tukiainen 2000 [1047]	Incorrect interventions
Ulrik 2009 [1052]	Not review population
Valovirta 2011 [1055]	Not review population
Van der molen 1998 [1060]	Less than minimum duration
Verberne 1997 [1075]	Not review population
Walters 2007 [1090]	Systematic review is not relevant to review question or unclear PICO
Wang 2011 [1092]	Not review population
Wasserman 1995 [1095]	Incorrect interventions
Wasserman 1996 [1096]	Not review population
Wasserman 2006 [1094]	Not review population
Weinstein 2002 [1099]	Conference abstract
Wennergren 1996 [1103]	Incorrect interventions
Wheatley 1983 [1106]	Not review population
White 199 [1108]	Not review population
Williams 2001[1111]	Not review population
Wisniewski 2008 [1119]	Letter
Wolfe 2000 [1121]	Not review population
Wolfe 2006 [1120]	Not review population
Yang 2013 [1124]	Systematic review is not relevant to review question or unclear PICO
Yurdakul 2003 [1133]	Not review population
Zetterstrom 2001 [1139]	Not review population
Zhang 2014 [1140]	Systematic review is not relevant to review question or unclear PICO
Zheng 1998 [1142]	Not in English

Zuwallack 2000 [1147]	Not review population

L.3 Escalating pharmacological treatment in patients poorly controlled on first-line preventer treatment

L.3.1 Second-line preventer

Table 88: Studies excluded from the clinical review

Study	Exclusion reason
Agarwal 2009[10]	Systematic review checked for references
Aguirre 1998[16]	Not review population
Akazawa 2006[22]	Systematic review checked for references
Allayee 2007[27]	Not review population
Allison 2014[31]	Protocol only
Andersson 2001[38]	Not review population
Antoniu 2011[50]	Commentary
Armenio 1993[57]	Not review population
Atienza 2013[63]	Not review population
Aubier 1999[66]	Not review population
Aubier 2010[64]	Incorrect interventions
Aubier 2011[65]	Incorrect interventions
Bailey 2008[73]	Not review population
Baker 2007[77]	Abstract only
Barnes 2000[89]	Abstract only
Barnes 2007[88]	Not review population
Bateman 2001[92]	Abstract
Bateman 2001[92]	Abstract
Bateman 2001[93]	Not review population
Bateman 2003[91]	Not review population
Bateman 2004[94]	Not review population. Incorrect interventions
Bateman 2007[96]	Incorrect interventions
Bateman 2008[97]	Not review population
Bateman 2008[95]	Not review population. Incorrect interventions
Bateman 2011[99]	Not review population
Bateman 2014[100]	Not review population
Befekadu 2014[105]	Systematic review checked for references
Beg 2012[106]	Abstract
Bensch 2002[114]	Incorrect interventions
Berger 2002[121]	Incorrect interventions
Berger 2006[123]	Not review population
Berger 2010[120]	Not review population
Berger 2010[122]	Not review population
Bernstein 1999[130]	Not review population
Bianco 1989[133]	Not review population
Bisgaard 2004[136]	Not review population
Bjermer 2000[143]	Protocol only
Boonsawat 2008[158]	Not review population
Boskovska 2001[157]	Abstract
Bruce 2005[186]	Not review population
Buhl 2003[193]	Not review population

Busse 2003[206]	Not review population
Busse 2013[211]	Not review population
Cai 2000[221]	Not in English
Canonica 2004[224]	Incorrect interventions
Cash 2001[231]	Abstract only
Cekic 2001[236]	Abstract
Chapman 2005[246]	Not review population
Chauhan 2013[250]	Systematic review checked for references
Chauhan 2014[251]	Systematic review checked for references
Chen 2013[256]	Not in English
Chervinsky 2008[258]	Not review population
Chowdhury 2011[266]	Commentary
Colice 2014[277]	Commentary
Condemi 1999[280]	Not review population
Corren 2001[285]	Not review population
Corren 2007[283]	Not review population
Corren 2013[284]	Not review population
Cserhati 2000[295]	Not review population
Dal negro 2001[308]	Abstract
Deepa latha 2011[317]	Abstract only
Demoly 2009[321]	Not review population
Demuro mercon 2001[322]	Abstract
Dente 2001[325]	Abstract
Ducharme 2004[345]	Systematic review checked for references
Ducharme 2006[348]	Systematic review checked for references
Ducharme 2010[350]	Systematic review checked for references
Ducharme 2010[351]	Systematic review checked for references
D'urzo 2001[301]	Crossover study
D'urzo 2005[300]	Not review population
Edmunds 1994[362]	Less than minimum duration
Eid 2010[367]	Abstract only
Evans 1997[379]	Not review population
Fernandes 2001[384]	Less than minimum duration
Filiz 2002[385]	Crossover study
Finn 2000[386]	Abstract
Finn jr 2000[387]	Abstract
Fish 2000[389]	Abstract
Fish 2001[390]	Not review population
Fitzgerald 1999[394]	Not review population
Fitzgerald 2003[397]	Incorrect interventions
Fitzgerald 2014[396]	Abstract
Fournier 1990[405]	Not in English
Fowler 2001[406]	Abstract
Frost 1998[412]	Not review population
Fyans 1989[416]	Not review population
Geller-bernstein 1980[432]	Not review population
Goossens 2009[446]	Incorrect interventions
Green 2002[450]	Abstract
Greenstone 2005[452]	Systematic review checked for references
Grosclaude 2003[454]	Not in English
Guo 2002[460]	Not in English
Gupta 2007[463]	Abstract
Guyer 2013[465]	Narrative review

Hoshino 2012[498]	Not review population
Howland 2000[501]	Abstract
Hozawa 2013[502]	Abstract
Hyde 1974[509]	Crossover study
Irvin 2007[520]	Not review population
Ismaila 2014[521]	Not review population
Jenkins 2000[532]	Abstract
Jenkins 2006[531]	Not review population
Johansson 2001[535]	Not review population
Johnson 1994[538]	Less than minimum duration
Johnston 1997[539]	Not review population
Jones 1994[543]	Not review population
Jung 2002[548]	Not in English
Juniper 1990[552]	Not review population
Juniper 1999[553]	Not review population
Juniper 2002[549]	Not review population
Kaiser 2008[554]	Not review population
Kalberg 1998[555]	Abstract
Kelsen 1999[566]	Not review population
Kemp 1998[569]	Not review population
Kemp 1999[571]	Not review population
Kerstjens 2015[573]	Not review population
Kew 2014[579]	Protocol only
Kew 2015[581]	Protocol only
Kew 2015[582]	Systematic review checked for references
Koopmans 2006[589]	Not review population
Laforce 2005[606]	Not review population
Lalloo 2001[610]	Abstract
Lalloo 2003[611]	Not review population
Leflein 2002[620]	Not review population
Lipworth 2013[639]	Not review population
Loymans 2014[644]	NMA
Mahr 2011[656]	Commentary
Malolepszy 2002[662]	Not in English
Martinat 2003[674]	Not in English
Maspero 2010[680]	Not review population
Mathison 1971[683]	Crossover study
Meltzer 1992[706]	Not review population
Meltzer 2007[703]	Not review population
Mitchell 2003[721]	Not review population
Molimard 2001[725]	Incorrect interventions
Murray 1999[743]	Not review population
Nakaji 2013[747]	Not review population
Narmadha 2011[749]	Not review population
Nathan 2006[753]	Not review population
Nathan 2010[753]	Not review population
Nathan 2012[751]	Not review population
Nelson 2001[760]	Less than minimum duration
Noonan 2001[769]	Not review population
Noonan 2006[771]	Not review population
Noonan 2009[770]	Not review population. Incorrect interventions
Nsouli 2000[772]	Abstract
O'byrne 2008[780]	Not review population

O'connor 2001[783]	Not review population
O'connor 2007[785]	Not review population
Ohta 2015[789]	Not review population
Ortega-cisneros 1998[796]	Abstract
Paggiaro 2014[802]	Abstract
Papi 2007[805]	Not review population
Pastorello 1998[812]	Not in English
Pauwels 1997[817]	Not review population
Pearlman 2002[821]	Abstract
Pertseva 2013[831]	Not review population
Peters 2008[835]	Not review population
Peters 2011[832]	Commentary
Phipatanakul 2003[841]	Not review population
Pieters 2005[843]	Not review population
Pijaskic kamenov 2001[844]	Abstract
Price 2002[864]	Abstract
Price 2003[865]	Not review population
Price 2014[860]	Abstract
Quon 2010[874]	Systematic review checked for references
Rabe 2006[875]	Not review population
Rajanandh 2014[880]	Not review population
Rajanandh 2014[878]	Not review population
Rajanandh 2014[879]	Not review population
Rajanandh 2015[881]	Not review population
Rabe 2006[876]	Not review population
Ram 2005[882]	Systematic review checked for references
Reddel 2000[894]	Incorrect interventions
Rees 1993[896]	Not review population
Reid 2008[897]	Not review population
Reiss 1998[899]	Not review population
Rely 2011[900]	Not in English
Rickard 2000[909]	Abstract
Ringdal 2002[913]	Not review population
Scicchitano 2004[945]	Not review population
Spector 2012[984]	Not review population
Stelmach 2015[994]	Not review population
Stirbulov 2012[999]	Not review population
Tal 2002[1015]	Not review population
Tasche 1998[1022]	Not in English
Tee 2007[1024]	Systematic review checked for references
Thomas 2014[1030]	Abstract
Tian 2014[1035]	Systematic review checked for references
Tohda 2002[1039]	Not review population. Incorrect interventions
Tomlinson 2005[1040]	Not review population
Ulrik 2010[1053]	Not review population
Van der molen 1997[1061]	Not review population
Van noord 1999[1063]	Not review population
Van schayck 2012[1065]	Incorrect interventions
Vandewalker 2014[1067]	Abstract
Vaquerizo 2003[1068]	Not review population
Vermetten 1999[1077]	No usable outcomes
Villaran 1979[1078]	Not review population
Virchow 2010[1080]	Incorrect interventions

Wallin 2003[1089]	Not review population
Wang 2011[1093]	Systematic review checked for references
Westall 2000[1104]	Abstract
Westby 2004[1105]	Systematic review checked for references
White 2001[1107]	Abstract
Williams 1986[1110]	Not review population
Woolcock 1996[1122]	Not review population
Yildirim 2001[1126]	Abstract
Yurdakul 2002[1132]	Not review population
Zangrilli 2011[1135]	Not review population
Zimmerman 2002[1144]	Abstract
Zimmerman 2004[1145]	Not review population

L.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

Table 89: Studies excluded from the clinical review

Study	Exclusion reason
Anonymous 2012[44]	Erratum
Atienza 2012[62]	Abstract only
Aubier 2011	Inappropriate comparison
Bateman 2011[98]	Systematic review is not relevant to review question or unclear PICO
Bell 2007[109]	Commentary
Buhl 2007[195]	Systematic review is not relevant to review question or unclear PICO
Buhl 2012[194]	Systematic review is not relevant to review question or unclear PICO
Edwards 2010[363]	Systematic review is not relevant to review question or unclear PICO
Hozawa 2014[503]	Less than minimum duration
Kuna 2010[602]	Inappropriate comparison
Lin dr 2012[635]	Subgroup of Asian patients in included study
Louis 2009[642]	Inappropriate comparison
Lundborg 2006[648]	Inappropriate comparison
Naji 2012[746]	Systematic review is not relevant to review question or unclear PICO
Pavord 2009[820]	Inappropriate comparison
Sears 2008[946]	Inappropriate comparison
Sears 2009[947]	Systematic review is not relevant to review question or unclear PICO
Stallberg 2015[989]	Incorrect study design
Takeyama 2014[1014]	No usable outcomes
Tamminen 2008[1016]	No additional outcomes to master study
Vogelmeier 2005[1084]	Erratum
Vogelmeier 2005[1083]	Duplicate of other included study
Vogelmeier 2012[1086]	Subgroup of master study (Asian patients)

L.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

Table 90: Studies excluded from the clinical review

Study	Exclusion reason
Amar 2016[36]	Abstract only
Antilla 2014[45]	Not review population
Antoniu 2009[48]	Incorrect interventions
Antoniu 2013[49]	Commentary
Atienza 2013[63]	Incorrect interventions
Bateman 2008[97]	Incorrect interventions
Bateman 2011[99]	Not review population
Bateman 2014[100]	Incorrect interventions
Bernstein 1999[130]	Not review population
Bernstein 2015[129]	Not review population
Boonsawat 2010[157]	No additional outcomes to master study
Bozek 2012[172]	Not review population
Brown 2012[184]	Not review population
Brown 2014[183]	Abstract only
Casale 2015[230]	Abstract only
Chong 2015[265]	Systematic review not review population
Currie 2002[296]	Abstract only
Dahl 2013[306]	Abstract only
Dahl 2014[304]	Abstract only
Dahl 2015[303]	Commentary
Depietro 2015[326]	Abstract only
Doherty, 2015[334]	Abstract only
Donohue 2016[337]	Crossover study
Dupont 2005[356]	Less than minimum duration
Emad 1996[371]	Not review population
Fitzgerald 2005[393]	Incorrect interventions
FitzGerald 2015[395]	Abstract only
Friday 1973[411]	Crossover study
Halpin 2013[472]	Abstract only
Huang 2016[504]	Not review population
Ichinose 2015[510]	Abstract only
Ind 2002[515]	Not review population
Inoue 2007[516]	Crossover study
Johansson 2006[534]	No additional outcomes to master publication
Kerstjens 2016[576]	Data previously reported and extracted
Lin 2015[636]	Not review population
Lin 2016[637]	Not review population

Miller 2007[720]	No additional outcomes from master publication
Miller 2008[719]	No additional outcomes from master study
Nathan 2012[751]	No usable outcomes
Noonan 2006[771]	Not review population
O'connor 2010[784]	Incorrect interventions
Okamoto 1996[790]	Not review population
Papi 2007[810]	Incorrect interventions
Papi 2013[806]	Incorrect interventions
Patel 2013[813]	Not review population
Peters 2016[834]	Not review population
Pohunek 2006[849]	Incorrect interventions
Price 2007[866]	Incorrect interventions
Rajanandh 2014[880]	Not review population
Russell 1995[924]	No usable outcomes
Sovani 2008[983]	Incorrect interventions
Spector 2012[984]	Not review population
Stempel 2016[996]	Not review population
Van der mark 2012[1056]	Systematic review is not relevant to review question or unclear PICO
Virchow 2000[1079]	Less than minimum duration
Vogelberg 2015[1081]	Commentary
Vogelberg 2015[1082]	Commentary
Weinstein 2010[1100]	Not review population
Willson 2014[1113]	No additional outcomes from master publication
Ye 2015[1125]	Not review population
Zetterstrom 2001[1139]	Incorrect interventions

L.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

Table 91: Studies excluded from the clinical review

Study	Exclusion reason
Anon 2005[517]	Commentary
Anon 2007[869]	Commentary
Bacharier 2008 [70]	Incorrect interventinos
Bisgaard 2006 [139]	Not guideline condition. Not review population. Episodic wheeze (not asthma). Not clinician diagnosed asthma. ICS versus placebo
Chong 2014 [264]	Protocol only
Connett 1993 [281]	Less than minimum duration. Intermittent ICS versus placebo
Ducharme 2007 [349]	Conference abstract
Ducharme 2012 [344]	Conference abstract

Study	Exclusion reason
Fitzgerald 2004 [392]	Incorrect interventions
Foresi 2000 [400]	Incorrect interventions
Gerald 2015 [433]	Master study already included
Gionfriddo 2015 [439]	Systematic review, not matching PICO
Goswami 2009 [447]	Incorrect interventions
Kovesi 2011 [594]	Commentary
Oborne 2009 [787]	Incorrect interventions
Papi 2015 [807]	Not review population.
Reddel 2008 [892]	Not review population
Rodrigo 2014 [917]	Incorrect study design
Simons 2011 [964]	Commentary
Smart 2012 [969]	Commentary
Stankovic 2007 [990]	Incorrect interventions
Svedmyr 1999 [1006]	Incorrect interventions
Turpeinen 2010 [1050]	Master study already included
Turpeinen 2010 [1051]	Master study already included

L.5 Improving adherence to treatment

Table 92: Studies excluded from the clinical review

Study	Exclusion reason
Adams 2004 [5]	Abstract
Ahmedani 2013 [20]	Incorrect study design
Allen 1991 [29]	Abstract
Allen 1995 [30]	Not review population
Anonymous 1998 [43]	Not review population
Apter 2005 [51]	Records/citations only
Apter 2011 [52]	Not review population
Armour 2007 [58]	Less than minimum duration
Armour 2013 [59]	Not review population
Baddar 2014 [71]	Incorrect study design
Bailey 1987[76]	Study protocol. Incorrect study design
Bailey 1990[75]	Not review population
Bailey 1999[74]	Not review population
Bailey 2009 [72]	Not review population
Baptist 2013 [81]	Not review population
Baren 2006 [85]	Not review population
Barnes 2015 [87]	Cross-referenced for included studies
Bauman 2002 [101]	Incorrect study design
Bender 2007 [111]	Incorrect study design. Abstract

Bender 2010 [110]	Less than minimum duration
Bender 2014 [112]	Paper not available
Bender 2015 [113]	Less than minimum duration
Berg 1997 [119]	Less than minimum duration
Berg 1998 [118]	Less than minimum duration
Berger 2009 [125]	Incorrect study design
Bheekie 2001 [131]	Less than minimum duration. Not review population
Bhogal 2006 [132]	Not review population
Blais 2008 [146]	Not review population
Blais 2011 [145]	Incorrect study design
Bolton 1991 [154]	Not review population
Bonner 2002 [155]	Less than minimum duration. Not review population
Bosley 1994 [162]	Incorrect interventions
Bragt 2015 [173]	Not review population
Braido 2013 [175]	Incorrect study design
Brooks 2014 [180]	Incorrect study design
Bruzzese 2012 [191]	Incorrect study design
Bruzzese 2014 [188]	Incorrect study design
Burgess 2007 [198]	Incorrect interventions
Burgess 2008 [200]	Incorrect study design
Burgess 2010 [199]	Less than minimum duration. Not review population
Burkhart 2001 [202]	Less than minimum duration. Not review population
Burkhart 2002 [201]	Less than minimum duration
Burkhart 2005 [203]	Incorrect study design. Less than minimum duration
Burkhart 2007 [205]	Less than minimum duration. Not review population
Butz 2012 [216]	Not review population
Byrne 1993 [218]	Less than minimum duration. Not review population
Chan 2003 [242]	Not review population
Chan 2007 [241]	Not review population
Chan 2015 [240]	Not review population
Chaney 2004 [243]	Incorrect interventions
Chan-yeung 2002 [239]	Incorrect interventions. Not review population
Charles 2007 [247]	Not review population
Chatkin 2006 [249]	Incorrect study design
Chen 2010 [254]	Less than minimum duration
Chiu 2014 [262]	Incorrect study design
Choi 2008 [263]	Incorrect study design
Christakis 2012 [267]	Not review population
Da costa 1997 [302]	Incorrect study design
Demiralay 2002 [319]	No relevant outcome

Demiralay 2004 [320]	No comparator for education intervention
Denford 2014 [324]	Not review population
Devine 1996 [327]	Not review population
Dhein 2006 [328]	Paper not available
Dibello 2014 [330]	Review protocol
Dogra 2010 [333]	Incorrect interventions
Drotar 2005 [343]	Not full text
D'souza 1996 [299]	Incorrect study design
Ducharme 2011 [352]	Not review population
Duncan 2013 [354]	Not review population
Ellis 2014 [370]	Not review population
Fischer 2015 [388]	Not review population. Not guideline condition
Fonseca 2006 [399]	Less than minimum duration
Foster 2014 [404]	Not review population
Foster 2016 [403]	Not review population
Francis 2001 [407]	Not review population
Fujita 2002 [413]	Conference abstract only
Garcia-cardenas 2013 [426]	Less than minimum duration
Gebert 1998 [429]	Not review population
Gerald 2009 [434]	Less than minimum duration
Gheonea 2009 [435]	Not review population
Goeman 2013 [443]	Not review population
Goldberg 2014 [444]	Incorrect interventions
Grzeskowiak 2014 [456]	Not review population
Guendelman 2002 [457]	Not review population
Gustafson 2012 [464]	Less than minimum duration
Halterman 2006 [473]	Study records/citation only
Hederos 2005 [479]	Not review population
Hederos 2009 [480]	Not review population
Hinchageri 2012 [484]	Incorrect study design
Holzheimer 1998 [491]	Not review population
Huss 1991 [507]	Not review population
Hussain-rizvi 2009 [508]	Less than minimum duration
Iqbal 2004 [518]	Incorrect interventions
Jan 2007 [524]	Not review population
Janson 2005 [525]	Records/citations only
Janson 2009 [527]	Not review population
Jat 2016 [529]	Incorrect interventions
Johnson 2016 [537]	Less than minimum duration
Jones 1995 [544]	Not review population

Joseph 2011 [547]	Not review population. Incorrect study design
Joseph 2013 [546]	Not review population
Kamps 2008 [556]	Incorrect interventions
Koufopoulos 2016 [593]	Incorrect interventions
Kritikos 2007 [596]	Not review population
Kumar 2009 [599]	Not review population
Lavoie 2011 [615]	Abstract
Lebaron 1985 [617]	Not review population
Lewis 1984 [626]	Not review population
Licskai 2013 [631]	Incorrect study design
Lu 2008 [645]	Not review population
Lv 2012 [649]	Not review population
Margolis 2013 [669]	Not guideline condition
Marosi 2001 [670]	Incorrect study design
Martin 2015 [672]	Not review population
Mcardle 1997 [686]	Conference abstract only
Mcclure 2008 [689]	Not review population
Mcgrady 2013 [691]	Not guideline condition
Mehring 2013 [698]	Incorrect study design
Mehuys 2008 [699]	Paper not available
Mehuys 2008 [700]	Not review population
Meischke 2011 [701]	Not review population
Milgrom 1996 [718]	Not review population
Mohammed saji 2012 [724]	Not review population
Morell 2014 [726]	Not review population
Morice 2001 [729]	Not review population
Mosnaim 2008 [734]	Not review population
Mosnaim 2016 [735]	Cross-referenced for included studies
Moullec 2012 [736]	Cross-referenced for included studies
Muhlhauser 1991 [738]	Incorrect study design
Ngamvitroj 2007 [763]	Incorrect study design
Nides 1993 [765]	Not guideline condition
Nikander 2003 [767]	Not review population. Incorrect interventions
Oei 2011 [788]	Not review population
Ostojic 2005 [798]	Not review population
Otsuki 2009 [800]	Not review population
Patel 2004 [815]	Incorrect study design
Patel 2013 [814]	Incorrect interventions
Petitto 2012 [836]	Incorrect interventions
Pokladnikova 2013 [850]	Not review population

Poureslami 2012 [854]	Not review population
Prabhakaran 2010 [857]	Not review population
Put 2003 [871]	Not review population
Rasmussen 2005 [888]	Not review population
Rastogi 2013 [889]	Incorrect study design
Riekert 2011 [910]	Incorrect study design
Saini 2008 [927]	Incorrect study design
Saito 2013 [928]	Incorrect study design
Salisbury 2002 [929]	Not review population
Santos dde 2010 [931]	Not review population
Sarkar 2015 [932]	Not guideline condition.
Schatz 2012 [936]	Incorrect study design. Not review population
Schmaling 2001 [938]	Less than minimum duration
Schonberger 2004 [940]	Not review population
Schulte 2008 [941]	Incorrect study design
Schultz 2010 [942]	Conference abstract only
Schultz 2012 [943]	Incorrect study design
Segura méndez 2001 [948]	Paper not available
Seid 2012 [949]	Not review population
Shah 2011 [952]	Not review population
Shames 2004 [953]	Not review population
Sherman 2001 [961]	Incorrect study design
Slader 2007 [968]	Not review population
Smith 1986 [974]	Not review population
Smith 2004 [976]	Less than minimum duration. Not review population
Smith 2005 [972]	Not review population
Smith 2008 [975]	Not review population
Spiess 1988 [985]	Not in English
Steurer-stey 2015 [997]	Paper not available
Strandbygaard 2010 [1001]	Not review population
Takemura 2012 [1013]	Incorrect study design. Not review population
Tapp 2011 [1019]	Study protocol
Terpstra 2012 [1027]	Not review population
To 2013 [1038]	Review protocol
Tran 2014 [1043]	Included studies already identified in search
Van schayck 2002 [1064]	Not review population. Incorrect study design
Van wijk 2005 [1066]	Not guideline condition
Vasbinder 2013 [1071]	Study protocol. Not review population
Vasbinder 2016[1070]	Less than minimum duration
Vollmer 2011 [1087]	Less than minimum duration

Weinberger 2002 [1098]	Not review population
Weng 2007 [1102]	Incorrect study design
Wiecha 2015 [1109]	Less than minimum duration
Williams 2010 [1112]	Less than minimum duration
Wilson 1993 [1116]	Not review population
Wilson 2005 [1115]	Records/citations only
Wilson 2010 [1117]	Not review population
Windsor 1990 [1118]	Not review population
Wu 2014 [1123]	Not guideline condition
Yoo 2005 [1127]	Paper not available
Yorke 2006 [1129]	Not review population
Yorke 2015 [1128]	Not review population
Young 2012 [1130]	Study protocol
Zhang 2014 [1141]	Not guideline condition
Zorc 2003 [1146]	Not review population

L.6 Self-management plans

Table 93: Studies excluded from the clinical review

Study	Exclusion reason
Abdulwadud 1999[2]	Incorrect interventions
Ahmad 2011[17]	Incorrect study design
Ahmed 2011[18]	Incorrect study design
Ahmed 2011[19]	Study protocol
Allen 1995[30]	No written PAAP
Al-sheyab 2012[24]	Incorrect interventions
Altay 2013[34]	Incorrect interventions
Andrews 2014[39]	Systematic review: literature search not sufficiently rigorous
Angelini 2010[40]	Conference abstract
Anon 2000[11]	Incorrect study design
Anon 2005[3]	Incorrect study design
Anon 2005[1029]	Incorrect study design
Antoniu 2003[46]	Not relevant
Arguel 2013[55]	Study protocol
Arikan ayyildiz 2014[56]	Conference abstract
Atherton 2000[61]	Incorrect study design
Bailey 1987[76]	Incorrect study design
Bailey 1990[75]	No written PAAP
Bailey 1999[74]	Not relevant

Baptist 2011[82]	Incorrect study design
Barbanel 2003[84]	No extractable outcomes
Barlow 2004[86]	Not relevant
Bartholomew 2000[90]	Incorrect interventions
Behera 2006[107]	Incorrect study design
Berg 1997[119]	Incorrect study design
Berg 1997[119]	Not relevant
Bernard-bonnin 1995[128]	No written PAAP
Blixen 2001[150]	Incorrect study design
Blonstein 2016 [151]	Interventions not asthma specific
Bolton 1991[154]	No written PAAP. Incorrect interventions
Bowen 2013[167]	No written PAAP
Boyd 2009[171]	Incorrect study design
Bragt 2014[174]	Incorrect study design
Bramson 1996[176]	Incorrect study design
Britto 2014[179]	Not relevant
Brown 2002[181]	Incorrect interventions
Brown 2006[182]	Intervention in the control arm
Bruzzese 2001[189]	Not relevant
Bruzzese 2008[192]	Not relevant
Bunjaroonsilp 2002[197]	Not relevant
Burkhart 2007[204]	Not relevant
Butz 2005[215]	Not relevant
Butz 2005[217]	Cross-sectional analysis in ongoing trial
Cano-garcinuno 2007[223]	Not relevant
Caplin 2001[225]	Not relevant
Catov 2005[234]	Incorrect study design
Cave 2010[235]	Incorrect study design
Cevik guner 2015[238]	Incorrect study design
Charrois 2006[248]	Incorrect interventions
Chiang 2004[260]	Incorrect interventions
Chiang 2009[261]	No written PAAP
Cicutto 2005[272]	Incorrect interventions
Clark 2005[274]	Incorrect interventions
Colland 1993[278]	Incorrect interventions
Couturaud 2002[289]	No usable outcomes
De asis ma 2004[313]	Incorrect study design
Espinoza-palma 2009[377]	Action plan is not personalised to the individual patient
Evans 2015[378]	Study protocol
Fischer 2015 [388]	Not asthma specific

Fornell 2014[402]	Conference abstract
Gaalen 2013[417]	Incorrect interventions
Gabriela perez 1999[418]	Incorrect study design
Gallefoss 1999[421]	Not relevant
Gallefoss 2000[422]	No extractable outcomes
Gallefoss 2000[423]	Not relevant
Gallefoss 2001[424]	Incorrect interventions
Gebert 1998[429]	Incorrect study design
Gibson 1999[436]	Incorrect study design
Gibson 2003[437]	Incorrect study design
Guendelman 2002[457]	Not relevant
Hesselink 2004[482]	Not relevant
Holzheimer 1998[491]	Incorrect interventions
Hoskins 1996[500]	Incorrect interventions
Janson 2003[526]	Less than minimum duration
Janson 2009[527]	Less than minimum duration
Kauppinen 1997[561]	Incorrect study design
Kauppinen 1998[560]	Incorrect study design
Kauppinen 1999[562]	Incorrect interventions
Kauppinen 2001[563]	Incorrect study design. Incorrect interventions.
Kauppinen 2011[564]	All patients received a PAAP
Kotses 1995[591]	No written PAAP
Kotses 1996[592]	Incorrect study design
Kuijer 2007[598]	Not relevant
Lahdensuo 1996[608]	Not relevant
Lemaigre 2010[621]	No written PAAP
Lorig 2014[641]	Not relevant
Lucas 2001[646]	Incorrect study design
Magar 2005[652]	No relevant outcomes
Mair 2014[657]	Study protocol
Mancuso 2010[665]	No relevant outcomes
Mancuso 2011[664]	Incorrect interventions
Martynenko 2015[676]	Incorrect study design
Mcnabb 1985[696]	Not relevant
Mesters 1994[712]	Not relevant
Milenkovi 2007[716]	Incorrect interventions
Morrison 2014[731]	Not relevant
Morrison 2016[732]	Incorrect interventions
Olivera 2016[791]	No written PAAP
Persaud 1996[830]	Incorrect interventions

Pinnock 2015[848]	Incorrect study design
Powell 2003[855]	Relevant studies extracted. Incorrect interventions
Put 2003[871]	Not relevant
Ronchetti 1997[919]	Incorrect study design
Roy 2011[921]	Incorrect study design
Schermer 2002[937]	No extractable outcomes
Sommaruga 1995[980]	No extractable outcomes
Tagaya 2005[1011]	No extractable outcomes
Tagaya 2006[1010]	Incorrect study design
Taitel 1995[1012]	Incorrect study design
Tieffenberg 2000[1036]	Not relevant
Tousman 2010[1041]	Not relevant
Tousman 2011[1042]	Incorrect interventions
Van der meer 2009[1057]	Not review population. Action plan is not personalised.

L.7 Dose variation within self-management plans

Table 94: Studies excluded from the clinical review

Reference	Reason for exclusion
Aalbers 2004[1]	Inappropriate interventions
Busse 2008[213]	Inappropriate interventions
Canonica 2004[224]	Inappropriate interventions
Currie 2003[298]	Systematic review, not matching this review
Currie 2003[297]	Inappropriate interventions
FitzGerald 2005[393]	Different drugs, mixed step-up
Garrett 1998[428]	No extractable outcomes
Holzheimer 1998[490]	Inappropriate interventions
Kankaanranta 2004[557]	Systematic review, not matching this review
Keskin 2016[578]	Inappropriate interventions
Leuppi 2003[625]	Inappropriate interventions
Leuppi 2002[623]	Inappropriate interventions
Menezes 2008[711]	Inappropriate interventions
Murray 1999[743]	Inappropriate interventions
Nathan 1997[752]	Inappropriate interventions
Phillips 2004[840]	Inappropriate study design

Reference	Reason for exclusion
Quon 2010[874]	Systematic review, checked for references
Razi 2008[890]	Inappropriate interventions
Reddel 2006[891]	Systematic review, checked for references
Rees 1993[896]	Inappropriate interventions
Shapiro 1998[954]	Inappropriate interventions
Simons 2005[965]	Commentary
Thomas 2011[1031]	Commentary
van der Meer 2010[1059]	Inappropriate study design
Vondra 1999[1088]	Not in English

L.8 Decreasing regular maintenance treatment

Table 95: Studies excluded from the clinical review

Reference	Reason for exclusion
Adachi 2001[4]	No prognostic values reported
Akasawa 2009[21]	Conference abstract
Alpaydin 2011[32]	Conference abstract
Ali 2014 [26]	Conference abstract
Alpaydin 2012[33]	No prognostic values reported
Baba 2002[68]	No prognostic values reported
Berger 2010[120]	No prognostic values reported
Brozek 2012[185]	Systematic review is not relevant to review question
Cabral 2009[220]	Incorrect study design
Domingo 2011[336]	Conference abstract
Frears 1975[408]	No prognostic values reported
Gelb 2006[430]	Not relevant analysis
Godard 2008[442]	No prognostic values reported
Haahtela 1994[467]	No prognostic values reported
Hagan 2014[470]	Systematic review is not relevant to review question
Hagiwara 2010[471]	No prognostic values reported
Hawkins 2003[478]	No prognostic values reported
Hojo 2012[487]	No prognostic values reported

Reference	Reason for exclusion
Honkoop 2015 [493]	Not relevant analysis
Juniper 1991[550]	No prognostic values reported
Kersten 2010[572]	No prognostic values reported
Kew 2015[580]	Systematic review - no included studies
Knox 2007[586]	No prognostic values reported
Kuna 2003[601]	No relevant prognostic values reported
Leuppi 2001[624]	Unadjusted data
Martinez 2011[675]	Incorrect intervention
Malerba 2012[658]	No prognostic values reported
Malinovschi 2014[659]	Conference abstract
Matsuda 1999[684]	No usable outcome
Murphy 2015[741]	Conference abstract
Obase 2013[786]	No prognostic values reported
O'Hogan 2012[774]	Not relevant analysis
Papi 2007[805]	Incorrect intervention
Papi 2012[809]	No prognostic values reported
Peirsman 2014[828]	Not relevant analysis
Perera2005 [829]	No prognostic values reported
Petsky 2014 [838]	Not relevant analysis
Phuong 2011[842]	Conference abstract
Pijnenburg 2005 [845]	Not relevant analysis
Pijnenburg 2005[846]	Not relevant analysis
Prieto 2003[868]	Unadjusted data
Rank 2015[886]	Conference abstract
Rank 2016[887]	No prognostic values reported
Reddel 2010[893]	No prognostic values reported
Reshetnikova 2010[902]	Conference abstract
Riccionni 2005[904]	No prognostic values reported
Self 1998[950]	No prognostic values reported
Shaw 2007[958]	Not relevant analysis
Smith 2005[970]	Not relevant analysis

Reference	Reason for exclusion
Syk 2013[1007]	Not relevant analysis
Tsurikisawa 2010[1045]	No useable outcome
Tsuzuki 2013[1046]	Conference abstract
Verini 2010[1076]	Not relevant analysis
Zaremba 2010[1136]	Conference abstract

L.9 Breathing exercises in addition to pharmacological treatment

Table 96: Studies excluded from the clinical review

Study	Exclusion reason
Agnihotri 2013[12]	Conference abstract
Agnihotri 2014[13]	No outcomes of interest
Anon 2013[275]	Commentary
Bidwell 2012[134]	Less than minimum duration
Bowler 1998[168]	Less than minimum duration
Bowler 1999[169]	Less than minimum duration
Cabradilla 2011[219]	Conference abstract
Carvalho 2014[229]	Conference abstract
Ceugniet 1996[237]	Less than minimum duration
Charrois 2006[248]	Incorrect interventions
Chiang 2009[261]	Less than minimum duration
Cooper 2003[261]	Incorrect interventions.
Cowie 2002[291]	Incorrect interventions.
Cowie 2008 [1072]	Incorrect interventions (head-to-head trial)
Cramer 2014[292]	Systematic review - references checked
Del Giacco 2016[318]	Commentary
Evaristo 2014[380]	Protocol
Fluge 1994[398]	Not in English
Freitas 2013[410]	Systematic review - references checked
Gimenez 2011[438]	Non-systematic review
Girodo 1992[441]	No relevant outcomes of interest
Holloway 2009[488]	Systematic review – references checked
Huntley 2002[506]	Less than minimum duration
Jain 1991[523]	Not an RCT
Khare 1991[584]	Not an RCT
Kligler 2011[584]	Incorrect interventions
Lima 2008[633]	Less than minimum duration
Lowhagen 2014[643]	Less than minimum duration
Manocha 2002[666]	Less than minimum duration
Martin 1999[671]	Commentary

Study	Exclusion reason
Mccall 2013[687]	Systematic review
Mchugh 2003[692]	Conference abstract
Mendes 2010[708]	Less than minimum duration. Incorrect interventions
Mendes 2011[707]	Less than minimum duration. Incorrect interventions
Mendonca 2013[709]	Conference abstract
Nagarathna 1985 [966]	No outcomes of interest
Opat 2000[793]	Less than minimum duration
Prem 2013[859]	Less than minimum duration
Ritz 2014[916]	Incorrect interventions. Not an RCT
Sabina 2005[926]	Less than minimum duration
Saxena 2009[934]	Less than minimum duration
Shaw 2011[957]	Less than minimum duration
Singh 2012[966]	Less than minimum duration
Sodhi 2009[978]	Less than minimum duration
Sodhi 2014[977]	Less than minimum duration
Soni 2011[981]	Conference abstract
Tanu 2011[1018]	Conference abstract
Varray 1995[1069]	Less than minimum duration. Incorrect interventions
Vedanthan 1998[1072]	Less than minimum duration
Vempati 2009[1073]	Less than minimum duration
Venugopal 2012[1074]	Conference abstract

L.10 Managing patients in relation to risk of poor outcomes

None.

Appendix M: Excluded health economic studies

M.1 Treatment in patients not on regular preventers

None.

M.2 Choice of first-line preventer in patients with poor asthma control

None.

M.3 Escalating pharmacological treatment in patients poorly controlled on first-line preventer treatment

M.3.1 Second-line preventer

Table 97: Studies excluded from the health economic review

Reference	Reason for exclusion
Doull 2007 [339]	This study was assessed as partially applicable with very serious limitations due to clinical outcomes being based on unpublished clinical trial data not included in the clinical review.

M.3.2 ICS + LABA preventer and reliever therapy versus ICS + LABA as preventer therapy and SABA as reliever therapy

Table 98: Studies excluded from the health economic review

Reference	Reason for exclusion
Bruggenjurgen 2010[187]	This study was assessed as not applicable as the comparison focused on combination inhaler versus two single inhalers.
Goossens 2009[446]	This study was assessed as not applicable as individuals did not necessarily receive a LABA in the comparison arm.
Lundborg[648]	This study was assessed as not applicable as the clinical evidence the analysis was built on (Kuna 2010[602]) was excluded from the clinical review.
Miller 2008[719]	This study was assessed as not applicable as the clinical evidence the analysis was built on [602] was excluded from the clinical review.
Price 2007[866]	This study was assessed as not applicable as the clinical evidence the analysis was built on [602] was excluded from the clinical review.
Tamminen 2008[1016]	This study was assessed as not applicable as the clinical evidence the analysis was built on[194] was excluded from the clinical review.

M.3.3 Inadequate control with optimal preventer therapy beyond low dose ICS

None.

M.4 Intermittent versus daily ICS with seasonal or trigger specific symptoms

None.

M.5 Improving adherence to treatment

None.

M.6 Self-management plans

Table 99: Studies excluded from the health economic review

Reference	Reason for exclusion
Gallefoss 2001 [424]	Selectively excluded as comparative costing only in the presence of cost utility economic evaluations. Resource use and cost from 1994.
Van der Meer 2011 [1058]	Wrong intervention. Internet based using algorithm to create PAAP.

M.7 Dose variation within self-management plans

None.

M.8 Decreasing regular maintenance treatment

Table 100: Studies excluded from the economic review

Reference	Reason for exclusion
Paggiaro 2013 [804]	No prognostic values reported

M.9 Breathing exercises in addition to pharmacological treatment

None.

M.10 Managing patients in relation to risk of poor outcomes

None.

Appendix N: Cost-effectiveness analysis for second line preventers

N.1 Introduction

This analysis will focus on the cost effectiveness of second-line preventers for adults over 16 years of age, whose asthma has remained uncontrolled using routine low dose inhaled corticosteroids (ICSs) and short acting beta agonists (SABAs) for symptom relief. Although studies have attempted to evaluate the cost effectiveness of such asthma therapies,[545 ,1114] these have been based on single trials and have not involved more than two comparators. This analysis will use data gathered from systematic reviews and will use the most up-to-date costs which incorporate the movement to dual inhalers and the expiration of the patent on leukotriene receptor antagonists (LTRAs). The committee prioritised this area for original health economic modelling because this constitutes a large spend of the NHS budget. 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 was too low in quality.

N.2 Methods

N.2.1 Model overview

N.2.1.1 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.

N.2.1.2 Comparators

The clinical review systematically searched for evidence on all possible treatment options available for individuals at this step. These included:

A) Continue to use SABAs for short-term symptom relief and:

1. Continue on ‘low dose’ ICS (do nothing approach)
2. Increase ICS dose to ‘moderate dose’
3. Increase ICS dose to ‘high dose’
4. Replace ‘low dose’ ICS with a long acting beta agonist (LABA)
5. Replace ‘low dose’ ICS with a leukotriene receptor antagonist (LTRA)
6. Replace ‘low dose’ ICS with theophylline or aminophylline
7. Replace ‘low dose’ ICS with cromolyns

B) Continue to use ‘low dose’ ICS and SABAs for symptom relief and:

8. Add a long acting beta agonist (LABA)
9. Add a leukotriene receptor antagonist (LTRA)
10. Add theophylline or aminophylline
11. Add cromolyns

C) Continue to use ‘low’ dose ICS combined with:

12. LABA (formoterol) for maintenance and reliever therapy (MART)

The clinical review found evidence on exacerbations and/ or quality of life for the relevant population for the following comparisons:

- A1 (low dose ICS) versus A3 (high dose ICS)
- A1 (low dose ICS) versus B8 (low dose ICS + LABA)
- A1 (low dose ICS) versus B10(low dose ICS + theophylline)
- A2 (moderate dose ICS) versus B8 (low dose ICS + LABA)
- A3 (high dose ICS) versus B10 (low dose ICS + theophylline)
- B8 (low dose ICS + LABA) versus B9 (low dose ICS + LTRA)

The committee felt that for the purpose of the economic model the clinical-effectiveness data sufficient to make recommendations were only obtainable for the following comparisons:

- A1 (low dose ICS) versus B8 (low dose ICS + LABA)
- A2 (moderate dose ICS) versus B8 (low dose ICS + LABA)
- B8 (low dose ICS + LABA) versus B9 (low dose ICS + LTRA)

Data on the other comparisons excluded from the list above (A1 versus A3, A1 versus B10 and A3 versus B10) came from one study by Lim et al.[632] The committee noted the short length of time the study was conducted (6 months) alongside the small number of individuals included in the study (approximately 50 in each arm), the high risk of bias and the fact that no quality of life outcomes were measured. For these reasons the committee decided not to use the study in the model and those comparisons were removed.

Therefore, the four comparisons under consideration for this analysis are:

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 a decision was then made whether the cost effectiveness of other treatment options could be inferred from the results based on these four comparisons.

N.2.1.3 Time horizon, perspective, discount rate used

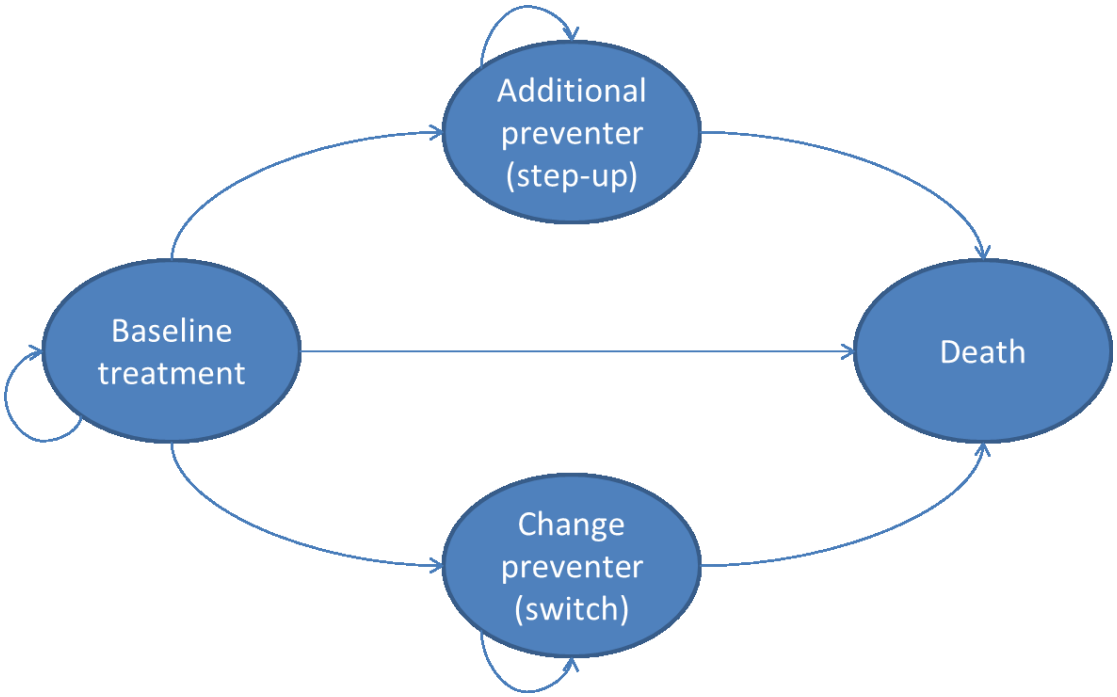
The analysis followed the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects. A sensitivity analysis using a discount rate of 1.5% for costs and health effects was conducted. A lifetime time horizon was adopted and a 10-year time horizon was looked 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 are crucial in determining the cost effectiveness. The analysis was undertaken using an NHS/PSS perspective.

N.2.2 Approach to modelling

N.2.2.1 Model structure

N.2.2.2

Figure 409: Markov 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 then if their asthma remains uncontrolled they will always have an additional preventer added (step-up) as opposed to having their ICS inhaler replaced (switch). 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 and exacerbation rates, 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 can be found in section N.2.3.4. 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 given in section N.2.3.3.

Costs attached to each state

The costs experienced in each state mainly correspond to the treatment the individual is receiving as detailed in section N.2.3.6, therefore if a patient experiences a step-up or switch they move to the corresponding health state where the cost takes into account the new management 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 section N.2.3.7.

N.2.2.3 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean quality-adjusted life-years (QALYs) were calculated using these values. The model was run repeatedly – 10,000 times for the base case and each sensitivity analysis.

The way in which distributions are defined reflects the nature of the data, for example probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a probability will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 101 and in the relevant input summary table in section N.2.3.1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 101: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Utilities	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $mean^2 \times [(1-mean)/SE^2] - mean$ Beta = Alpha×[(1−mean)/mean]
Reliever medication use, rate ratios, risk ratios	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: Alpha = $(mean/SE)^2$ Beta = $SE^2/Mean$
Duration of exacerbation, NHS Reference Costs, rate ratios, risk ratios	Lognormal	Where appropriate, the lognormal distribution may provide a better fit than the gamma distribution. The natural log of the mean was calculated as follows: Mean = ln(mean cost) − SE2/2 Where the natural log of the standard error was calculated by: SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2)

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

- the cost-effectiveness threshold (which was deemed to be fixed by NICE)

- cost of staff required to implement each strategy (assumed to be fixed according to national pay scales and programme content)
- cost of medication.

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

N.2.3 Model inputs

N.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 102 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 102: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Population characteristics				
Proportion Male : Female	0.4 : 0.6	Deterministic		Clinical review
Starting age	44	Deterministic		Clinical review
Probability death	This value changes over time to reflect increasing mortality with age.			England and Wales ONS Life Tables
Rate of asthma deaths for individuals on step 3 asthma treatment per 100 person years	0.05			De Vries 2010
Costs (£)				
Low-dose ICS + LABA (per year if taken as indicated)	£208.55	Drug costs were kept deterministic in the base case as there is no indication as to how these may change. The impact of drug costs was explored in a sensitivity analysis. A full breakdown of how these costs were derived can be found in Appendix O.		Drug Tariff Oct 2016, BNF Oct 2016, PCA 2016 See section N.2.3.6
LTRA (per year if taken as indicated)	£28.85			
Low-dose ICS (per year if taken as indicated)	£57.34			
Moderate-dose ICS (per year if taken as indicated)	£135.80			
Moderate-dose ICS + LABA (per year if taken as indicated)	£399.69			
SABA (per puff)	£0.02			
Hospitalised exacerbation	£871.36	Lognormal	Meanlog=6.42 Sdlog=0.83	NHS reference cost
Non-hospitalised exacerbation	£75.33	Lognormal	Meanlog=4.32 Sdlog=0.18	Expert opinion, PSSRU, BNF July 2016
Non-exacerbation related healthcare costs (LABA)	£51	See section N.2.3.7 for more details		Price 2011[861]

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
NHS activity costs (LTRA, low dose ICS, moderate dose ICS)	£64	See section N.2.3.7 for more details		Price 2011[861], assumption
Adherence and treatment switching				
Mean % prescriptions picked up (LTRA)	59.3%	Uncertainty explored in a deterministic sensitivity analysis		Price 2011[861]
Mean % prescriptions picked up (ICS – single inhaler)	62.4%			Price 2011[861]
Mean % prescriptions picked up (ICS/LTRA – dual inhaler)	60.2%			Price 2011[861]
Probability of changing to LABA preventer after 2 years (for those starting on LTRA)	25.39% (14.76% replace LTRA with LABA) (10.63% add a LABA)	See section N.2.3.6 for more details		Price 2011[861] Price 2011[861]
Probability of adding a LABA preventer after 2 years (for those starting on low dose or moderate dose ICS)	12.7% (0% replace ICS with LABA) (12.7% add a LABA)			Assumption
Utilities				
Average utility	0.8	Deterministic		Price 2011[861]
Quality of life decrease for those starting on low dose ICS + LTRA	0.006	See section N.2.3.4 for more details		Price 2011[861]
Quality of life decrease from a hospitalised exacerbation	0.57	Beta	Alpha=0.15 Beta=0.30	Llyod et al[640]
Quality of life decrease from a non-hospitalised exacerbation	0.33	Beta	Alpha=0.51 Beta=0.38	Llyod et al[640]
Duration hospitalised exacerbation (years)	0.077 (~4 weeks)	Lognormal	Meanlog=-2.57 Sdlog=0.26	Expert opinion
Duration non-hospitalised exacerbation (years)	0.038 (~2 weeks)	Lognormal	Meanlog=-3.26 Sdlog=0.42	Expert opinion
Clinical effectiveness of treatments				
Yearly exacerbation rate (low dose ICS + LABA)	0.305	Gamma	Alpha=0.35 Lambda=0.57	Price 2011[861]
Exacerbation rate ratio (low dose ICS+LTRA versus low dose ICS+LABA)	1.13	Lognormal	Meanlog=0.12 Sdlog=0.07	Bjermer 2003[144]
Exacerbation rate ratio (low dose ICS versus low dose ICS+LABA)	2.08	Lognormal	Meanlog=-0.74 Sdlog=0.11	O'Bryne 2001[776]

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Exacerbation rate ratio (moderate dose ICS versus low dose ICS+LABA)	1.21	Lognormal	Meanlog=0.16 Sdlog=0.29	Greening 1994
Yearly hospitalisation rate (low dose ICS + LABA)	0.01	Gamma	Alpha=49 Lambda=3,500	Price 2011[861]
Hospitalisation rate ratio (low dose ICS + LABA versus low dose ICS + LTRA)	0.83	Lognormal	Meanlog=-0.43 Sdlog=0.71	Price 2011[861]
Hospitalisation rate ratio (low dose ICS + LABA versus low dose ICS)	7.23	Lognormal	Meanlog=1.98 Sdlog=0.06	O'Bryne 2001
Hospitalisation rate ratio- (low dose ICS + LABA versus moderate dose ICS)	1	Deterministic		Assumption
SABA use difference, puffs per day (low dose ICS + LABA versus low dose ICS + LTRA)	0.52	Normal	Mean = 0.52 SE = 0.08	Ilowite 2004[513]
SABA use difference, puffs per day (low dose ICS + LABA versus low dose ICS + moderate dose)	0.20	Normal	Mean = 0.21 SE = 0.21	Greening 1994
SABA use difference, puffs per day (low dose ICS + LABA versus low dose ICS)	0.48	Normal	Mean = 0.48 SE = 0.17	O'Byrne 2001
Additional modelling parameters				
Discount rate (cost and effects)	0.035 (3.5% as per the NICE reference case)			
Cycle length (years)	0.083 (1 month)			

Abbreviations: ICS: low-dose inhaled corticosteroids; LABA: long-acting beta-agonist; LTRA: leukotriene receptor agonist; SABA: short-acting beta-agonist; SE: standard error

N.2.3.2 Baseline mortality risk

The average starting age, along with the proportion of individuals who are male was informed by the clinical review. The only impacts these factors have are on all-cause mortality and the length of time the model runs when adopting a lifetime horizon.

All-cause mortality risk was accounted for by using the life tables for Wales and England. Asthma-related mortality risk was accounted for using data taken from De Vries 2010, in particular the asthma-related mortality risk for people on ICS + LABA. It was assumed there were no mortality differences between treatments so this mortality effect was applied equally to all treatments. The rate of asthma-related deaths in individuals on step 3 treatment was found to be 0.05 per 100 person years. This value was added onto the all-cause mortality rate from the Wales and England life tables and then turned into a monthly probability.

N.2.3.3 Relative treatment effects

Exacerbations

One of the main outcomes reported by the clinical review was the impact treatments have on the probability of a person exacerbating. Most studies report a risk ratio that captures the impact the

treatment has on preventing the individual from exacerbating. This statistic therefore only captures the impact of preventing an exacerbation from occurring rather than capturing the impact on the total number of exacerbations. The committee felt that having an exacerbation was likely to alter the probability of the individual having another exacerbation. To take this into account for the economic model it was important to capture the impact a treatment has on total exacerbation numbers as every exacerbations has a cost and quality of life impact.

There are some limitations with this approach. Firstly, if a single individual who was very prone to exacerbations, regardless of treatment, was randomised to one arm then they may have many exacerbations that could skew the results. This issue may be a problem in smaller studies with few people however is less of an issue in large studies where randomisation of such a large number would allow these 'at risk' individuals to be equally distributed amongst both arms.

Secondly it has to be assumed that any impact an exacerbation has on the probability of having a further exacerbation is captured within the follow-up period of the trials. The committee felt that the impact an exacerbation has on future exacerbations would likely be captured within a six-month time frame at a minimum, however ideally a one-year time frame would be needed due to seasonal impacts.

Low dose ICS + LABA was the only comparator that appeared in all the studies collected in the review. Therefore this allowed indirect comparisons between treatments where no direct evidence was available.

A sensitivity analysis was run whereby it was assumed having an exacerbation has no impact on the probability of having a future exacerbation. Therefore this assumption allows the use of risk ratios as reported in the clinical review.

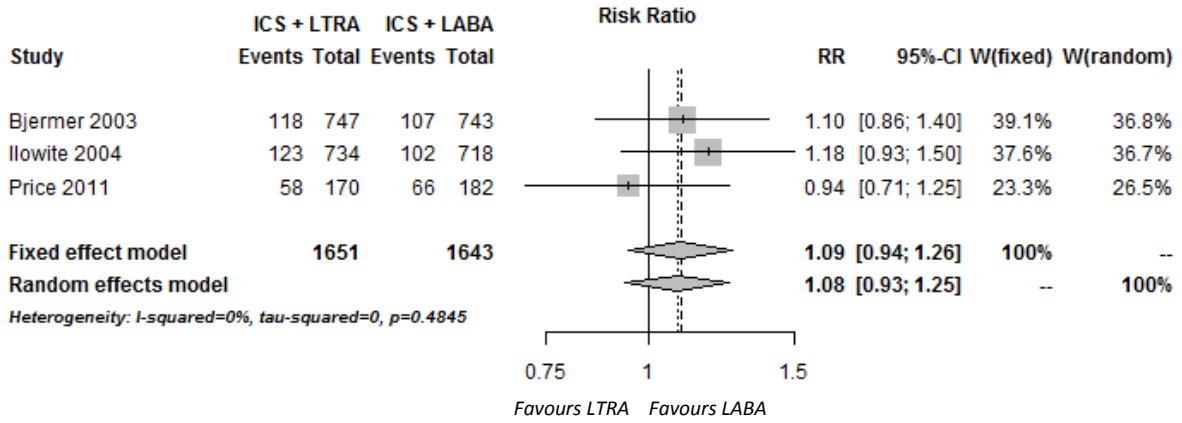
Low dose ICS + LABA

As low dose ICS + LABA was the only common comparison across all studies the exacerbation rate for low dose ICS + LABA was used as a baseline and then a rate ratio was applied to this figure for each comparison. The exacerbation rate for low dose ICS + LABA was available from five studies identified in the clinical review. However, for the model only the value reported in the study by Price et al. was used in the base case. This was done for several reasons. Firstly, the studies by O'Byrne et al., Bjermer et al. and Ilowite et al. used a broader definition for exacerbation than that adopted in the guideline. This means the exacerbation rate, defined in this guideline as the need for oral steroids, will be overestimated in these studies. Secondly, the study by Greening was only across 6 months as opposed to Price et al.'s 2 years and therefore less likely to capture the impact that an initial exacerbation has on future exacerbations. Therefore in the model the annual average rate of exacerbations for those taking low dose ICS + LABA was 0.305 per patient per year. Although Price et al. was a pragmatic study that allowed treatment switching, no individuals who started on LABA switched medication therefore this exacerbation rate represents entirely the population receiving low dose ICS + LABA.

Low dose ICS + LABA vs low dose ICS + LTRA

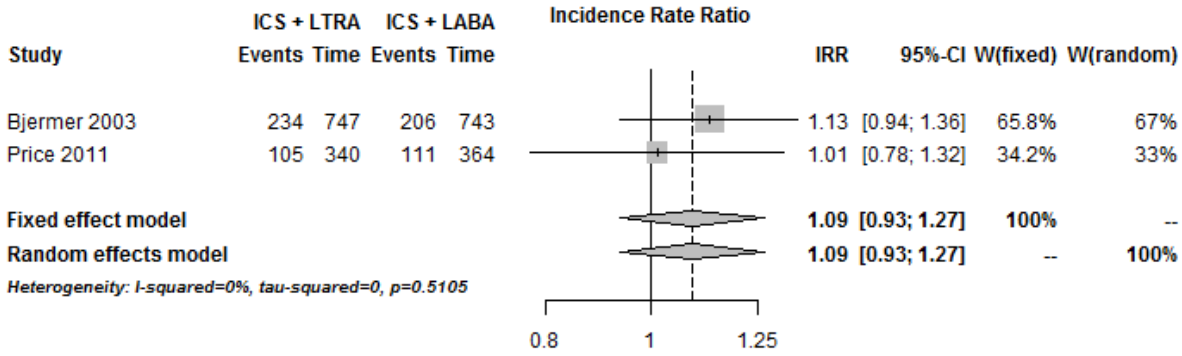
Figure 410 below shows the meta-analysis of the risk ratio for preventing an exacerbation from occurring when comparing low dose ICS+ LTRA and low dose ICS + LABA.

Figure 410: Meta-analysed risk ratio for exacerbations (low dose ICS + LTRA versus low dose ICS + LABA)



The clinical data show that the risk of exacerbating is slightly higher for those taking LTRAs with low dose ICS rather than LABAs with low dose ICS, albeit statistically non-significant. These data are based on the number of patients experiencing exacerbations as opposed to the total number of exacerbations among the cohorts. Only two of the three studies included in the clinical review above reported the total number of exacerbations that occurred in both arms. Therefore, only these studies could be used to calculate a meta-analysed rate-ratio. Figure 411 below shows the meta-analysis of the incidence rate ratio between the two treatment arms.

Figure 411: Meta-analysed rate ratio for exacerbations (low dose ICS + LTRA versus low dose ICS + LABA)



The meta-analysis in Figure 411 shows that ICS+LABAs have a slight, non-statistically significant, impact on reducing total exacerbations relative to ICS+LTRA. Whereas Figure 410 represents the difference in people who had an exacerbation, Figure 411 shows the difference in total exacerbations. For example although fewer people starting on ICS+LTRA in the Price et al. study had an exacerbation when compared to ICS+LABA (shown by a risk ratio <1); those who did exacerbate, exacerbated more frequently (shown by a rate ratio >1). However both meta-analysed results show similar effect sizes in the same direction.

One limitation with the data provided by Bjermer used in Figure 411 is that exacerbation was defined as the need for oral steroids or the need for an unscheduled medical visit; this is therefore inconsistent with the rest of the guideline's definition as just the need for oral steroids. It therefore has to be assumed that the rate ratio is the same for the difference between all exacerbations and exacerbations resulting in oral steroids.

The committee noted that in the study by Price et al. individuals were allowed to switch medications. Therefore as some individuals ended up on ICS+LABA in the LTRA arm this could reduce the rate ratio. This may explain why it is slightly lower than that of other studies. As treatment switching was built into the model two scenarios were considered:

1. In the basecase those who remain on ICS + LTRA have an exacerbation rate as described in Bjermer 2003 applied to the ICS+LABA exacerbation rate. Those who switch to LABA have no rate ratio adjusted to the ICS+LABA exacerbation rate.
2. In a sensitivity analysis, the exacerbation rate ratio calculated from Price et al. would be used for the entire cohort of people starting on LTRA regardless of whether they have switched to LABA or not. This is because the impact treatment switching may have on exacerbations will have been captured in this rate ratio.

In the basecase using this method could bias the model in favour of ICS + LABA as those who do not respond well to LTRA are likely to have a higher than average exacerbation rate relative to the rest of the cohort starting on LTRAs. Therefore when we remove these people from the cohort and place them on LABAs then one would expect the average exacerbation of those who remain in the LTRA cohort to drop. The importance of this bias was therefore tested by employing scenario 2.

As Ilowite et al. did not report total exacerbations it could not be used in the model. However Figure 410 shows that the results of Ilowite et al. are largely consistent with those of Bjermer et al. and Price et al., highlighted by a 0% I-squared term signifying minimal heterogeneity between the studies. Therefore its exclusion should not impact the results. Another sensitivity analysis conducted increased the exacerbation rates of LTRAs by using the upper limit calculated in the 95% confidence interval in Figure 411.

Low dose ICS + LABA versus low dose ICS

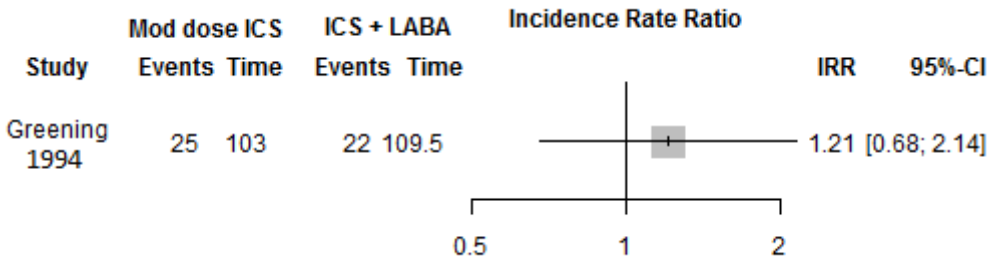
Only one study from O'Bryne et al. was identified that compared low-dose ICS + LABA to low-dose ICS. This study found that adding a LABA to low dose ICS reduced the rate of severe exacerbations by 52% (rate ratio = 0.48, 95% CI = 0.39 to 0.59). However one limitation with this data is that severe exacerbation was defined as the need for oral steroids or a decrease in morning PEF >25% from baseline; this is inconsistent with the rest of the guideline's definition as just the need for oral steroids. Therefore again it has to be assumed that the rate ratio is the same for the difference between all exacerbations as well as the exacerbations resulting in oral steroids. As treatment switching can occur in those who start on only a low dose ICS inhaler it was assumed that those who switch to low dose ICS+LABA will have the same exacerbation rate as those in the LABA arm. Those who do no switch retain the same exacerbation rate. As discussed above this will introduce a potential bias whereby those who do not switch will likely have a lower exacerbation rate.

Low dose ICS + LABA versus moderate dose ICS

Only one study was identified that compared low-dose ICS + LABA to moderate-dose ICS. In this study, across 6 months, 37 exacerbations occurred in the low-dose ICS + LABA arm across 220 people and 25 exacerbations occurred in the moderate dose ICS arm across 206 people. However the committee noted that 15 of the 37 exacerbations that occurred in the LABA arm came from one individual. This extremely high rate of exacerbations in one individual was concerning and therefore these exacerbations were excluded from the rate calculation as they were likely not treatment related. Therefore across 6 months the rate of exacerbations for those taking low-dose ICS + LABA was 0.10 and for moderate-dose ICS the rate was 0.12. The rate ratio was calculated by:

$$Rate\ ratio = \left(\frac{events_a}{participant\ years_a}\right) \div \left(\frac{events_b}{participant\ years_b}\right)$$

$$Rate\ ratio = \left(\frac{25}{206 * 0.5}\right) \div \left(\frac{22}{219 * 0.5}\right) = 1.21$$



As treatment switching can occur in those who start on only a moderate dose ICS inhaler it was assumed that those who switch to moderate dose ICS+LABA will have the same exacerbation rate as those in the LABA arm. Those who do no switch retain the same exacerbation rate. One limitation with this is that no data were found on moderate dose ICS + LABA and this may be of higher efficacy than low dose ICS + LABA; this limitation was explored in a sensitivity analysis.

Incorporating hospitalisation

If an exacerbation is hospitalised then the costs and quality of life impact will be significantly different. Therefore it was important to capture the differences in hospitalisations across treatments.

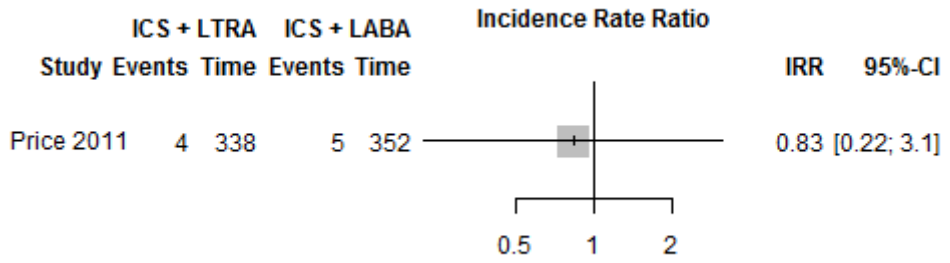
Rate of hospitalisation for those ICS + LABA

The rate of hospitalisations for individuals taking ICS+LABA was taken from Price et al. This was the only study that reported total number of hospital visits as opposed to number of people who were hospitalised. As with exacerbations a rate ratio was applied to this value to represent the differences in hospitalisations across comparisons.

Rate of hospitalisation for those ICS + LTRA

The rate of hospitalisations for those taking ICS+LTRA was calculated by applying a rate ratio to the hospitalisation rate calculated for ICS + LABA.

Figure 412: Hospitalisation rate ratio (ICS + LTRA versus ICS + LABA)



This shows that the difference in hospitalisation rates is highly uncertain, this is driven by the small numbers of hospitalisations that occur relative to the size of trial's cohort.

Rate of hospitalisation for those taking low dose ICS

The study by Jonsson et al. 2002, which is based on data from the O'Byrne study, reports the number of patients that were hospitalised but also reports the number of days spent in hospital.

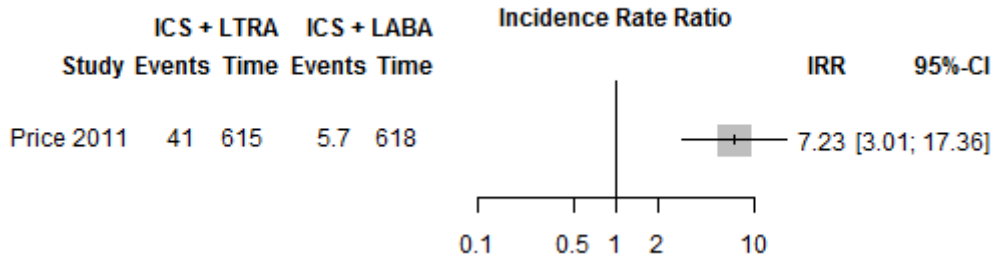
Table 103: Hospitalisation data from Jonsson (2002)

Parameter	Low dose ICS (n=615)	ICS + LABA (n=618)
Patients hospitalised (Nh)	9	5
Number of days spent in hospital (Dh)	123	17
Average days spent in hospital per patient hospitalised (Md = Dh/Nh)	13.67	3.4
Hospitalisation rate, assuming an average length of stay (LoS) of 3 days. (Md/LoS * Nh)	41	5.7

Source: Jonsson et al.

There are two potential reasons for the large disparity between the average days spent in hospital. One reason is that the exacerbations occurring in the low dose ICS arm could be of higher severity. However a more likely reason is that the individuals who are hospitalised are being hospitalised more than once. If we assume the average length of stay for an individual with asthma is 3 days then there are 41 individual hospital events for those taking low dose and 5.7 for those taking ICS + LABA. It is worth noting in the NHS reference costs that 60% of non-elective visits for asthma are short stay, defined as less than a 2-day stay. Although an average length of stay of 3 days is a very plausible value this is also explored in a sensitivity analysis. The resulting estimated incidence rate ratio for low dose ICS vs ICS+LABA is shown in Figure 413 below.

Figure 413: Hospitalisation incidence rate ratio (Low dose ICS versus low dose ICS + LABA)



Low dose ICS + LABA versus moderate dose ICS

It was assumed that those taking moderate dose ICS would have the same proportion of hospitalisations as those taking ICS+LABAs. In the study by Greening only one hospitalised exacerbation occurred in the trial and although this was experienced by an individual taking ICS + LABA it was felt this was not sufficient to draw any conclusions from given the 6 month trial length.

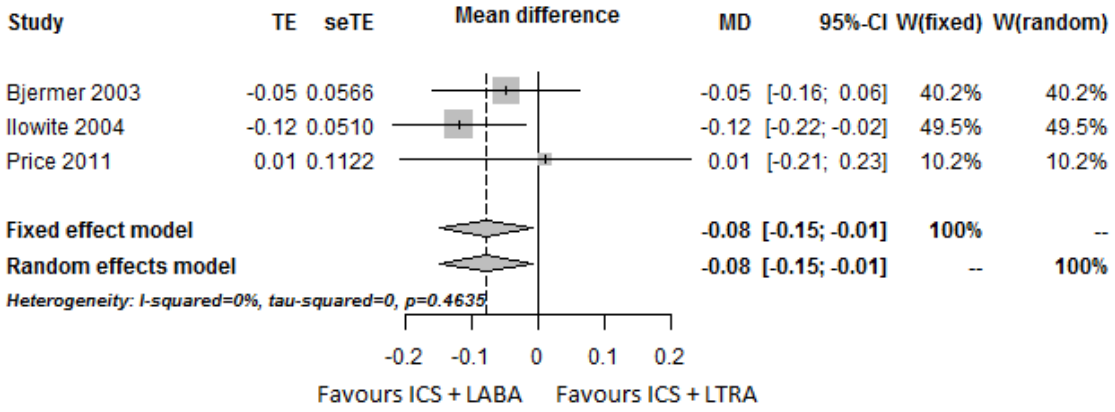
N.2.3.4 Utilities

Low dose ICS + LABA versus low dose ICS + LTRA

Of the three studies identified in the clinical review comparing ICS+LTRA to ICS+LABA only one measured quality of life using EQ-5D and valued this using the UK tariff as per the NICE reference case. This study showed that those taking ICS+LTRA experienced a small improvement in quality of

life of 0.001 at 2 years, however at 2 months those taking ICS+LABA had a higher quality of life by 0.006. As the trial was pragmatic and individuals were able to switch medication it was noted at the end of the trial 25% of individuals starting on LTRA had switched to LABA. Therefore, the small quality of life difference at 2 months may reflect the sub-optimal management for the individuals not responding to LTRAs. All other studies reported quality using asthma specific questionnaires as shown below.

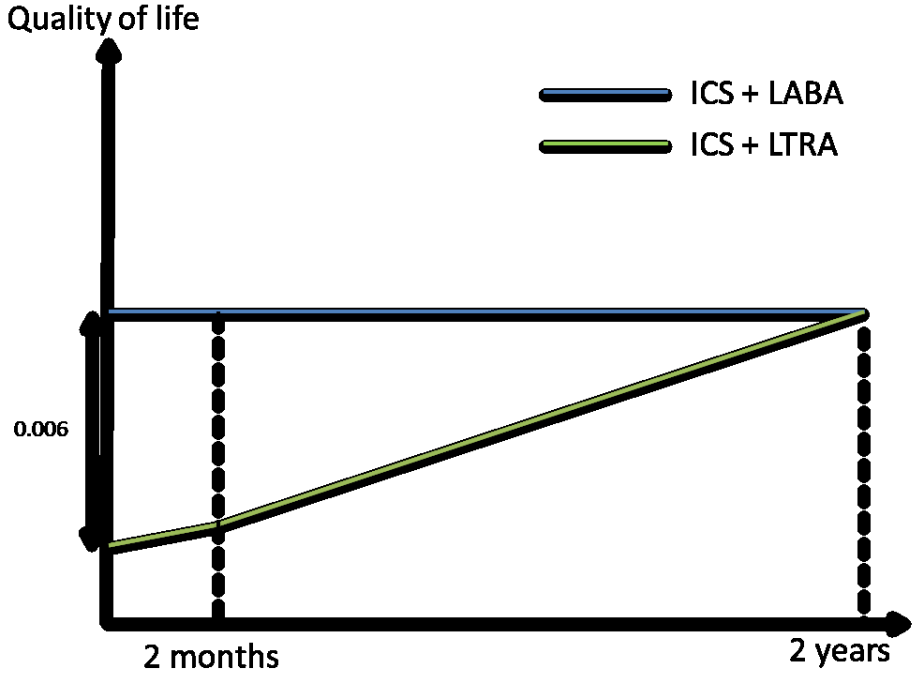
Figure 414: Quality of life (AQLQ/miniAQLQ, 1–7, higher is better outcome)



Source/Note: *TE: treatment effect, seTE: standard error of the treatment effect*

Looking at the asthma-specific quality of life data the differences between interventions do not cross the minimally important difference threshold (0.5) even at the highest end of the 95% confidence interval. However the committee felt it would be appropriate to incorporate this small potential quality of life difference into the model. In the model it was assumed there would be a disutility for those starting on ICS+LTRA, which gradually decreased to reach no disutility at 2 years. This reflects the potential quality of life impairment for individuals in the trial who did not respond to LTRAs straight away and eventually switched to LABAs. At two years it is assumed there is no quality of life difference between the two treatments as those who did not respond to LTRAs would have switched to a LABA. This appears to be in line with quality of life data in Price et al.

Figure 415: Changes in quality of life over time for those starting on ICS+LABA and ICS+LTRA



As shown in Figure 415 the quality of life difference between the two treatments was assumed to be 0.006 until 2 months, as per the Price study, and then decrease linearly with time until the difference reaches zero at two years, whereby it is assumed there is no quality of life difference between the two treatments. It was noted at this point that everyone who needed to switch treatments would have likely done so already. It is also worth noting that this graph focuses on incremental differences. Although both treatments may increase quality of life from the baseline this graph focuses on how the differences in quality of life between the two treatments changes over time.

In the base case the disutility associated with treatment switching was not applied to those starting on moderate or low dose ICS as no evidence was collected to attach a value to. This assumption biases against the use LTRAs and was therefore explored in a sensitivity analysis.

Low dose ICS + LABA versus low dose ICS

In the one study by O'Bryne et al. comparing ICS+LABA to low dose ICS there was no evidence captured on quality of life using validated quality of life questionnaires. An assumption was made that there was no quality of life difference between low dose ICS and low dose ICS + LABA. The committee recognised this was a very conservative assumption and that there would be quality of life benefits by adding an additional preventer.

Low dose ICS + LABA versus moderate dose ICS

No data was found concerning quality of life for the moderate dose ICS comparison. Therefore, an assumption was made that the quality of life for those taking moderate dose ICS would be the same as those taking ICS+LABA. As with the low-dose ICS comparison this assumption is likely to bias in favour of moderate dose ICS.

Baseline utility for all treatments

As the disutility applied to treatments is not dependent on the baseline utility a value of 0.8 was applied to each treatment and then adjusted for disutilities. This value does not impact the incremental analysis, for example if a baseline utility of 0.5 was used the difference in utility for the

first two years for LTRA versus LABA, as expressed above, remains 0.006. The 0.8 value chosen was in line with the baseline utilities shown in Price et al.

N.2.3.5 Disutility from exacerbating

One concern with using EQ-5D in asthma trials is that it is unlikely to capture the short term impacts on quality of life that occur when the individual experiences an exacerbation. To account for the disutility associated with exacerbating, a systematic search of the quality of life literature was conducted. This search identified one study by Lloyd et al. that measured EQ-5D in a cohort of people with asthma over four weeks. The study was able to measure the quality of life of an individual who had experienced an exacerbation within these four weeks as well as those whose exacerbation was hospitalised. To calculate the full disutility an assumption had to be made concerning how long the reduction in utility from exacerbating lasts for. A further assumption being that an individual returns to pre-exacerbation quality of life.

Table 104: Disutility a patient experiences with an exacerbation

Severity of exacerbation	Quality of life (QoL) decrease during exacerbation†	Duration of exacerbation in years‡	(QoL decrease)*duration = Disutility
Hospitalised	0.56	0.077 (4 weeks)	0.043
Non-hospitalised	0.32	0.038 (2 weeks)	0.012

†Source: Lloyd et al.
‡Source: Committee opinion

One limitation with the values presented by Lloyd et al. is that they may reflect that those who exacerbate have a lower general quality of life than those who do not exacerbate. Therefore the reduction in quality of life may not be as severe if they have a lower baseline quality of life to begin with. This issue was explored in a sensitivity analysis along with varying the duration of exacerbations as this was estimated from expert consensus.

N.2.3.6 Drug costs

To cost a class of medication, firstly of all the various brands of medication that are currently being prescribed for that class were identified. Different brands have different costs so to find the average cost of prescribing a drug within a certain class we needed to find out how much a certain brand is prescribed over the other. Once this was established, a weighted cost was calculated by giving more weight to brands that are more commonly prescribed. The prescription cost analysis was used to identify the proportion of brands prescribed for a given class. The NHS drug tariff along with the BNF and expert consensus was then used to calculate recommended preparations and costs.

Prescriptions picked up and changing medications

Two things that will alter the cost to the NHS of prescribing a certain medication will be the level of adherence, and whether the individual changes the treatment course due to ineffectiveness.

If an individual is not adherent to the prescribed medication regime, then they will pick up fewer prescriptions per year meaning the annual cost will be lower than if the medication was taken as prescribed. Price et al. was the only study identified in the clinical review that measured adherence, defined as '*the rate at which prescriptions are re-filled for asthma therapy'* and found that it was significantly lower than 100% for all medications. The study reported the percentage of prescriptions picked up for:

- LTRAs

- single ICS inhalers for those taking ICS + LTRA
- single ICS inhalers for those taking ICS + LABA
- single LABA inhalers for those taking ICS + LABA.

The committee noted that the majority of individuals now placed on an ICS + LABA regime would be prescribed a dual inhaler. This was confirmed by the prescription data that showed a very small number of people being prescribed single LABA inhalers. Therefore an assumption was made that the percentage of dual inhalers picked up would be the same as the percentage of single ICS inhalers picked up for those taking ICS + LABA. Likewise no data was gathered on the percentage of ICS inhalers picked up for those taking just low dose or moderate dose ICS. An assumption was made that this would be the same as the number of inhalers picked up for those taking ICS + LTRA. It is worth noting that the values presented by Price et al. were given as median values along with an inter-quartile range. Using this data a distribution was fit using the software package RRiskdistributions in R. Once a distribution was fit the mean value was taken from this distribution.

Table 105: Mean (%) prescriptions picked up

Prescription	Median (IQR) proportion of prescriptions picked up	Beta distribution attached	Median (IQR) of fitted beta distribution	Mean from fitted beta distribution
LTRA	0.74 (0.14 – 1.0)	Alpha = 0.298 Beta = 0.205	0.75 (0.14 – 0.99)	0.59
ICS/LABA (dual inhaler)	0.64 (0.31 – 0.91)	Alpha = 0.811 Beta = 0.537	0.66 (0.32 – 0.90)	0.60
ICS (single inhaler)	0.76 (0.27 – 1.0)	Alpha = 0.466 Beta = 0.278	0.76 (0.27 – 0.98)	0.63

Source: Price et al. (2011)

The table shows the mean percentage of prescriptions picked up is always lower than the median, indicating that the distributions are negatively skewed.

This value was not run probabilistically as the committee noted that the level of adherence would likely correlate with the number of exacerbations an individual would have. Therefore rather than assume a correlation this was explored in a two-way sensitivity analysis whereby exacerbation rates and adherence was changed simultaneously. As the adherence rates were taken from Price et al. an assumption was made that these would be the same across all studies. This assumption is explored in the sensitivity analysis above.

The second thing that could alter medication costs is people changing medication regimes. As Price et al. was the only pragmatic trial identified in the clinical review they were the only study that allowed the individual to change medications during the trial. This study showed that after 2 months 3.5% of individuals who started in the LTRA arm had switched to LABAs and 0.5% had a LABA added onto their therapy. After 2 years 14.76% had switched to LABAs and 10.63% had a LABA added to their therapy. Using these values a cumulative probability distribution was calculated in the software R, using the package RRiskdistributions, which reflected the change in this probability over time. In the base case it was assumed after two years no more people would change medications and therefore the probability of switching falls to zero. In the LABA arm no-one changed treatment and therefore the probability of changing medication was 0% throughout the model. Although this was a significant difference between the two groups the clinical review identified two other RCTs that had similar findings, with regards to clinical effectiveness, to this study and these did not allow for treatment switching. This would indicate that treatment switching was having minimal impact on improving exacerbations in these patients.

Data on treatment switching were not available for the low or moderate-dose ICS comparisons in the model and therefore it was assumed this would occur at half the rate it would do for those starting on ICS + LTRA. In total 25.39% of people who started on LTRA had LABA either replace or added onto their therapy. The model therefore assumed that 12.7% of people who start on a single ICS inhaler will have a LABA added onto their therapy.

In the model when the individual switches to the ICS + LABA or steps-up to ICS + LABA + LTRA the exacerbation rate and hospitalisation rate for that individual changes to that of an individual taking ICS + LABA. Apart from the cost of treatment, no other parameters change. The parameters of those remaining on the initial treatment remains unchanged. In reality this is unlikely to be the case as the people who change medication are likely to be those who perform the worst and therefore removing them from the cohort would likely drive the exacerbation rate, for example, for that group down. This assumption will therefore slightly over-estimate the benefits of starting on ICS + LABA in the model. Likewise if the individual steps up to ICS+LABA+LTRA then it is assumed the exacerbation rate is the same as ICS+LABA, which is likely to bias the results against those starting on ICS+LTRA. This was explored in a sensitivity analysis.

N.2.3.7 Healthcare utilisation

Exacerbation costs

In the model exacerbation costs are dependent on whether or not the exacerbation leads to hospitalisation. If the exacerbation does not require hospitalisation then the cost includes two GP appointments (£37) and a course of oral steroids with prednisolone (cost=£1.33). If the exacerbation requires hospitalisation then the cost of asthma hospitalisation will be added (cost = £873.74 from NHS reference cost). Therefore, the cost of exacerbations per year is:

$$Annual\ cost\ of\ exacerbation = [Total\ exacerbation\ rate - Hospitalised\ exacerbation\ rate] * (cost\_non\_hospitalised\_exacerbation) + [Hospitalised\ exacerbation\ rate] * (cost\_hospitalisation\ )$$

Non-exacerbation related resource use

If an individual's symptoms worsen then they may visit the GP despite not having an exacerbation. In the clinical review an exacerbation was defined as the need for a course of oral steroids. Price et al. gathered information on all resource use and found that those receiving ICS+LTRA cost the NHS £94 a year and those receiving ICS+LABAs cost the NHS £88 a year. This cost however includes the costs associated with exacerbations which are included separately in the model.

In total this cost included:

GP visits, GP home visits, out-of-hours GP time, GP telephone consultations, nurse in clinic time, nurse on the phone time, outpatient visits, inpatient admissions, A&E visits and diagnostics.

First of all each of the components was costed using the most up-to-date costs from the NHS reference costs and the PSSRU 2016.

In the model, as discussed above, it is assumed that a non-hospitalised exacerbation results in two additional GP appointments. Therefore to prevent double counting, the number of GP appointments in Price's calculation was reduced by (2*[non-hospitalised exacerbation rate]) and the cost of inpatient admissions was removed. Therefore the cost of NHS activity not related to exacerbations was calculated to be £64 for those taking ICS+LTRA and £51 for those taking ICS+LABA. It is worth noting this cost potentially includes the cost of additional GP visits for those taking ICS+LTRA who switch medications. In the model this cost difference remains throughout the whole simulation

where in reality the cost difference may decrease over time once those that switched treatments are put onto the optimal therapy. This would bias the results against ICS+LTRA.

Finally, as no data on resource use were collected for the low or moderate dose ICS comparisons an assumption was made that non-exacerbation related resource use was the same as those taking ICS+LTRAs. This means non-exacerbation costs would be lower for those taking ICS+LABA than those taking just ICS. This decision was made as both moderate and low dose ICS had poorer clinical outcomes than ICS + LABA, and as it was assumed some people would switch medication the additional resource use associated with those unscheduled healthcare visits would be captured.

N.2.4 Computations

The model was constructed in TreeAge 2015 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohort's age as a respective risk factor for mortality.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities.

Transition probabilities for changing medications change over time for two years and then fall to zero under the assumption that after two years the treatment is unlikely to be switched.

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in the alive state of the model (1 month or 0.08 years) was weighted by a utility value that is dependent on the treatment effect on exacerbations. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first year were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

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

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$

Where:
r=discount rate per annum
n=time (years)

N.2.5 Sensitivity analyses

The model was re-run multiple times using the following assumptions:

SA1 Use the cheapest medication brands as the cost of medication.

In the model to account for different brands of medication used in the same drug class, a weighted cost was used based on which medications were currently prescribed the most. To look into the impact of this the model was re-run using the cheapest branded medication for each comparison as follows:

Table 106: Difference in cost between base case and cheapest medication

Class	Drug	Cost	Difference from base case
Moderate dose ICS	Asmabec Clickhaler_D/P Inh 100 mcg(200 D)	£71.61	-£66.62
LTRA	Montelukast_Tab 10 mg	£21.70	-£7.15
ICS + LABA[a]	Flutiform_Inha 50/5 mcg (120 D)	£175	-£33.35
Low dose ICS	Clenil Modulite_Inha 100 mcg (200 D)	£35.81	-£21.56

[a] This assumes only dual inhalers are prescribed and single LABA inhalers are no longer provided alongside ICS.

SA2/SA3 Change the length of exacerbations

In the model an assumption was made, based on expert consensus, concerning the length of time quality of life would be affected due to an exacerbation. Therefore the model was re-run using the lowest (SA2) and highest (SA3) values the committee felt could be appropriate for average duration of disutility from an exacerbation. For non-hospitalised the model was run using 1 week and 3 weeks. For hospitalised the model was run for 2 weeks and 6 weeks.

SA4 Decrease disutility associated with exacerbations

The quality of life decrement arising from an exacerbation was taken from Lloyd et al. In this study they report the difference in quality of life between those who have had an exacerbation and those who have not. However it is plausible that those who have an exacerbation will have a lower baseline quality of life than those who do not exacerbate, prior to the exacerbation occurring. This means the quality of life decrement from having an exacerbation is not the difference between those who exacerbate and those who do not, rather it is the difference in quality of life from baseline for those who exacerbate. Using this data from the study, the quality of life decrement from a non-hospitalised exacerbation is 0.1 and 0.2 for a hospitalised exacerbation.

SA5 Run a 10-year time horizon

As per the NICE reference case the model was run using a lifetime horizon. However due to introduction of new medications and changing management the model was run for a 10 year time horizon to see if the cost effectiveness results would hold over a shorter time horizon where things are unlikely to dramatically change.

SA6/SA7 Treatment switching

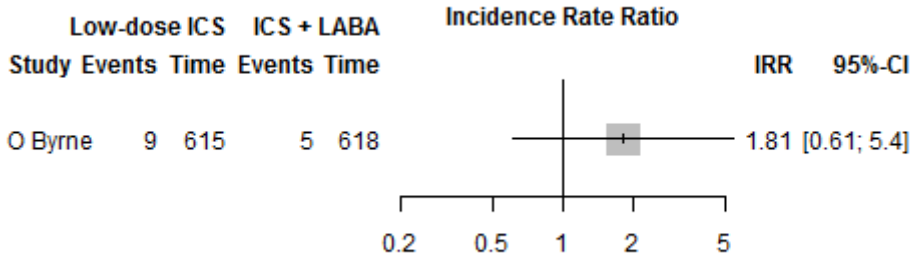
In the base case treatment switching occurs at half the rate for those taking moderate or low dose ICS. The model was re-run assuming treatment switching was the same across the moderate dose, low dose and LTRA arms (SA6). The model was then re-run assuming no treatment switching occurred in the low dose and moderate dose arms (SA7).

SA8 Adherence

In the model costs were altered by what percentage of prescriptions were picked up. This is likely linked to the effectiveness of the intervention. Therefore this value was changed in a two-way sensitivity analysis along with the number of exacerbations to see how changing these values simultaneously could influence the results.

SA9 Hospitalisation for low dose

In the base case an assumption was made concerning the hospitalisation rate for those taking low-dose ICS. This sensitivity analysis uses the most conservative estimates for calculating the lowest plausible exacerbation rate for those taking low dose ICS.



Here we assume that individuals who were hospitalised were only hospitalised once. Therefore in this sensitivity analysis only the additional length of stay in hospital experienced in the low-dose ICS group is taken into account. In the NHS reference costs the additional cost of an excess bed day is £263.97, weighted by severity of asthma admission. Therefore as those taking low-dose ICS spent an additional 10 days in hospital, an additional £2,639 is added on for each hospitalisation for those taking low-dose ICS.

SA10 Run the analysis with a 1.5% discount rate for both costs and effects

In the base case a discount rate of 3.5% was applied; this was reduced to 1.5% for both costs and effects.

SA11 Running the exacerbation rate ratio from Price et al.

In the study by Price et al. individuals were allowed to switch treatments during the trial. Therefore the exacerbation rate ratio compares a cohort of people who started on ICS + LABA to a cohort of people who started on ICS + LTRA (however some switched to LABAs). In the base case the exacerbation rate ratio from Bjermer was used. In this sensitivity analysis the exacerbation rate ratio from Price et al. is used. This does not impact the rate of hospitalised exacerbations which are treated as an independent variable in this sensitivity analysis.

SA12 Using upper limit of 95% confidence interval for exacerbation rate ratio

This sensitivity analysis increases the number of exacerbations experienced by those taking ICS + LTRAs to the upper limit of the 95% confidence interval.

SA13 Increase the number of GP appointments of those starting on LTRAs

The number of GP appointments of those starting on ICS + LTRA was taken from the study by Price et al. This sensitivity analysis assumes that everyone starting on ICS + LTRA will receive an additional GP appointment on top of what is already used in the model.

SA14 Increase the disutility from starting on ICS+LTRA

Price et al. reported a small and non-significant difference in quality of life at 2 months between those starting on ICS+LTRA and those starting on ICS+LABA. This impact was doubled to see if this short-term quality of life impact would influence the cost-effectiveness results.

SA15 Reduce the cost of LABA + ICS

Following development and consultation on this model, we were informed of a price reduction to a LABA + ICS combined inhaler. This reduces the cost of low dose LABA + ICS from £208.55 to £197.19 and moderate dose LABA + ICS from £399.69 to £387.57. The effect of this change was tested in an additional sensitivity analysis.

N.2.6 Model validation

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

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

N.2.7 Estimation of cost-effectiveness

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

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost-effective if: ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost, with options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost-effective if: • Highest net benefit

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

N.2.8 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[755] sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

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

As we have several interventions, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

N.3 Results

N.3.1 Base case

The results below in Table 107 show that LTRAs have the highest net monetary benefit and are therefore the most cost effective way of managing asthma for this patient population. 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.

Table 107: 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 CE 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%

N.3.2 Sensitivity analyses

SA1) Use the cheapest medication brands as the cost of medication

Table 108: Results from SA1

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.222	£3,572	£320,888	1	-
Moderate dose ICS	16.220	£3,820	£320,607	2	Dominated
ICS + LABA	16.234	£4,229	£320,479	3	£52,910
Low dose ICS	16.113	£4,786	£317,540	4	Dominated

Using the cheapest brand of medication for each drug class changed the cost-effectiveness rankings of moderate dose ICS and low dose ICS + LABA. ICS+LTRA remained the most cost effective option and low dose ICS remained the least preferred option.

SA2) Double the length of exacerbations

Table 109: Results from SA2

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.132	£3,929	£318,703	1	-
Moderate dose ICS	16.122	£4,657	£317,788	3	Dominated
ICS + LABA	16.150	£4,641	£318,366	2	£37,999
Low dose ICS	15.912	£5,079	£313,164	4	Dominated

Doubling the length of exacerbations did not change the cost-effectiveness rankings relative to the base case.

SA3) Halving the length of exacerbations

Table 110: Results from SA3

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.269	£3,929	£321,447	1	-
Moderate dose ICS	16.271	£4,657	£320,763	3	Dominated
ICS + LABA	16.278	£4,641	£320,919	2	£76,973
Low dose ICS	16.218	£5,079	£319,290	4	Dominated

Halving the length of exacerbations did not change the cost-effectiveness rankings relative to the base case.

SA4) Decrease the disutility associated with exacerbations

Table 111: Results from SA4

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.285	£3,954	£321,780	1	-
Moderate dose ICS	16.289	£4,621	£321,123	3	Dominated
ICS + LABA	16.293	£4,643	£321,227	2	£89,066
Low dose ICS	16.253	£5,079	£319,986	4	Dominated

Reducing the disutility of exacerbations did not change the cost-effectiveness rankings relative to the base case.

SA5) Reduce time horizon to 10 years

Table 112: Results from SA5

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	6.637	£1,599	£131,130	1	-
Moderate dose ICS	6.639	£1,896	£130,891	3	Extendedly Dominated
ICS + LABA	6.645	£1,900	£131,004	2	£34,439
Low dose ICS	6.600	£2,079	£129,842	4	Dominated

Reducing the time horizon to 10 years did not change the cost-effectiveness rankings relative to the base case.

SA6) Assume no treatment switching for those taking low dose/moderate dose ICS

Table 113: Results from SA6

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.223	£3,929	£320,532	1	-
Moderate dose ICS	16.219	£4,657	£320,133	2	Dominated
ICS + LABA	16.235	£4,641	£320,068	3	£57,362
Low dose ICS	16.098	£5,061	£316,901	4	Dominated

Assuming no treatment switching for those taking low or moderate dose ICS did change the cost-effectiveness rankings relative to the base case. Now moderate dose ICS is more cost effective than low dose ICS + LABA. Low dose ICS+LTRA remains the most cost-effective option.

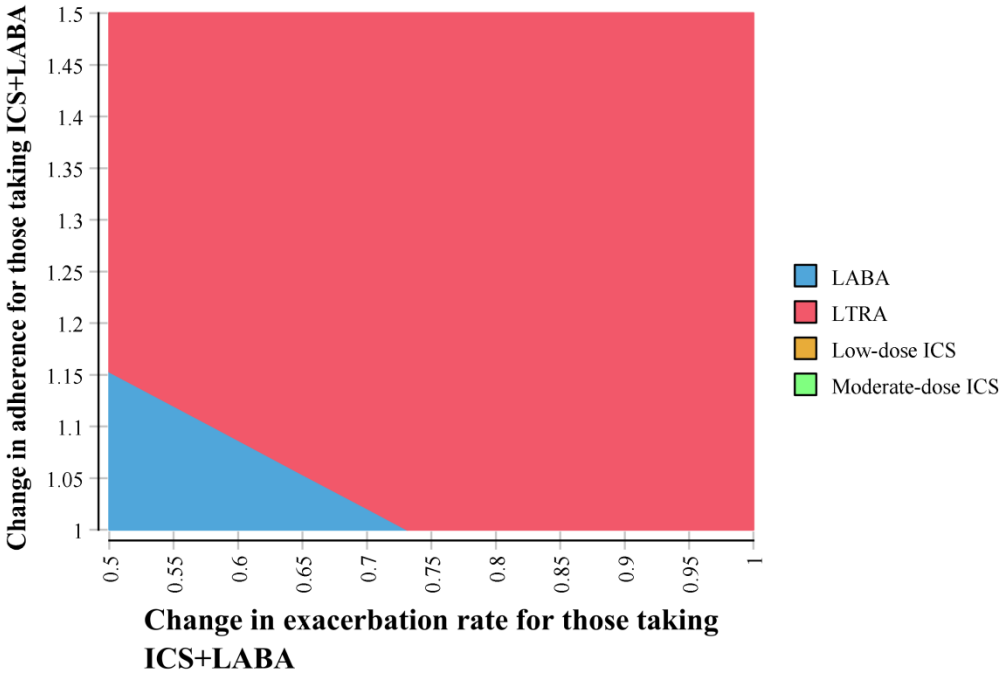
SA7) Assume equal treatment switching

Table 114: Results from SA7

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.223	£3,929	£320,532	1	-
ICS + LABA	16.235	£4,642	£320,068	2	£57,362
Moderate dose ICS	16.223	£5,010	£319,456	3	Dominated
Low dose ICS	16.132	£5,067	£317,579	4	Dominated

Assuming equal treatment switching for those taking ICS + LTRA, low or moderate dose ICS did not change the cost-effectiveness rankings relative to the base case.

SA8) Two-way sensitivity analysis concerning adherence and exacerbation rates



The graph above shows what change is needed in exacerbation rates and adherence levels for there to be a change in the most cost effective option. A change of 1.5 represents the variable increasing by 50%, 0.5 represents a decrease of 50% and 1 represents no change from the base case. The y axis represents changes to adherence and the x-axis represents changes in exacerbation rates. The only scenario where LABA becomes cost effective is when exacerbation rates drop by 27% (0.73 on the x-axis of the graph) relative to the base case and adherence remains unchanged. In the base case exacerbation rates for ICS+LABA are 0.305 per year, therefore in this scenario exacerbation rates would decrease to 0.22 for those taking ICS+LABA, adherence would remain at 60% and exacerbation rates for ICS+LTRA would be 0.32. Realistically for any reduction in exacerbations to be achieved adherence would need to improve. The graph above shows that if adherence improves by 15% exacerbation rates would need to significantly fall by 50% to make ICS+LABA cost effective relative to ICS+LTRA. Therefore even if adherence rates improved for those taking ICS+LABA it is highly unlikely they would achieve the clinical effect needed to make them cost effective relative to ICS+LTRA.

SA9) Hospitalisation for low dose

Table 115: Results from SA9

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.223	£3,929	£320,532	1	-
Low dose ICS	16.158	£5,289	£317,864	4	Dominated
Moderate dose ICS	16.221	£4,657	£319,771	3	Dominated
ICS + LABA	16.235	£4,641	£320,068	2	£57,362

Using a more conservative estimate, concerning low-dose ICS hospitalisation rates, did not change the cost-effectiveness rankings relative to the base case. Low dose ICS is now considerably less costly.

SA10) Use a 1.5% discount rate for costs and effects

Table 116: Results from SA10

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	22.502	£5,455	£444,578	1	-
Moderate dose ICS	22.497	£6,465	£443,477	3	Dominated
ICS + LABA	22.517	£6,438	£443,893	2	£65,835
Low dose ICS	22.35	£7,044	£439,989	4	Dominated

Using a 1.5% discount rate did not change the cost-effectiveness rankings relative to the base case.

SA11) Use the exacerbation rate calculated in Price et al.

Table 117: Results from SA11

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.230	£3,887	£320,707	1	-
Moderate dose ICS	16.221	£4,657	£319,771	3	Dominated
ICS + LABA	16.235	£4,641	£320,068	2	£131,549
Low dose ICS	16.116	£5,079	£317,248	4	Dominated

Using the exacerbation rate from Price et al. did not change the cost-effectiveness rankings relative to the base case.

SA12) Using highest exacerbation rate for LTRA

Table 118: Results from SA12

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold (per QALY)
	QALYs	Cost			
ICS + LTRA	16.215	£3,947	£320,353	1	-
Moderate dose ICS	16.225	£4,625	£319,803	3	
ICS + LABA	16.235	£4,641	£320,068	2	£33,976
Low dose ICS	16.116	£5,079	£317,280	4	Dominated

Using the highest exacerbation rate for ICS + LTRA did not change the cost-effectiveness rankings relative to the base case.

SA13) adding an additional GP visit for those starting on ICS+LTRA

Table 119: Results from SA13

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold
	QALYs	Cost			
ICS + LTRA	16.222	£3,991	£320,495	1	-
Moderate dose ICS	16.220	£4,657	£319,771	3	Dominated

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold
	QALYs	Cost			
ICS + LABA	16.234	£4,641	£320,068	2	£54,385
Low dose ICS	16.113	£5,079	£317,248	4	Dominated

Increasing the number of GP appointments did not change the cost-effectiveness rankings relative to the base case.

SA14) increasing the disutility from starting on ICS+LTRA

Table 120: Results from SA14

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold
	QALYs	Cost			
ICS + LTRA	16.217	£3,929	£320,410	1	-
Moderate dose ICS	16.220	£4,657	£319,771	3	Dominated
ICS + LABA	16.234	£4,641	£320,068	2	£38,487
Low dose ICS	16.113	£5,079	£317,248	4	Dominated

Doubling the disutility from starting on ICS+LTRA did not change the cost-effectiveness rankings relative to the base case.

SA15) reducing the cost of LABA + ICS

Table 121: Results from SA15

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Incremental cost-effectiveness threshold
	QALYs	Cost			
ICS + LTRA	16.223	£3,894	£320,567	1	-
Moderate dose ICS	16.221	£4,624	£319,804	3	Dominated
ICS + LABA	16.235	£4,502	£320,208	2	£48,929
Low dose ICS	16.116	£5,061	£317,267	4	Dominated

Reducing the cost of LABA + ICS did not change the cost-effectiveness rankings relative to the base case.

N.4 Discussion

N.4.1 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 0.012 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 lead to better outcomes than moderate or low dose ICS. Although low dose ICS costs less than ICS + LTRA it becomes a dominated option when the additional costs of exacerbations are 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. Sensitivity analyses 3 extended 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 high enough amount to change the cost-effectiveness rankings. It is worth noting that the PCA data 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 + LTRAs 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 including treatment switching for moderate dose ICS made it a more costly option than starting individuals on ICS + LABA straight away.

N.4.2 Limitations and interpretation

The main limitation of the model is 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 would 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 at the time of the trial 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 + LTRAs 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 all non-LABA comparators throughout the model. The committee felt that over time these costs would be much closer once people who did not respond to initial treatment had switched to LABAs.

Overall using the clinical evidence obtained from the systematic review this model attempted to fully test the clinical benefits and costs of each treatment option assessed. The committee felt that there was no evidence of substantial benefit of choosing ICS + LABA over ICS + LTRA. The potential benefit of choosing ICS + LABA was fully explored however the use of LTRA was always significantly cheaper. Therefore the committee felt it was appropriate to trial LTRAs prior to using LABAs as the cost savings could be substantial given the size of the population of people with asthma. Although the amount of clinical evidence for moderate dose ICS informing the model was weak the committee felt comfortable with the conclusion that these would not be a cost-effective treatment option unless they offered higher clinical benefits that ICS + LABA.

N.4.3 Generalisability to other populations or settings

The committee agreed that the results could not be fully extrapolated to children as it was likely the clinical benefits of each treatment option would vary, impacting the cost effectiveness. Likewise as children would be on lower doses the cost of medication would also be lower.

The main driver of cost effectiveness in the model is the cost of medication as opposed to unscheduled healthcare costs; therefore in settings (for example other countries) where the difference in treatment cost is not the same as the one used in this model, our results are not applicable.

N.4.4 Comparisons with published studies

Two studies were identified concerning the cost effectiveness of treatments analysed in this model.

Price et al. looked at the cost effectiveness of ICS + LTRA versus ICS + LABA. Although they reached the same conclusion of ICS + LTRA being cost effective, the committee felt that their model may have overestimated the benefit of ICS + LTRA. In their model ICS + LTRA produced more QALYs than ICS + LABA; however some EQ-5D data was generated by imputation due to missing values. Likewise an additional disutility was not added due to exacerbating meaning that it was assumed the impact on quality of life would have been captured in the EQ-5D questionnaire. As the clinical review identified two additional large studies comparing ICS + LTRA and ICS + LABA, the committee felt an original model would be appropriate that took all of the evidence into account. This was especially the case given that the Price study was a pragmatic trial, so if it did introduce unwanted biases these could be resolved by also looking at data from non-pragmatic trials. It is worth noting that the Price study was conducted when LTRA was on patent. The cost of a 28 tablet pack of Singulair (Montelukast) was £26.97 whereas today a generic version, which is more commonly prescribed, is £1.90. Therefore if the Price analysis was redone using today's prices ICS + LTRA would have been a dominant option.

Jonsson et al. looked at the cost effectiveness of low dose ICS versus ICS + LABA. This study was conducted in 2004 using Swedish healthcare costs. At the time dual inhalers were not prescribed therefore in the study the cost of ICS + LABA is higher than it is today. In the study the cost of 200 micrograms of budesonide + 4.5 micrograms of formoterol was calculated to be £282 a year. The cost of 200 micrograms of budesonide + 6 micrograms of formoterol is £200 and that is assuming 100% adherence. However the committee noted that the cost of 200 micrograms of budesonide alone was also very high at £103. The cost of 200 micrograms of budesonide using the BNF is £32–£43 depending on the brand. Given that the study also did not report QALYs, the committee felt using the clinical results from O'Bryne to inform the health economic model would give a clearer picture regarding the cost effectiveness of low dose ICS. Jonsson showed that the ICER for low dose

ICS (200 micrograms) versus ICS + LABA was £11 per symptom-free day alongside £53 per severe exacerbation avoided, although severe exacerbation included exacerbations that did not require oral steroids. Regardless the committee felt that this result agreed with the model's conclusion that low dose ICS alone was not cost effective relative to ICS + LABA for those who remained uncontrolled after taking low dose ICS.

The model results differed from Jonsson in the sense that ICS + LABA dominated low dose ICS. The cost difference from medication in Jonsson was calculated to be £180 whereas in the model the cost difference was £90, without any treatment switching. This cost difference gets smaller over time as people switch from low dose ICS to ICS + LABA in the model, something which does not occur in the Jonsson study. The main cost of being on low dose ICS in the model comes from the increased hospitalisations which make it a dominated option. Therefore given large changes in medication prices and the use of NHS costs it is not surprising that the cost difference between the two treatments is substantially different.

N.4.5 Conclusions

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 of starting on ICS + LABA was £56,977 per QALY, above the £20,000 per QALY threshold.

N.4.6 Implications for future research

Although the model is fairly conclusive for adults the results cannot be fully extrapolated to children. Further research therefore needs to be conducted to evaluate the cost effectiveness of treatment options at this treatment step for children under 16 years old.

Appendix O: Unit costs

O.1 Unit costs for adults

O.1.1 Low dose ICS (adult dose)

Table 122: Costs for single ICS inhaler (adult low dose)

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Qvar 50_Inha 50 mcg (200 D)	50	200	200	£7.74	£0.04	£0.00	£0.15	£56.50
Qvar 50_Autohaler 50 mcg (200 D)	50	200	200	£7.87	£0.04	£0.00	£0.16	£57.45
Qvar 50 E-Breathe_Inha 50 mcg (200 D)	50	200	200	£7.87	£0.04	£0.00	£0.16	£57.45
Clenil Modulite_Inha 100 mcg (200 D)	100	200	400	£7.42	£0.04	£0.00	£0.15	£54.17
Pulmicort_Turbohaler 100 mcg (200 D)	100	200	400	£11.84	£0.06	£0.00	£0.24	£86.43
Easyhaler_Budesonide 100 mcg (200 D)	100	200	400	£8.86	£0.04	£0.00	£0.18	£64.68
Flixotide_Accuhaler 100 mcg (60 D)	100	60	200	£8.93	£0.15	£0.00	£0.30	£108.65
Flixotide_Evohaler 125 mcg (120 D)	125	120	250	£21.26	£0.18	£0.00	£0.35	£129.33
Asmanex Twisthaler_D/P Inh 200 mcg (60 D)	200	60	200	£23.54	£0.39	£0.00	£0.39	£143.20
Alvesco 80_Inh 80 mcg (120 D) CFF	80	120	160	£32.83	£0.27	£0.00	£0.55	£199.72
Asmabec Clickhaler_D/P Inh 100 mcg (200 D)	100	200	200	£9.81	£0.05	£0.00	£0.10	£35.81
Pulmicort_Turbohaler 200 mcg (100 D)	200	100	400	£11.84	£0.12	£0.00	£0.24	£86.43
Qvar 100_Inha 100 mcg (200 D)	100	200	200	£16.95	£0.08	£0.00	£0.17	£61.87
Qvar 100_Autohaler 100 mcg (200 D)	100	200	200	£17.21	£0.09	£0.00	£0.17	£62.82
Qvar 100 E-Breathe_Inha 100 mcg (200 D)	100	200	200	£17.21	£0.09	£0.00	£0.17	£62.82

O.1.2 Moderate dose ICS (adult dose)

Table 123: Costs for single ICS inhaler (adult moderate dose)

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Asmabec Clickhaler_D/P Inh 100 mcg (200 D)	100	200	400	£9.81	£0.05	£0.00	£0.20	£71.61
Qvar 100_Inha 100 mcg (200 D)	100	200	400	£16.95	£0.08	£0.00	£0.34	£123.74
Qvar 100_Autohaler 100 mcg (200 D)	100	200	400	£17.21	£0.09	£0.00	£0.34	£125.63
Qvar 100 E-Breathe_Inha 100 mcg (200 D)	100	200	400	£17.21	£0.09	£0.00	£0.34	£125.63
Clenil Modulite_Inha 200 mcg (200D)	200	200	800	£16.17	£0.08	£0.00	£0.32	£118.04
Pulmicort_Turbohaler 200 mcg (100 D)	200	100	800	£11.84	£0.12	£0.00	£0.47	£172.86
Pulmicort_Turbohaler 400 mcg (50 D)	400	50	800	£13.86	£0.28	£0.00	£0.55	£202.36
Budelin Novolizer_Inh 200 mcg (100 D)	200	100	800	£14.86	£0.15	£0.00	£0.59	£216.96
Budelin Novolizer_Inh 200 mcg 100D Ref	200	100	800	£9.59	£0.10	£0.00	£0.38	£140.01
Easyhaler_Budesonide 200 mcg (200 D)	200	200	800	£17.71	£0.09	£0.00	£0.35	£129.28
Flixotide_Accuhaler 250 mcg (60 D)	250	60	500	£21.26	£0.35	£0.00	£0.71	£258.66
Flixotide_Evohaler 125 mcg (120 D)	125	120	500	£21.26	£0.18	£0.00	£0.71	£258.66
Asmanex Twisthaler_D/P Inh 400 mcg (60 D)	400	60	400	£36.05	£0.60	£0.00	£0.60	£219.30
Alvesco 160_Inh 160 mcg (120 D) CFF	160	120	320	£38.62	£0.32	£0.00	£0.64	£234.94

O.1.3 High dose ICS (adult dose)

Table 124: Costs for single ICS inhaler (adult high dose)

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Qvar 100_Inha 100 mcg (200 D)	100	200	800	£16.95	£0.08	£0.00	£0.68	£247.47
Qvar 100_Autohaler 100 mcg (200 D)	100	200	800	£17.21	£0.09	£0.00	£0.69	£251.27
Qvar 100 E-Breathe_Inha 100 mcg (200 D)	100	200	800	£17.21	£0.09	£0.00	£0.69	£251.27
Pulmicort_Turbohaler 400 mcg (50 D)	400	50	1600	£13.86	£0.28	£0.00	£1.11	£404.71

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Budelin Novolizer_Inh 200 mcg (100 D)	200	100	1600	£14.86	£0.15	£0.00	£1.19	£433.91
Budelin Novolizer_Inh 200 mcg 100D Ref	200	100	1600	£9.59	£0.10	£0.00	£0.77	£280.03
Easyhaler_Budesonide 400 mcg (100 D)	400	100	1600	£17.71	£0.18	£0.00	£0.71	£258.57
Flixotide_Accuhaler 250 mcg (60 D)	250	60	1000	£21.26	£0.35	£0.00	£1.42	£517.33
Flixotide_Accuhaler 500 mcg (60 D)	500	60	1000	£36.14	£0.60	£0.00	£1.20	£439.70
Flixotide_Evohaler 250 mcg (120 D)	250	120	1000	£36.14	£0.30	£0.00	£1.20	£439.70
Clenil Modulite_Inha 250 mcg (200 D)	250	200	1000	£16.29	£0.08	£0.00	£0.33	£118.92

O.1.4 Low dose ICS + LABA combined inhaler (adult dose)

Table 125: Costs for ICS + LABA combined inhaler (adult low dose)

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Fostair_Inh 100 mcg/6 mcg (120 D) CFF (extrafine formulation	100	120	200	£29.32	£0.24	£0.00	£0.49	£178.36
Fostair NEXThaler_Inh 100 mcg/6 mcg (120 D) (extrafine formulation	100	120	200	£29.32	£0.24	£0.00	£0.49	£178.36
Symbicort_Turbohaler 100 mcg/6 mcg (120 D)[(a)]	100	120	400	£33.00	£0.28	£0.00	£1.10	£401.50
Symbicort_Turbohaler 200 mcg/6 mcg (120 D)[(a)]	200	120	400	£38.00	£0.32	£0.00	£0.63	£231.17
Seretide 100_Accuhaler 100 mcg/50 mcg(60 D)	100	60	200	£18.00	£0.30	£0.00	£0.60	£219.00
Seretide 50_Evohaler 50 mcg/25 mcg (120 D)	50	120	200	£18.00	£0.15	£0.00	£0.60	£219.00
Flutiform_Inha 50/5 mcg (120 D)	50	120	200	£14.40	£0.12	£0.00	£0.48	£175.20
DuoResp Spiromax_Inh 160 mcg/4.5 mcg(120 D)	160	120	320	£29.97	£0.25	£0.00	£0.50	£182.32

(a) Costs have recently changed to £28.00 per pack, but were correct at the time of development of and consultation on this guideline. See sensitivity analysis SA15 in appendix N.

O.1.5 Moderate dose ICS + LABA combined inhaler (adult dose)

Table 126: Costs for ICS + LABA combined inhaler (adult moderate dose)

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Fostair_Inh 100 mcg/6 mcg (120 D) CFF (extrafine formulation	100	120	400	£29.32	£0.24	£0.00	£0.98	£356.73
Fostair NEXThaler_Inh 100 mcg/6 mcg (120 D) (extrafine formulation	100	120	400	£29.32	£0.24	£0.00	£0.98	£356.73
Symbicort_Turbohaler 100 mcg/6 mcg (120 D)[(a)]	100	120	800	£33.00	£0.28	£0.00	£2.20	£803.00
Symbicort_Turbohaler 200 mcg/6 mcg (120 D)[(a)]	200	120	800	£38.00	£0.32	£0.00	£1.27	£462.33
Symbicort_Turbohaler 400 mcg/12 mcg (60 D)[(a)]	400	60	800	£38.00	£0.63	£0.00	£1.27	£462.33
DuoResp Spiromax_Inh 160 mcg/4.5 mcg(120 D)	160	120	640	£29.97	£0.25	£0.00	£1.00	£364.64
DuoResp Spiromax_Inh 320 mcg/9 mcg (60 D)	320	60	640	£29.97	£0.50	£0.00	£1.00	£364.64
Seretide 250_Accuhaler 250 mcg/50 mcg (60 D)	250	60	500	£35.00	£0.58	£0.00	£1.17	£425.83
Seretide 125_Evohaler 125 mcg/25 mcg (120 D)	125	120	500	£35.00	£0.29	£0.00	£1.17	£425.83
Flutiform_Inha 125/5 mcg (120 D)	125	120	500	£28.00	£0.23	£0.00	£0.93	£340.67
Relvar Ellipta_Inha 92 mcg/22 mcg (30 D)	92	30	92	£22.00	£0.73	£0.01	£0.73	£267.67

(a) Costs have recently changed to £28.00 per pack, but were correct at the time of development of and consultation on this guideline. See sensitivity analysis SA15 in appendix N.

O.1.6 High dose ICS + LABA combined inhaler (adult dose)

Table 127: Costs for ICS + LABA combined inhaler (adult high dose)

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Symbicort_Turbohaler 400 mcg/12 mcg (60 D)[(a)]	400	60	1600	£38.00	£0.63	£0.00	£2.53	£924.67
DuoResp Spiromax_Inh 320 mcg/9 mcg (60 D)	320	60	1280	£29.97	£0.50	£0.00	£2.00	£729.27
Seretide 500_Accuhaler 500 mcg/50 mcg (60 D)	500	60	1000	£40.92	£0.68	£0.00	£1.36	£497.86
Seretide 250_Evohaler 250 mcg/25 mcg (120 D)	250	120	1000	£59.48	£0.50	£0.00	£1.98	£723.67
Flutiform_Inha 250/10 mcg (120 D)	250	120	1000	£45.56	£0.38	£0.00	£1.52	£554.31
Relvar Ellipta_Inha 184 mcg/22 mcg (30 D)	184	30	184	£29.50	£0.98	£0.01	£0.98	£358.92

(a) Costs have recently changed to £28.00 per pack, but were correct at the time of development of and consultation on this guideline. See sensitivity analysis SA15 in appendix N.

O.1.7 Single LABA inhaler

Table 128: Costs for LABA single inhaler

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Salmeterol_Inha 25 mcg (120 D) CFF	25	120	100	£29.96	£0.25	£0.01	£1.00	£364.51
Serevent_Accuhaler 50 mcg (60 D)	50	60	100	£29.26	£0.49	£0.01	£0.98	£356.00
Serevent_Evohaler 25 mcg (120 D)	25	120	100	£29.96	£0.25	£0.01	£1.00	£364.51
Foradil_Inh Cap 12 mcg + Inha	12	60	24	£28.06	£0.47	£0.04	£0.94	£341.40
Oxis 6_Turbohaler 6 mcg (60 D)	6	60	24	£24.80	£0.41	£0.07	£1.65	£603.47
Oxis 12_Turbohaler 12 mcg (60 D)	12	60	24	£24.80	£0.41	£0.03	£0.83	£301.73
Atimos Modulite_Inh 12 mcg (100 D)	12	100	24	£30.06	£0.30	£0.03	£0.60	£219.44
Formoterol Easyhaler_12 mcg (120 D)	12	120	24	£23.75	£0.20	£0.02	£0.40	£144.48

O.1.8 LTRA

Table 129: Costs for LTRA

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Accolate_Tab 20 mg	20	56	40	£17.75	£0.32	£0.02	£0.63	£231.38
Montelukast_Tab 10 mg	10	28	10	£1.75	£0.06	£0.01	£0.06	£22.29
Singulair_Tab 10 mg	10	28	10	£26.97	£0.96	£0.10	£0.96	£351.57

O.1.9 LAMA

Table 130: Costs for LAMA

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Respimat	2.5	60	5	£23.00	£0.38	£0.15	£0.77	£279.83

O.1.10 Sodium cromoglicate

Table 131: Costs for sodium cromoglicate

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Intal_Inha 5 mg (112 D) CFF	5	112	40	£18.33	£0.16	£0.03	£1.31	£477.89

O.1.11 Theophylline (adult dose)

Table 132: Costs for theophylline

Brand	Mcg/unit	Unit/pack	Mcg/day	Cost/pack	Cost/unit	Cost/mcg	Cost/day	Cost/year
Nuelin SA_Tab 175 mg	175	60	350	£6.38	£0.11	£0.00	£0.21	£77.62
Nuelin SA-250_Tab 250 mg	250	60	500	£8.92	£0.15	£0.00	£0.30	£108.53
Slo-Phyllin_Cap 60 mg	60	56	250	£2.76	£0.05	£0.00	£0.21	£74.96
Slo-Phyllin_Cap 125 mg	125	56	250	£3.48	£0.06	£0.00	£0.12	£45.36
Slo-Phyllin_Cap 250 mg	250	56	250	£4.34	£0.08	£0.00	£0.08	£28.29
Uniphyllin Continus_Tab 400 mg	400	56	400	£5.65	£0.10	£0.00	£0.10	£36.83
Uniphyllin Continus_Tab 200 mg	200	56	400	£4.77	£0.09	£0.00	£0.17	£62.18
Uniphyllin Continus_Tab 300 mg	300	56	400	£2.96	£0.05	£0.00	£0.07	£25.72

O.2 Finding the average cost for each drug class for use in the economic model

As shown in the tables above there are many brands that can be prescribed for a given drug class. For the economic model a single cost was required for each drug class that represented the 'average' cost of recommending that drug class. To find this 'average' cost the cost of each brand was weighted by how often it is prescribed. These data are available from the prescription cost analysis. The most recent July 2016 version was used for this purpose. The table below outlines how often each brand of medication is prescribed.

Table 133: Summary of how often each brand is prescribed (July 2016 PCA data)

BNF Chemical Name	Drug Name	Items Dispensed
Beclometasone dipropionate	Asmabec Clickhaler_D/P Inh 100 mcg (200 D)	213
Beclometasone dipropionate	Asmabec Clickhaler_D/P Inh 250 mcg (100 D)	6
Beclometasone dipropionate	Qvar 50_Inha 50 mcg (200 D)	26232
Beclometasone dipropionate	Qvar 100_Inha 100 mcg (200 D)	48862 (2)
Beclometasone dipropionate	Qvar 50_Autohaler 50 mcg (200 D)	2967
Beclometasone dipropionate	Qvar 100_Autohaler 100 mcg (200 D)	7292 (2)
Beclometasone dipropionate	Qvar 50 E-Breathe_Inha 50 mcg (200 D)	6148
Beclometasone dipropionate	Qvar 100 E-Breathe_Inha 100 mcg (200 D)	10786 (2)
Beclometasone dipropionate	Pulvinal Beclomet_Inha 200 mcg (100 D)	43
Beclometasone dipropionate	Pulvinal Beclomet_Inha 100 mcg (100 D)	80
Beclometasone dipropionate	Pulvinal Beclomet_Inha 400 mcg (100 D)	6
Beclometasone dipropionate	Clenil Modulite_Inha 50 mcg (200 D)	66652 (1)
Beclometasone dipropionate	Clenil Modulite_Inha 100 mcg (200 D)	233613
Beclometasone dipropionate	Clenil Modulite_Inha 200 mcg (200 D)	56478
Beclometasone dipropionate	Clenil Modulite_Inha 250 mcg (200 D)	12656
Beclometasone dipropionate	Fostair_Inh 100 mcg/6 mcg (120 D) CFF (extrafine formulation	188696 (2)
Beclometasone dipropionate	Fostair NEXThaler_Inh 100 mcg/6 mcg (120 D) (extrafine formulation	15601 (2)
Beclometasone dipropionate	Fostair_Inh 200 mcg/6 mcg (120 D) CFF (extrafine formulation	7416
Beclometasone dipropionate	Fostair NEXThaler_Inh 200 mcg/6 mcg (120 D) (extrafine formulation	2214
Budesonide	Pulmicort_Turbohaler 200 mcg (100 D)	12198
Budesonide	Pulmicort_Turbohaler 400 mcg (50 D)	4393
Budesonide	Pulmicort_Turbohaler 100 mcg (200 D)	3113
Budesonide	Symbicort_Turbohaler 100 mcg/6 mcg (120 D)	25864 (1)
Budesonide	Symbicort_Turbohaler 200 mcg/6 mcg (120 D)	123076 (3)
Budesonide	Symbicort_Turbohaler 400 mcg/12mcg (60 D)	74296
Budesonide	Easyhaler_Budesonide 100 mcg (200 D)	3084
Budesonide	Easyhaler_Budesonide 200 mcg (200 D)	1026
Budesonide	Easyhaler_Budesonide 400 mcg (100 D)	343
Budesonide	DuoResp Spiromax_Inh 160 mcg/4.5 mcg(120D)	40599

BNF Chemical Name	Drug Name	Items Dispensed
Budesonide	DuoResp Spiromax_Inh 320 mcg/9 mcg (60 D)	31764 (2)
Fluticasone propionate (Inh)	Flixotide_Accuhaler 50 mcg (60 D)	957 (1)
Fluticasone propionate (Inh)	Flixotide_Accuhaler 100 mcg (60 D)	3712
Fluticasone propionate (Inh)	Flixotide_Accuhaler 250 mcg (60 D)	2203
Fluticasone propionate (Inh)	Flixotide_Accuhaler 500 mcg (60 D)	1166
Fluticasone propionate (Inh)	Flixotide_Evohaler 125 mcg (120 D)	6523
Fluticasone propionate (Inh)	Flixotide_Evohaler 250 mcg (120 D)	7052
Fluticasone propionate (Inh)	Flixotide_Evohaler 50 mcg (120 D)	7142
Fluticasone propionate (Inh)	Seretide 100_Accuhaler 100 mcg/50 mcg (60 D)	20607
Fluticasone propionate (Inh)	Seretide 250_Accuhaler 250 mcg/50 mcg (60 D)	43817
Fluticasone propionate (Inh)	Seretide 500_Accuhaler 500 mcg/50 mcg (60 D)	76562
Fluticasone propionate (Inh)	Seretide 50_Evohaler 50 mcg/25 mcg (120 D)	45130
Fluticasone propionate (Inh)	Seretide 125_Evohaler 125mcg/25 mcg (120 D)	40987
Fluticasone propionate (Inh)	Seretide 250_Evohaler 250 mcg/25mcg (120 D)	52560
Fluticasone propionate (Inh)	Flutiform_Inha 125/5 mcg (120 D)	21730
Fluticasone propionate (Inh)	Flutiform_Inha 250/10 mcg (120 D)	21057
Fluticasone propionate (Inh)	Flutiform_Inha 50/5 mcg (120 D)	5955
Fluticasone propionate (Inh)	Relvar Ellipta_Inha 184 mcg/22 mcg (30 D)	4956
Fluticasone propionate (Inh)	Relvar Ellipta_Inha 92 mcg/22 mcg (30 D)	25825
Mometasone furoate	Asmanex Twisthaler_D/P Inh 200 mcg (30 D)	77
Mometasone furoate	Asmanex Twisthaler_D/P Inh 200 mcg (60 D)	132
Mometasone furoate	Asmanex Twisthaler_D/P Inh 400 mcg (30 D)	85
Mometasone furoate	Asmanex Twisthaler_D/P Inh 400 mcg (60 D)	133
Ciclesonide	Alvesco 80_Inh 80 mcg (120 D) CFF	709
Ciclesonide	Alvesco 160_Inh 160 mcg (120 D) CFF	1271
Ciclesonide	Alvesco 160_Inh 160 mcg (60 D) CFF	1431
Zafirlukast	Accolate_Tab 20 mg	2699
Montelukast	Montelukast_Tab 10 mg	144369
Montelukast	Singulair_Tab 10 mg	1240
Salmeterol	Salmeterol_Inha 25 mcg (120 D) CFF	34519 (3)
Salmeterol	Serevent_Accuhaler 50mcg (60 D)	9082 (3)
Salmeterol	Serevent_Evohaler 25 mcg (120 D)	5005 (3)
Formoterol fumarate	Foradil_Inh Cap 12 mcg + Inha	699 (3)
Formoterol fumarate	Oxis 6_Turbohaler 6 mcg (60 D)	1361 (3)
Formoterol fumarate	Oxis 12_Turbohaler 12 mcg (60 D)	3469 (3)
Formoterol fumarate	Atimos Modulite_Inh 12 mcg (100 D)	2868 (3)
Formoterol fumarate	Formoterol Easyhaler_12 mcg (120 D)	4327 (3)
Tiotropium	Spiriva Respimat_Inha 2.5 mcg (60 D) + Dev	16423
Theophylline	Nuelin SA_Tab 175 mg	411
Theophylline	Nuelin SA-250_Tab 250 mg	415
Theophylline	Slo-Phyllin_Cap 60 mg	681
Theophylline	Slo-Phyllin_Cap 125 mg	2270

BNF Chemical Name	Drug Name	Items Dispensed
Theophylline	Slo-Phyllin_Cap 250 mg	5636
Theophylline	Uniphyllin Continus_Tab 400 mg	5515
Theophylline	Uniphyllin Continus_Tab 200 mg	20668
Theophylline	Uniphyllin Continus_Tab 300 mg	5711
Sodium cromoglicate	Intal_Inha 5 mg (112 D) CFF	564

Source/Note: the quantities here are taken from the PCA July 2016 data. The cells with bracketed numbers next to them are adjusted in the final analysis based on assumptions below. (1) are assumed to only be prescribed to children and excluded from the adult costings. (2) are adjusted due to the fact that these brands are commonly prescribed across multiple dosages. (3) are LABA brands that are adjusted due to the fact that they are commonly prescribed for both adults and children. More details are given below.

Before the PCA data could be used to find the average cost for each brand, a few considerations needed to be made.

The first thing to note is that items dispensed was the data taken from the PCA. This is defined as: *'single medicine prescribed by a doctor (or dentist/nurse/etc.) on a prescription form. This is different to quantity i.e. if salbutamol inhaler x 2 was prescribed. This is one item with a quantity of two*.' This is important as some medications require higher quantities to fulfil a yearly prescription. Therefore we would expect higher quantities of these medications to be prescribed, however that doesn't indicate that more people are on that treatment. Therefore to calculate the weighted average, 'items dispensed' was deemed more appropriate than 'quantity'.

The first adjustment to make to the data is with regards to whether a brand can be prescribed across multiple dosages. For example, when offered a low dose ICS + LABA treatment the person could be given a Fostair 100/6mcg inhaler and told to take one puff twice a day. Likewise if offered to be placed on a moderate dose ICS + LABA treatment they could also be given the same Fostair 100/6mcg inhaler, however this time told to take two puffs twice a day. Some brands, like Flutiform, come in different forms such as 50/5mcg and 125/5mcg. In this case if an individual was starting on low dose they would receive the 50/5mcg preparation whereas if starting on moderate dose they would likely receive the 125/5mcg preparation.

The PCA data does not break down who the Fostair 100/6mcg inhaler is provided for; rather it just gives the total number of prescriptions. Therefore when trying to calculate the most commonly prescribed brand for those starting on low dose ICS + LABA if a brand can be prescribed across multiple dosages an assumption needs to be made regarding what proportion of these prescriptions are for those taking low, moderate or high dose.

To account for this it was assumed that if a brand comes in multiple forms then each form would exclusively be prescribed for either low, moderate or high dose. For example it was assumed that Flutiform 50/5mcg would **only** be prescribed for those on low dose ICS + LABA. This assumption tends to reduce the average cost of prescribing ICS + LABA as it costs more to prescribe low dose brands more often. For example it costs nearly twice as much to prescribe Symbicort 100mcg/6mcg (120 D) for someone taking 400mcg a day than it does to prescribed Symbicort 200mcg/6mcg (120 D).

A second assumption that was made was that for brands that do not come in multiple forms and are prescribed for both low and moderate dose these will be prescribed for low dose 50% of the time and prescribed for moderate dose 50% of the time. Likewise brands that do not come in multiple forms and are prescribed for both moderate and high dose will be prescribed for moderate dose 50% of the time and prescribed for high dose 50% of the time. The brands this assumption affects are highlighted with a (2) in Table 133 above. These assumptions will likely overestimate the proportion

of prescriptions given for moderate and high dose treatments. However it was noted that this assumption had minimal impact on the average costs.

Another method that was explored was to calculate how often a brand is prescribed across all dosages and assume this weighting was the same across low, moderate and high. The concern with this approach is that some brands are not prescribed across all dosages. For example Fostair 100/6mcg cannot be prescribed for high dose; likewise some brands are specifically targeted towards treating a high dose population. Therefore if this method was chosen, when trying to calculate the average cost of prescribing low dose ICS + LABA, brands that can be prescribed at a higher dose would incorrectly receive a higher weighting across lower dosages. This over-estimates the cost of prescribing ICS + LABA at lower dosages.

The second consideration concerned brands that could be prescribed for both adults and children. Some brands are only licensed for adults and some are licensed for both children and adults. Therefore when trying to calculate how often a brand is prescribed for a certain comparator consideration needs to be given as to whether the brand is prescribed for both adults and children. For example when looking at what brands are most commonly prescribed for ICS + LABA in adults there is a choice between Fostair and Symbicort amongst many others. For children Symbicort is licensed whereas Fostair is not. When trying to calculate how often each brand is prescribed in adults, ideally the brands that can also be prescribed in children should be adjusted downwards otherwise the weighting will be overstated. To account for this some brands that are predominantly prescribed in children, such as those with a very low dose, were excluded from the adult costing. These are highlighted with a (1) in Table 133 above. If a brand can be prescribed for both adults and children it was assumed 20% of the prescriptions would be for children and 80% would be for adults, this assumption was based on the fact that 20% of individuals with asthma in the UK are children. These brands are highlighted with a (3) in Table 133 above. These adjustments were not made for any of the ICS brands as all are licenced for use in both adults and children.

Various different assumptions were applied to the data however the average weighted cost did not change much. This is because a few brands tended to dominate. For single ICS inhalers this is Clenil and for ICS + LABA this is Fostair and Symbicort. Therefore the average costs tend to be close to the cost of prescribing these brands.

These assumptions were tested in a sensitivity analysis in the model by assuming that the cheapest brand would always be prescribed.

Table 134: Costs for single ICS inhaler (adult doses)

Drug Name	Annual cost (low dose)	Annual cost (moderate dose)	Annual cost (high dose)
Asmabec Clickhaler_D/P Inh 100 mcg (200 D)	£35.81	£71.61	-
Qvar 50_Inha 50 mcg (200 D)	£56.50	-	-
Qvar 100_Inha 100 mcg (200 D)	-	£123.74	£247.47
Qvar 50_Autohaler 50 mcg (200 D)	£57.45	-	-
Qvar 100_Autohaler 100 mcg (200 D)	-	£125.63	£251.27
Qvar 50 E-Breathe_Inha 50 mcg (200 D)	£57.45	-	-
Qvar 100 E-Breathe_Inha 100 mcg (200 D)	-	£125.63	£251.27
Clenil Modulite_Inha 100 mcg (200 D)	£54.17	-	-
Clenil Modulite_Inha 200 mcg (200 D)	-	£118.04	-
Clenil Modulite_Inha 250 mcg (200 D)	-	-	£118.92
Pulmicort_Turbohaler 200 mcg (100 D)	-	£172.86	-
Pulmicort_Turbohaler 400 mcg (50 D)	-	-	£404.71
Pulmicort_Turbohaler 100 mcg (200 D)	£86.43		-
Easyhaler_Budesonide 100 mcg (200 D)	£64.68	-	-
Easyhaler_Budesonide 200 mcg (200 D)	-	£129.28	-
Easyhaler_Budesonide 400 mcg (100 D)	-	-	£258.57
Flixotide_Accuhaler 100 mcg (60 D)	£108.65	-	-
Flixotide_Accuhaler 250 mcg (60 D)	-	£258.66	-
Flixotide_Accuhaler 500 mcg (60 D)	-	-	£439.70
Flixotide_Evohaler 125 mcg (120 D)	-	£258.66	-
Flixotide_Evohaler 250 mcg (120 D)	-	-	£439.70
Flixotide_Evohaler 50 mcg (120 D)	£97.03	-	-
Asmanex Twisthaler_D/P Inh 200 mcg	£143.20	-	-

Drug Name	Annual cost (low dose)	Annual cost (moderate dose)	Annual cost (high dose)
Asmanex Twisthaler_D/P Inh 400 mcg	-	£219.30	-
Alvesco 80_Inh 80 mcg (120 D) CFF	£199.72	-	-
Alvesco 160_Inh 160 mcg (120 D) CFF	-	£234.94	-

Table 135: Weighted costs for single ICS inhaler (adult doses)

How often brands are prescribed overall (1)			Weighted cost for low dose ICS			Weighted cost for moderate dose ICS			Weighted cost for high dose ICS		
Brand	Items dispensed	Weight	Items dispensed	Weight	Weighted cost	Items dispensed	Weight	Weighted cost	Items dispensed	Weight	Weighted cost
Asmabec	219	0.00	110	0.000	£0.01	110	0.00	£0.07	0	-	-
Qvar inha	75094	0.17	26232	0.09	£5.11	32575	0.27	£33.66	16287	0.38	£93.24
Qvar auto	10259	0.02	2967	0.01	£0.59	4861	0.04	£5.10	2431	0.06	£14.13
Qvar E	16934	0.04	6148	0.02	£1.22	7191	0.06	£7.54	3595	0.08	£20.90
Clenil	302747	0.67	233613	0.805	£43.59	56478	0.47	£55.67	12656	0.29	£34.82

How often brands are prescribed overall (1)			Weighted cost for low dose ICS			Weighted cost for moderate dose ICS			Weighted cost for high dose ICS		
Pulmicort	19704	0.04	7656	0.026	£2.28	7656	0.06	£11.05	4393	0.10	£41.13
Easyhaler	4453	0.01	3084	0.011	£0.69	1026	0.01	£1.11	343	0.01	£2.05
Flixotide accuhaler	6339	0.01	2970	0.010	£1.11	2203	0.02	£4.76	1166	0.03	£11.86
Flixotide evohaler	13575	0.03	6523	0.022	£2.18	4701	0.04	£10.15	2351	0.05	£23.91
Asmanex	427	0.00	209	0.001	£0.10	218	0.00	£0.40	0	-	-
Alvesco	3411	0.01	709	0.002	£0.49	2702	0.02	£5.30	0	-	-

How often brands are prescribed overall (1)			Weighted cost for low dose ICS			Weighted cost for moderate dose ICS			Weighted cost for high dose ICS		
			Average cost for low dose ICS:		**£57.37**	**Average cost for moderate dose ICS:**		**£138.23**	**Average cost for high dose ICS:**		**£242.06**

(1) this column is just used to demonstrate how often each brand is prescribed overall, it is not used in any of the average cost calculations.

Table 136: Costs for combined ICS+LABA inhaler (adult doses)

Drug Name	Annual cost (low dose)	Annual cost (moderate dose)	Annual cost (high dose)
Fostair_Inh 100 mcg/6 mcg (120 D) CFF	£178.36	£356.73	-
Fostair NEXThaler_Inh 100 mcg/6 mcg (120 D)	£178.36	£356.73	-
Fostair_Inh 200 mcg/6 mcg (120 D) CFF	-	-	£356.73
Fostair NEXThaler_Inh 200 mcg/6 mcg (120 D)	-	-	£356.73
Symbicort_Turbohaler 200 mcg/6 mcg (120 D)[(a)]	£231.17	£462.33	-
Symbicort_Turbohaler 400 mcg/12 mcg (60 D)[(a)]	-	£462.33	£924.67
DuoResp Spiromax_Inh 160 mcg/4.5 mcg (120 D)	£182.32	£364.64	-
DuoResp Spiromax_Inh 320 mcg/9 mcg (60 D)	-	£364.64	£729.27
Seretide 100_Accuhaler 100 mcg/50 mcg (60 D)	£219.00	-	-
Seretide 250_Accuhaler 250 mcg/50 mcg (60 D)	-	£425.83	-
Seretide 500_Accuhaler 500 mcg/50 mcg (60 D)	-	-	£497.86
Seretide 50_Evohaler 50 mcg/25 mcg (120 D)	£219.00	-	-
Seretide 125_Evohaler 125 mcg/25 mcg (120 D)	-	£425.83	-
Seretide 250_Evohaler 250 mcg/25 mcg (120 D)	-	-	£723.67
Flutiform_Inha 125/5 mcg (120 D)	-	£340.67	-

Drug Name	Annual cost (low dose)	Annual cost (moderate dose)	Annual cost (high dose)
Flutiform_Inha 250/10 mcg (120 D)	-	-	£554.31
Flutiform_Inha 50/5 mcg (120 D)	£175.20	-	-
Relvar Ellipta_Inha 184 mcg/22 mcg (30 D)	-	-	£358.92
Relvar Ellipta_Inha 92 mcg/22 mcg (30 D)	-	£267.67	-

(a) Costs have recently changed, but were correct at the time of development of and consultation on this guideline. See sensitivity analysis SA15 in appendix N.

Table 137: Weighted average for ICS + LABA (adult doses)

How often brands are prescribed overall[a]			Weighted cost for low dose ICS + LABA			Weighted cost for moderate dose ICS + LABA			Weighted cost for high dose ICS + LABA		
Brand	Items dispensed	Weight	Items dispensed	Weight	Weighted cost	Items dispensed	Weight	Weighted cost	Items dispensed	Weight	Weighted cost
Fostair	205742	0.25	98056	0.3740	£66.70	98056	0.3579	£127.67	9630	0.0369	£13.18
Symbicort[b]	172757	0.22	49230	0.1878	£43.40	49230	0.1797	£83.07	74296	0.2850	£263.51
Duoresp	72363	0.10	40599	0.1548	£28.23	15882	0.0580	£21.14	15882	0.0609	£44.43
Seretide Acc	136865	0.17	16486	0.0629	£13.77	43817	0.1599	£68.10	76562	0.2937	£146.21
Seretide Evo	129651	0.16	36104	0.1377	£30.15	40987	0.1496	£63.70	52560	0.2016	£145.89

How often brands are prescribed overall[a]			Weighted cost for low dose ICS + LABA			Weighted cost for moderate dose ICS + LABA			Weighted cost for high dose ICS + LABA		
Flutiform	48742	0.06	21730	0.0829	£14.52	21057	0.0769	£26.18	5955	0.0228	£12.66
Relvar	30781	0.04	0	0.0000	-	4956	0.0181	£4.84	25825	0.0991	£35.55
Single LABA[c]	49064	*See table 137 below*	-	0.0587	£23.45	-	0.0587	£28.00	-	0.0580	£34.10
			Average cost for low dose ICS+LABA:		£208.55	**Average cost for moderate dose ICS+LABA:**		£399.69	**Average cost for high dose ICS+LABA:**		£657.17

(a) This column is just used to demonstrate how often each brand is prescribed overall, it is not used in any of the average cost calculations.
(b) Costs have recently changed, but were correct at the time of development of and consultation on this guideline. See sensitivity analysis SA15 in appendix N.
(c) The cost of a single LABA inhaler was taken from Table 137 below.

Table 138: Weighted average for single ICS+LABA inhaler (adult doses)

Brand	Annual cost	items dispensed	Weight	Weighted cost
Salmeterol_Inha 25 mcg (120 D) CFF	£364.51	34519	0.56284	£205.16
Serevent_Accuhaler 50 mcg (60 D)	£356.00	9082	0.148084	£52.72
Serevent_Evohaler 25 mcg (120 D)	£364.51	5005	0.081608	£29.75
Foradil_Inh Cap 12 mcg + Inha	£341.40	699	0.011397	£3.89
Oxis 6_Turbohaler 6 mcg (60 D)	£603.47	1361	0.022191	£13.39
Oxis 12_Turbohaler 12 mcg (60 D)	£301.73	3469	0.056563	£17.07
Atimos Modulite_Inh 12 mcg (100 D)	£219.44	2868	0.046763	£10.26
Formoterol Easyhaler_12 mcg (120 D)	£144.48	4327	0.070553	£10.19
			Average cost for single LABA inhaler:	£342.43

Table 139: Weighted average for LTRA (adult doses)

Brand	Annual cost	Items Dispensed	Weight	Weighted cost
Accolate_Tab 20 mg	£231.38	2699	0.018198614	£4.21
Montelukast_Tab 10 mg	£22.29	144369	0.973440408	£21.70
Singulair_Tab 10 mg	£351.57	1240	0.008360979	£2.94
			Average cost for LTRA:	£28.85

Table 140: Weighted average for Theophylline (adult doses)

Brand	Cost/year	Items Dispensed	Weight	Weighted cost
Nuelin SA_Tab 175 mg	£77.62	411	0.009949887	£0.77
Nuelin SA-250_Tab 250 mg	£108.53	415	0.010046723	£1.09
Slo-Phyllin_Cap 60 mg	£74.96	681	0.01648631	£1.24

Brand	Cost/year	Items Dispensed	Weight	Weighted cost
Slo-Phyllin_Cap 125 mg	£45.36	2270	0.054954366	£2.49
Slo-Phyllin_Cap 250 mg	£28.29	5636	0.136441765	£3.86
Uniphyllin Continus_Tab 400 mg	£36.83	5515	0.13351248	£4.92
Uniphyllin Continus_Tab 200 mg	£62.18	20668	0.50035103	£31.11
Uniphyllin Continus_Tab 300 mg	£25.72	5711	0.138257438	£3.56
			Average cost for theophylline:	£49.04

Both LAMAs and sodium cromoglicate only come in one form therefore a weighted average was not needed. The table below summarises the cost of prescribing each brand for adults.

Summary of costs for adults

Table 141: Summary of adult costs

Drug class	Cost/year
Low dose ICS	£57.34
Moderate dose ICS	£138.23
High dose ICS	£242.06
Low dose ICS + LABA	£208.55
Moderate dose ICS + LABA	£399.69
High dose ICS + LABA	£657.17
LAMA	£407.58
Theophylline	£49.04
Sodium cromoglicate	£477.89
LTRA	£28.85

O.3 Unit costs for children

O.3.1 Low dose ICS (child dose)

Table 142: Single ICS inhaler (child low dose)

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Clenil Modulite_Inha 50 mcg (200 D)	50	200	200	£3.70	£0.02	£0.00	£0.07	£27.01
Pulmicort_Turbohaler 100 mcg (200 D)	100	200	200	£11.84	£0.06	£0.00	£0.12	£43.22
Flixotide_Accuhaler 50 mcg (60 D)	50	60	100	£6.38	£0.11	£0.00	£0.21	£77.62
Flixotide_Evohaler 50 mcg (120 D)	50	120	100	£5.44	£0.05	£0.00	£0.09	£33.09

O.3.2 Moderate dose ICS (child dose)

Table 143: Single ICS inhaler (child moderate dose)

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Asmabec Clickhaler_D/P Inh 100 mcg (200 D)	100	200	200	£9.81	£0.05	£0.00	£0.10	£35.81
Qvar 50_Inha 50 mcg (200 D)	50	200	200	£7.74	£0.04	£0.00	£0.15	£56.50
Qvar 50_Autohaler 50 mcg (200 D)	50	200	200	£7.87	£0.04	£0.00	£0.16	£57.45
Qvar 50 E-Breathe_Inha 50 mcg (200 D)	50	200	200	£7.87	£0.04	£0.00	£0.16	£57.45
Clenil Modulite_Inha 100 mcg (200 D)	100	200	400	£7.42	£0.04	£0.00	£0.15	£54.17
Pulmicort_Turbohaler 100 mcg (200 D)	100	200	400	£11.84	£0.06	£0.00	£0.24	£86.43
Pulmicort_Turbohaler 200 mcg (100 D)	200	100	400	£11.84	£0.12	£0.00	£0.24	£86.43
Easyhaler_Budesonide 100 mcg (200 D)	100	200	400	£8.86	£0.04	£0.00	£0.18	£64.68
Flixotide_Accuhaler 100 mcg (60 D)	100	60	200	£8.93	£0.15	£0.00	£0.30	£108.65
Flixotide_Evohaler 50 mcg (120 D)	50	120	200	£5.44	£0.05	£0.00	£0.18	£66.19
Asmanex Twisthaler_D/P Inh 200 mcg (60 D)	200	60	400	£23.54	£0.39	£0.00	£0.78	£286.40
Alvesco 80_Inh 80 mcg (120 D) CFF	80	120	160	£32.83	£0.27	£0.00	£0.55	£199.72

O.3.3 High dose ICS (child dose)

Table 144: Single ICS inhaler (child high dose)

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Asmabec Clickhaler_D/P Inh 100 mcg (200 D)	100	200	400	£16.95	£0.08	£0.00	£0.34	£123.74
Qvar 100_Inha 100 mcg (200 D)	100	200	400	£16.95	£0.08	£0.00	£0.34	£123.74
Qvar 100_Autohaler 100 mcg (200 D)	100	200	400	£17.21	£0.09	£0.00	£0.34	£125.63
Qvar 100 E-Breathe_Inha 100 mcg (200 D)	100	200	400	£17.21	£0.09	£0.00	£0.34	£125.63
Pulmicort_Turbohaler 200 mcg (100 D)	200	100	800	£11.84	£0.12	£0.00	£0.47	£172.86
Pulmicort_Turbohaler 400 mcg (50 D)	400	50	800	£13.86	£0.28	£0.00	£0.55	£202.36
Easyhaler_Budesonide 200 mcg (200 D)	200	200	800	£17.71	£0.09	£0.00	£0.35	£129.28
Flixotide_Accuhaler 250 mcg (60 D)	250	60	500	£21.26	£0.35	£0.00	£0.71	£258.66
Flixotide_Evohaler 125mcg (120 D)	125	120	500	£21.26	£0.18	£0.00	£0.71	£258.66
Alvesco 160_Inh 160 mcg (120 D) CFF	160	120	320	£38.62	£0.32	£0.00	£0.64	£234.94

O.3.4 Low dose combined ICS + LABA inhaler (child dose)

Table 145: ICS + LABA combined inhaler (child low dose)

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Symbicort_Turbohaler 100 mcg/6 mcg (120 D)[(a)]	100	120	200	£33.00	£0.28	£0.00	£0.55	£200.75

(a) Costs have recently changed to £28.00 per pack, but were correct at the time of development of and consultation on this guideline. See sensitivity analysis SA15 in appendix N.

O.3.5 Moderate dose combined ICS + LABA inhaler (child dose)

Table 146: ICS + LABA combined inhaler (child moderate dose)

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Symbicort_Turbohaler 100 mcg/6 mcg (120 D)[(a)]	100	120	400	£33.00	£0.28	£0.00	£1.10	£401.50
Symbicort_Turbohaler 200 mcg/6 mcg (120 D)[(a)]	200	120	400	£38.00	£0.32	£0.00	£0.63	£231.17
Seretide 100_Accuhaler 100 mcg/50 mcg (60 D)	100	60	200	£18.00	£0.30	£0.00	£0.60	£219.00
Seretide 50_Evohaler 50 mcg/25 mcg (120 D)	50	120	200	£18.00	£0.15	£0.00	£0.60	£219.00

(a) Costs have recently changed to £28.00 per pack, but were correct at the time of development of and consultation on this guideline. See sensitivity analysis SA15 in appendix N.

O.3.6 LTRA (child dose)

Table 147: LTRA (child dose)

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Montelukast_Tab 5 mg	5	28	5	1.61	£0.06	£0.01	£0.06	£20.99
Singulair_Tab 5 mg	5	28	5	25.69	£0.92	£0.18	£0.92	£334.89

O.3.7 Sodium cromoglicate

Table 148: Sodium cromoglicate

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Intal_Inha 5 mg (112 D) CFF	5	112	40	£18.33	£0.16	£0.03	£1.31	£477.89

O.3.8 Theophylline

Table 149: Theophylline (child dose)

Brand	Mg/unit	Unit/pack	Mg/day	Cost/pack	Cost/unit	Cost/mg	Cost/day	Cost/year
Nuelin SA_Tab 175 mg	175	60	350	£6.38	£0.11	£0.00	£0.21	£77.62
Nuelin SA-250_Tab 250 mg	250	60	250	£8.92	£0.15	£0.00	£0.15	£54.26
Slo-Phyllin_Cap 60 mg	60	56	60	£2.76	£0.05	£0.00	£0.05	£17.99
Slo-Phyllin_Cap 125 mg	125	56	125	£3.48	£0.06	£0.00	£0.06	£22.68
Slo-Phyllin_Cap 250 mg	250	56	250	£4.34	£0.08	£0.00	£0.08	£28.29
Uniphyllin Continus_Tab 200 mg	200	56	200[1]	£4.77	£0.09	£0.00	£0.09	£31.09

Source/Note: represents the maximum dosage that would be prescribed according to the BNF

As a model was not built for children an exact cost was not needed for each class of medication. The committee were presented with the PCA data outlining how often each brand was prescribed along with the most commonly prescribed brand.

O.3.9 Summary of costs for children

Table 150: Summary of child costs (using the most commonly prescribed brand)

Brand	Cost/year
Low dose ICS	£27.01
Moderate dose ICS	£54.17
High dose ICS	£118.04
Low dose ICS + LABA	£200.75
Moderate dose ICS + LABA	£231.17
Theophylline	£31.09
Sodium cromoglicate	£477.89
LTRA	£20.99

Appendix P: Research recommendations

The guideline committee identified a number of uncertainties during the development of this guideline. Five of these uncertainties were chosen as priorities for research recommendations and are outlined in detail in the sections below.

1. Starting asthma treatment
2. Second line preventer in children and young people (under 16)
3. Addition of preventers beyond ICS high dose + LABA
4. Decreasing pharmacological treatment
5. Improving adherence to asthma medication.

Other uncertainties are discussed in the linking evidence to recommendations sections of the relevant reviews and include the optimal method of delivering self-management, the clinical and cost effectiveness of intermittent ICS (particularly as triggered by seasonal periods) and the clinical and cost effectiveness of breathing exercises or breathing retraining.

P.1 Starting asthma treatment

Research question: In adults, children and young people 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 beta$_2$ 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?

Why this is important:

Recently best practice has shifted from starting people with asthma on a SABA as a reliever alone and starting maintenance therapy only if the person continues to have persistent asthma symptoms, to starting people on a low dose inhaled corticosteroid (ICS) as maintenance therapy alongside the SABA at the first instance. The committee agree with this shift and have included consensus based recommendations in line with this pattern. However the shift is not based on direct clinical evidence comparing these two strategies for the general population of newly diagnosed asthmatics. There is also little evidence to support the particular groups in which one option or other is more appropriate.

PICO question	Population: children, young people and adults with asthma who have not been prescribed a SABA or preventer previously. The population should be stratified by the presence or absence of potential prognostic factors such as high FeNO, eosinophilia, atopy. Intervention(s): ICS low dose + PRN SABA, PRN SABA alone Comparison: ICS low dose + PRN SABA versus PRN SABA alone Outcome(s): Severe exacerbations and quality of life should be prioritised, additional outcomes as per the review protocol for this question in the guideline. The duration of any research should be at least 12 months in order to capture longer term benefits.
Importance to patients or the population	If there is a group of people who would benefit from bypassing treatment solely with a PRN SABA then this study could identify that population and potentially provide significant long-term benefits.

Relevance to NICE guidance	Research in this area could allow NICE recommendations for specific groups of people to bypass a period of asthma management solely with a PRN SABA.
Relevance to the NHS	Early treatment with a preventer could potentially prevent longer term deterioration and reduce severe exacerbations although it would increase treatment costs.
Current evidence base	There is currently no evidence addressing this specific question.
Study design	This should be a randomised trial with prospective stratification of the trial population by prognostic markers.
Feasibility	The trial will have to account for the need of some participants to progress to a preventer during the time period that they are assigned to PRN SABA alone.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.2 Second-line preventer in children and young people (under 16)

Research question: 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 beta2 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?

Why this is important:

There is a lack of evidence on managing asthma in children and young people under 16. Many of the recommendations for children and young people in this guideline were made using extrapolation from the adult evidence and the consensus of the guideline committee. The guideline committee would like to encourage more research in this age group. This particular question was prioritised because it affects the early stages of the treatment pathway and could have significant clinical and cost implications for the managing asthma in this age group.

PICO question	Population: children and young people (aged 16 and under) with asthma that is uncontrolled on low dose ICS + PRN SABA. Intervention(s): ICS low dose + LABA + PRN SABA, ICS low dose + LTRA + PRN SABA Comparison: ICS low dose + LABA + PRN SABA vs ICS low dose + LTRA + PRN SABA Outcome(s): Severe exacerbations and quality of life should be prioritised, additional outcomes as per the review protocol for this question in the guideline. The duration of any research should be at least 12 months in order to capture longer term benefits.
Importance to patients or the population	Currently the recommendations to use LTRAs prior to LABAs in the under 16 age group are principally driven by extrapolations from adult data. If there are different effects in the under 16 age group this could impact upon clinical outcomes for this population.
Relevance to NICE guidance	Evidence in this area could either strengthen the current weak recommendations for this age group or justify a deviation from the recommendations for adults.
Relevance to the NHS	Optimising preventer therapy for children could potentially both improve clinical

	outcomes as well as reduce costs if a significant reduction in severe exacerbations and hospitalisations is seen.
Current evidence base	The current evidence base in this age group is limited, it principally revolves around a handful of very small studies or is an extrapolation from adult evidence.
Study design	This study should be a randomised controlled trial with blinding of participants, likely requiring a double dummy design due to the different formulations (oral and inhaled) of the two preventer strategies.
Feasibility	As the study focuses on children, ethical approval may be more challenging but due to the uncertainties in this area further research is justified.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.3 Additional maintenance therapy for asthma uncontrolled on a moderate dose of ICS plus LABA with or without LTRA

Research question: 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?

Why this is important:

The evidence is insufficient in quantity and quality to support strong recommendations for the use of additional maintenance therapy beyond moderate dose ICS plus LABA. The clinical evidence tends to favour the addition of a long-acting muscarinic antagonist (LAMA) but the guideline committee did not consider this to be conclusive, particularly because the addition of a LAMA is not cost effective compared with treatment with a placebo. In current practice, the alternative treatment options to adding a LAMA at this stage are increasing ICS dose to high, addition of theophyllines or a course of oral steroids. Therefore to truly understand the cost effectiveness of LAMAs, an RCT and health economic analysis taking into account the impact of LAMAs on oral steroid use and comparing the addition of LAMAs to any alternative strategy (as opposed to just placebo) is needed. The guideline committee felt the body of evidence, supported by consensus agreement and current practice, was sufficient to weakly recommend the options of ICS high dose plus LABA, addition of a LAMA or theophylline or seeking advice from a healthcare professional with expertise in asthma. However a study comparing these various strategies would be critical for stronger recommendations or a more specific order of options.

PICO question	Population: children, young people and adults with asthma that is uncontrolled on moderate or high dose ICS + LABA + PRN SABA. Intervention(s): ICS high dose + LABA + PRN SABA, ICS moderate/high dose + LABA + LAMA + PRN SABA, ICS moderate/high dose + LABA + theophyllines + PRN SABA Comparison: Any of the above strategies compared to each other, continuing on previous preventer treatment (+ placebo) should also be included but the priority should be comparing different additional strategies. Outcome(s): Severe exacerbations and quality of life should be prioritised, additional outcomes as per the review protocol for this question in the guideline. The duration of any research should be at least 12 months in order to capture longer term benefits.
Importance to patients	There is a group of people with asthma whose asthma will still be uncontrolled on ICS moderate/high dose + LABA. This research could provide sufficient

or the population	evidence for recommendations on additional preventer strategies at that stage.
Relevance to NICE guidance	This research would allow for a stronger and more hierarchical set of recommendations beyond ICS moderate dose + LABA.
Relevance to the NHS	Optimising preventer therapy at this stage could improve clinical outcomes and reduce erroneous use of costly medication.
Current evidence base	The current evidence base is limited. Studies in this area typically recruit a heterogenous population of people on a number of different preventer treatments and often not all participants have asthma that is uncontrolled on ICS + LABA. The majority of the evidence compares intervention strategies to placebo and not to each other.
Study design	Studies in this area should be randomised controlled trials with blinding of participants, likely requiring a double dummy design due to the different formulations (oral and inhaled) of the various preventer strategies. The studies should include a cost-effectiveness analysis, particularly to take into account the cost of oral steroid use in placebo arms. The studies should stratify their population by the presence of prognostic factors (for example high FeNO, eosinophilia, atopy) to determine if certain subgroups may benefit from different strategies.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.4 Decreasing pharmacological treatment

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

Why this is important:

There is consensus within the guideline committee and across healthcare professionals managing asthma that people with well-controlled asthma should not remain on high dose or multiple preventer medicines for long periods of time. However, there is little evidence available about which people might benefit most from decreasing regular maintenance therapy. This guideline identified 3 studies attempting to answer this question but none of them included a sufficiently large population, with suitable decrease in treatment throughout and assessment of multiple prognostic markers.

PICO question	Population: children, young people and adults with asthma that is currently controlled on preventer therapy. Intervention(s): decreasing regular preventer therapy, stratified by specific step (for example stopping LABA, reducing ICS dose, ceasing ICS treatment) Prognostic markers: duration of asthma control, time since last exacerbation, use of reliever medication, ACQ/ACT score, FeNO Outcome(s): successful step down as defined by maintained step down without exacerbation beyond at least 4 weeks
Importance to patients or the population	Identifying evidence-based prognostic markers for the success of step down would give people with asthma and their healthcare professionals more confidence to step down when appropriate and avoid inappropriate step downs.
Relevance to NICE guidance	Answering this question would allow recommendations to step down (or not) based on specific characteristics of people with asthma.
Relevance to the NHS	Appropriate and successful step downs of preventer therapy reduce unnecessary medication costs without incurring adverse clinical outcomes, identifying useful

	prognostic markers will increase the likelihood of step downs being appropriate.
Current evidence base	There is very limited evidence in this area; the studies identified by this guideline were limited by their small size or inappropriate study design.
Study design	Studies looking to answer this question should be prospective and involve step downs that are initiated by the person with asthma in conjunction with a healthcare professional. Prognostic accuracy data should be collected demonstrating the sensitivity, specificity, positive predictive value and negative predicitive value of each of the potential prognostic markers for identifying people who will have a successful step down.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.5 Improving adherence to asthma medication

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

Why this is important:

There is a consensus within the guideline committee and across healthcare professionals that medicines adherence is an important determinant of asthma control, and that non-adherence is a common problem. However, there is a lack of high-quality evidence on methods to improve adherence to asthma medicines. The guideline identified a number of studies focusing on this question, but there was not a strong body of evidence behind any specific intervention strategy. In addition, the guideline committee had concerns about the applicability of studies that did not report outcomes after a prolonged follow-up and studies that only used self-reported measures to assess adherence. The guideline committee felt further and higher quality research is needed to recommend specific interventions for this common and significant problem.

PICO question	Population: children, young people and adults with asthma who are prescribed preventer therapy but are non-adherent (taking ≤80% of their prescribed medication) Intervention(s): more frequent review, asthma adherence-specific education, inhaler alarms, behavioural change interventions Comparison: usual care or any other intervention Outcome(s): Severe exacerbations, quality of life and adherence should be prioritised, additional outcomes as per the review protocol for this question in the guideline. The duration of any research should be at least 3 months beyond the end of the intervention in order to assess for long-term behaviour change.
Importance to patients or the population	New or altered guidance in this area may increase the options available to people who are non-adherent to their asthma preventer therapy and wish to improve their adherence.
Relevance to NICE guidance	Further evidence in this area could allow for recommendations to use or not use the specific interventions outlined above. The current recommendations to follow the generic NICE guidance in this area do not specifically endorse any one intervention category.
Relevance to the NHS	Non-adherence leads to wasted medication and poor clinical outcomes. If a clinically and cost-effective strategy to improve adherence can be identified this could both reduce costs and improve clinical outcomes.
Current evidence base	The current evidence base involves mostly small trials with short-term follow-up.

	Outcomes are usually only focused on adherence, which is assessed using measures that the committee considers sub-optimal (for example self-reported).
Study design	Research in this area should involve randomised clinical trials, ideally with some sort of sham component for the usual care arm. The trials need to assess clinical outcomes at least 3 months after the end of the intervention to demonstrate any lasting effects and therefore a greater chance of long-term cost effectiveness. The trials should also use objective measures of assessing adherence, ideally some sort of inhaler that monitors actual use.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

Appendix Q: Additional information

Q.1 Dose equivalency tables

Adults and adolescents	Low dose	Moderate dose	High dose
Beclometasone dipropionate (CFC)	200–500 µg	>500–1000 µg	>1000 µg
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	>440µg
Triamcinolone acetonide	400–1000 µg	>1000–2000 µg	>2000 µg

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

Appendix R: NICE technical team

Name	Role
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Judith Thornton	Technical Lead
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