

CHAPTER 16

RESPIRATORY DISORDERS

16.1 ASTHMA, ACUTE EXACERBATION

J45.0-1/J45.8-9/J46

DESCRIPTION

Acute asthma is an emergency and presents with one or more of the following:

- » wheeze
- » chest tightness
- » breathlessness
- » cough
- » respiratory distress

Risk factors for asthma-related death

- » History of near-fatal asthma requiring intubations and mechanical ventilation.
- » Hospitalisation or emergency care visit for asthma in the past year.
- » Currently using or recent discontinuation of oral corticosteroids.
- » Not currently using inhaled corticosteroids.
- » Frequent use of short acting β_2 -agonists (SABA), defined as average SABA usage ≥ 1 metered dose inhaler (MDI) canister, or ≥ 1 unit of nebuliser solution, per month.
- » Poor adherence to ICS-containing medications.
- » A history of psychiatric disease or psychosocial problems.
- » Food allergy in a patient with asthma.
- » Presence of pneumonia, diabetes or arrhythmias (each individually associated with an increased risk of death after hospitalisation for an asthma exacerbation).

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DIAGNOSIS

Classify the patient according to the most severe clinical features present, e.g., if a patient has some features of mild-moderate exacerbation, but a single severe or life-threatening feature, manage them according to the higher severity assessment.

Table 16.1: Recognition and assessment of severity of asthma exacerbation in adults and adolescents ≥ 12 years

	Mild-Moderate	Severe	Life-Threatening
Oxygen saturation	$\geq 90\%$	$< 90\%$ on room air	$< 90\%$ on oxygen
Talks in	Phrases	Words	Unable to speak
Alertness	Normal	Usually agitated	Agitated, drowsy or confused
Respiratory rate	≤ 30 breaths/minute	> 30 breaths/minute	> 30 breaths/minute, OR feeble effort

Wheeze	Present	Present	Silent chest
Heart rate	100–120 beats/minute	> 120 beats/minute	< 60 beats/minute
PEFR (%)	≥ 60% of predicted	33–60% of predicted PEF	< 33% of expected, or unable to perform test

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PEFR is expressed as percentage of predicted normal (or personal best if known). See PEF charts in Appendix V: Asthma monitoring.

Differential Diagnosis

- » For patients 50 years of age or older, with a first presentation of asthma, consider pulmonary oedema due to heart failure as an alternate diagnosis.
- » In patients who do not respond within one hour of initiating the acute asthma algorithm, exclude upper airway obstruction/stridor, pneumothorax, and anaphylaxis.

GENERAL MEASURES

- » Assess the severity of the exacerbation and treat according to the management algorithm below.
- » Monitor response to treatment with repeated PEFR and clinical signs. Assess need to escalate therapy hourly, or sooner if worsening clinically.
- » Exclude upper airway obstruction/stridor, pneumothorax, and anaphylaxis.
- » Ideally, patients with a moderate, severe, or life-threatening asthma exacerbation should be closely monitored in a high care- or intensive care unit.

Table 16.2: Features of clinical response to treatment in adults and adolescent ≥12 years

	No response	Response
PEFR (if possible)	Improvement by < 20%	Improvement by ≥ 20%
Respiratory rate	> 20 breaths/ minute	≤ 20 breaths/ minute
Speech	Impaired	Normal

MEDICINE TREATMENT

Bronchodilator administration:

- » Salbutamol administered via spacer is as effective as via nebuliser.
- » When using metered dose inhalers (MDIs), shake inhaler between each puff.
- » For guidance on inhaler, spacer and nebuliser device techniques, see Appendix VI: Devices for Respiratory Conditions.

Mild to moderate exacerbations

- Salbutamol, 100 mcg metered-dose inhaler (MDI).
 - Salbutamol inhaler 400–1000 mcg (4–10 puffs) using a spacer.
 - Shake the inhaler between each puff.
 - If no relief, repeat every 20 minutes in the first hour.
 - Thereafter, repeat every 2–4 hours if needed.

LoE:IIIbⁱⁱⁱ**OR**

- Salbutamol 0.5% (5 mg/mL), nebuliser solution.
 - Administer 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL solution by adding 3 mL sodium chloride 0.9%.
 - Recommended delivery at a flow rate of 8 L/minute with oxygen.
 - If no relief, repeat every 20 minutes in the first hour.
 - Thereafter, repeat every 2–4 hours if needed.

LoE:IIIb^{iv}**PLUS**

- Prednisone, oral, 40 mg immediately if patient is known to have asthma/COPD.
 - Follow with prednisone, oral, 40 mg daily for 5 days.

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Severe exacerbations

- Oxygen to keep oxygen saturation 93–95%.

AND

- Salbutamol 0.5% (5 mg/mL), nebuliser solution.
 - Administer 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL solution by adding 3 mL sodium chloride, 0.9%.
 - Recommended delivery at a flow rate of 8 L/minute with oxygen.
 - If no relief, repeat every 20 minutes until PEF > 60% of predicted.
 - Once clinical improvement is noted, repeat every 2–4 hours if needed.

LoE:IIIb^v**OR (if no oxygen required)**

- Salbutamol 100 mcg MDI.
 - Salbutamol 400–1000 mcg (4–10 puffs), using a spacer.
 - If no relief, repeat every 20 minutes until PEF > 60% of predicted.
 - Once clinical improvement is noted, repeat every 2–4 hours if needed.

LoE:IIIb^{vi}If response is poor after first salbutamol nebulisation/inhalation:

Continue oxygen and salbutamol nebuliser therapy described above, and:

ADD

- Ipratropium bromide 0.5 mg/2 mL, nebuliser solution.
 - Administer ipratropium bromide 0.5 mg (2 mL of 0.5 mg/2 mL solution) every 4 hours.
 - Where ipratropium bromide dose coincides with 2 hourly salbutamol, add ipratropium bromide 0.5 mg (2 mL of 0.5 mg/2 mL solution) to salbutamol 5 mg (1 mL of 5 mg/mL solution) and make up to 4 mL with sodium chloride, 0.9%, i.e. add 1 mL sodium chloride, 0.9%.
 - Once clinical improvement is noted, taper the dose frequency until patient is stable.

LoE:IVb^{vii}

Example: Dosing schedule for nebulisation if patient has a poor response to initial dose of salbutamol

Timeline*	Nebuliser treatment
0 hours [‡]	Salbutamol 5mg + Ipratropium bromide 0.5 mg
2 hours	Salbutamol 5mg
4 hours	Salbutamol 5mg + Ipratropium bromide 0.5 mg
6 hours	Salbutamol 5mg
8 hours	Salbutamol 5mg + Ipratropium bromide 0.5 mg
10 hours	Salbutamol 5mg
12 hours	Salbutamol 5mg + Ipratropium bromide 0.5 mg
*Once clinical improvement is noted, taper down dose frequency until patient is stable	
[‡] Time at which poor response is noted	

AND

- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 40 mg immediately.
 - Follow with prednisone, oral, 40 mg daily for 5 days.

LoE:IVb^{vii}

Note: If response to treatment remains poor, consider alternative diagnoses and refer urgently.

In patients who cannot tolerate oral therapy, are vomiting, or are suspected to have gastric atony from a severe asthma exacerbation:

- Hydrocortisone, IM/slow IV, 100 mg immediately, then 6 hourly until oral therapy is tolerated.

LoE:IVb^{ix}

Once oral medication can be taken, switch parenteral corticosteroids to:

- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 40 mg daily for 5 days.

CAUTION

Avoid sedation of any kind.

Life-threatening exacerbations

Urgently refer patient for high care or intensive care. While awaiting referral, administer:

- Oxygen, to keep oxygen saturation 93–95%.

AND

- Salbutamol 0.5% (5 mg/mL) with ipratropium bromide 0.5 mg/2mL, nebuliser solution:
 - Salbutamol 0.5%, 2 mL (10 mg) plus ipratropium bromide, 2 mL (0.5 mg) every 15 minutes until asthma severity category improves from life-threatening to severe.

- Recommended delivery at a flow rate of 8 L/minute with oxygen.

AND

- Parenteral corticosteroids (intermediate-acting), e.g.:
- Hydrocortisone, IM/slow IV, 100 mg immediately, then 6 hourly until oral therapy is tolerated.

LoE:IVb^x

In patients with a poor response despite corticosteroid therapy:

ADD

- Magnesium sulfate, IV, (50 mg/kg, maximum dose 2 g) in 100 mL sodium chloride 0.9%, as a single dose, administered over 20 minutes.
 - A single dose of intravenous magnesium sulfate has been shown to reduce the likelihood of hospital admissions.

LoE:IVb^{xi}

In patients where nebulised treatment cannot be given effectively, e.g., silent chest, agitation with mask intolerance, repeated mask removal, or cyanosis:

In a high care or intensive care setting where adequate monitoring is accessible, consult a specialist for use of:

- Salbutamol, IV, 1mg/mL injection for IV infusion.
 - Dilute one 5 mg/mL ampoule in 500 mL sodium chloride, 0.9% to produce a 10 mcg/mL solution of salbutamol.
 - Administer loading dose of 750 mcg over 10 minutes at an infusion rate of 450 mL/hour.
 - Continue maintenance infusion by reducing infusion rate to 30 mL/hour (5 mcg/minute).
 - Adjust the infusion rate every 15 minutes according to clinical response by maintaining a rate between 18 to 120 mL/hour (3 to 20 mcg/minute).
 - Monitor for tachycardia and arrhythmias, hypokalaemia, hyperglycaemia (particularly in diabetic patients receiving concomitant corticosteroids), and lactic acidosis (uncommon).

LoE:IVb^{xii}**Note:**

- » There is good evidence to recommend **against** the use of IV aminophylline in the management of acute asthma exacerbations in adults, as its use is not associated with additional bronchodilation and may result in increased toxicity (e.g. vomiting and dysrhythmias) with concurrent high-dose nebulised β 2-agonists.
- » As the clinical condition responds to treatment and severity improves from life-threatening to severe, treat as per severe asthma exacerbation above.

LoE:IVb^{xiii}**CAUTION**

Avoid sedation of any kind.

Intercurrent bacterial respiratory infections

- » Acute asthma exacerbations rarely involve bacteria.

- » Yellow sputum suggests eosinophilia, not infection.
- » Antibiotics are unnecessary unless chest X-ray shows consolidation (see Section 16.6: Pneumonia, community acquired).

REFERRAL

- » If patient fails to respond within one hour (i.e., symptomatic improvement and PEF > 60% of predicted/personal best):
 - Discuss management with a specialist.
 - Intubation and ventilator support may be required.
- » If referral to another facility is required, stabilise the patient prior to transfer and utilise the appropriate level of ambulant care – discuss with the referral centre.

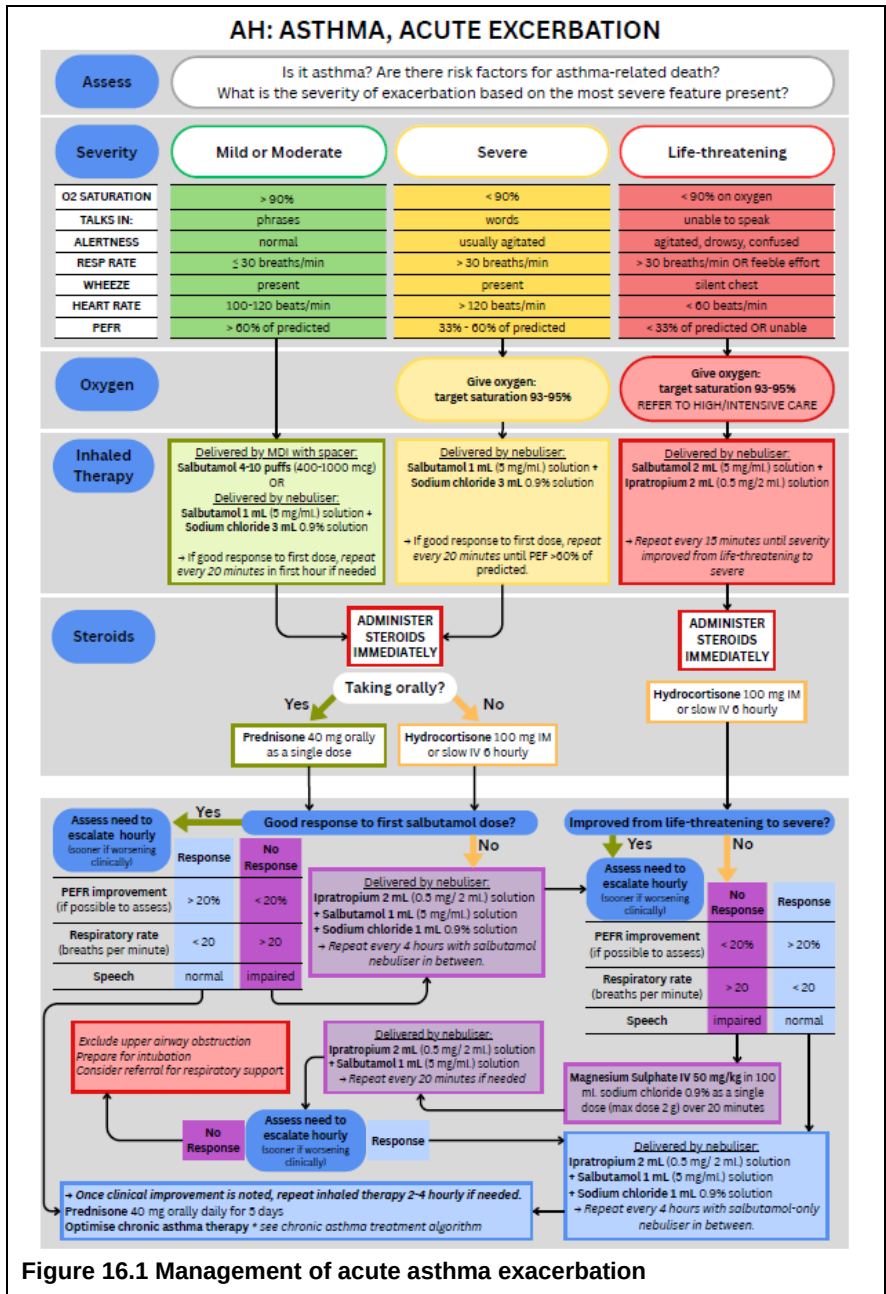


Figure 16.1 Management of acute asthma exacerbation

16.2 ASTHMA, CHRONIC

J45.0-1/J45.8-9

DESCRIPTION

Asthma is a chronic, heterogeneous disease of the airways, and is characterised by airway inflammation. Asthma is usually associated with airway hyperresponsiveness and structural remodelling, however, these are not necessary or required to make a diagnosis.

DIAGNOSIS

Chronic obstructive pulmonary disease is often mistaken for asthma. Asthma must be distinguished from chronic obstructive pulmonary disease (COPD) through history taking to aid in selecting appropriate treatment.

Features suggestive of asthma:

- » **Respiratory symptoms:** wheeze, cough, chest tightness, shortness of breath.
- » **History and examination:** intermittently symptomatic, night-time symptoms, identified triggers, atopy, family history.
- » **Reversibility test:** Increase in PEF $\geq$ 20% when performed 15 minutes after short-acting β_2 agonist (SABA) use (See Appendix V: Asthma Monitoring for details).

Typical features	Asthma	COPD
Age of onset	< 20 years	Usually > 40 years
History	Eczema, hay fever, familial	Heavy smoking (tobacco, cannabis), TB
Symptom pattern	Intermittent	Persistent, progressive
Triggers	URTIs, weather, stress	N/A
Nocturnal symptoms	Common	Less prominent
Cough onset	Variable	Precedes dyspnoea
PEF post β_2 -agonist	Increases 20% after 10 minutes	Little improvement

GENERAL MEASURES

Patient Education

- » All patients should be counselled on smoking cessation, inhaler technique, treatment adherence and decreasing exposure to triggers (e.g., house dust mite, pollens, grasses, pets, smoke, fumes, etc.).
- » See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Assessment

- » Initial diagnosis, treatment initiation and follow up should be accompanied by:

- An assessment of the patient's future risk, including addressing all modifiable risk factors.
- Inhaler technique (See Appendix VI: Devices for Respiratory Conditions).
- » Follow up consultations should include assessment of asthma control, future asthma risk, and appropriateness of current treatment to determine if escalation or de-escalation of therapy is required.

Table 16.3: Future asthma outcome risk assessment

Risk factors for exacerbations		
Poor control	» Uncontrolled asthma (as assessed below)	
Inappropriate medication use	» High SABA use (more than 3 inhalers per year) » Inadequate ICS use (not prescribed, poor adherence, poor inhaler technique)	
Co-morbidities	» Obesity » Gastro-oesophageal reflux disease (GORD) » Chronic rhinosinusitis » Pregnancy » Confirmed food allergy	
Exposures	» Smoking (including e-cigarettes) » Air pollution	» Known allergen exposure » Indoor smoke exposure
Social factors	» Major psychosocial and socioeconomic issues	
Poor lung function	» FEV1 < 60% predicted » High bronchodilator responsiveness	
Inflammatory markers	» Eosinophilia (blood)	
Exacerbations	» Any prior intubation or ICU admission for asthma » Severe exacerbation in the past year	
Risk factors for developing persistent airflow limitation		
History	» Preterm birth, LBW and greater infant weight gain » Chronic mucus hypersecretion	
Medications	» History of severe exacerbation (see Section 16.1: Asthma, acute exacerbation) without ICS treatment thereafter.	
Exposures	» Tobacco smoke » Noxious chemicals	» Occupational or domestic exposures
Investigations	» Low initial FEV1	» Sputum/blood eosinophilia

Asthma severity

Classify asthma severity based on a patient's *response* to treatment. Historic definitions of mild, moderate, and severe asthma, do not accurately reflect a patient's symptom frequency, intensity, or risk, and their use is no longer recommended.

MEDICINE TREATMENT**Corticosteroid and bronchodilator combination therapy**

The use of an anti-inflammatory reliever (AIR) (usually an inhaled corticosteroid/ICS with the rapid onset LABA reliever, formoterol) is more

effective than SABA use alone, even in asthma with low symptom frequency. In more severe disease, the same ICS-formoterol combination inhaler can be used for symptom relief as well as maintenance therapy, and is called maintenance-and-reliever therapy (MART).

Patient therapy should be determined as follows (see the chronic asthma algorithm below):

- » Initiate patients with newly diagnosed asthma at the highest step that correlates with their symptoms, e.g., if a patient has some features requiring step 2 or 3 therapy, but also has a recent history of acute exacerbation, initiate therapy according to step 4 and review after a period of therapy.
- » Step up treatment to the next level if patient is uncontrolled, partially controlled, or at high risk of exacerbations.
- » Consider treatment step down if patient has been well-controlled for 2–3 months.
- » **Note:** There is a significant drug interaction between the budesonide component of budesonide/formoterol inhalers and protease inhibitors (PIs). See the recommended therapy for patients on PIs below.

Table 16.4: Assessment of asthma severity at baseline & recommended entry point for stepwise treatment for adults and adolescents aged 12 years and older

Presenting Symptoms	Initial Treatment
Asthma symptoms: two days/week or less	Step 1 Low dose ICS-formoterol as AIR ONLY
Asthma symptoms: less than 3–5 days/week Normal or mildly reduced lung function	Step 2 Low dose ICS-formoterol as AIR only
Asthma symptoms: Most days (≥ 4 days/week) OR Night waking once a week or more OR Reduced lung function	Step 3 Low-dose ICS-formoterol as MART (once daily maintenance dose)
Asthma symptoms: Daily OR Night waking once a week or more AND Reduced lung function OR recent exacerbation	Step 4 Low-dose ICS-formoterol as MART (twice daily maintenance dose) OR Refer
Abbreviations: ICS = Inhaled corticosteroids; AIR ONLY = Anti-inflammatory reliever only; MART = Maintenance-and-reliever therapy; SABA = Short-acting β_2 agonist.	

LoE:IIIb^{xiv}

Inhaled corticosteroids (ICS) improve asthma control when used for reliever/rescue therapy & maintenance therapy.

Stepwise treatment of chronic asthma

Patients who are unable to use aerosol inhalers correctly after adequate counselling, may benefit from the use of a spacer with metered dose inhalers. See Appendix VIII for Comparative dosing across various ICS products.

STEP 1 and STEP 2:

(Asthma symptoms < 5 days per week; and no nocturnal symptoms; and normal or mildly reduced lung function; and no history of recent acute exacerbation).

Reliever/rescue therapy:

- Low dose corticosteroid/formoterol inhaler (AIR therapy), e.g.:
- Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, one inhalation as needed.
 - Maximum daily dose: 1920 mcg/54 mcg (12 inhalations) doses per day.
 - Patients should be counselled to present to their healthcare facility for review if they require maximum doses of inhaler therapy for more than one week within a month.

Note: Insufficient asthma control on maximum therapeutic doses should trigger a review to step up treatment.

Maintenance therapy:

No maintenance therapy required. Continue with reliever/rescue therapy using ICS/formoterol combination inhaler and monitor asthma control.

STEP 3:

(Asthma symptoms most days ≥ 4 per week; or weekly nocturnal symptoms; or reduced lung function; and no history of recent acute exacerbation).

Maintenance therapy:

- Low dose corticosteroid/formoterol inhaler (MART therapy), e.g.:
- Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, one inhalation 12 hourly.

ANDReliever/rescue therapy:

- Low dose corticosteroid/formoterol inhaler, e.g.:
- Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, one inhalation as needed.
 - Maximum daily dose: 1920 mcg/54 mcg (12 inhalations) considering maintenance and reliever doses per day. This equates to 10 additional reliever inhalations on top of 2 maintenance inhalations.
 - Patients should be counselled to present to their healthcare facility for review if they require maximum doses of inhaler therapy for more than one week within a month.

Note: Insufficient asthma control on maximum therapeutic doses should trigger a review to step up treatment.

STEP 4:

(Daily asthma symptoms; or weekly nocturnal symptoms; and reduced lung function; or has history of recent acute exacerbation).

Maintenance therapy:

- Medium dose corticosteroid/formoterol (using low dose ICS/formoterol inhaler), e.g.:
- Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, two inhalations 12 hourly.

ANDReliever/rescue therapy:

- Low dose corticosteroid/formoterol inhaler, e.g.:
- Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, one inhalation as needed.
 - Maximum daily dose: 1920 mcg/54 mcg (12 inhalations) considering maintenance and reliever doses per day. This equates to 8 additional reliever inhalations on top of 4 maintenance inhalations.

Note: Insufficient asthma control on maximum therapeutic doses should trigger a review to discuss with a specialist/refer for further treatment.

LoE:IVb^{iv}**CAUTION**

Formoterol has a rapid onset of action and **CAN be used as reliever** therapy, but only in combination with an ICS.

Salmeterol is not rapid acting and **CANNOT** be used as reliever therapy.

Table 16.5: Assessment of recent asthma control over the past 4 weeks (or since last review):

	Yes / No (Assign one point for each “yes” answer)	
	Yes	No
Daytime asthma symptoms more than twice weekly		
Night waking due to asthma (any)		
Activity limitation due to asthma (any)		
IF using SABA-only inhaler: SABA-only reliever use > twice/week for symptoms*		
Total points	Control	
0 points	Well controlled	
1–2 points	Partially controlled	
3–4 points	Uncontrolled	

*Only applicable if patient is using an inhaler containing short-acting β_2 -agonist only, i.e. not a corticosteroid containing inhaler (e.g. salbutamol only inhaler).

- » Consider whether level of treatment needs to be adjusted:
 - If patient is well-controlled: STEP DOWN treatment.
 - If patient is partially controlled or uncontrolled: STEP UP treatment.

- » Complete the following assessment before initiating change of therapy:

Before STEPPING DOWN treatment	Before STEPPING UP treatment
» Ensure that control has been good for at least 2–3 months. » Ensure that there have been no exacerbations in the past year. » Ensure that the patient does not have 2 or more risk factors for exacerbations (see “Assessment of risk factors” above). » Do not step down while pregnant or travelling.	» Ensure that medication adherence is good. » Ensure that inhaler technique is correct. » Ensure that all exposures have been minimised and modifiable risk factors addressed. » Ensure that co-morbidities are controlled and/or are not interfering with asthma control. » Ensure that there is no inappropriate medication use (e.g. β-blockers or HIV protease inhibitors).

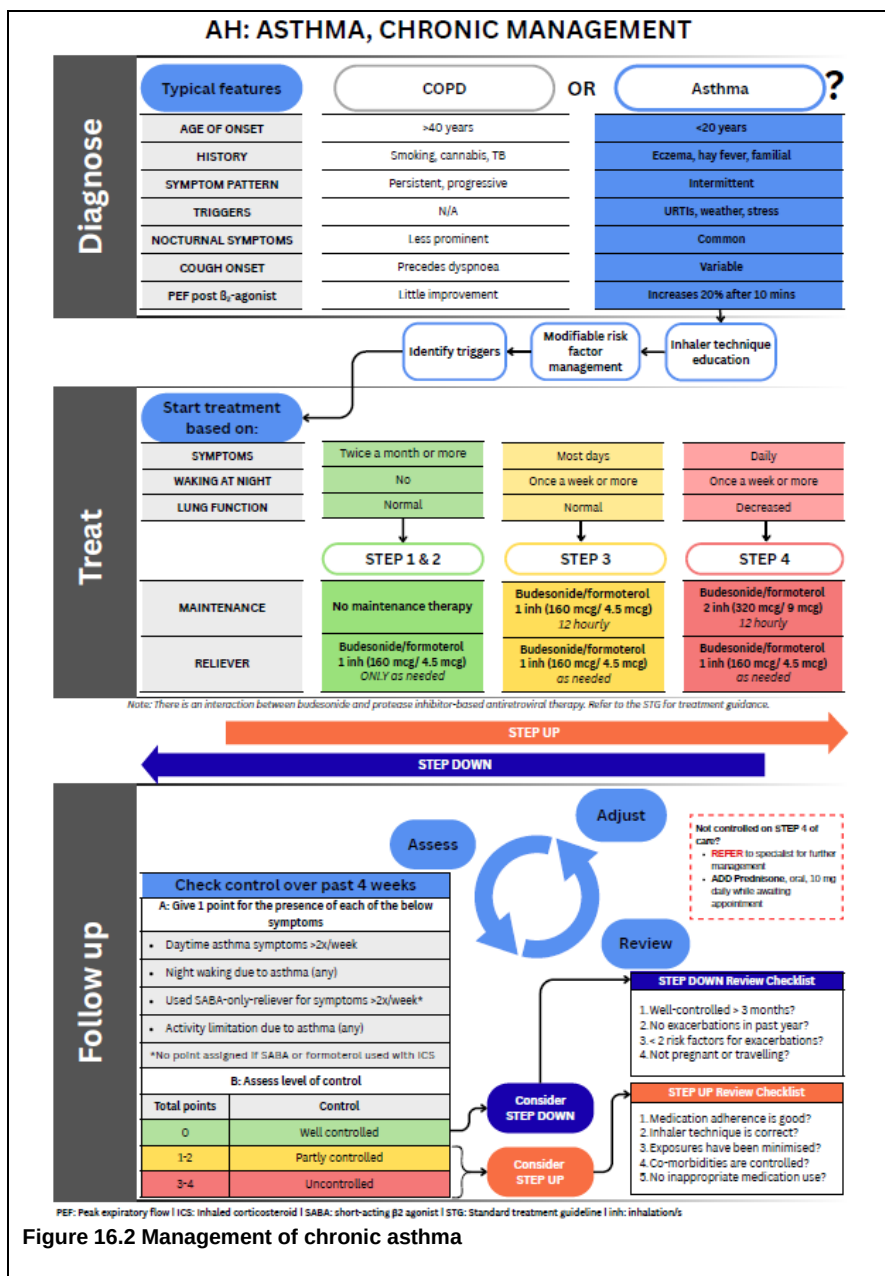


Figure 16.2 Management of chronic asthma

CAUTION

Budesonide has significant drug-drug interactions with HIV protease inhibitors and should be replaced with beclometasone where indicated.

Regimen for patients on protease inhibitors

Beclometasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide:

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STEP 1:Reliever/rescue therapy:

- Short acting β_2 -agonists, e.g.:
- Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed.

AND

- Low dose beclometasone, 100 mcg MDI, to take 200 mcg (two inhalations) as needed.

Maintenance therapy:

No maintenance therapy required. Continue with reliever/rescue therapy and monitor asthma control.

STEP 2:Reliever/rescue therapy:

- Short acting β_2 -agonists, e.g.:
- Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed.

Maintenance therapy:

- Low dose beclometasone, 100 mcg MDI, to take 200 mcg (two inhalations), 12 hourly.
 - Well and stable after 6 months: can attempt to reduce beclometasone dose to 200 mcg daily or STEP 1 therapy.
 - Dose adjustments may be required at change of seasons.

STEP 3:Reliever/rescue therapy:

- Short acting β_2 -agonists, e.g.:
- Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed.

Maintenance therapy:

- Low dose beclometasone, 100 mcg MDI, to take 200 mcg (two inhalations) 12 hourly.

AND

- Formoterol, MDI, 12 mcg, 12 hourly.

STEP 4:

Reliever/rescue therapy:

- Short acting β_2 -agonists, e.g.:
- Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed.

Maintenance therapy:

- Medium dose beclometasone, 100 mcg MDI, to take 400 mcg (four inhalations) 12 hourly.

AND

- Formoterol, MDI, 12 mcg, 12 hourly.

Management of patients poorly controlled on step 4:

- » Refer to specialist for further management.

While awaiting appointment with specialist:

Continue current therapy and add corticosteroids:

- Corticosteroids (intermediate-acting) , e.g.:
- Prednisone, oral, 10 mg daily.

Note:

- » Prednisone should only be used as a bridging step while awaiting review by specialist and **SHOULD NOT** be used for long-term maintenance therapy. Ideally, patient should be referred within 4 weeks.
- » Consider steroid tapering if used for more than 2 weeks (see “Appendix II: Prescribing Information for Specific Medicines, Prednisone, Oral”).

REFERRAL

- » Patients with poor asthma control on maximum ICS/reliever therapy.

16.3 BRONCHIECTASIS

J47

GENERAL MEASURES

Advice on early self-referral for suspected acute infections.

Physiotherapy: Regular chest clearance exercises (20 minutes morning and night) are the mainstay of therapy and must be emphasised and demonstrated to the patients, including cough and chest drainage techniques, and must be emphasised repetitively.

MEDICINE TREATMENT**Antimicrobial therapy**

Antibiotic therapy in patients with bronchiectasis should only be used when there is either systemic evidence of sepsis such as pyrexia, or there is a history of increasing sputum purulence or volume. Antibiotic choices should be guided by sputum microscopy, culture and sensitivity. The number and duration of physiotherapy sessions should be increased.

Treatment may need to be prolonged for two weeks, depending on the extent of the bronchiectasis and the organisms suspected.

In patients otherwise stable and before culture results:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 10 days, or longer, depending on the response. A LoE:III^{xvii}

Severe penicillin allergy: (Z88.0)

- Azithromycin, oral, 500 mg daily for 10 days. W

LoE:IVb

More severely ill patients may require hospitalisation and initiation of parenteral antibiotic therapy.

Sputum microscopy, culture and sensitivity determination are indicated in all cases.

- Ceftriaxone 2 g, IV, daily, until patient afebrile for 24 hours. W

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

LoE:III^{xviii}

LoE:II^{ix}

If Pseudomonas infection is confirmed on culture, change to: (B96.5)

- Ciprofloxacin, oral, 750 mg 12 hourly for 7 days. W

If penicillin allergic and unable to tolerate oral therapy: (Z88.0)

Management of these patients should be discussed with a specialist for possible referral and alternative parenteral therapy:

- Moxifloxacin, IV, 400 mg daily infused over 60 minutes. W

Switch to oral treatment once able to take orally:

- Moxifloxacin, oral, 400 mg daily to complete a total of 7 days of treatment with moxifloxacin i.e. total duration of 7 days for IV and oral combined. W

LoE:II^{ix}

Subsequent antibiotic therapy should be based on results of sputum investigations. A sputum smear for Acid Fast Bacilli (AFB), followed by culture if positive, is recommended in patients with a poor response to antibiotics as patients with bronchiectasis are at increased risk for infection with non-tuberculous Mycobacteria which will not be detected by Xpert® MTB/RIF PCR assay. If tuberculosis is a consideration, also send a sputum for TB-NAAT testing.

Inhaled bronchodilators

Bronchodilators may be used, as for COPD, if airflow obstruction is present. There is no indication for inhaled corticosteroids in the management of bronchiectasis.

Any asthmatic component (i.e. reversible obstruction) should be treated in the usual way, as for asthma. (See Sections 16.1: Asthma, acute, and 16.2:

Asthma, chronic persistent.)

See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Prophylaxis (Z25.1)

- Annual influenza vaccine. See Section 9.2: Adult vaccination.

For frequent severe exacerbations, consult a specialist.

REFERRAL

- » For exclusion of a possible foreign body.
- » For assessment for surgical removal of a bronchiectatic segment.
- » Major haemoptysis.

16.4 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

J43.0-2/J43.8-9/J44.0-1/J44.8-9

DESCRIPTION

COPD is characterised by persistent respiratory symptoms (dyspnoea, chronic cough and sputum production), and airflow limitation. Spirometry is required to diagnose COPD, where the post-bronchodilator FEV1/FVC ratio is <0.7. COPD is likely to worsen over time, even with optimal care.

Regular follow-up is necessary to monitor lung function, symptoms, exacerbations, co-morbidities, and the need for treatment regimen changes.

COPD can be graded on severity of symptoms and frequency of exacerbations to assist in treatment selection and to monitor treatment success:

LoE:III^{poxi}

GOLD group	mMRC breathlessness score	Exacerbations/hospitalisations in past year
A	0–1	<2 exacerbations (and no hospitalisations)
B	≥2	<2 exacerbations (and no hospitalisations)
E	N/A	≥2 exacerbations (or ≥1 leading to hospitalisation)

Assess breathlessness using the mMRC dyspnoea scale:

Grade	Exacerbations in past year
0	Dyspnoea with strenuous exercise
1	Dyspnoea when hurrying on level ground or walking up a slight hill
2	Walks slower than people of same age group, due to dyspnoea
3	Stops for breath after walking 91m, or after a few minutes on level ground
4	Too breathless to leave the house, or dyspnoea when dressing/undressing

URL to the modified Medical Research Council (mMRC) dyspnoea scale calculator:

<https://www.mdcalc.com/mmrcc-modified-medical-research-council-dyspnea-scale>.

LoE:III^{poxi}

GENERAL MEASURES

Patients with clinical COPD must undergo spirometry to confirm and grade the severity of obstruction.

Patients should be screened for ongoing smoking and advised to stop at each visit. Smoking cessation and avoidance of noxious respiratory particles should form the mainstay of management.

MEDICINE TREATMENT

Note: Correct inhaler technique should be demonstrated and checked regularly. See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Management of acute exacerbations

Progression of disease (measured by symptoms and deterioration in lung function) in COPD is variable, but is greater in patients who experience COPD exacerbations which are defined as:

- » worsening of dyspnoea,
- » increased cough,
- » increased sputum production or purulence or,
- » greater than usual day to day variability of symptoms.

Severe exacerbations are defined as being sufficiently severe to prompt use of an oral corticosteroid course and/or an antibiotic.

COPD exacerbations are not always associated with significant decreases in PEF or FEV₁, and are defined by symptoms and, when severe, measures of respiratory failure. Most are precipitated by viral and/or bacterial infection and are more common in winter.

Patients should be admitted if there is a marked increase in dyspnoea, symptoms disturb eating or sleeping, change in mental status or poor social circumstances. Causes of worsening symptoms other than an acute exacerbation of COPD such as cardiac failure, pulmonary embolus, or pneumonia must be considered.

If available, check blood gases for the presence of hypoxaemia and hypercapnia. In some patients with long-standing lung disease the drive to respiration switches from hypercapnia (increases in PaCO₂) to hypoxaemia (level of respiratory failure). In such patients, relief of hypoxaemia with uncontrolled oxygen therapy may result in hypoventilation, with consequent rise in PaCO₂ to dangerous levels and associated respiratory acidosis leading to coma and death. For this reason, hypoxaemia should be corrected using controlled use of supplemental oxygen, preferably starting with a nasal cannula 1-2 litres/minute.

If the patient's arterial PaCO₂ does not rise, the FiO₂ may be increased until a PaO₂ of 8 kPa (60 mmHg), or oxygen saturation of 90%, is reached. The FiO₂ must be reduced, or oxygen removed, if worsening hypercapnia occurs; these patients might require non-invasive ventilation or intubation for mechanical ventilation.

Where blood gas facilities are not readily available, the patient's clinical status should be reviewed regularly to check for increasing drowsiness, headache, or confusion, which may precede coma.

Where resources for mechanical ventilation are scarce, oxygen saturation targets for patients with long-standing COPD and limited effort tolerance may be relaxed if the patient is improving clinically.

- Salbutamol, 0.5% (5 mg/mL) nebuliser solution.
 - 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 6-8 L/min with oxygen.
 - Nebulise continuously (refill the nebuliser reservoir every 20 minutes).

If a poor response to nebulised salbutamol:

ADD

- Ipratropium bromide 0.5 mg (UDV) with the first refill of the nebuliser reservoir.
 - Patients who fail to respond within 1 hour must be discussed with a specialist. (Patients with COPD have fixed airway disease. Unlike asthmatics, PEF is not a reliable measure of disease.)

Once clinically stabilised, nebulise with:

- Salbutamol, 0.5% (5 mg/mL) nebuliser solution
 - 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 6-8 L/min with oxygen.
 - Repeat 4–6 hourly.

AND

- Corticosteroids (intermediate-acting), e.g.: LoE: ^{pxiii}
- Prednisone, oral, 40 mg immediately.
- Follow with: Prednisone, oral, 40 mg daily to complete 5 days.

OR

In patients who cannot use oral therapy:

- Hydrocortisone, IV, 100 mg 6 hourly until patient can take oral medication.

Once oral medication can be taken, follow with:

- Corticosteroids (intermediate-acting), e.g.: LoE: ^{pxiv}
- Prednisone, oral, 40 mg daily to complete 5 days of corticosteroids in total.
 - Monitor response and clinical signs.

Antibiotic therapy for acute exacerbations

Indications:

- » Patients with increased sputum purulence AND either increased sputum volume or increased dyspnoea LoE: ^{IIIIb^{xxv}}

OR

- » Patients with a severe exacerbation (respiratory acidosis, severe dyspnoea, or persistent hypoxaemia despite supplemental oxygen).
- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days. A

Severe penicillin allergy: (Z88.0)

- Azithromycin, oral, 500 mg daily for 3 days. 

LoE:III^{xxvi}

LoE:III^{xxvii}

Chronic therapy

FOR ALL STAGES:

- Short acting β_2 -agonists, e.g.:
- Salbutamol, MDI, 200 mcg 6 hourly as needed (educate on correct inhaler use - use a large volume spacer if inhaler technique remains poor).

GROUP B:

ADD

- Long acting β_2 -agonist (LABA), e.g.:
- Formoterol, inhalation, 12 mcg 12 hourly.

LoE:III^{xxviii}

LoE:I^{xxx}

GROUP E (frequent exacerbations (≥ 2 per year)):

If blood eosinophils <0.1 cells $\times 10^9$ /L:

ADD

- Long acting β_2 -agonist (LABA), e.g.:
- Formoterol, inhalation, 12 mcg 12 hourly.

LoE:I^{xxx}

If blood eosinophils ≥ 0.1 cells $\times 10^9$ /L:

ADD

- LABA/ICS combination, e.g.:
- Salmeterol/fluticasone, inhalation, 50/250 mcg 12 hourly.

LoE:I^{xxxi}

Note: Do not measure blood eosinophils while taking oral corticosteroids, as this may temporarily lower the eosinophil count.

Patients on protease inhibitors:

Replace LABA/ICS combination with:

- Beclometasone, inhalation, 400 mcg 12 hourly.

AND

- Formoterol, inhalation, 12 mcg 12 hourly.

LoE:III^{xxxii}

If inadequate control with above therapy:

- Theophylline, slow release, oral, 200 mg at night (Specialist consultation).
 - Ongoing use of theophylline should be re-evaluated periodically. If there is no benefit after 12 months, discontinue theophylline.

AND

Refer patients for additional assessment and management.

LoE:II^{xxxiii}

Corticosteroids

Oral corticosteroids are not recommended for stable COPD.

Pre-operative assessment for surgical procedures:

Patients with chronic lung disease are at an increased risk of post-operative

pulmonary complications. Risk is increased with increasing severity of pulmonary disease, and with upper abdominal or thoracic surgery.

Patients undergoing elective surgery must be optimised pre-operatively by following the recommended treatment for their disease. Clinical assessment is generally sufficient, as further investigations such as spirometry, CXR and ABGs are reserved for patients with clinically severe disease/ unstable disease, or where the diagnosis is uncertain. COPD patients should be wheeze free and without dyspnoea on moderate exertion (carrying shopping walking up a flight of stairs), or a history of frequent exacerbations. As COPD is a disease characterised by fixed airway obstruction, some patients may have continuous wheezing and will require further pre-operative assessment. Peri-operative oral corticosteroids may be used to gain optimal control but are not advocated for routine use:

- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 30 mg daily for not longer than 5 days.

AND

LoE:III

Inhaled therapy must be continued and may be administered via nebulisation peri-operatively:

- Short acting β_2 -agonists, e.g.:
- Salbutamol MDI, 200 mcg, 30 minutes pre-intubation.

LoE:III

Prophylaxis (Z25.1)

- Annual influenza vaccination. See Section 9.2: Adult vaccination.

REFERRAL

- » Assessment for long-term home-based oxygen therapy, if COPD with $\text{PaO}_2 < 7.3 \text{ kPa}$ (55 mmHg) and non-smoker for at least 3 months.
- » Recent onset of respiratory failure or signs of cor pulmonale.
- » Symptoms that appear disproportionate to the level of airflow obstruction, as judged by spirometry or clinical evaluation (absence of hyperinflation or unusual pattern of symptoms).
- » Onset <40 years of age.
- » COPD with a history of little or no smoking.
- » Recurrent exacerbations, i.e. ≥ 2 per year.
- » Failure to respond to treatment.

16.5 LUNG ABSCESS

J85.0-3

GENERAL MEASURES

Physiotherapy and regular emphasis on postural drainage is essential for management.

Instruct patient to do chest clearance exercises (taught by a physiotherapist where possible) for at least 20 minutes, 6 hourly.

Nutritional support.

MEDICINE TREATMENT

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient apyrexial for 24 hours. **A**

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. **A** LoE:III

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, IV, 400 mg daily, until patient apyrexial for 24 hours. **W**

Follow with:

- Moxifloxacin, oral, 400 mg daily. **W** LoE:II^{poxxv}

Duration of therapy

Usually 4-6 weeks – monitor with repeat CXR every 1-2 weeks, which should show disappearance of air-fluid level and reduction in size of abscess.

REFERRAL

- » No response to treatment.
- » CXR not resolving or worsening.
- » Complications, such as empyema or severe haemoptysis.

16.6 PNEUMONIA, COMMUNITY ACQUIRED

J13/J14/J15.0-9/J16.0/J16.8/J18.0-2/J18.8-9

DESCRIPTION

Pneumonia is an acute infection of the lung parenchyma. Early appropriate antibiotic therapy decreases mortality. The decision to hospitalise a patient and choice of initial antibiotic therapy is guided by age, comorbid diseases (such as HIV infection, diabetes or chronic respiratory disease), and severity. Socioeconomic circumstances should form part of the clinical assessment when deciding if a patient is suitable for outpatient treatment.

GENERAL MEASURES**Diagnosis:**

LoE:III^{poxxv}

Clinical features include cough, fever, tachypnoea, and signs of consolidation on chest examination.

CXR almost invariably shows a focal area of opacification or consolidation. However, empiric antibiotic therapy can be considered for severely ill, hospitalised patients with suspected pneumonia, and a negative CXR. Pneumonia may be excluded if a repeat CXR after 24-48 hours still shows no opacification. Diffuse, bilateral, interstitial infiltrates in a patient with HIV infection and hypoxaemia is suggestive of *Pneumocystis jirovecii* pneumonia.

All patients should be offered HIV testing, as HIV infection is associated with a markedly increased risk of bacterial pneumonia.

Even in typical cases of pneumonia, exclude tuberculosis by sending sputum for Xpert® MTB/RIF Ultra.

A follow-up CXR should be done 4–6 weeks after completion of therapy in patients >50 years of age, or if symptoms persist.

LoE:III^{xxxxvi}

Follow-up CXRs are indicated earlier only when complications are suspected, e.g. empyema, abscess, or pneumothorax.

MEDICINE TREATMENT

LoE:I^{xxxxvii}

- Oxygen, if saturation <94%.

Adequate analgesia for pleuritic chest pain, if present. See Section 25.2.1: Medical conditions associated with severe pain.

Antimicrobial therapy

Duration of antibiotic therapy is guided by clinical response, but should be 5–7 days, with a minimum of 7 days for MRSA or *Pseudomonas*.

Longer duration of antibiotic therapy is recommended for:

- » identified pathogen that is not susceptible to initial empiric therapy,
- » extrapulmonary infection (e.g. meningitis or endocarditis),
- » empyema, lung abscess or necrotizing pneumonia,
- » unusual organism present.

LoE:I^{xxxxviii}

Prolonged fever and clinical signs may be due to unrecognised TB, complications (such as empyema), incorrect choice of antibiotic (e.g. atypical bacteria), or an underlying bronchial obstruction (foreign body or carcinoma). These patients should be further investigated.

Community-acquired pneumonia without features of severe pneumonia (see below for definition) and without co-morbidity and in patients <65 years of age:

- Ampicillin, IV, 1 g 6 hourly. A

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Amoxicillin, oral, 1 g 8 hourly for 5 days i.e. total duration of 5 days for IV and oral antibiotics combined. A

LoE:I^{xxxxix}

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, oral, 400 mg daily for 5 days. W

If response is poor after 48 hours, exclude TB and consider atypical bacterial pneumonia, which requires treatment with a macrolide.

Community-acquired pneumonia without features of severe pneumonia (see below for definition) in patients >65 years of age or co-morbidity (e.g. COPD, HIV, cardiac failure, diabetes):

- Ceftriaxone, IV, 2 g daily. **W**

LoE: I^{kl}

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days. **A**

LoE: III^{cd}

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, oral, 400 mg daily for 5 days. **W**

If response is poor after 48 hours, exclude TB and consider atypical bacterial pneumonia, which requires treatment with a macrolide.

Severe pneumonia (cyanosis, confusion, hypotension or respiratory rate >30 breaths/min):

- Ceftriaxone, IV, 2 g daily. **W**

Mechanical ventilation may be required (refer to a centre, if needed).

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days. **A**

LoE: III^{cd}

AND

- Azithromycin, 500 mg, slow IV (minimum infusion duration of 60 minutes) daily for 3 days. **W**

LoE: II^{xiii}

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, IV, 400 mg daily. **W**

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Moxifloxacin, oral, 400 mg daily for 5 days. **W**

Note: There is no need to add a macrolide as moxifloxacin has adequate cover for atypical bacteria.

HIV infected with bilateral diffuse interstitial infiltrates on CXR:

Clinical presentation includes a dry cough of <12 weeks' duration and significant tachypnoea.

Treat as *Pneumocystis jirovecii* pneumonia (exclude TB) - see Section 10.2.9: Pneumocystis pneumonia.

16.7 PNEUMONIA, ASPIRATION

J69.0-1/J69.8

DESCRIPTION

Following aspiration, a patient may develop pneumonitis or pneumonia. Aspiration pneumonitis develops within hours of the aspiration event and is more common in previously healthy people who aspirate gastric acid. Antibiotics will not benefit these patients unless infection is present.

Pneumonia following aspiration of gastric contents and/or commensal organisms from the oropharynx usually occurs in debilitated patients and presents with symptoms and signs of community-acquired pneumonia. However, it may also have a more indolent onset and is more frequently complicated by lung abscess or empyema.

There may be solid (food) particles or other foreign bodies aspirated. The organisms involved are polymicrobial, i.e. Gram-positive and anaerobes. Aspiration pneumonia should be suspected in patients with episodic or prolonged decreased level of consciousness, e.g. in alcoholics, drug overdoses, epileptics, strokes, or those with swallowing problems.

MEDICINE TREATMENT

Antimicrobial therapy

Treatment duration: Continue therapy until there are no features of sepsis.

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient is apyrexial and stable for 24 hours. A

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

Severe penicillin allergy: (Z88.0)

LoE:III

- Moxifloxacin, IV, 400 mg daily, until patient is apyrexial for 24 hours. W

Follow with:

- Moxifloxacin, oral, 400 mg daily. W

LoE:II^{mod}

If **nosocomial infection** is present (develops >48 hours post admission), see Section 9.1.3: Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

REFERRAL

- » Hypoxaemia non-responsive to facemask oxygen.
- » Suspected foreign body aspiration.
- » Suspected chemical aspiration pneumonia.
- » Non-resolving pneumonia.

16.8 EMPYEMA

J86.0/J86.9

DESCRIPTION

Pus in the pleural cavity and/or bacteria present in a pleural effusion. An empyema is always secondary to another process, e.g. pneumonia (especially aspiration pneumonia), lung abscess, tuberculosis, bacteraemia, penetrating chest wall, or oesophageal injury.

GENERAL MEASURES

Aspirate and analyse all pleural effusions.

A parapneumonic effusion should be distinguished from an empyema by biochemical analysis, fluid microscopy and culture (MCS) – tube drainage is indicated if the aspirated fluid pH is <7.2, shows bacteria on MCS, or is purulent. The primary management of empyema is early and complete drainage by insertion of an intercostal drain to prevent long-term complications.

MEDICINE TREATMENT

Antimicrobial therapy

If an empyema occurs due to a complication of pneumonia, antimicrobial therapy should be prescribed as guided in Section 16.6: Pneumonia, community acquired (the duration of therapy should be prolonged until drainage is complete).

If not a complication of pneumonia:

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient is afebrile for 24 hours. **A**

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. **A**

Continue treatment until drainage is complete.

LoE:III

Severe penicillin allergy (and not a complication of pneumonia): (Z88.0)

- Moxifloxacin, IV, 400 mg daily, until patient is afebrile for 24 hours. **W**

Follow with:

- Moxifloxacin, oral, 400 mg daily. **W**

Continue treatment until drainage is complete.

LoE:III

REFERRAL

- » Loculated empyema or inadequate drainage.
- » Chronic empyema with pleural thickening and restrictive lung disease, for consideration for surgical decortication.

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**SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
NEMLC SUMMARY REPORT ON UPDATES MADE TO THE
THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE
PRODUCTS
AH Chp 16 RESPIRATORY DISORDERS**

Document Version Control

Report Version	Date	Detail
V1.0	27/11/2025	Draft 1 for external comment - Update – Asthma, acute - Update – Asthma, chronic persistent
V1.1	30/07/2026	Draft 2 for external comment
V1.2	30/09/2026	Published as NEMLC ratified

Summary Tables

Medicine Amendments

Medicine amendment recommendations, with supporting evidence and rationale are listed below. If appropriate can include non-medicine amendments if appropriate (for example if item has a large impact on how medicine is accessed). Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG). Include updates post initial publication first or mark/highlight appropriately.

STG): include updates post initial publication first of many highlight appropriately.

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / DELETED / AMENDED	TI* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Report Version 1.1: Asthma, acute							
Section 16.1 Asthma, acute	✓	✓	✓		Ipratropium bromide MDI	Deleted	
		✓	✓		Salbutamol IV 1mg/mL injection for IV infusion	Added	
Report Version 1.0 : Asthma, chronic persistent							
Section 16.2 Asthma, chronic	✓	✓			SABA – reliever/rescue therapy	Deleted	
	✓	✓			ICS-controller therapy	Deleted	
	✓	✓	✓		ICS/formoterol for MART therapy	Added	Yes
	✓	✓			Budesonide 160mcg/formoterol 4.5mcg MDI	Added	Yes
Section 16.2 Asthma, chronic – patients on	✓	✓	✓		SABA – reliever/rescue therapy	Retained	

PI-based ART	✓	✓			Beclometasone 200mcg MDI controller therapy	-	Added	
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*Therapeutic Interchange

AH Respiratory Chapter 16

Section 16.1. Asthma, acute

Ipratropium bromide MDI: Deleted

Ipratropium bromide MDI has been removed from the EML for the management of acute exacerbations of asthma, following notification of its withdrawal by local suppliers¹. Ipratropium bromide solution for nebulisation is retained in the STG as the alternative to the MDI.

Recognition and assessment of severity of asthma exacerbations in adults and adolescents ≥ 12 years – oxygen saturation

In response to external comments, guidance on assessing the severity of acute exacerbations of asthma has been clarified with respect to oxygen saturation i.e. an indicator for severe asthma is oxygen saturation <90% on room air and for life-threatening exacerbations oxygen saturation <90% with oxygen supplementation, respectively.

Dose and duration of corticosteroids

Prednisone/Prednisolone, oral – acute exacerbations of asthma in adults and adolescents 12 years and older: Amended

The NEMLC recommendation for the use of oral prednisone/prednisolone has been standardised to 40mg once daily for 5 days, for the management of acute exacerbations of asthma in adults and adolescents older than 12 years.

Life-threatening exacerbations of asthma

Guidance has been clarified that patients presenting with life-threatening exacerbations of asthma must be referred to a higher level of care i.e. patients presenting at PHC level of care should call for emergency response support and for patients presenting at AH level of care, patients should be referred for high care or intensive care. Guidance on the management of patients while awaiting transfer, has also been amended, for PHC and AH level of care respectively.

Salbutamol IV 1mg/mL injection for IV infusion: Added

The EML indication for salbutamol IV infusion for the management of children with life-threatening asthma exacerbations has been extended to include use in adults and adolescents. Salbutamol IV infusion has been added to the STG for the management of adults and adolescents with life-threatening asthma exacerbations in patients where nebulised treatment cannot be given effectively, e.g., silent chest, agitation with mask intolerance, repeated mask removal, or cyanosis. Use should be limited high care or intensive care setting where adequate monitoring is accessible, and should be initiated in consultation with a specialist.

STG Update

¹ Correspondence from Boehringer Ingelheim. Discontinuation of Atrovent®20 HFA MDI. 2 December 2025.

AMENDED FROM**16.1 ASTHMA, ACUTE****J45.0-1/J45.8-9****DESCRIPTION**

This is an emergency recognised by various combinations of:

- » wheeze
- » tightness of the chest
- » chest indrawing
- » breathlessness
- » respiratory distress
- » cough

In adults, bronchospasm is usually associated with asthma (where the bronchospasm is usually completely reversible) or chronic obstructive pulmonary disease (COPD; where the bronchospasm is partially reversible).

The clinical picture of pulmonary oedema due to left ventricular heart failure may be similar to that of asthma. If patients >50 years of age present with asthma for the first time, consider pulmonary oedema due to left ventricular heart failure.

All PHC facilities must have peak expiratory flow rate (PEFR) meters as asthma cannot be correctly managed without measuring PEFR.

Recognition and assessment of severity of asthma attacks in adults

	Mild-Moderate	Severe	Life threatening
Oxygen saturation	>90%	<90%	<90%
Talks in	phrases	words	Unable to speak
Alertness	normal	Usually agitated	agitated, drowsy or confused
Respiratory rate	20–30 breaths/minute	often >30 breaths/minute	often >30 breaths/minute OR feeble effort
Wheeze	present	present	absent
Heart rate	100–120 beats/minute	>120 beats/minute	bradycardia
PEFR	>60% of predicted	<60% of predicted	<33% of expected or unable to blow

AMENDED TO**16.1 ASTHMA, ACUTE EXACERBATION**

J45.0-1/J45.8-9/J46

DESCRIPTION

Acute asthma is an emergency and presents with one or more of the following:

- » wheeze
- » chest tightness
- » breathlessness
- » cough
- » respiratory distress

Risk factors for asthma-related death

- » History of near-fatal asthma requiring intubations and mechanical ventilation.
- » Hospitalisation or emergency care visit for asthma in the past year.
- » Currently using or recent discontinuation of oral corticosteroids.
- » Not currently using inhaled corticosteroids.
- » Frequent use of short acting β_2 -agonists (SABA), defined as average SABA usage ≥ 1 metered dose inhaler (MDI) canister, or ≥ 1 unit of nebuliser solution, per month.
- » Poor adherence to ICS-containing medications.
- » A history of psychiatric disease or psychosocial problems.
- » Food allergy in a patient with asthma.
- » Presence of pneumonia, diabetes or arrhythmias (each individually associated with an increased risk of death after hospitalisation for an asthma exacerbation).

DIAGNOSIS

Classify the patient according to the most severe clinical features present, e.g., if a patient has some features of mild-moderate exacerbation, but a single severe or life-threatening feature, manage them according to the higher severity assessment.

Table 16.1: Recognition and assessment of severity of asthma exacerbation in adults and adolescents ≥ 12 years

	Mild-Moderate	Severe	Life-Threatening
Oxygen saturation	$\geq 90\%$	< 90% on room air	< 90% on oxygen
Talks in	Phrases	Words	Unable to speak
Alertness	Normal	Usually agitated	Agitated, drowsy or confused
Respiratory rate	≤ 30 breaths/minute	> 30 breaths/minute	> 30 breaths/minute, OR feeble effort
Wheeze	Present	Present	Silent chest
Heart rate	100–120 beats/minute	> 120 beats/minute	< 60 beats/minute
PEFR (%)	$\geq 60\%$ of predicted	33–60% of predicted PEF	< 33% of expected, or unable to perform test

Note: PEFR is expressed as a percentage of the predicted normal value for the individual, or of the patient's personal best value obtained previously when on optimal treatment. See PEF charts in Appendix V: Asthma monitoring). GENERAL MEASURES Patients with moderate-severe or life threatening asthma should ideally be closely monitored in a High Care- or Intensive Care Unit. MEDICINE TREATMENT See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques. Mild to moderate attacks - Salbutamol 100 mcg metered-dose inhaler (MDI), - Salbutamol inhaler 400–1000 mcg (4-10 puffs) using a spacer if required and available. - Shake the inhaler between each puff. - If no relief, repeat every 20–30 minutes in the first hour. - Thereafter, repeat every 2–4 hours if needed. Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser. OR - Salbutamol 0.5% (5 mg/mL), solution, 1 mL (5 mg) salbutamol 0.5% solution made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen. - If no relief, repeat every 20–30 minutes in the first hour. - Thereafter, repeat every 2–4 hours if needed. PLUS - Prednisone, oral, 40 mg immediately if patient known to have asthma/COPD. - Follow with prednisone, oral, 40 mg daily for 7 days. Severe attacks - Oxygen to keep oxygen saturation 93-95%. AND - Salbutamol 0.5% (5 mg/mL) nebuliser solution, 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen. - If no relief, repeat every 20–30 minutes until PEF > 60% of predicted. - Once PEF > 60% of predicted, repeat every 2–4 hours if needed. OR - Salbutamol, inhalation using a MDI, - Salbutamol 400–1000 mcg (4–10 puffs), up to 20 puffs, using a spacer. - Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs. - If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.	PEFR is expressed as percentage of predicted normal (or personal best if known). See PEF charts in Appendix V: Asthma monitoring. Differential Diagnosis - For patients 50 years of age or older, with a first presentation of asthma, consider pulmonary oedema due to heart failure as an alternate diagnosis. - In patients who do not respond within one hour of initiating the acute asthma algorithm, exclude upper airway obstruction/stridor, pneumothorax, and anaphylaxis. GENERAL MEASURES - Assess the severity of the exacerbation and treat according to the management algorithm below. - Monitor response to treatment with repeated PEFR and clinical signs. Assess need to escalate therapy hourly, or sooner if worsening clinically. - Exclude upper airway obstruction/stridor, pneumothorax, and anaphylaxis. - Ideally, patients with a moderate, severe, or life-threatening asthma exacerbation should be closely monitored in a high care- or intensive care unit. Table 16.2: Features of clinical response to treatment in adults and adolescent ≥12 years <table><tr><th></th><th>No response</th><th>Response</th></tr><tr><td>PEFR (if possible)</td><td>Improvement by < 20%</td><td>Improvement by ≥ 20%</td></tr><tr><td>Respiratory rate</td><td>> 20 breaths/ minute</td><td>≤ 20 breaths/ minute</td></tr><tr><td>Speech</td><td>Impaired</td><td>Normal</td></tr></table> MEDICINE TREATMENT Bronchodilator administration: - Salbutamol administered via spacer is as effective as via nebuliser. - When using metered dose inhalers (MDIs), shake inhaler between each puff. - For guidance on inhaler, spacer and nebuliser device techniques, see Appendix VI: Devices for Respiratory Conditions. Mild to moderate exacerbations - Salbutamol, 100 mcg metered-dose inhaler (MDI). - Salbutamol inhaler 400–1000 mcg (4–10 puffs) using a spacer. - Shake the inhaler between each puff. - If no relief, repeat every 20–30 minutes in the first hour. - Thereafter, repeat every 2–4 hours if needed. OR - Salbutamol 0.5% (5 mg/mL), nebuliser solution. - Administer 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL solution by adding 3 mL sodium chloride 0.9%. - Recommended delivery at a flow rate of 8 L/min with oxygen. - If no relief, repeat every 20 minutes in the first hour. - Thereafter, repeat every 2–4 hours if needed. PLUS - Prednisone, oral, 40 mg immediately if patient is known to have asthma/COPD.		No response	Response	PEFR (if possible)	Improvement by < 20%	Improvement by ≥ 20%	Respiratory rate	> 20 breaths/ minute	≤ 20 breaths/ minute	Speech	Impaired	Normal
	No response	Response											
PEFR (if possible)	Improvement by < 20%	Improvement by ≥ 20%											
Respiratory rate	> 20 breaths/ minute	≤ 20 breaths/ minute											
Speech	Impaired	Normal											

- Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

If response is poor after first salbutamol nebulisation/inhalation:

ADD

- Ipratropium bromide 0.5 mg/2mL; nebuliser solution.
 - Ipratropium bromide, 2 mL (0.5 mg) added to salbutamol 1 mL (5 mg) solution and made up to 4 mL with sodium chloride 0.9%.
 - Administer every 20–30 minutes for 3 doses depending on clinical response.

OR

- Ipratropium bromide, MDI, 80–160 mcg (2–4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours.

AND

Corticosteroids (intermediate-acting) e.g.:

- Prednisone, oral, 40 mg immediately.
 - Follow with prednisone, oral, 40 mg daily for 7 days.

OR

In patients who cannot use oral therapy, are vomiting, or are suspected to have gastric atony from a severe asthma exacerbation:

- Hydrocortisone IM/slow IV, 100 mg 6 hourly. Once oral medication can be taken, switch to:
 - Corticosteroids (intermediate-acting) e.g.: Prednisone, oral, 40 mg daily for 7 days.

CAUTION

Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently.

Life-threatening attacks

- Oxygen, to keep oxygen saturation 93–95%.

AND

- Salbutamol 0.5% (5 mg/mL) with ipratropium bromide 0.5 mg/2mL nebuliser solution:
 - Salbutamol 0.5%, 2 mL (10 mg) plus ipratropium bromide, 2 mL (0.5 mg) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.
 - Delivered at a flow rate of 8 L/min with oxygen.
 - If no relief, repeat every 20–30 minutes until asthma severity category moves from life-threatening to severe.

AND

- Parenteral corticosteroids (intermediate-acting), e.g.:
- Hydrocortisone IM/slow IV, 100 mg 6 hourly. Once oral medication can be taken, switch to:
 - Corticosteroids (intermediate-acting) e.g.: Prednisone, oral, 40 mg daily for 7 days.

CAUTION

Avoid sedation of any kind.

Note: As clinical condition responds to treatment and severity improves to becomes severe but not life

- Follow with prednisone, oral, 40 mg daily for 5 days.

Severe exacerbations

- Oxygen to keep oxygen saturation 93–95%.

AND

- Salbutamol 0.5% (5 mg/mL), nebuliser solution.
 - Administer 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL solution by adding 3 mL sodium chloride, 0.9%.
 - Recommended delivery at a flow rate of 8 L/minute with oxygen.
 - If no relief, repeat every 20 minutes until PEF > 60% of predicted.
 - Once clinical improvement is noted, repeat every 2–4 hours if needed.

OR (if no oxygen required)

- Salbutamol 100 mcg MDI.
 - Salbutamol 400–1000 mcg (4–10 puffs), using a spacer.
 - If no relief, repeat every 20 minutes until PEF > 60% of predicted.
 - Once clinical improvement is noted, repeat every 2–4 hours if needed

If response is poor after first salbutamol nebulisation/inhalation:

Continue oxygen and salbutamol therapy described above, and:

ADD

- Ipratropium bromide 0.5 mg/2 mL, nebuliser solution.
 - Administer ipratropium bromide 0.5 mg (2 mL of 0.5 mg/2 mL solution) every 4 hours.
 - Where ipratropium bromide dose coincides with 2 hourly salbutamol, add ipratropium bromide 0.5 mg (2 mL of 0.5 mg/2 mL solution) to salbutamol 5 mg (1 mL of 5 mg/mL solution) and make up to 4 mL with sodium chloride, 0.9%, i.e. add 1 mL sodium chloride, 0.9%.
 - Once clinical improvement is noted, taper the dose frequency until patient is stable.

Example: Dosing schedule for nebulisation if patient has a poor response to initial dose of salbutamol

Timeline*	Nebuliser treatment
0 hours†	Salbutamol 5mg + Ipratropium bromide 0.5 mg
2 hours	Salbutamol 5mg
4 hours	Salbutamol 5mg + Ipratropium bromide 0.5 mg
6 hours	Salbutamol 5mg
8 hours	Salbutamol 5mg + Ipratropium bromide 0.5 mg
10 hours	Salbutamol 5mg
12 hours	Salbutamol 5mg + Ipratropium bromide 0.5 mg

*Once clinical improvement is noted, taper down dose frequency until patient is stable

†Time at which poor response is noted

AND

- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 40 mg immediately.

threatening, treat as per severe asthma exacerbation above.	• Follow with prednisone, oral, 40 mg daily for 5 days.												
Assessment of response in adults	Note: If response to treatment remains poor, consider alternative diagnoses and refer urgently.												
<table><tr><th></th><th>Response</th><th>No response</th></tr><tr><td>PEFR (if possible)</td><td>improvement by >20%</td><td>improvement by <20%</td></tr><tr><td>Respiratory rate</td><td><20 breaths/minute</td><td>>20 breaths/minute</td></tr><tr><td>Speech</td><td>normal</td><td>impaired</td></tr></table>		Response	No response	PEFR (if possible)	improvement by >20%	improvement by <20%	Respiratory rate	<20 breaths/minute	>20 breaths/minute	Speech	normal	impaired	<u>In patients who cannot tolerate oral therapy, are vomiting, or are suspected to have gastric atony from a severe asthma exacerbation:</u> • Hydrocortisone, IM/slow IV, 100 mg 6 hourly until oral therapy is tolerated.
	Response	No response											
PEFR (if possible)	improvement by >20%	improvement by <20%											
Respiratory rate	<20 breaths/minute	>20 breaths/minute											
Speech	normal	impaired											
Monitor response with PEF and clinical signs. Patients who fail to respond within 1 hour (symptomatic improvement and PEF >60% of predicted/personal best): » Exclude upper airway obstruction/stridor, pneumothorax, and anaphylaxis. » Discuss management with a specialist. » Intubation and ventilator support may be required. » If referral to another facility is required, the patient needs to be stabilised prior to transfer and transported by the appropriate level of transport –discuss with the referral centre.	<u>Once oral medication can be taken, switch parenteral corticosteroids to:</u> • Corticosteroids (intermediate-acting), e.g.: • Prednisone, oral, 40 mg daily for 5–7 days.												
<u>In patients with a poor response:</u> ADD Magnesium sulfate, IV, (50 mg/kg, maximum dose 2 g) in 100 mL sodium chloride 0.9%, as a single dose, administered over 20 minutes. ○ Intravenous magnesium, single dose, has been shown to reduce the rate of hospitalisation.	CAUTION Avoid sedation of any kind.												
There is good evidence to recommend against the use of intravenous aminophylline in acute asthma as its use, together with high-dose nebulised β_2 -agonists, does not result in significant additional bronchodilation, and leads to a significant increase in toxicity (vomiting and dysrhythmias).	Life-threatening exacerbations Urgently refer patient for high care or intensive care. While awaiting referral, administer: • Oxygen, to keep oxygen saturation 93–95%.												
Intercurrent bacterial respiratory infections Bacterial infections are seldom present in acute exacerbations of asthma and yellow sputum production is usually related to presence of eosinophils. Antibiotics do not play a role in the management of asthma unless there is air space consolidation on CXR. See Section 16.6: Pneumonia, community acquired.	AND • Salbutamol 0.5% (5 mg/mL) with ipratropium bromide 0.5 mg/2mL, nebuliser solution: ○ Salbutamol 0.5%, 2 mL (10 mg) plus ipratropium bromide, 2 mL (0.5 mg) every 15 minutes until asthma severity category improves from life-threatening to severe. ○ Recommended delivery at a flow rate of 8 L/minute with oxygen.												
	AND • Parenteral corticosteroids (intermediate-acting), e.g.: • Hydrocortisone, IM/slow IV, 100 mg 6 hourly until oral therapy is tolerated.												
	<u>In patients with a poor response despite corticosteroid therapy:</u> ADD • Magnesium sulfate, IV, (50 mg/kg, maximum dose 2 g) in 100 mL sodium chloride 0.9%, as a single dose, administered over 20 minutes. ○ A single dose of intravenous magnesium sulfate has been shown to reduce the likelihood of in-hospital admissions.												
	<u>In patients where nebulised treatment cannot be given effectively, e.g., silent chest, agitation with mask intolerance, repeated mask removal, or cyanosis:</u> In a high care or intensive care setting where adequate monitoring is accessible, consult a specialist for use of: • Salbutamol, IV, 1mg/mL injection for IV infusion. ○ Dilute one 5 mg/mL ampoule in 500 mL sodium chloride, 0.9% to produce a 10 mcg/mL solution of salbutamol. ○ Administer loading dose of 750 mcg over 10 minutes at an infusion rate of 450 mL/hour. ○ Continue maintenance infusion by reducing infusion rate to 30 mL/hour (5 mcg/minute).												

STG guidance on the management of acute asthma has been subject to editorial updates as detailed below.

	○ Adjust the infusion rate every 15 minutes according to clinical response by maintaining a rate between 18 to 120 mL/hour (3 to 20 mcg/minute). ○ Monitor for tachycardia and arrhythmias, hypokalaemia, hyperglycaemia (particularly in diabetic patients receiving concomitant corticosteroids), and lactic acidosis (uncommon). Note: • There is good evidence to recommend against the use of IV aminophylline in the management of acute asthma exacerbations in adults as its use is not associated with additional bronchodilation and may result in increased toxicity (e.g. vomiting and dysrhythmias) with concurrent high-dose nebulised β_2-agonists. • As the clinical condition responds to treatment and severity improves from life-threatening to severe, treat as per severe asthma exacerbation above. CAUTION Avoid sedation of any kind. Intercurrent bacterial respiratory infections • Acute asthma exacerbations rarely involve bacteria. • Yellow sputum suggests eosinophilia, not infection. • Antibiotics are unnecessary unless chest X-ray shows consolidation (see Section 16.6: Pneumonia, community acquired). REFERRAL » If patient fails to respond within one hour (i.e., symptomatic improvement and PEF > 60% of predicted/personal best): – Discuss management with a specialist. – Intubation and ventilator support may be required. » If referral to another facility is required, stabilise the patient prior to transfer and utilise the appropriate level of ambulant care – discuss with the referral centre.
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AH: ASTHMA, ACUTE EXCERBATION

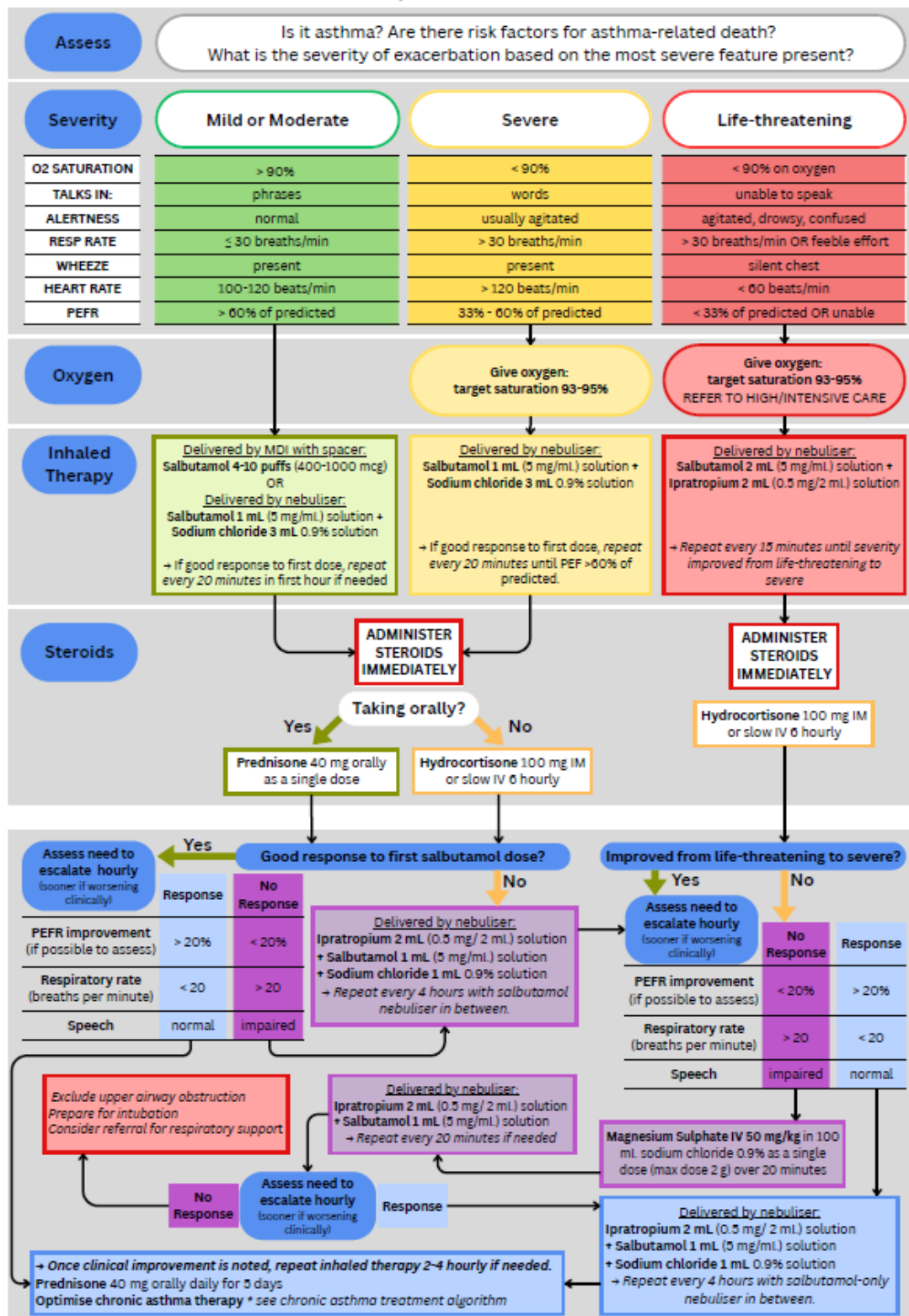


Figure 16.1 Management of acute asthma exacerbation

Section 16.2 Asthma, chronic

MAINTENANCE AND RELIEVER THERAPY (MART)

Short-acting beta agonist (SABA) – asthma reliever/rescue therapy: Deleted

The use of inhaled corticosteroid therapy with a short-acting beta agonist (SABA) for maintenance and reliever therapy in adults and adolescents 12 years and older has been replaced with the use of corticosteroid/formoterol inhaled combination therapy for maintenance and/or reliever therapy for different degrees of asthma severity, as appropriate.

Inhaled Corticosteroid (ICS) therapy- asthma controller therapy: Deleted

The use of inhaled corticosteroid maintenance/controller therapy with a short-acting beta agonist (SABA) for reliever therapy in adults and adolescents 12 years and older has been replaced with the use of corticosteroid/formoterol inhaled combination therapy for maintenance and/or reliever therapy for different degrees of asthma severity, as appropriate.

ICS/formoterol combination inhaler for maintenance and reliever therapy (MART): Added

The Asthma Sub-Committee established during the NEMLC 2020-4 review cycle conducted 3 evidence reviews on the use of ICS/formoterol combination inhalers for maintenance and/or reliever therapy for different degrees of asthma severity as tabulated below:

	Asthma Severity	Research question
PICO 1	Intermittent asthma or asthma symptoms < twice a month	In adults and adolescents aged 12 years and older with asthma symptoms less than two times per month, what is the efficacy and safety of formoterol/ICS taken as needed compared with intermittent short-acting beta ₂ agonist (SABA) reliever plus low-dose ICS as needed for symptom relief?
PICO 2	Mild persistent asthma	In adults and adolescents aged 12 years and older with mild persistent asthma, what is the efficacy and safety of formoterol/ICS taken as needed compared with daily low-dose ICS and a SABA reliever?
PICO 3	Moderate to severe persistent asthma or uncontrolled asthma in patients on maintenance LABA/ICS	In asthmatic adults and adolescents aged 12 years and older using daily inhaled LABA plus ICS fixed-dose combination (FDC), what is the efficacy and safety of formoterol/ICS taken as maintenance therapy and as needed reliever therapy compared with LABA plus ICS FDC and as needed SABA reliever for symptom relief?

The NEMLC recommendation from these 3 evidence reviews is detailed below. A copy of the consolidated evidence review for the 3 PICOs can be found at the end of this report or on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATIONS					
Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	

Recommendation PICO 1:

The ASC suggests that the ICS/formoterol combination, as needed, be used for symptom relief in adults and adolescents aged 12 years and older with intermittent asthma or asthma symptoms less than two times per month (*conditional recommendation, very low certainty evidence*).

Recommendation PICO 2:

The ASC recommends that the ICS/formoterol combination be used for symptom relief in adults and adolescents aged 12 years and older with mild persistent asthma (*strong recommendation, moderate certainty evidence*).

Recommendation PICO 3:

The ASC recommends that the ICS/formoterol combination be used as a maintenance and reliever therapy in adults and adolescents aged 12 years and older with moderate to severe persistent asthma (*strong recommendation, moderate certainty evidence*).

Remarks:

- Beta-2-agonists should not be used as sole reliever therapy in asthma without concomitant inhaled corticosteroids, ideally co-formulated as a fixed-dose combination
- PICO 1: Network meta-analysis evidence (Rayner, 2024) and expert opinion were used to determine the efficacy and safety of ICS/FABA compared to ICS with SABA
- Across all PICOs: Sensitivity analysis of the budget impact analysis indicated uncertainty regarding several model parameters, and further research is required in this area (costs of emergency room visits, hospitalisations and ICU admissions, the proportion of asthmatics referred from PHC for hospitalisation, utilisation patterns of inhalers for the standard of care and the proportion of adults with severe asthma)
- The environmental impact of the different types of inhaler devices needs to be considered when prescribing these products

Rationale: The committee considers the combination of interventions; the benefits outweigh the risks and are considered feasible and acceptable. It makes programmatic sense to use the same reliever therapy across all levels of asthma severity as asthma symptoms change over time.

Review indicator: New high-quality evidence of a clinically relevant benefit, a change in the price of medicines.

Monitoring and evaluation (M&E) considerations: The ASC recognises the importance of M&E programmes, which require careful planning and implementation to monitor clinical outcomes such as acute severe asthma exacerbations, hospitalisations, referrals from primary healthcare (PHC) facilities, as well as utilisation data.

Research priorities: There is a need for prevalence data for our populations of interest, better direct evidence for PICO 1 as well as more local acceptability, feasibility and costing data.

NEMLC RECOMMENDATION (27 Nov 2025):

NEMLC supports the ERC recommendation as detailed above.

Additionally, an economic evaluation was undertaken to assess the cost effectiveness and budget impact of switching from the current standard of care (ICS+SABA) to ICS/formoterol for both maintenance and reliever therapy for chronic asthma management in adults and adolescents ≥ 12 years. The NEMLC recommendation from this economic analysis is detailed below. A copy of economic analysis can be found at the end of this report or on the NHI webpage.

Economic analysis - Conclusion

The budget impact analysis demonstrates that adopting ICS/formoterol treatment strategies for asthma, has the potential to yield cost savings for the South African public health sector. Across the different PICO scenarios, the reduction in healthcare utilisation costs (primarily from fewer hospitalisations, emergency visits, and ICU admissions) and the lower medicine costs for PICOs 1 and 2 lead to net savings. The higher medicine costs for the intervention group in PICO 3 are also offset by the lower healthcare utilisation costs, due to improved patient outcomes.

Key factors influencing the budget impact include the price of budesonide/formoterol inhalers, the prevalence of asthma, the relative population cohorts based on disease severity, and uncertainties surrounding healthcare utilisation patterns. While the analysis highlights potential economic benefits, successful implementation of revised asthma guidelines requires additional investments in procurement, health provider training, and patient education to ensure adherence and optimal treatment outcomes. Given the limited availability of local epidemiological data, further research is needed to refine cost estimates and validate assumptions. Policymakers may also consider engaging in price monitoring and negotiations for budesonide/formoterol inhalers to enhance affordability and sustainability. By aligning treatment strategies with cost-effective interventions, the health system can improve asthma management, while optimising resource allocation.

ICS/fomoterol 4.5mcg MDI or DPI – chronic asthma for adults and adolescents 12 years and older: Added

Comparative ICS doses for adults and adolescents 12 years and older are tabulated below. The recommended doses do not necessarily imply dose equivalence or equipotency (i.e. switching patients from low dose of one medicine to low dose of another medicine may represent an increase or decrease in potency). Refer to Appendix VIII: Comparative dose tables for further detail and the therapeutic interchange tables at the end of this report.

Adults and adolescents ≥12 years			
Drug	Daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate CFC	200–500	>500–1 000	>1 000
Beclometasone dipropionate HFA	100–200	>200–400	>400
Budesonide DPI or HFA	200–400	>400–800	>800
Ciclesonide HFA	80–160	>160–320	>320
Fluticasone furoate DPI	100	n/a	200
Fluticasone propionate DPI	100–250	>250–500	>500
Fluticasone propionate HFA	100–250	>250–500	>500
Mometasone furoate	110–220	220–440	>440
CFC: chlorofluorocarbon propellant HFA: hydrofluoroalkane propellant MDI: metered dose inhaler DPI: dry powder inhaler			

Budesonide 160mcg/fomoterol 4.5mcg MDI: Added (as example from therapeutic class)

Budesonide 160mcg/fomoterol 4.5mcg MDI has been added to the STG as an example of the corticosteroids/formoterol inhaler therapeutic class, following publication of the most recent HP07 contract circular².

² HP07-2026DAI: Supply and delivery of pharmaceutical products: drops, aerosols and inhaled medicines to the department of health for the period 01 September 2026 to 31 August 2029. Ref: HP07-2026DAI

Budesonide 160mcg/fomoterol 4.5mcg MDI – maximum daily dose: Amended

In response to external comment received, guidance on the maximum dose of budesonide 160mcg/fomoterol 4.5mcg when used as AIR/MART therapy for chronic asthma in adults and adolescents 12 years and older, has been amended to a maximum of 12 inhalations per day (equivalent to budesonide 1920 mcg/formoterol54 mcg), and aligned with recommendations in the GINA guideline³.

PATIENTS ON PROTEASE-INHIBITOR-BASED ANTIRETROVIRAL THERAPY

Short-acting beta agonist (SABA) – asthma reliever/rescue therapy for patients on protease inhibitors: Retained

Beclomethasone 200mcg MDI HFA- asthma controller therapy for adults and adolescents ≥ 12 years on protease inhibitors: Added

Beclomethasone is the preferred ICS for people living with HIV and on protease inhibitor based antiretroviral therapy, as there are drug interactions between protease inhibitors and budesonide. For adults and adolescents 12 years and over, GINA guidelines recommend:

- Patients on Step 1-3: low dose beclometasone dipropionate HFA (100-200mcg) as a total daily dose when used as reliever (Step 1) or maintenance therapy (Step 2 and 3)
- Patients on Step 4: medium dose beclometasone dipropionate HFA (>200-400 mcg) as a total daily dose when used for maintenance therapy

Note: Beclometasone 100 mcg MDI has been awarded on the most recent HP07 tender circular.⁴ Dosing guidance in the STG has therefore been aligned to the beclometasone 100mcg formulation.

STG Update

Guidance on the management of asthma and adolescents ≥ 12 years has been updated to include the use of corticosteroid/formoterol inhaler for maintenance and/or reliever therapy based on the degree of asthma severity. The updated STG guidance is detailed below.

AMENDED FROM: 16.2 ASTHMA, CHRONIC PERSISTENT J45.0-1/J45.8-9 DESCRIPTION Asthma must be distinguished from chronic obstructive pulmonary disease, which is often mistaken for asthma. The history is a reliable diagnostic guideline and may be of value in assessing treatment response. GENERAL MEASURES Patient education: including advice on smoking cessation. <table><tr><td>Asthma</td><td>COPD</td></tr></table> Decrease exposure to triggers, e.g. house dust mite, pollens, grasses, pets, smoke, fumes, etc.	Asthma	COPD	AMENDED TO 16.2 ASTHMA, CHRONIC J45.0-1/J45.8-9 DESCRIPTION Asthma is a chronic, heterogeneous disease of the airways, and is characterised by airway inflammation. Asthma is usually associated with airway hyperresponsiveness and structural remodelling, however, these are not necessary or required to make a diagnosis. DIAGNOSIS Chronic obstructive pulmonary disease is often mistaken for asthma. Asthma must be distinguished from chronic obstructive pulmonary disease (COPD) through history taking to aid in selecting appropriate treatment. Features suggestive of asthma: » Respiratory symptoms: wheeze, cough, chest tightness, shortness of breath. » History and examination: intermittently symptomatic, night-time symptoms, identified triggers, atopy, family history.
Asthma	COPD		

³ Global Initiative for Asthma (GINA). (2024). *Global Strategy for Asthma Management and Prevention, 2024*. <https://ginasthma.org/2024-report/>

⁴ HP07-2026DAI: Supply and delivery of pharmaceutical products: drops, aerosols and inhaled medicines to the department of health for the period 01 September 2026 to 31 August 2029. Ref: HP07-2026DAI

» Young age onset, usually <20 years. » History of hay fever, eczema and/or allergies. » Family history of asthma. » Symptoms are intermittent with periods of normal breathing in between. » Symptoms are usually worse at night or in the early hours of the morning, during an upper respiratory tract infection, when the weather changes or when upset. » Increase 20% in PEF 10 minutes after receiving a β_2-agonist.	» Older age onset, usually >40 years. » Symptoms slowly worsen over a long period of time. » Long history of daily/frequent cough, before the onset of shortness of breath. » Symptoms are persistent and not only at night or during the early morning. » History of heavy smoking (>20 cigarettes/day for ≥ 15 years), heavy cannabis use or previous TB. » Little improvement in PEF with β_2-agonist.	» Reversibility test: Increase in PEF $\geq 20\%$ when performed 15 mins after short-acting β_2 agonist (SABA) use (See Appendix V: Asthma Monitoring for details).																		
MEDICINE TREATMENT																				
Nocturnal symptoms of cough and wheeze, the need for bronchodilators more than twice a week, or PEF <80% of the patient's best value, indicates poor asthma control.																				
Patients with poorly controlled asthma need to step up their maintenance therapy as described below.																				
The Asthma Control Test®, a validated measure of clinical asthma control, can be completed by the patient (after initial instruction) at each visit to the clinic prior to consultation. A value of ≥ 20 suggests adequate asthma control (see Appendix V: Asthma monitoring).																				
See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.																				
A patient with poorly controlled asthma should be assessed for the following and identified problems addressed prior to stepping up therapy: 1) Correct inhaler technique should be demonstrated and checked regularly, as many asthmatic patients do not use their inhalers correctly. 2) Adherence to medication, especially the inhaled corticosteroid. 3) Ensure a spacer is being used for all MDIs and patient has been trained in its use. 4) Exposure to triggers of bronchospasm. 5) Use of medications that may aggravate asthma, e.g. NSAIDs. 6) Other medical conditions such as cardiac disease. 7) Treat allergic rhinitis (see Section 17.2: Rhinitis, allergic, persistent) and GORD (see Section 1.1.3: Gastro-																				
GENERAL MEASURES																				
Patient Education																				
» All patients should be counselled on smoking cessation, inhaler technique, treatment adherence and decreasing exposure to triggers (e.g., house dust mite, pollens, grasses, pets, smoke, fumes, etc.). » See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.																				
Assessment																				
» Initial diagnosis, treatment initiation and follow up should be accompanied by: - An assessment of the patient's future risk, including addressing all modifiable risk factors. - Inhaler technique (See Appendix VI: Devices for Respiratory Conditions). » Follow up consultations should include assessment of asthma control, future asthma risk, and appropriateness of current treatment to determine if escalation or de-escalation of therapy is required.																				
Table 16.3: Future asthma outcome risk assessment																				
<table> <tr> <th colspan="3">Risk factors for exacerbations</th></tr> <tr> <td>Poor control</td><td colspan="2">» Uncontrolled asthma (as assessed below)</td></tr> <tr> <td>Inappropriate medication use</td><td colspan="2"> » High SABA use (more than 3 inhalers per year) » Inadequate ICS use (not prescribed, poor adherence, poor inhaler technique) </td></tr> <tr> <td>Co-morbidities</td><td> » Obesity » Chronic rhinosinusitis » Confirmed food allergy </td><td> » Gastro-oesophageal reflux disease (GORD) » Pregnancy </td></tr> <tr> <td>Exposures</td><td> » Smoking (including e-cigarettes) » Air pollution </td><td> » Known allergen exposure » Indoor smoke exposure </td></tr> <tr> <td>Social factors</td><td colspan="2">» Major psychosocial and socioeconomic issues</td></tr> </table>			Risk factors for exacerbations			Poor control	» Uncontrolled asthma (as assessed below)		Inappropriate medication use	» High SABA use (more than 3 inhalers per year) » Inadequate ICS use (not prescribed, poor adherence, poor inhaler technique)		Co-morbidities	» Obesity » Chronic rhinosinusitis » Confirmed food allergy	» Gastro-oesophageal reflux disease (GORD) » Pregnancy	Exposures	» Smoking (including e-cigarettes) » Air pollution	» Known allergen exposure » Indoor smoke exposure	Social factors	» Major psychosocial and socioeconomic issues	
Risk factors for exacerbations																				
Poor control	» Uncontrolled asthma (as assessed below)																			
Inappropriate medication use	» High SABA use (more than 3 inhalers per year) » Inadequate ICS use (not prescribed, poor adherence, poor inhaler technique)																			
Co-morbidities	» Obesity » Chronic rhinosinusitis » Confirmed food allergy	» Gastro-oesophageal reflux disease (GORD) » Pregnancy																		
Exposures	» Smoking (including e-cigarettes) » Air pollution	» Known allergen exposure » Indoor smoke exposure																		
Social factors	» Major psychosocial and socioeconomic issues																			

oesophageal reflux disease (GORD) and dyspepsia, if present.

Asthma therapy

Inhaled corticosteroids (ICS) are the mainstay of treatment in asthma.

For patients with infrequent asthma symptoms < twice a month:

As reliever/rescue therapy:

- Short acting β_2 -agonists, e.g.:
- Salbutamol, MDI, 200 mcg, as needed.

AND

- Inhaled corticosteroids, e.g.:
- Budesonide, inhalation, 200 mcg whenever salbutamol is taken.

In patients on protease inhibitors, beclomethasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide.

- Beclomethasone, inhalation, 200 mcg whenever salbutamol is taken.

For patients with asthma symptoms $\geq$ twice a month:

As controller therapy:

- Inhaled corticosteroids, low dose, e.g.:
- Budesonide, inhalation, 200 mcg 12 hourly.
 - Well and stable after 6 months: can attempt to reduce budesonide dose to 200 mcg daily.
 - Dose adjustments may be required at change of seasons.

In patients on protease inhibitors, beclomethasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide.

- Beclomethasone, inhalation, 200 mcg 12 hourly for 6 months; reduced to 200 mcg daily once well and stable.

AND

As reliever/rescue therapy:

- Short acting β_2 -agonists, e.g.:
- Salbutamol, MDI, 200 mcg, 6 hourly as necessary.

For patients with asthma symptoms almost daily or waking due to asthma at least once a week:

- Long-acting β_2 -agonist/corticosteroid combination inhaler, e.g.:
- Salmeterol/fluticasone, inhalation, 50/250 mcg 12 hourly.

Poor lung function	» FEV1 < 60% predicted » High bronchodilator responsiveness
Inflammatory markers	» Eosinophilia (blood)
Exacerbations	» Any prior intubation or ICU admission for asthma » Severe exacerbation in the past year
Risk factors for developing persistent airflow limitation	
History	» Preterm birth, LBW and greater infant weight gain » Chronic mucus hypersecretion
Medications	» History of severe exacerbation (see Section 16.1: Asthma, acute exacerbation) without ICS treatment thereafter.
Exposures	» Tobacco smoke » Noxious chemicals » Occupational or domestic exposures
Investigations	» Low initial FEV1 » Sputum/blood eosinophilia

Asthma severity

Classify asthma severity based on a patient's *response* to treatment. Historic definitions of mild, moderate, and severe asthma, do not accurately reflect a patient's symptom frequency, intensity, or risk, and their use is no longer recommended.

MEDICINE TREATMENT

Corticosteroid and bronchodilator combination therapy

The use of an anti-inflammatory reliever (AIR) (usually an inhaled corticosteroid/ICS with the rapid onset LABA reliever, formoterol) is more effective than SABA use alone, even in asthma with low symptom frequency. In more severe disease, the same ICS-formoterol combination inhaler can be used for symptom relief as well as maintenance therapy, and is called maintenance-and-reliever therapy (MART).

Patient therapy should be determined as follows (see the chronic asthma algorithm below):

- » Initiate patients with newly diagnosed asthma at the highest step that correlates with their symptoms, e.g., if a patient has some features requiring step 2 or 3 therapy, but also has a recent history of acute exacerbation, initiate therapy according to step 4 and review after a period of therapy.
- » Step up treatment to the next level if patient is uncontrolled, partially controlled, or at high risk of exacerbations.
- » Consider treatment step down if patient has been well-controlled for 2–3 months.
- » **Note:** There is a significant drug interaction between the budesonide component of budesonide/formoterol inhalers and protease inhibitors (PIs). See the recommended therapy for patients on PIs below.

Table 16.4: Assessment of asthma control & recommended entry point for stepwise treatment

Presenting Symptoms	Initial Treatment
Asthma symptoms: two days/week or less	Step 1

○ Maximum dose: 50/500 mcg 12 hourly. ○ Well and stable for 6 months: step down to budesonide, inhaled, 200 mcg 12 hourly. AND <u>As reliever/rescue therapy:</u> ▪ Short acting β_2-agonists, e.g.: • Salbutamol, MDI, 200 mcg, 6 hourly as necessary. <u>In patients on protease inhibitors:</u> • Beclomethasone, inhalation, 400 mcg 12 hourly. AND • Formoterol, inhalation, 12 mcg 12 hourly. <u>Failure of above therapy:</u> While awaiting appointment with specialist. ADD ▪ Corticosteroids (intermediate-acting) e.g.: Prednisone, oral, 10 mg daily. Note: Prednisone should not be used as maintenance therapy but only as a bridging step while awaiting review by specialist. <u>For short-term exacerbations in patients not responding to the above, while awaiting review with specialist:</u> ▪ Corticosteroids (intermediate-acting) e.g.: Prednisone, oral, 40 mg daily for 10 days. PATIENT AND CAREGIVER EDUCATION ON INHALER AND SPACER TECHNIQUES: See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques. <u>Spacer devices</u> ▪ Patients on step 3 therapy and above, and patients on step 1 and 2 who are unable to use aerosol inhalers correctly after adequate counselling, may benefit from the use of a spacer with metered dose inhalers.	<table border="1"> <tr> <td></td><td>Low dose ICS-formoterol as AIR ONLY</td></tr> <tr> <td>Asthma symptoms: less than 3–5 days/week Normal or mildly reduced lung function</td><td>Step 2 Low dose ICS-formoterol as AIR only</td></tr> <tr> <td>Asthma symptoms: Most days (≥ 4 days/week) <i>OR</i> Night waking once a week or more <i>OR</i> Reduced lung function</td><td>Step 3 Low-dose ICS-formoterol as MART (once daily maintenance dose)</td></tr> <tr> <td>Asthma symptoms: Daily <i>OR</i> Night waking once a week or more <i>AND</i> Reduced lung function <i>OR</i> recent exacerbation</td><td>Step 4 Low-dose ICS-formoterol as MART (twice daily maintenance dose) OR Refer</td></tr> <tr> <td colspan="2">Abbreviations: ICS = Inhaled corticosteroids; AIR ONLY = Anti-inflammatory reliever only; MART = Maintenance-and-reliever therapy; SABA = Short-acting β_2 agonist.</td></tr> </table> Inhaled corticosteroids (ICS) improve asthma control when used for reliever/rescue therapy & maintenance therapy. Stepwise treatment of chronic asthma Patients who are unable to use aerosol inhalers correctly after adequate counselling, may benefit from the use of a spacer with metered dose inhalers. STEP 1 and STEP 2: (<i>Asthma symptoms < 5 days per week; and no nocturnal symptoms; and normal or mildly reduced lung function; and no history of recent acute exacerbation</i>). <u>Reliever/rescue therapy:</u> ▪ Low dose corticosteroid/formoterol inhaler (AIR therapy), e.g.: • Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, one inhalation as needed. ○ Maximum daily dose: 1920 mcg/54 mcg (12 inhalations) doses per day. ○ Patients should be counselled to present to their healthcare facility for review if they require maximum doses of inhaler therapy for more than one week within a month. Note: Insufficient asthma control on maximum therapeutic doses should trigger a review to step up treatment. <u>Maintenance therapy:</u> No maintenance therapy required. Continue with reliever/rescue therapy using ICS/formoterol combination inhaler and monitor asthma control. STEP 3: (<i>Asthma symptoms most days ≥ 4 per week; or weekly nocturnal symptoms; or reduced lung function; and no history of recent acute exacerbation</i>).		Low dose ICS-formoterol as AIR ONLY	Asthma symptoms: less than 3–5 days/week Normal or mildly reduced lung function	Step 2 Low dose ICS-formoterol as AIR only	Asthma symptoms: Most days (≥ 4 days/week) <i>OR</i> Night waking once a week or more <i>OR</i> Reduced lung function	Step 3 Low-dose ICS-formoterol as MART (once daily maintenance dose)	Asthma symptoms: Daily <i>OR</i> Night waking once a week or more <i>AND</i> Reduced lung function <i>OR</i> recent exacerbation	Step 4 Low-dose ICS-formoterol as MART (twice daily maintenance dose) OR Refer	Abbreviations: ICS = Inhaled corticosteroids; AIR ONLY = Anti-inflammatory reliever only; MART = Maintenance-and-reliever therapy; SABA = Short-acting β_2 agonist.	
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Abbreviations: ICS = Inhaled corticosteroids; AIR ONLY = Anti-inflammatory reliever only; MART = Maintenance-and-reliever therapy; SABA = Short-acting β_2 agonist.											

	<u>Maintenance therapy:</u> ▪ Low dose corticosteroid/formoterol inhaler (MART therapy), e.g.: • Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, one inhalation 12 hourly. AND <u>Reliever/rescue therapy:</u> ▪ Low dose corticosteroid/formoterol inhaler, e.g.: • Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, one inhalation as needed. ○ Maximum daily dose: 1920 mcg/54 mcg (12 inhalations) considering maintenance and reliever doses per day. This equates to 10 additional reliever inhalations on top of 2 maintenance inhalations. ○ Patients should be counselled to present to their healthcare facility for review if they require maximum doses of inhaler therapy for more than one week within a month. Note: Insufficient asthma control on maximum therapeutic doses should trigger a review to step up treatment. STEP 4: <i>(Daily asthma symptoms; or weekly nocturnal symptoms; and reduced lung function; or has history of recent acute exacerbation).</i> <u>Maintenance therapy:</u> ▪ Medium dose corticosteroid/formoterol (using low dose ICS/formoterol inhaler), e.g.: • Budesonide/formoterol, 160 mcg/4.5 mcg MDI, 160 mcg/4.5 mcg, two inhalations 12 hourly. AND <u>Reliever/rescue therapy:</u> ▪ Low dose corticosteroid/formoterol inhaler, e.g.: • Budesonide/formoterol, 160 mcg/4.5 mcg MDI,160 mcg/4.5 mcg, one inhalation as needed. ○ Maximum daily dose: 1920 mcg/54 mcg (12 inhalations) considering maintenance and reliever doses per day. This equates to 8 additional reliever inhalations on top of 4 maintenance inhalations. Note: Insufficient asthma control on maximum therapeutic doses should trigger a review to discuss with a specialist/refer for further treatment.								
	CAUTION Formoterol has a rapid onset of action and CAN be used as reliever therapy, but only in combination with an ICS. Salmeterol is not rapid acting and CANNOT be used as reliever therapy.								
	Table 16.5: Assessment of recent asthma control over the past 4 weeks (or since last review): <table><tr><th rowspan="2"></th><th colspan="2">Yes / No (Assign one point for each “yes” answer)</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td></td><td></td><td></td></tr></table>		Yes / No (Assign one point for each “yes” answer)		Yes	No			
	Yes / No (Assign one point for each “yes” answer)								
	Yes	No							

	Daytime asthma symptoms more than twice weekly		
	Night waking due to asthma (any)		
	Activity limitation due to asthma (any)		
	IF using SABA-only inhaler: SABA-only reliever use > twice/week for symptoms*		
	Total points	Control	
	0 points	Well controlled	
	1–2 points	Partially controlled	
	3–4 points	Uncontrolled	
	*Only applicable if patient is using an inhaler containing short-acting β_2 -agonist only, i.e. not a corticosteroid containing inhaler (e.g. salbutamol only inhaler).		
	» Consider whether level of treatment needs to be adjusted: – If patient is well-controlled: STEP DOWN treatment. – If patient is partially controlled or uncontrolled: STEP UP treatment. » Complete the following assessment before initiating change of therapy:		
	Before STEPPING DOWN treatment	Before STEPPING UP treatment	
	» Ensure that control has been good for at least 2–3 months. » Ensure that there have been no exacerbations in the past year. » Ensure that the patient does not have 2 or more risk factors for exacerbations (see “Assessment of risk factors” above). » Do not step down while pregnant or travelling.	» Ensure that medication adherence is good. » Ensure that inhaler technique is correct. » Ensure that all exposures have been minimised and modifiable risk factors addressed. » Ensure that co-morbidities are controlled and/or are not interfering with asthma control. » Ensure that there is no inappropriate medication use (e.g. β-blockers or HIV protease inhibitors).	
	See Figure 16.2 chronic asthma treatment algorithm below		
	CAUTION Budesonide has significant drug-drug interactions with HIV protease inhibitors and should be replaced with beclometasone where indicated.		
	Regimen for patients on protease inhibitors Beclometasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide:		

See Figure 16.2 chronic asthma treatment algorithm below

CAUTION Budesonide has significant drug-drug interactions with HIV protease inhibitors and should be replaced with beclometasone where indicated.

Regimen for patients on protease inhibitors
 Beclometasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide:

	STEP 1: <u>Reliever/rescue therapy:</u> ▪ Short acting β2-agonists, e.g.: • Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed. AND • Low dose beclometasone, 100 mcg MDI, to take 200 mcg (two inhalations) as needed. <u>Maintenance therapy:</u> No maintenance therapy required. Continue with reliever/rescue therapy and monitor asthma control. STEP 2: <u>Reliever/rescue therapy:</u> ▪ Short acting β2-agonists, e.g.: • Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed. <u>Maintenance therapy:</u> • Low dose beclometasone, 100 mcg MDI, to take 200 mcg (two inhalations), 12 hourly. ○ Well and stable after 6 months: can attempt to reduce beclometasone dose to 200 mcg daily or STEP 1 therapy. ○ Dose adjustments may be required at change of seasons. STEP 3: <u>Reliever/rescue therapy:</u> ▪ Short acting β2-agonists, e.g.: • Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed. <u>Maintenance therapy:</u> • Low dose beclometasone, 100 mcg MDI, to take 200 mcg (two inhalations) 12 hourly. AND • Formoterol, MDI, 12 mcg, 12 hourly. STEP 4: <u>Reliever/rescue therapy:</u> ▪ Short acting β2-agonists, e.g.: • Salbutamol 100 mcg MDI, to take 200 mcg (two inhalations) as needed. <u>Maintenance therapy:</u> • Medium dose beclometasone, 100 mcg MDI, to take 400 mcg (four inhalations) 12 hourly. AND • Formoterol, MDI, 12 mcg, 12 hourly. Management of patients poorly controlled on step 4: » Refer to specialist for further management. <u>While awaiting appointment with specialist:</u> Continue current therapy and add corticosteroids: ▪ Corticosteroids (intermediate-acting) , e.g.: • Prednisone, oral, 10 mg daily. Note:
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	» Prednisone should only be used as a bridging step while awaiting review by specialist and <u>SHOULD NOT</u> be used for long-term maintenance therapy. Ideally, patient should be referred within 4 weeks. » Consider steroid tapering if used for more than 2 weeks (see "Appendix II: Prescribing Information for Specific Medicines, Prednisone, Oral"). REFERRAL » Patients with poor asthma control on maximum ICS/reliever therapy.
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AH: ASTHMA, CHRONIC MANAGEMENT

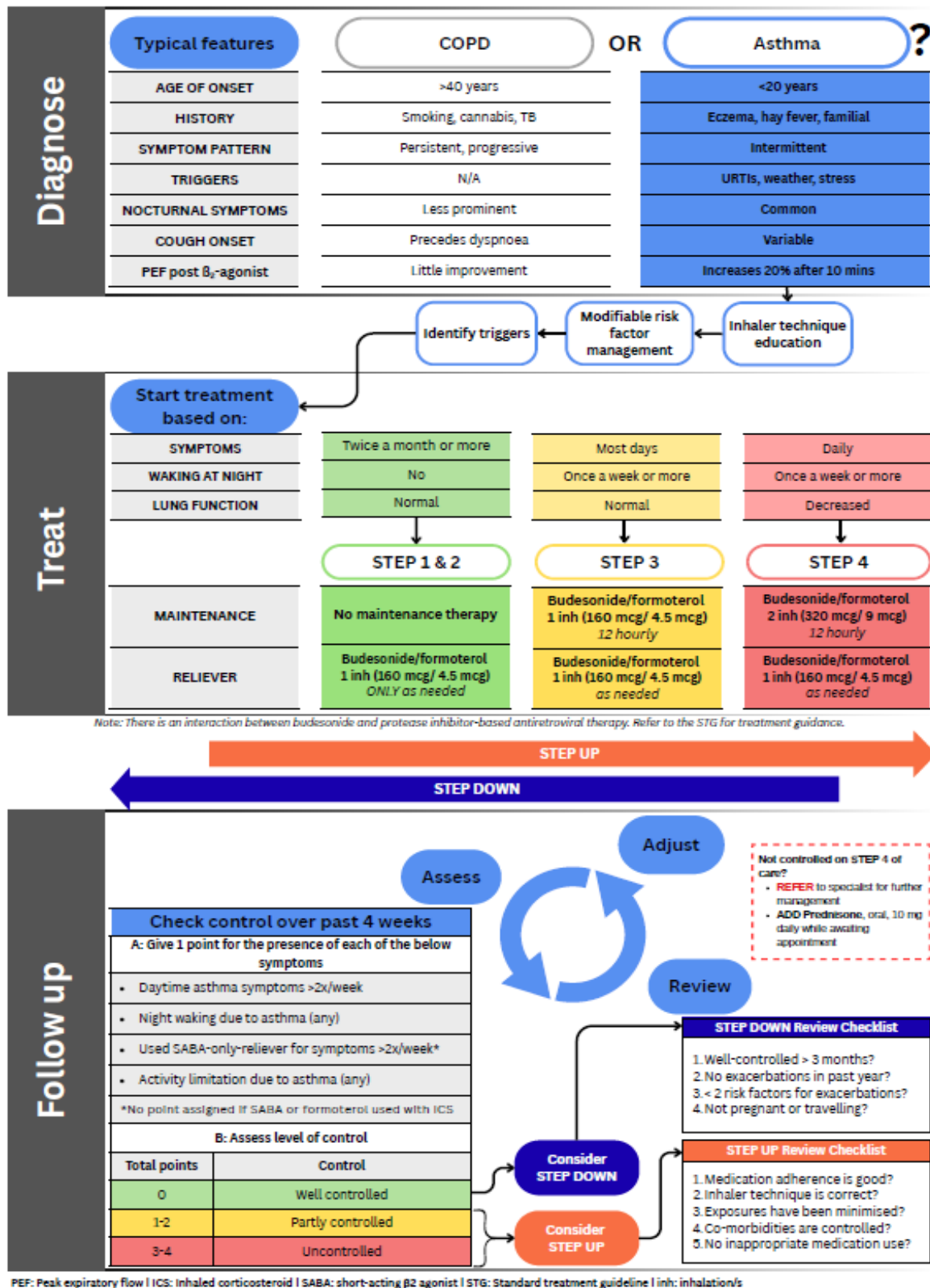


Figure 16.2 Management of chronic asthma

Section 16.9 Tuberculosis, pulmonary

This STG has been updated and transferred to the newly develop AH Chp 27: Tuberculosis chapter.

Section 16.10 Tuberculosis, pleural (TB pleurisy)

This STG has been updated and transferred to the newly develop AH Chp 27: Tuberculosis chapter.

Section 16.11 Drug-resistant TB

This STG has been updated and transferred to the newly develop AH Chp 27: Tuberculosis chapter.

AH Appendix V: ASTHMA MONITORING

Appendix V: Asthma monitoring, has been retained in the AH publication and may be found at the end of this report or on the NHI webpage.

AH Appendix VI: DEVICES FOR RESPIRATORY CONDITIONS

Nebulisers: Amended

An editorial amendment has been made as tabulated below:

Amended from:

Ensure the nebuliser cup is filled sufficiently to allow effective nebulisation (approx. 4 L minimum volume).

Amended to:

Ensure the nebuliser cup is filled sufficiently to allow effective nebulisation (approx. 4 mL minimum volume).

The amended Appendix VI: Devices for Respiratory Conditions, may be found at the end of this report or on the NHI webpage.

AH Appendix VIII: COMPARATIVE DOSE TABLES

NEMLC approved recommendations for comparative dosing across therapeutic classes of inhaled corticosteroids have been included in the newly developed AH Appendix VIII: Comparative dose tables. Appendix VIII: Comparative Dose tables, may be found at the end of this report or on the NHI webpage.

Comparative Interchange

NEMLC approved categories and products for inclusion on the therapeutic interchange database are detailed below (note that recommended doses do not necessarily imply dose equivalence or equipotency).

The delivered dose of inhaled medication may be influenced by several factors, including the drug chemical composition (e.g. fluticasone propionate versus fluticasone furoate), device type (e.g. MDI vs DPI), particle size (e.g. standard vs extra fine) and propellant type for MDIs (e.g. chlorofluorocarbon (CFC) vs hydrofluoroalkane (HFA)). The list below is not an exhaustive list of all SAHPRA approved products and it is therefore recommended that the individual product information be consulted for guidance on the delivered dose and comparative potency.

Product information last sourced from SAHPRA Registered Health Products database: 19 July 2026.

Therapeutic class	No. of doses/ inhaler	Trade name	strength	unit	Device type	Dosing interval (times per day)	Adult/ child	SAHPRA Approved indication /Off-label	DDD	No. of inhalers modelled per annum. Estimated equivalent	Comments
ICS/formoterol Combination - anti-inflammatory reliever therapy (patients with mild intermittent/persistent disease): GINA step 1& 2 (low dose ICS)											
Budesonide, Formoterol fumarate dihydrate	60	Symbicord	160/4.5	mcg	DPI	1p prn	Adult	Approved	prn (1-8p per day). Max 12p/day	3 to 6	Mild/intermittent asthma - assume 3 inhalers per annum. Mild/persistent asthma - assume 6 inhalers per annum.
Budesonide, Formoterol fumarate dihydrate	120	Symbicord	160/4.5	mcg	DPI	1p prn	Adult	Approved	prn (1-8p per day). Max 12p/day	2 to 3	Mild/intermittent asthma - assume 2 inhalers per annum. Mild/persistent asthma - assume 3 inhalers per annum.
Budesonide, Formoterol	120	Halecord	200/6	mcg	DPI	1p prn	Adult	Approved	prn. Max 8p/day	2 to 3	No SEP and does not seem to be actively marketed locally. No local experience with this device which precludes comments on feasibility and acceptability.
Budesonide, Formoterol fumarate dihydrate	120	Vannair	160/4.5	mcg	MDI	1p prn	Adult	Off-label	prn. Max 12p/day	2 to 3	Shelf life reduced to 3 months once the foil wrapper is opened
Beclomethasone dipropionate, formoterol fumarate dihydrate	120	Innuvair	100/6	mcg	MDI	1p prn	Adult	Off-label	prn. Max 8p/day	4 (fridge)	Extrafine particle size - 100mcg of extrafine equivalent to 250mcg of standard formulation. Requires refrigeration - Maximum 3 months storage outside of fridge
Mometasone furoate, formoterol fumarate dihydrate	120	Dulera 100/5	100/5	mcg	MDI	1p prn	Adult	Off-label	prn (Max 11p/day)	2 to 3	There are no current studies on using mometasone/formoterol for SMART. However, if considered, the preferred formulation for adults is 100/5mcg with a maximum dose of 11 puffs a day and 50/5mcg for children with a maximum dose of 7 puffs a day. ref: https://www.aaaai.org/tools-for-the-public/conditions-library/asthma/smart

Budesonide, Formoterol fumarate dihydrate	120	Budofo 160/4.5	160/4.5	mcg	MDI	1p prn	Adult	Off-label	prn (1-8p per day). Max 12p/day	4	Mild/intermittent asthma - assume 4 inhalers per annum. Mild/persistent asthma - assume 4 inhalers per annum. Shelf life reduced to 3 months once the foil wrapper is opened
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Therapeutic class	Number of dose s/inhaler	Trade name	strength	unit	Inhaler device type	Dosing interval (times per day)	Adult/child	SAHPRA Approved indication /Off-label	DDD	No. of inhalers modelled per annum. Estimated equivalent	Comments
ICS/formoterol Combination - Anti-inflammatory and Reliever Plus Maintenance Therapy: GINA Step 3-4 (low-med dose ICS)											
Budesonide, Formoterol fumarate dihydrate	60	Symbicord	160/4.5	mcg	DPI	1p BD or 2p BD <i>plus</i> 1p prn	Adult	Approved	320/9 to 640/18 (max 12p/day)	18-30	The higher-dose budesonide-formoterol formulation (320/9 mg delivered dose [400/12 mg metered dose]) is not approved or recommended for SMART because the total dose of formoterol with multiple as-needed dosing would increase too rapidly. (Ref: Reddel H et al. A Practical Guide to Implementing SMART in Asthma Management. Journal of Allergy and Clinical Immunology: In Practice. 2021)
Budesonide, Formoterol fumarate dihydrate	120	Symbicord	160/4.5	mcg	DPI	1p BD or 2p BD <i>plus</i> 1p prn	Adult	Approved	320/9 to 640/18 (max 12p/day)	12 to 18	The higher-dose budesonide-formoterol formulation (320/9 mg delivered dose [400/12 mg metered dose]) is not approved or recommended for SMART because the total dose of formoterol with multiple as-needed dosing would increase too rapidly. (Ref: Reddel H et al. A Practical Guide to Implementing SMART in Asthma Management. Journal of Allergy and Clinical Immunology: In Practice. 2021)
Budesonide, Formoterol	120	Halecord	200/6	mcg	DPI	1p BD or 2p BD <i>plus</i> 1p prn	Adult	Approved	400/12 to 800/24 (max 8p/day)	12 to 18	No SEP and does not seem to be actively marketed locally. No local experience with this device which precludes comments on feasibility and acceptability.
Budesonide, Formoterol fumarate dihydrate	120	Vannair	160/4.5	mcg	MDI	1p BD or 2p BD <i>plus</i> 1p prn	Adult	Off-label	320/9 to 640/18 (max 12p/day)	12 to 18	
Beclomethasone dipropionate, formoterol fumarate dihydrate	120	Innuvair	100/6	mcg	MDI	1p BD or 2pBD <i>plus</i> 1p prn	Adult	Off-label	200/12 to 400/24 (max 8p/day)	12 to 18	Extrafine particle size - 100mcg of extrafine equivalent to 250mcg of standard formulation. Requires refrigeration - Maximum 3 months storage outside of fridge
Mometasone furoate, formoterol fumarate dihydrate	120	Dulera 100/5	100/5	mcg	MDI	1p BD or 2pBD <i>plus</i> 1p prn	Adult	Off-label	200/10 to 400/20 (max 11p/day)	12 to 18	There are no current studies on using mometasone/formoterol for SMART. However, if considered, the preferred formulation for adults is 100/5mcg with a maximum dose of 11 puffs a day ref: https://www.aaaai.org/tools-for-the-public/conditions-library/asthma/smart .

Budesonide, Formoterol fumarate dihydrate	120	Budofor 160/4.5	160/4.5	mcg	MDI	1p BD or 2p BD <i>plus</i> 1p prn	Adult	Off-label	320/9 to 640/18 (max 12p/day)	12 to 18	Shelf life reduced to 3 months once the foil wrapper is opened
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Therapeutic class	Number of doses/inhaler	Trade name	strength	unit	Inhaler device type	Dosing interval (times per day)	Adult/ child	SAHPRA Approved indication/Off- label	DDD
Acute exacerbations asthma & COPD									
Salbutamol	200	–	100	mcg	MDI	prn	Adult	Approved	
SABA - Chronic management of COPD - (All groups)									
Salbutamol	200	–	100	mcg	MDI	2p 6hrly prn	Adult	Approved	200-800 mcg
Terbutaline	200	Bricanyl	0,5	mg	DPI	1p prn max 12	Adult	Approved	0.5-6mg
Fenoterol	200	Berotec	100	mcg	MDI	1-2p prn max 8	Adult	Approved	100- 800mcg
LABA - Chronic management of COPD (Group B + Group E eosinophils <0.1)									
Formoterol	60	Foratec caps	12	mcg	DPI	1p BD	Adult	Approved	24mcg
Formoterol	60	Oxis	9	mcg	DPI	1p BD	Adult	Approved	18 mcg
Formoterol	120	Foratec HFA	12	mcg	MDI	1-2p BD	Adult	Approved	24-48 mcg
Salmeterol	120	Serevent	25	mcg	MDI	2p BD	Adult	Approved	100 mcg
Salmeterol	60	Serevent	50	mcg	DPI	1p BD	Adult	Approved	100 mcg
LABA/ICS Combination - Chronic management of COPD (Group E eosinophils >= 0.1)									
Salmeterol/fluticasone	60+60	Serehale	50/250	mcg	DPI	1p BD	Adult	Approved	100/500
Salmeterol/fluticasone	60	Spirodisc	50/250	mcg	DPI	1p BD	Adult	Approved	100/500
Salmeterol/fluticasone	60	Airflusal	50/250	mcg	DPI	1p BD	Adult	Approved	100/500
Salmeterol/fluticasone	60	Sereflo	50/250	mcg	DPI	1p BD	Adult	Approved	100/500
Salmeterol/fluticasone	60	Foxair accuhaler	50/250	mcg	DPI	1p BD	Adult	Approved	100/500
Formoterol/budesonide	60	Symbicord	320/9	mcg	DPI	1p BD	Adult	Approved	640/18
Formoterol/budesonide	120	Symbicord	160/4.5	mcg	DPI	2p BD	Adult	Approved	640/18
Budesonide, Formoterol fumarate dihydrate	120	Vannair	160/4.5	mcg	MDI	2p BD	Adult	Approved	640/18
Formoterol/Mometasone furoate	120	Dulera	200/5	mcg	MDI	2p BD	Adult	Approved	800/20

SOUTH AFRICAN NATIONAL ESSENTIAL MEDICINE LIST

PHC MEDICATION REVIEW PROCESS

COMPONENT: FORMOTEROL PLUS INHALED CORTICOSTEROID (ICS) FIXED-DOSE COMBINATION FOR SYMPTOM RELIEF IN CHRONIC ASTHMA MANAGEMENT

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EXECUTIVE SUMMARY

Date: 27 February 2025

Medicine (INN): Formoterol/inhaled corticosteroid (as maintenance-and-reliever therapy [MART])

Medicine (ATC): R03AK07 (formoterol and budesonide), R03AK08 (formoterol and mometasone) R03AK11 (formoterol and fluticasone), R03AK08 (formoterol and beclomethasone)

Indication (ICD10 code): Chronic asthma (J45.0-1/J45.8-9)

Patient population: Adults and adolescents aged 12 years and older

Prevalence of condition: South Africa is ranked as having the fourth-highest asthma mortality in the world and the fifth-highest asthma mortality among 5–35-year-olds (Cazzoletti, 2009). Despite this, local epidemiological data for adult asthma is lacking (Kalla, 2022). However, a systematic analysis and modelling study estimated the asthma prevalence aged 5–69 years to be 11.3% (95% CI 9.0–14.1%) in the African region, based on population studies published between 1 January 1990 to 31 December 2019 (Song, 2022). In the Western Cape, a substantial increase in asthma prevalence in adolescents as measured by self-reported current wheeze, from 16.0% in 1995 (ISAAC I) to 20.3% in 2002 (ISAAC III) (Zar, 2007) and 21.3% in 2017 (GAN Phase 1) (Baard, 2021), which was higher than the global prevalence of 14.1% among 5–69-year-olds. A more recent cross-sectional survey conducted in Durban, South Africa, between May 2019 and June 2021 estimated the prevalence of lifetime, current, and severe asthma as 24.6%, 13.7%, and 9.1%, respectively, among adolescents (Mphahlele, 2023).

Level of Care: Primary Healthcare

Prescriber Level: Medical doctor

Reviewers: Sumayyah Ebrahim, Trudy D Leong, Michael McCaul, Gayle Tatz, Karen Cohen

Motivators: *Asthma Sub-Committee:* Karen Cohen (Chair), Michael McCaul (Vice-chair), Prakash Jeena, Michael Levin, Jeremy Nel, Michelle Wong, Gustav Thom, Gayle Tatz, Sumayyah Ebrahim, Trudy D Leong

Secretariat: Zahiera Adams, Maropeng Rapetsoa, Derusha Frank

PTC affiliation: N/A

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATIONS

Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	
Recommendation PICO 1: The ASC suggests that the ICS/formoterol combination, as needed, be used for symptom relief in adults and adolescents aged 12 years and older with intermittent asthma or asthma symptoms less than two times per month (<i>conditional recommendation, very low certainty evidence</i>). Recommendation PICO 2: The ASC recommends that the ICS/formoterol combination be used for symptom relief in adults and adolescents aged 12 years and older with mild persistent asthma (<i>strong recommendation, moderate certainty evidence</i>). Recommendation PICO 3: The ASC recommends that the ICS/formoterol combination be used as a maintenance and reliever therapy in adults and adolescents aged 12 years and older with moderate to severe persistent asthma (<i>strong recommendation, moderate certainty evidence</i>).					

Remarks:

- Beta-2-agonists should not be used as sole reliever therapy in asthma without concomitant inhaled corticosteroids, ideally co-formulated as a fixed-dose combination
- PICO 1: Network meta-analysis evidence (Rayner, 2024) and expert opinion were used to determine the efficacy and safety of ICS/FABA compared to ICS with SABA
- Across all PICOs: Sensitivity analysis of the budget impact analysis indicated uncertainty regarding several model parameters, and further research is required in this area (costs of emergency room visits, hospitalisations and ICU admissions, the proportion of asthmatics referred from PHC for hospitalisation, utilisation patterns of inhalers for the standard of care and the proportion of adults with severe asthma)
- The environmental impact of the different types of inhaler devices needs to be considered when prescribing these products

Rationale: The committee considers the combination of interventions; the benefits outweigh the risks and are considered feasible and acceptable. It makes programmatic sense to use the same reliever therapy across all levels of asthma severity as asthma symptoms change over time.

Review indicator: New high-quality evidence of a clinically relevant benefit, a change in the price of medicines.

Monitoring and evaluation (M&E) considerations: The ASC recognises the importance of M&E programmes, which require careful planning and implementation to monitor clinical outcomes such as acute severe asthma exacerbations, hospitalisations, referrals from primary healthcare (PHC) facilities, as well as utilisation data.

Research priorities: There is a need for prevalence data for our populations of interest, better direct evidence for PICO 1 as well as more local acceptability, feasibility and costing data.

NEMLC RECOMMENDATION (27 Nov 2025):

NEMLC supports the ERC recommendation as detailed above.

NAME OF MOTIVATOR(S)/CONTRIBUTORS

Asthma Sub-Committee: Karen Cohen (Chair) (KC), Michael McCaul (Vice-chair) (MM), Prakash Jeena (PJ), Michael Levin (ML), Jeremy Nel (JN), Michelle Wong (MW), Gustav Thom (GTa), Gayle Tatz (GTb), Sumayyah Ebrahim (SE), Trudy D Leong (TDL)

PICO 2 contributors: Natasha Gloeck (NG) and Tamara Kredo (TK)

Economic analysis: Donela Besada (DB)

Secretariat: Zahiera Adam (ZA), Maropeng Rapetsoa (MR), Derusha Frank (DF)

CONFLICT OF INTEREST DETAILS

Declarations of interest: The motivators have no interests related to the reviewed interventions to declare. South African GRADE Network members are SE, TDL, MM, and KC.

Funding: SE, TDL and MM are partly supported by the Research, Evidence, and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies. ZA is a consultant for the Clinton Health Access Initiative (CHAI).

ACKNOWLEDGEMENTS

- Joy Oliver for support with the search strategy from the Health Systems Research Unit, South African Medical Research Council
- *PICO 2:* (Crossingham, 2021; Hatter, 2021). The economic data (medicine costs) provided by ZA was sourced from the Master Health Product List and Single Exit Price (SEP) master file with a Quality Assurance (QA) check from fellow secretariat, Dr M Reddy.

BACKGROUND

Asthma is a major non-communicable disease affecting people of all ages and the most common chronic disease among children (World Health Organization [WHO], 2023). The World Health Organization (WHO) describes asthma as “inflammation and narrowing of the small airways in the lungs cause asthma symptoms, which can be any combination of cough, wheeze, shortness of breath and chest tightness”, with an estimated worldwide prevalence of 262 million and mortality of 455 000 deaths in 2019 (WHO, 2023; Vos, 2020). Asthma symptoms vary in intensity over time with variable expiratory airflow limitation. They are associated with airway hyperresponsiveness to direct or indirect stimuli (allergen or irritant exposure, viral or bacterial respiratory infections, exercise, seasonal variation, etc.) (Global Initiative for Asthma [GINA], 2024). Avoiding these triggers may assist in reducing asthma symptoms (GINA, 2024). Most asthma-related asthma deaths occur in low- and middle-income countries (LMICs), where there are challenges with the diagnosis and treatment of asthma (WHO, 2023).

The updated 2024 Global Initiative for Asthma (GINA) guidelines describe asthma control as “the extent to which features of asthma are observed in an individual or have been reduced or removed by treatment” (GINA, 2024, p. 35). GINA recommends that for asthma control and symptom control, the risk of adverse outcomes and exacerbations should be assessed using a stepwise approach to treat chronic asthma (see Figure 1) (GINA, 2024). Updated asthma severity classification is based on the level of treatment intensity required rather than on symptoms. GINA no longer distinguishes between “intermittent” and “mild persistent” asthma because this was an arbitrary classification, with no evidence of a difference in the treatment response (Reddel, 2022, p. S3). Asthma severity is assessed retrospectively after 2–3 months of treatment and is based on the level of treatment required to control symptoms and exacerbations (Reddel, 2022).

Inhaler therapies for asthma are usually classified as controllers or relievers (GINA, 2024; Crossingham, 2021). Short-acting beta₂-agonists (SABA) are used to relieve symptoms due to bronchoconstriction rapidly; however, they do not affect the underlying primary pathological process of inflammation. Since 2019, the GINA guidelines no longer recommend treatment of asthma in adolescents and adults with short-acting β₂-agonist (SABA) alone, for mild intermittent asthma, or where patients experience asthma symptoms less than twice per month due to the associated safety concerns and SABA overuse (Reddel, 2022). Inhaled corticosteroids (ICs) are an effective preventer therapy in adults, leading to better control of asthma symptoms (GINA, 2024; Crossingham, 2021). Longer-acting beta₂-agonists (LABA) are also available and are generally used as controller therapy, together with an ICS (Crossingham, 2021).

Some LABAs, such as formoterol, have a rapid onset of action and thus can rapidly relieve symptoms (GINA, 2024; Crossingham, 2021). Fixed-dose combination inhalers contain both a steroid and a beta₂ agonist in the same device, delivering both therapies simultaneously (Crossingham, 2021). Advantages include simplifying the inhaler regimen, improving adherence, and ensuring that LABA therapy is always administered with an ICS (Crossingham, 2021). The latter is important as LABA use without an ICS was shown to be associated with a significantly increased risk of asthma-related mortality (Nelson, 2006). Combination inhalers with a fast-acting beta₂ agonist (FABA), such as formoterol, make the inhaler suitable for as-needed use (Crossingham, 2021). FABAs act immediately on the smooth muscle to relieve airway narrowing and symptoms (Crossingham, 2021). ICS therapy suppresses type 2 inflammation at the epithelial level (Barnes, 2010). Combining ICS and FABA therapy, especially during increased symptoms, may result in symptomatic improvement and suppression of the underlying pathological inflammatory process, thus decreasing the risk of severe or life-threatening events (Crossingham, 2021; Beasley, 2019a).

In summary, the GINA guidelines recommend two tracks, depending on the choice of reliever (Figure 1). The preferred reliever is as-needed, low-dose ICS/formoterol (sometimes called ‘anti-inflammatory reliever’ or AIR) in track 1 at all steps:

as needed only in Steps 1-2 (mild asthma), and with daily maintenance ICS/formoterol (maintenance-and-reliever therapy, “MART”) in Steps 3-5 (moderate to severe persistent asthma) (GINA, 2024). Where ICS/formoterol therapy is unavailable, unaffordable, or not preferred by a patient due to no or low risk of exacerbations in the past year, track 2 (alternative) recommends as-needed SABA across all steps, plus regular ICS (Step 2) or ICS/LABA (Steps 3-5) (GINA, 2024; Reddel, 2022).

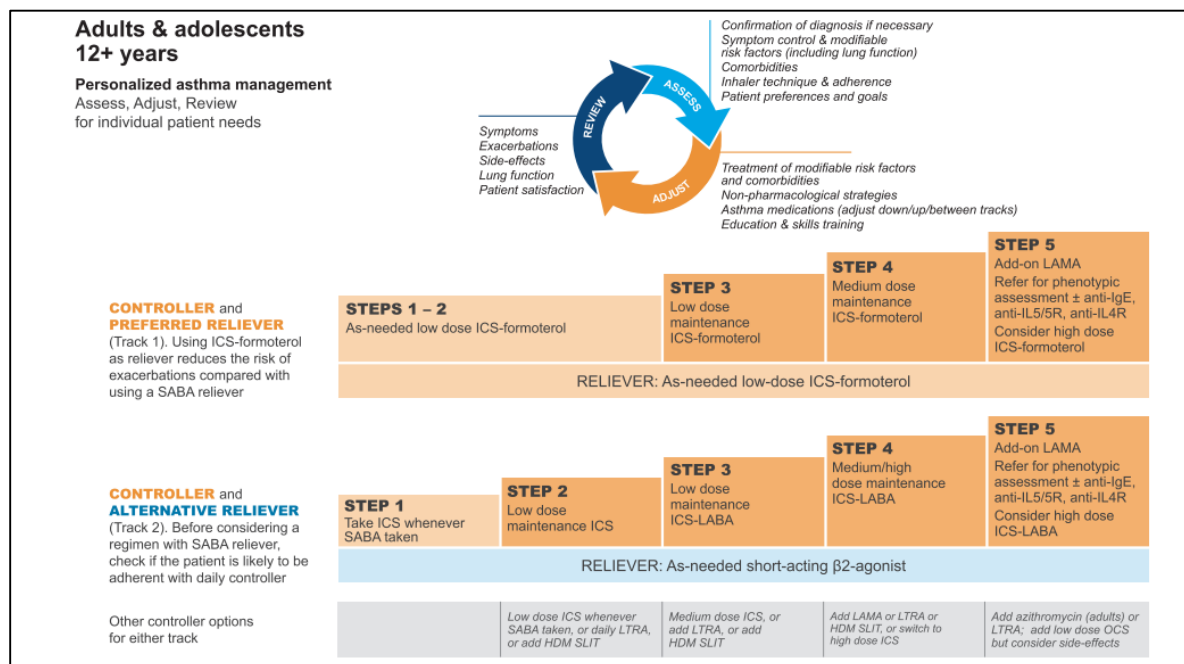


Figure 1: Personalized management for adults and adolescents to control symptoms and minimise risk

HDM = house dust mite; ICS = inhaled corticosteroid; LABA = long-acting β₂-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; SABA = short-acting β₂-agonist; SLIT = sublingual immunotherapy

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Many guidelines, including the GINA guidelines, define the ICS dose as “low”, “medium”, and “high” maintenance doses (Table 1). We use this standardised terminology for this review. However, we note that some argue that the terminology is not evidence-based, and using this categorisation in clinical practice may result in excessive use of ICS. An alternative classification proposed by Beasley *et al.* (Beasley, 2019b) is to dose ICS based on the standard daily dose, defined as 200–250µg of fluticasone propionate or equivalent, where 80–90% of the maximum achievable therapeutic benefit of ICS is obtained in adult asthma across the spectrum of severity (Beasley, 2019b). However, further research is required.

Table 1: Low, Medium and High doses of inhaled corticosteroids in adults/adolescents as defined by GINA Guidelines

Inhaled Corticosteroid	Dose (µg/d)			Bioequivalence*
	Low	Medium	High	
Beclomethasone dipropionate (CFC)	200–500	>500–1,000	>1,000	1.0
Beclomethasone dipropionate (HFA)	100–200	>200–400	>400	2.5
Budesonide (DPI)	200–400	>400–800	>800	1.25
Ciclesonide (HFA)	80–160	>160–320	>320	3.125
Fluticasone propionate (HFA)	100–250	>250–500	>500	2.0
Fluticasone furoate (DPI)	100	NA	200	5.0
Mometasone furoate	110–220	>220–440	>440	2.25

Definition of abbreviations: CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; NA = not applicable.

*Bioequivalence compared with beclomethasone dipropionate, derived from the stated “high dose.”

Source: Beasley, R., Harper, J., Bird, G., Majers, I., Weatherall, M., & Pavord, I. D. (2019b). Inhaled corticosteroid therapy in adult asthma: Time for a new therapeutic dose terminology. *American Journal of Respiratory and Critical Care Medicine*, 199(12), 1471-1477. <https://doi.org/10.1164/rccm.201810-1868CI>

The current South African Hospital-level (adult) standard treatment guidelines (STG) recommend using a salbutamol metered-dose inhaler together with an inhaled corticosteroid as reliever therapy for patients with asthma symptoms <twice per month (National Department of Health [NDoH], 2019). For patients with symptoms two or more times per month, the recommendation is to use an ICS regularly (e.g. 12 hourly dosing with budesonide) and reliever therapy with a SABA, e.g. salbutamol as needed for up to 6 hours (NDoH, 2019). Longer-acting beta₂-agonists (LABA) are also available and generally used as preventer therapy with an ICS (Crossingham, 2021). The local STG reserves the use of a LABA in combination with an ICS (e.g. Salmeterol/fluticasone, inhalation, 50/250 mcg 12 hourly) as preventer therapy for more severe asthmatics, specifically those with “asthma symptoms almost daily or waking due to asthma at least once a week” (NDoH, 2019, p. 16.4).

These recommendations may affect both direct and indirect costs. There are also potential benefits related to reduced healthcare utilisation due to improved symptom control, reduced exposure to systemic corticosteroids, and reduced asthma-related hospital admissions, the latter being a major contributor to the economic burden of asthma (Crossingham, 2021; Mukherjee, 2016). This review aimed to summarise the evidence on the efficacy and safety of ICS/formoterol¹ taken as needed in adults and adolescents aged 12 years and older with:

- Intermittent asthma or infrequent asthma symptoms <twice a month, corresponding to asthma that may be controlled by GINA Step 1 (Figure 1)
- Mild persistent asthma, corresponding to asthma that may be controlled by GINA Step 2 (Figure 1)
- Moderate to severe persistent asthma or uncontrolled asthma in patients on maintenance LABA/ICS, corresponding to asthma that may be controlled by GINA Steps 3-4 (Figure 1)

¹ The terms ICS/formoterol or formoterol/ICS may be used interchangeably in this report
NEMLC Evidence Review_ICS/formoterol for asthma_27 Nov 2025_final

GLOSSARY AND DEFINITIONS

Asthma severity: Intermittent¹	• Asthma symptoms requiring reliever therapy less than twice per month • No interference with normal activities between exacerbations • No exacerbations requiring oral glucocorticoids per year • No risk factors for exacerbations
Asthma severity: Mild persistent¹	Asthma symptoms twice monthly or more requiring reliever therapy (although less than 4-5 days per week)
Asthma severity: Moderate¹	• Asthma symptoms most days requiring reliever therapy OR • Nocturnal awakenings once per week or more requiring reliever therapy
Maintenance treatment²	Asthma treatment that is prescribed for use everyday (or on a regularly scheduled basis). Medications are intended to be used continuously, even when the person does not have asthma symptoms. Examples include ICS-containing medications (ICS, ICS-LABA, ICS-LABA-LAMA), LTRA, and biologic therapy. The term ‘maintenance’ describes the prescribed frequency of administration, not a particular class of asthma medicine.
Controller²	Medication targeting both domains of asthma control(symptom control and future risk) • In the past, ‘controller’ was primarily used for ICS-containing medications prescribed for regular daily treatment, so ‘controller’ and ‘maintenance’ became almost synonymous. However, this became confusing after introducing a combination of ICS-containing relievers for as-needed use. • To avoid confusion, ‘ICS-containing treatment’ and ‘maintenance treatment’ have been substituted as appropriate where the intended meaning was unclear.
Reliever²	Asthma inhaler taken as needed for quick relief of asthma symptoms • Sometimes called rescue inhalers. In addition to being used for symptom relief, reliever inhalers can be used before exercise to prevent exercise-induced asthma symptoms. • Includes SABAs (e.g., salbutamol [albuterol], terbutaline, ICS- salbutamol), as-needed ICS-formoterol, and as-needed ICS-SABA. • SABA-containing relievers should not be used for regular maintenance or taken when the person does not have asthma symptoms (except before exercise).
Anti-inflammatory reliever (AIR)²	• Reliever inhaler that contains both a low-dose ICS and a rapid-acting bronchodilator • Includes budesonide-formoterol, beclometasone-formoterol and • ICS-salbutamol combinations. Patients can also use AIRs as needed before exercise or allergen exposure to prevent asthma symptoms and bronchoconstriction. Non-formoterol LABAs, in combination with ICS, cannot be used as relievers. ICS-formoterol should not be used as the reliever with maintenance ICS-non-formoterol LABAs • The anti-inflammatory effect of as-needed ICS-formoterol was demonstrated by the reduction in FeNO in several studies. • Some anti-inflammatory relievers can be used as needed at Steps 1–2 as the person’s sole asthma treatment, without a maintenance (AIR-only) treatment. Almost all evidence for this is with ICS-formoterol. Some ICS-formoterol combinations can be used as maintenance and reliever treatments at Steps 3–5 (see MART below).
Maintenance- and-reliever therapy (MART)²	A treatment regimen in which the patient uses an ICS/formoterol inhaler every day (maintenance dose) and uses the same medication as needed to relieve asthma symptoms (reliever doses). MART (Maintenance-And-Reliever Therapy) can be used <u>only</u> with a combination of ICS-formoterol inhalers such as budesonide-formoterol and beclometasone-formoterol. Other ICS-formoterol inhalers can also potentially be used, but combinations of ICS with non-formoterolLABAs, or ICS-SABA, cannot be used for MART. MART is also sometimes called SMART (single-inhaler maintenance-and-reliever therapy); the meaning is the same.

Severe asthma exacerbation³	As defined in the trials - according to the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria: • The use of systemic corticosteroids for at least 3 days and/or • Hospitalisation or emergency department (ED) visits because of asthma, requiring systemic corticosteroids
Adverse events⁴	An adverse event is any untoward medical occurrence in a study subject temporally associated with participation in the trial and the administration of study medication, whether considered related to the medicine. An adverse event can be any unfavourable and unintended sign, symptom, or disease temporally associated with using the study treatment. A worsening of a pre-existing medical condition other than asthma will be considered an adverse event
Serious adverse events (SAEs)⁴	• Death • Life-threatening event • Permanently disabling or incapacitating event • Inpatient hospitalisation or prolongation of hospitalisation • Hospitalisation for SAE reporting is defined as an admission to hospital and does not include a presentation to the ED followed by discharge without admission or an admission for elective reasons • Consists of a congenital anomaly or birth defect • Any event considered serious by the study investigator
Adverse Drug Reaction⁵	An appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen, or withdrawal of the product.

¹National Asthma Education, Prevention Program (National Heart, Lung, & Blood Institute). (1997). *Expert panel report 2: Guidelines for the Diagnosis and Management of Asthma*. Diane Publishing. <https://www.govinfo.gov/content/pkg/GOVPUB-HE20-PURL-LPS3669/pdf/GOVPUB-HE20-PURL-LPS3669.pdf>

²Global Initiative for Asthma (GINA). (2024). *Global Strategy for Asthma Management and Prevention, 2024*. <https://ginasthma.org/2024-report/>

³Reddel, H. K., Taylor, D. R., Bateman, E. D., Boulet, L. P., Boushey, H. A., Busse, W. W., ... & Wenzel, S. E. (2009). An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *American Journal of Respiratory and Critical Care Medicine*, 180(1), 59–99. <https://doi.org/10.1164/rccm.200801-060ST>

⁴Protocol for: Beasley, R., Holliday, M., Reddel, H. K., Braithwaite, I., Ebmeier, S., Hancox, R. J., ... & Weatherall, M. (2019a). Controlled trial of budesonide–formoterol as needed for mild asthma. *New England Journal of Medicine*, 380(21), 2020-2030. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1901963/suppl_file/nejmoa1901963_protocol.pdf

⁵Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: Definitions, diagnosis, and management. *The Lancet*, 356(9237), 1255-1259. [https://doi.org/10.1016/S0140-6736\(00\)02799-9](https://doi.org/10.1016/S0140-6736(00)02799-9)

SCOPE AND QUESTIONS

Intermittent asthma or asthma symptoms < twice a month

Question: In adults and adolescents aged 12 years and older with asthma symptoms less than two times per month, what is the efficacy and safety of formoterol/ICS taken as needed compared with intermittent short-acting beta₂ agonist (SABA) reliever plus low-dose ICS as needed for symptom relief?

Table 2: PICO 1	
Population	Patients with asthma symptoms less than two times per month, 12 years and older
Intervention	Formoterol* plus inhaled corticosteroid (ICS) as needed for symptom relief
Comparator	Intermittent SABA plus low-dose ICS as needed for symptom relief
Outcomes	Acute severe exacerbations, asthma visits to the emergency room, asthma admissions, courses of systemic steroids, mortality, serious adverse events, adverse events and adverse reactions
Study designs	Randomised controlled trials (RCTs)

Mild persistent asthma

In adults and adolescents aged 12 years and older with mild persistent asthma, what is the efficacy and safety of Formoterol/ICS taken as needed compared with daily low-dose ICS and a SABA reliever?

Table 3: PICO 2	
Population	Patients with mild persistent asthma [asthma symptoms twice monthly or more requiring reliever therapy (although less than 4-5 days per week)], 12 years and older
Intervention	Formoterol* plus ICS as needed for symptom relief
Comparator	Low-dose ICS daily plus SABA as needed for symptom relief
Outcomes	Acute exacerbations, asthma visits to the emergency room, asthma admissions, courses of systemic steroids, mortality, adverse events, and adverse reactions
Study designs	RCTs

Moderate to severe persistent asthma or uncontrolled asthma in patients on maintenance LABA/ICS

Question: In asthmatic adults and adolescents aged 12 years and older using daily inhaled LABA plus ICS fixed-dose combination (FDC), what is the efficacy and safety of formoterol/ICS taken as maintenance therapy and as needed reliever therapy compared with LABA plus ICS FDC and as needed SABA reliever for symptom relief?

Table 4: PICO 3	
Population	Patients with asthma using daily inhaled LABA plus ICS fixed-dose combination (FDC), 12 years and older
Intervention	Daily maintenance ICS/LABA combination + Formoterol*/ICS combination as needed for symptom relief
Comparator	Daily maintenance ICS/LABA combination + SABA as needed for symptom relief
Outcomes	Acute severe exacerbations, asthma visits to the emergency room, asthma admissions, courses of systemic steroids, mortality, serious adverse events, adverse events and adverse reactions
Study designs	RCTs

**This PICO intends to compare a LABA with a rapid onset of action that would allow for use as asthma anti-inflammatory reliever therapy. Formoterol is currently the only LABA registered locally for this indication.*

METHODS

We used a prespecified protocol (PROSPERO registration: CRD42023485640) that followed the Cochrane methodology (Garritty, 2021) and the National Department of Health Technology Assessment Methods Guide for rapid systematic reviews (NDoH, 2023).

STUDY DESIGN

A tiered approach was used: first, we considered high-quality, relevant, and up-to-date clinical practice guidelines, followed by systematic reviews (SRs), then randomised controlled trials (RCTs) and other observational study designs as needed (Cochrane Collaboration, 2020). The GINA guideline (GINA, 2023) had no underlying SR that we could appraise, and the guideline group could not share the evidence synthesis included in the guideline. Additionally, the guideline group did not conduct a GRADE-based review or assessment. Hence, we could not use their Summary of Findings (SoF) tables or Evidence to Decision (EtD) for guideline adaptation as these were not available. Figure 2 shows a timeline and overview of the study phases.

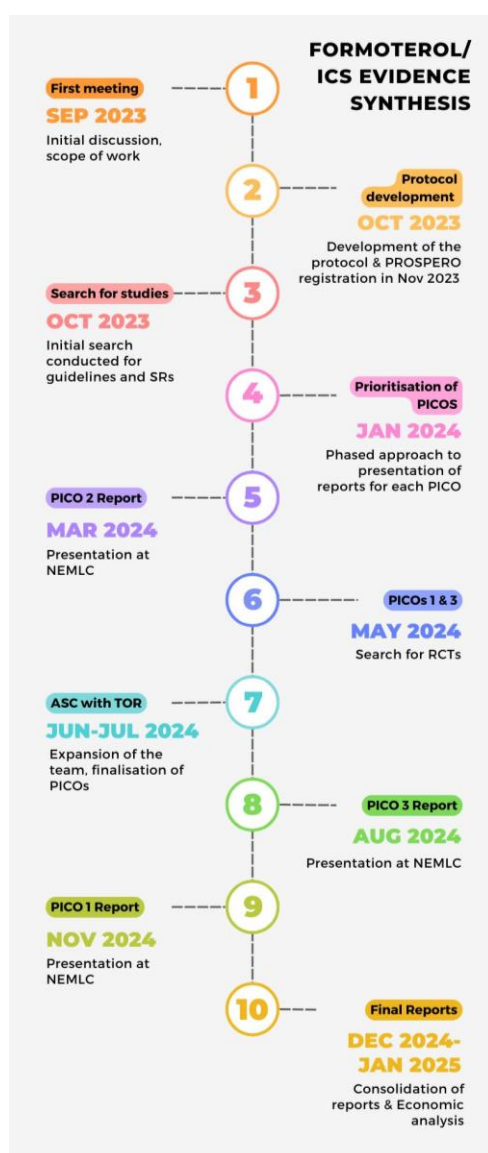


Figure 2: Overview of study phases

Data sources

PICO 2

On 10 October 2023, we searched the Trip database for asthma guidelines and recommendations in adolescents and adults aged 12 years and older. We then searched the PubMed (20 October 2023) and Epistemonikos (23 October 2023) databases for SRs of RCTs.

PICOs 1 and 3

Following the initial search for SRs described above, two studies (Sobieraj, 2018; Beasley, 2022) were identified as possibilities for inclusion to answer PICO 3. However, the trials included in these SRs were dated (10 years or older). Thus, we proceeded to conduct a rapid review of RCTs. We searched the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases for randomised controlled trials on 14 and 15 May 2024, respectively.

Search strategy

An experienced information specialist (JO) developed and conducted the search strategy without language or publication restrictions. Search terms used are found in Appendix 1: Search Strategy.

Study selection, data extraction, and analysis

PICOs 1 and 3

Screening of titles and abstracts, full-text screening, and selection of studies were done independently and in duplicate by two reviewers (SE, TDL). We used the Covidence software for screening. We summarised the selection process graphically in a PRISMA flow diagram (Figures 3 and 15). Data extraction was conducted independently and in duplicate (SE, TDL), and disagreements were resolved through discussion. The main characteristics of the included studies and study outcomes for PICO 3 are shown in Appendix 10. The reasons for full-text exclusion are described in the flow diagram and characteristics of excluded studies table (for PICO 1 in Appendix 2 and PICO 3 in Appendix 8). Appendix 9 presents the results of the search for planned/ongoing trials for PICO 3.

We appraised the RCTs using the Cochrane risk of bias tool (RoB 2.0) (Higgins, 2023; Sterne, 2019), assessing the risk of bias in duplicate for primary outcomes in the included studies and resolving disagreements through discussion (SE, TDL) or by adjudication. For each domain and overall risk of bias judgment, we summarised the risk of bias levels as 'low risk of bias', 'some concerns', or 'high risk of bias' (Appendix 11).

We used RevMan version 5.4.1 (2020) to perform data analysis. If pooled synthesis of data was possible, a meta-analysis was conducted using a random-effects model. We reported risk ratios for dichotomous data with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence, considering various factors that may decrease our confidence in the trial findings, including risk of bias, inconsistency, imprecision, publication bias, and indirectness (Guyatt, 2011). GRADE assessments were conducted using GRADEPro software by SE, TDL, and MM. Pooled effects across outcomes and certainty of evidence are reported in the GRADE Evidence Profile and SoF tables.

We reviewed and extracted the underlying evidence from the relevant trials for the effectiveness EtD criteria (benefit, harms, and balance of effects) (SE, TDL). Economic evaluations were conducted (DB, TDL): 1) rapid review of economic evaluations, 2) pricing analysis, and 3) budget impact analysis, and are reported in supplementary reports. We did not plan a qualitative or equity assessment for this review but extracted variables for qualitative criteria

(values, equity, feasibility, and acceptability) and variables on place of residence, gender, age, and other PROGRESS-PLUS variables from the eligible studies (O'Neill, 2014).

PICO 2

Screening of titles and abstracts, full-text screening, and selection of studies were done independently and in duplicate by two reviewers (SE and GT). We used the Covidence software for screening. Data extraction was conducted by one reviewer (SE) and cross-checked by a second reviewer (GT). The AGREE II tool (Brouwers, 2010) was used to appraise relevant guidelines by two reviewers (SE and NG). The AMSTAR II tool (Shea, 2017) was used to appraise all the included SRs by a single reviewer (SE) and checked by a second reviewer (GT). Any disagreements were resolved through discussion or consultation with a third reviewer (NG). Where multiple eligible SRs were included, we reported evidence from the most relevant, recent, and highest-quality-assessed review that provided evidence across the PICO domains. Results from reviews that were eligible but not up-to-date, credible, or failed to report on critical outcomes were not prioritised. However, the results and direction of effects were cross-checked. GRADE was used to assess the overall confidence of the evidence, considering various factors that may decrease our confidence in the trial findings, including risk of bias, inconsistency, imprecision, publication bias, and indirectness (Guyatt, 2011). GRADE assessments were conducted using GRADEPro software by SE, MM, and TK. Pooled effects across outcomes and certainty of evidence are reported in the GRADE Evidence Profile and Summary of Findings (SoFs) tables.

We reviewed and extracted the underlying evidence from the relevant SRs for the effectiveness EtD criteria (benefit, harms, and balance of effects). The economic data (medicine costs) provided by ZA was sourced from the Master Health Product List and SEP master file with a QA check from fellow secretariat, Dr M Reddy. Qualitative criteria (values, equity, feasibility, and acceptability) were sourced from a search on Epistemonikos (Appendix 7). We aimed to supplement this with local contextual evidence (e.g. resources, acceptability, equity) where feasible.

RESULTS

PICO 1

Key findings

- *The Global Initiative for Asthma (GINA) Guidelines, previously appraised as moderate quality (refer to the LABA/ICS PICO 2 report), recommends that asthma not be treated solely with short-acting β_2 -agonist (SABA) because of the risks of SABA-only treatment, SABA overuse, and evidence for the benefit of inhaled corticosteroid (ICS).*
- *GINA introduced two tracks for the stepwise management of asthma in adults and adolescents in 2021.*
 - *Track 1 (preferred) – As needed combination of inhaled low-dose ICS/formoterol as the reliever, to reduce the risk of severe exacerbations compared with SABA alone as the reliever (with/without a maintenance controller).*
 - *Track 2 (alternative approach) – As needed, inhaled SABA is co-administered with ICS (as combination or separate inhalers).*
- *The current 2019 Adult Hospital Level South African standard treatment guidelines (STG) are aligned with Track 2 of the GINA guidelines and recommend that adults and adolescents 12 years and older with mild intermittent asthma (or where patients experience asthma symptoms less than twice per month) use as-needed SABA with low-dose ICS. This is based on one randomised controlled trial (RCT) of adult patients with mild asthma (Papi, 2007) comparing as-needed ICS/SABA (n=122) to as-needed SABA (n=118), which showed:*
 - *A difference in peak expiratory flow (PEF) of 8.31 litres/minute (95% CI 0.58 to 16.04, p=0.04)*
 - *Fewer severe exacerbations (0% vs 3.4%, p=0.057)*
 - *Less use of reliever/rescue medication with a mean number of puffs/day (standard error) of 0.08 (0.006) vs 0.20 (0.09)*
 - *More symptom-free days within the last 2 weeks of the 6-month treatment period compared to baseline (difference of 4.93 days, p=0.18).*
- *A rapid review was conducted to evaluate the efficacy and safety of an as-needed formoterol/ICS combination inhaler compared to as-needed SABA with low-dose ICS in adults and adolescents aged 12 years and older who experience asthma symptoms less than twice a month.*
- *We searched electronic databases for randomised controlled trials (RCTs), but no eligible RCTs were identified.*
- *The preferred track 1 of the GINA guidelines recommends the combination of low-dose ICS/formoterol as needed. This recommendation is based on indirect and limited evidence, with pragmatic and safety considerations. A Cochrane review (Crossingham, 2021) of two RCTs (Beasley, 2019a; O'Byrne, 2018) demonstrated that compared to as-needed SABA alone, as-needed ICS/formoterol:*
 - *Reduced exacerbations requiring systemic corticosteroids: OR 0.45, 95% CI 0.34 to 0.60, 2 RCTs, n=2997, high certainty evidence (NNT 18).*
 - *Reduced the odds of asthma-related hospital admission, emergency department, or urgent care visit: OR 0.35, 95% CI 0.20 to 0.60, 2 RCTs, n=2997, low certainty evidence (NNT 46).*
 - *One RCT (Beasley, 2019a) reported a reduced mean number of β_2 -agonist-containing actuations per day in the as-needed low-dose ICS (budesonide)/formoterol compared to the as-needed SABA (Albuterol) only groups with a mean ($\pm$ standard deviation) of 0.53 ± 0.54 and 1.01 ± 1.60 actuations per day, respectively.*
 - *Regarding adverse events, the odds of an adverse event were about 18% lower in the as-needed ICS/formoterol group compared with the as-needed SABA group (OR 0.82, 95% CI 0.71 to 0.95; participants = 3,002; moderate certainty evidence (NNT 21).*
 - *There was no difference in mortality between as-needed ICS/formoterol and as-required SABA groups; one death was reported in the as-needed ICS/formoterol group (Beasley, 2019a).*

- *Currently, there are no SAHPRA-registered combination products of ICS/SABA, and patients would need to use two separate inhalers. This may have limited feasibility in our setting*
- *Available evidence of patient preferences comparing combined ICS/LABA to ICS/SABA is lacking. However, one study demonstrated patient preferences for a combination ICS/LABA inhaler rather than for the separate components of ICS and LABA, simplifying treatment and promoting adherence (Murphy, 2009). Another two studies showed greater health-related quality of life (HRQoL) with combined ICS/LABA using the Asthma Quality of Life Questionnaire (AQLQ[S]) compared to the separate ICS and LABA mono-components (Chervinsky, 2008; Bateman, 2004) – refer to the LABA/ICS PICO 2 report.*
- *In summary, limited data shows that SABA taken with ICS is better than SABA alone and that formoterol/ICS is better than SABA alone. We did not find RCTs comparing as-needed formoterol/ICS to SABA with ICS, but formoterol/ICS as needed may be preferred as:*
 - *As-needed ICS/formoterol was more efficacious in reducing exacerbations requiring corticosteroids and asthma-related hospital admission, emergency department, or urgent care visit than as-needed SABA alone.*
 - *Limited data from one RCT (Papi, 2007) suggests that as-needed ICS/SABA may be as effective as as-needed SABA alone.*
 - *Qualitative studies suggest that patients prefer combination inhalers of ICS/LABA over two separate inhalers of mono-components.*
 - *Combination therapy with fixed-dose formoterol/ICS simplifies treatment and promotes adherence. Patients may not consistently use their ICS with the SABA reliever if they are separate inhalers.*
 - *Safety concerns and increased risk of exacerbations are associated with SABA-only therapy.*
 - *Streamlining therapy for asthmatics across many spectrums of severity allows for programmatic ease and simplified patient care.*
 - *Using ICS as the mainstay of asthma control from the outset may reinforce the focus on maintenance therapy and discourage the overuse of SABA-only reliever therapy.*
- *In the absence of direct evidence to evaluate this PICO, the evidence is likely to be of very low certainty. Thus, we are very uncertain about the effect of an as-needed formoterol/ICS combination inhaler compared to as-needed SABA with low-dose ICS in adults and adolescents aged 12 years and older who experience asthma symptoms less than twice a month on the listed outcomes: acute severe exacerbations, asthma visits to the emergency room, asthma admissions, courses of systemic steroids, mortality, serious adverse events, adverse events, and adverse reactions. The as-needed formoterol/ICS combination inhaler may have little to no effect on the aforementioned outcomes, but the evidence is very uncertain. However, we believe that benefits may outweigh harms based on indirect evidence and thus favour the intervention.*

Search results

An electronic search of the databases, with no language or publication date restrictions, retrieved 1045 records, of which 1037 were RCTs. Following deduplication and identification of ineligible records by automation tools, 680 records were screened, of which 22 were identified for full-text screening. All studies were excluded for having the incorrect comparator and/or intervention and/or study design (See Figure 3 for the PRISMA flow diagram). See Appendix 2 for the list of excluded studies and the reason for exclusion.

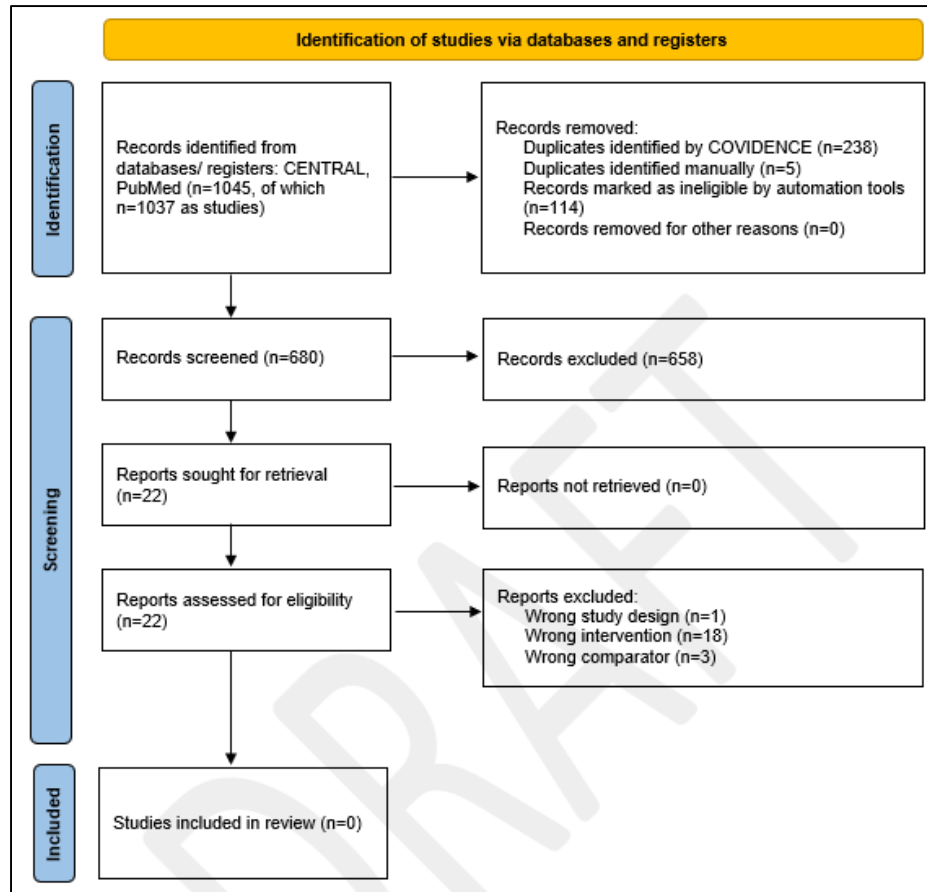


Figure 3: PRISMA flow diagram for review, PICO 1

Evidence synthesis

GINA guidelines and the rationale for removal of SABA-only treatment

As no available RCT evidence could be sourced comparing as-needed LABA/ICS (i.e. formoterol/ICS) to as-needed SABA inhaler therapy for intermittent asthma (i.e. symptoms less than twice per month) amongst asthmatics ≥ 12 years, a synopsis of the rationale provided by GINA guidelines follows:

- Safety concerns with SABA monotherapy**

Despite SABA being inexpensive with quick relief of symptoms, SABA alone has been associated with an increased risk of asthma deaths, as reported in the 2014 UK National Review of Asthma Deaths, where 9% of asthma deaths were reported in patients treated with SABA alone, and 39% were associated with excess use of SABA (Royal College of Physicians, 2014). Similarly, a Swedish cohort of asthmatic patients ($n=365,324$), aged 12-45 years, for the period 2006-2014, showed that SABA overuse was associated with increased mortality: ≥ 11 canisters, HR 2.35 (95% CI 2.02 to 2.72) compared to ≤ 2 canisters per year; and increased risks of exacerbation: ≥ 11 canisters of 150 doses of SABA

per year was associated with a hazard ratio (HR) of 1.77 (95% CI 1.72 to 1.83), compared to ≤ 2 canisters per year (Nwaru, 2020). Even modest overuse of SABA (3-5 canisters per annum was associated with mortality (HR 1.26, 95% CI 1.14 to 1.39) and severe exacerbations (HR 1.26, 95% CI 1.24 to 1.28) (Hancox, 2006). Various studies showed adverse effects such as reduced broncho-protection and bronchodilator response, increased airway hyperresponsiveness, exercise-induced bronchoconstriction, and allergic responses, and increased eosinophilic inflammation and mast cell mediator release associated with short-term regular use of SABA alone (Taylor, 1996; Hancox, 2006). Furthermore, starting treatment with SABA alone trains patients to perceive SABAs as their primary asthma treatment (GINA, 2024).

- *Inhaled corticosteroids to reduce asthma symptoms, hospitalisations and death*

In British Columbian health administrative database studies in 1995 of patients aged 5-50 years (n=23,986) using a lower ratio of ICS to SABA were at greater risk of hospitalisation with an adjusted relative risk (aRR) of 1.68, 95% CI 1.25 to 2.26 and emergency admission (aRR 1.93, 95% CI 1.35 to 2.77) compared to the appropriate use of SABAs (≤ 4 canisters of SABA containing 200 doses, per year, with daily ICS) (Anis, 2001). Population strategies in Brazil (Souza-Machado, 2010) and Finland (Haahtela, 2006) showed that regular, daily, low-dose ICS reduces asthma symptoms and risk of hospitalisations and death, including patients with infrequent symptoms, whilst a Saskatchewan population-based epidemiologic study (1975 to 1991) of subjects aged 5-44 years, on asthmatic medication (n=30,569) showed regular use of low-dose ICS was associated with a decreased risk of death from asthma (Suissa, 2000). Subsequently, large RCTs (Pauwels, 2003; O'Byrne, 2001) showed that low-dose ICS reduced severe asthma exacerbations in mild persistent asthma. However, adherence to ICS is poor, often only 25-35% of the prescribed dose (Boulet, 2012), with patients reverting to SABA-only treatment (Williams, 2011). Factors contributing to poor adherence to ICS include the lack of perceived necessity of taking daily ICS, especially if asymptomatic (Barnes, 2015).

- *GINA guidelines: Track 1 with a reliever, as-needed low-dose ICS/formoterol (preferred)*

The recommendation of as-needed low-dose ICS/formoterol for adult and adolescent asthmatics with symptoms < 2 times per month is based on indirect evidence from two RCTs (Beasley, 2019a; O'Byrne, 2005) in mild persistent asthma where patients were on maintenance ICS. The NOVEL Start trial (Beasley, 2019a) was an open-label trial of mild asthmatics ≥ 12 years of age (n=443) investigating the superiority of as-needed ICS/formoterol 200/6mcg to as-needed SABA 4mg to control asthma. The multi-centre SYGMA 1 trial (O'Byrne, 2018) assessed as-needed low-dose ICS/formoterol 200/6mcg compared with as-needed SABA 4mg amongst mild asthmatics aged ≥ 12 years (n=2554). For severe exacerbations, the risk for ICS/formoterol vs SABA was estimated as 4% vs 10% and 12% vs 6% for the NOVEL Start and SYGMA 1 trial, respectively. A Cochrane review (Crossingham, 2021) pooled data from these trials demonstrating that as-needed ICS/formoterol reduced exacerbations requiring systemic corticosteroids compared with as-required SABA alone (OR 0.45, 95% CI 0.34 to 0.60, 2 RCTs, n=2997, high certainty evidence – see Figure 4). The absolute effect is 57 fewer cases per 1,000 (69 fewer to 41 fewer); NNT 18 (95% CI 14 to 27). Similarly, as-needed ICS/formoterol reduced the odds of asthma-related hospital admission or emergency department or urgent care visit (OR 0.35, 95% CI 0.20 to 0.60, 2 RCTs, n=2997, low certainty evidence – see Figure 5) compared with as-required SABA alone. The absolute effect is 22 fewer cases per 1,000 (27 fewer to 13 fewer), NNT 47 (95% CI 32 to 95).

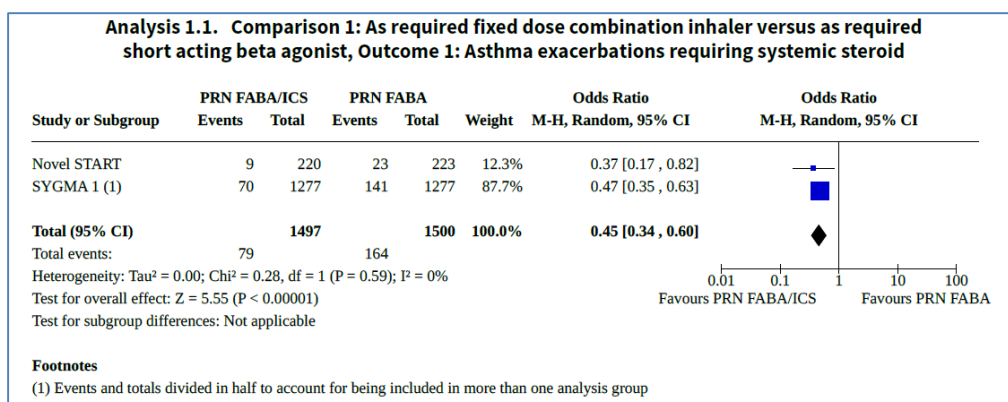


Figure 4: Forest plot of ICS/Formoterol reliever vs SABA reliever: Exacerbations requiring systemic corticosteroids

Source: Crossingham, I., Turner, S., Ramakrishnan, S., Fries, A., Gowell, M., Yasmin, F., ... & Hinks, T. S. (2021). Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. Cochrane Database of Systematic Reviews.

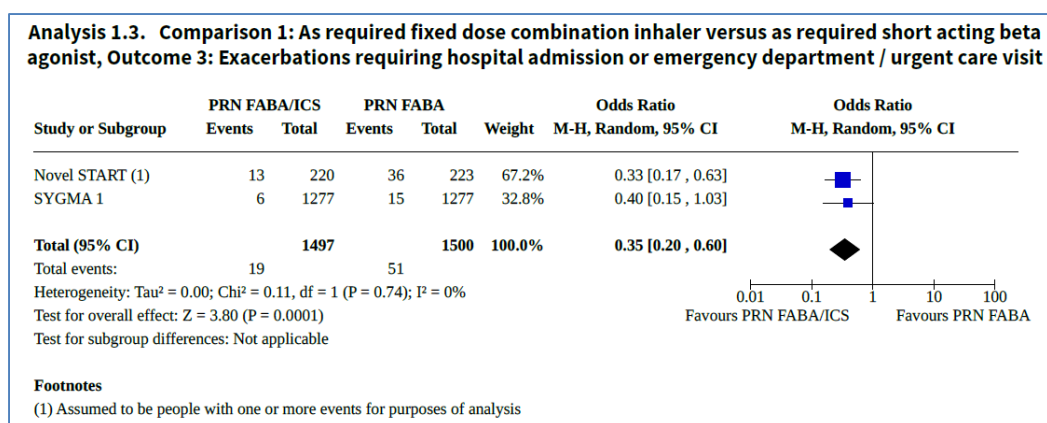


Figure 5: Forest plot of ICS/Formoterol reliever vs SABA reliever: Exacerbations requiring hospital admission or emergency department/urgent care visit

Source: Crossingham, I., Turner, S., Ramakrishnan, S., Fries, A., Gowell, M., Yasmin, F., ... & Hinks, T. S. (2021). Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. Cochrane Database of Systematic Reviews.

This evidence was extrapolated to asthmatics with intermittent symptoms of <2 times per month not on any maintenance controller asthma medication, supported by additional considerations by GINA (GINA, 2024), which included:

- Historically, recommendations for as-needed SABA alone were not supported by evidence of long-term safety or efficacy; early guidelines assumed patients with mild asthma would not benefit from ICS and were concerned about safety based on experience with oral corticosteroids (OCS).
- The past distinction between eligibility for Steps 1 and 2 treatment was based arbitrarily on symptom frequency.
- As-needed ICS/formoterol reduced severe exacerbations, compared with as-needed SABA, even in intermittent asthma (SABA use ≤twice per week at baseline) (Beasley, 2019a).
- A single day with more than two, four, six, or eight doses of as-needed ICS/formoterol reduced the short-term risk of severe exacerbations, compared with as-needed SABA alone (post-hoc analysis) (O'Byrne, 2018). This is similarly demonstrated with ICS/formoterol MART in Steps 3–4 (Buhl, 2012; Bousquet, 2007).
- Overuse of SABA (≥3 canisters per year) was associated with an increased risk of severe exacerbations and mortality (Nwaru, 2020; Stanford, 2012).

- Occasional short courses of OCS are associated with significant short-term risks (Waljee, 2017) and cumulative risks of long-term adverse effects (i.e. osteoporosis and diabetes) (Price 2018).
- Regular, daily, low-dose ICS treatment is effective in reducing asthma symptoms and risks, including intermittent asthma (Reddel, 2017). However, poor adherence to ICS is common (Barnes, 2015), risking overtreatment of SABA monotherapy.
- As-needed ICS/formoterol is well tolerated in mild asthma (Beasley, 2019a; Hardy, 2019; Bateman, 2018; O’Byrne, 2018).
- Starting treatment with SABA alone trains the patient to regard it as their primary asthma treatment.
- *As-needed reliever therapy*

Two RCTs reported on as-needed reliever therapy as either ICS/SABA or ICS/formoterol compared to SABA alone:

- ICS/SABA

Papi *et al.* (Papi, 2007) showed that less rescue medication was required for “mild” asthma in the group using an as-needed ICS/SABA (beclomethasone/albuterol) combination (n=122) compared to as-needed SABA (albuterol) alone (n=118). The mean scores (standard error) of rescue medication puffs per day were 0.08 (0.006) and 0.20 (0.09) at 6-months, respectively. The cumulative dose (mean $\pm$ SD) of as-needed short-acting β 2-agonists was lower among patients receiving as-needed combination therapy (7.39 $\pm$ 10.10 mg) than among those receiving as-needed albuterol therapy (9.74 $\pm$ 14.17 mg).

- ICS/formoterol

Beasley *et al.* (Beasley, 2019a) showed that the number of β -2 agonist actuations per day was reduced in the group using as-needed low-dose ICS (budesonide)/formoterol group (n=220), with mean scores ($\pm$ standard deviation) 0.53 $\pm$ 0.54 compared to 1.01 $\pm$ 1.60 in the as-needed SABA (albuterol) group (n=223) at 52 weeks.

In a recent systematic review and network meta-analysis (Rayner, 2024) that compared SABA alone with SABA combined with ICS and with the fast-onset LABA, formoterol combined with ICS for asthma, a total of 27 randomised clinical trials (N=50,496 adult and paediatric patients) were included.

- Compared with SABA alone, both ICS-containing relievers were associated with fewer severe exacerbations: (ICS-formoterol RR 0.65 [95% CI, 0.60-0.72]; risk difference [RD], -10.3% [95% CI, -11.8% to -8.3%]; ICS-SABA RR, 0.84 [95% CI, 0.73-0.95]; RD, -4.7% [95% CI, -8.0% to -1.5%]), high certainty evidence. Thus, ICS-formoterol was associated with a 10.3% reduction in severe exacerbations, and ICS-SABA was associated with a 4.7% reduction in the risk of severe exacerbations.
- *In a network comparison with ICS-SABA [(none of the identified RCTs directly compared ICS-formoterol with ICS-SABA (combined or separate as reliever inhalers)): ICS-formoterol was associated with fewer severe exacerbations (RD, -1.9% [95% CI, -3.0% to -0.7%]) moderate certainty evidence, in GINA Step 1 patients.*
- Compared with SABA alone, ICS-formoterol (RD, -0.6% [95% CI, -1.3% to 0%]) was not associated with increased risk of serious adverse events (high certainty evidence) and ICS-SABA (RD, 0% [95% CI, -1.1% to 1.2%]) was not associated with increased risk of serious adverse events (moderate certainty evidence).
- *In a network comparison with ICS-SABA, ICS-formoterol (RD, -0.7% [95% CI, -2.0% to 0.6%]) was not associated with increased risk of serious adverse events (moderate certainty evidence).*
- Mortality: ICS-formoterol vs. SABA alone: RD, 0% [95% CI, -0.1% to 0.1%], high certainty evidence.

Evidence to decision framework: PICO 1

QUESTION	
Should formoterol/ICS as needed versus intermittent SABA plus low-dose ICS as needed be used for symptom relief in adults and adolescents aged 12 years and older with asthma symptoms less than two times per month?	
POPULATION	Patients with asthma symptoms less than two times per month, 12 years and older
INTERVENTION	Formoterol plus inhaled corticosteroid (ICS) as needed for symptom relief
COMPARISON	Intermittent SABA plus low-dose ICS as needed for symptom relief
OUTCOMES	Acute severe exacerbations, asthma visits to the emergency room, asthma admissions, courses of systemic steroids, mortality, serious adverse events, adverse events and adverse reactions
SETTING	Public sector, South Africa
PERSPECTIVE	Public health/population

Recommendation PICO 1:

The ASC suggests that the ICS/formoterol combination, as needed, be used for symptom relief in adults and adolescents aged 12 years and older with intermittent asthma or asthma symptoms less than two times per month (*conditional recommendation, very low certainty evidence*).

	JUDGEMENT	RESEARCH EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	What is the certainty/quality of evidence? High Moderate Low Very low ☐ ☐ ☐ ☒ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect	We did not find direct evidence that compared ICS/LABA to ICS/SABA amongst adults and adolescents with asthma symptoms <twice a week. 1. A Cochrane review (Crossingham, 2021) of two RCTs (Beasley, 2019a; O'Byrne, 2018) demonstrated that compared to as-needed SABA alone, as-needed ICS/formoterol: • Reduced exacerbations requiring systemic corticosteroids: high certainty evidence • Reduced the odds of asthma-related hospital admission, emergency department, or urgent care visit: low certainty evidence 2. In a recent systematic review and network meta-analysis (NMA) (Rayner, 2024) that compared SABA alone with ICS-SABA and with the fast-onset LABA, formoterol combined with ICS: in an indirect comparison with ICS-SABA (none of the identified RCTs directly compared ICS-formoterol with ICS-SABA (combined or separate as reliever inhalers): ICS-formoterol was associated with fewer severe exacerbations, moderate certainty evidence, in GINA Step 1 patients (n=3,949). Additional considerations: In the absence of direct evidence to evaluate this PICO, the committee considers the evidence likely to be of very low certainty. However, indirect evidence from the (Rayner, 2024) SR and network meta-analysis shows moderate CoE.
EVIDENCE OF BENEFIT	What is the size of the effect for beneficial outcomes? Large Moderate Small None ☐ ☐ ☒ ☐	We did not find direct evidence that compared ICS/LABA to ICS/SABA amongst adults and adolescents with asthma symptoms <twice a week. 1. A Cochrane review (Crossingham, 2021) of two RCTs (Beasley, 2019a; O'Byrne, 2018) demonstrated that compared to as-needed SABA alone, as-needed ICS/formoterol: • Reduced exacerbations requiring systemic corticosteroids: OR 0.45, 95% CI 0.34 to 0.60, 2 RCTs, n=2997, NNT 18. • Reduced the odds of asthma-related hospital admission, emergency department, or urgent care visit: OR 0.35, 95% CI 0.20 to 0.60, 2 RCTs, n=2997, NNT 46. 2. In a recent systematic review and network meta-analysis (NMA) (Rayner, 2024): in an indirect comparison with ICS-SABA, ICS-formoterol was associated with

		fewer severe exacerbations (RD, -1.9% [95% CI, -3.0% to -0.7%]), in GINA Step 1 patients (n=3,949). However, according to the estimates reported by the (Rayner, 2024) SR and NMA, there may be small benefits of ICS-formoterol in GINA Step 1 patients.
QUALITY OF EVIDENCE OF HARM	What is the certainty/quality of evidence? High Moderate Low Very low ☐ ☐ ☐ ☒ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect	We did not find direct evidence that compared ICS/LABA to ICS/SABA amongst adults and adolescents with asthma symptoms <twice a week. 1. A Cochrane review (Crossingham, 2021) of two RCTs (Beasley, 2019a; O'Byrne, 2018) demonstrated that compared to as-needed SABA alone, as-needed ICS/formoterol: • Adverse events: moderate certainty 2. In a recent systematic review and network meta-analysis (Rayner, 2024): • In an indirect comparison with ICS-SABA, ICS-formoterol was not associated with an increased risk of serious adverse events, with moderate certainty evidence. • Mortality: ICS-formoterol vs SABA alone, high certainty evidence. Additional considerations: In the absence of direct evidence to evaluate this PICO, the committee considers the evidence likely to be of very low certainty. However, indirect evidence from the (Rayner, 2024) SR and network meta-analysis shows moderate CoE.
EVIDENCE OF HARMS	What is the size of the effect for harmful outcomes? Large Moderate Small None ☐ ☐ ☐ ☒	We did not find direct evidence that compared ICS/LABA to ICS/SABA amongst adults and adolescents with asthma symptoms <twice a week. 1. A Cochrane review (Crossingham, 2021) of two RCTs (Beasley, 2019a; O'Byrne, 2018) demonstrated that compared to as-needed SABA alone, as-needed ICS/formoterol: • Regarding adverse events, the odds of an adverse event were about 18% lower in the as-needed ICS/formoterol group compared with the as-needed SABA group (OR 0.82, 95% CI 0.71 to 0.95; participants = 3,002, NNT 21 • There was no difference in mortality between the as-needed ICS/formoterol and as-required SABA groups; one death was reported in the as-needed ICS/formoterol group (Beasley, 2019a). 2. In a recent systematic review and network meta-analysis (Rayner, 2024):

		- In an indirect comparison with ICS-SABA, ICS-formoterol (RD, −0.7% [95% CI, −2.0% to 0.6%]) was not associated with an increased risk of serious adverse events - Mortality: (ICS-formoterol vs SABA alone: RD, 0% [95% CI, −0.1% to 0.1%]) However, estimates from the (Rayner, 2024) SR and NMA show trivial to no harm.																																			
BENEFITS & HARMS	Do the desirable effects outweigh the undesirable harms? Favours intervention Favours control Intervention = Control <i>or</i> Uncertain ☒ ☐ ☐	We did not find direct evidence that compared ICS/LABA to ICS/SABA amongst adults and adolescents with asthma symptoms <twice a week. However, we believe that benefits may outweigh harms based on indirect evidence and thus favour the intervention.																																			
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes No ☒ ☐	There are currently no therapeutic alternatives on the EML as salmeterol has a slower onset of action and is, therefore, not a therapeutic equivalent for formoterol. The following ICS/formoterol combination inhalers are SAHPRA-approved. Only Symbicord® DPI is approved for use as MART. <table><tr><th>ICS/Formoterol combination product</th><th>Pack size</th><th>Trade name</th><th>Device</th><th>SAHPRA approved PI recommendations for the management of acute attacks/reliever therapy</th></tr><tr><td>Budesonide 80mcg, Formoterol 4.5mcg.</td><td>60</td><td>Symbicord Turbuhaler</td><td>DPI</td><td rowspan="3">SYMBICORD is taken as an anti-inflammatory reliever therapy, and in addition, patients take a daily maintenance dose of SYMBICORD. The as-needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have SYMBICORD TURBUHALER available to relieve symptoms at all times. A separate inhaler for relief of symptoms is not required.</td></tr><tr><td>Budesonide 160mcg, Formoterol 4.5mcg.</td><td>60 & 120</td><td>Symbicord Turbuhaler</td><td>DPI</td></tr><tr><td>Budesonide 320mcg Formoterol 9mcg</td><td>60</td><td>Symbicord Turbuhaler</td><td>DPI</td></tr><tr><td>Budesonide 80mcg, Formoterol 4.5mcg</td><td>120</td><td>Vannair</td><td>MDI</td><td rowspan="4">VANNAIR is taken as a regular maintenance treatment. Patients should be advised to always have their separate rapid-acting bronchodilator available for rescue use. Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy</td></tr><tr><td>Budesonide 160mcg, Formoterol 4.5mcg</td><td>120</td><td>Vannair</td><td>MDI</td></tr><tr><td>Mometasone furoate 50 mcg, formoterol fumarate dihydrate 5 mcg.</td><td>120</td><td>Dulera</td><td>MDI</td></tr><tr><td>Mometasone furoate 100 mcg, formoterol</td><td>120</td><td>Dulera</td><td>MDI</td></tr></table>	ICS/Formoterol combination product	Pack size	Trade name	Device	SAHPRA approved PI recommendations for the management of acute attacks/reliever therapy	Budesonide 80mcg, Formoterol 4.5mcg.	60	Symbicord Turbuhaler	DPI	SYMBICORD is taken as an anti-inflammatory reliever therapy, and in addition, patients take a daily maintenance dose of SYMBICORD. The as-needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have SYMBICORD TURBUHALER available to relieve symptoms at all times. A separate inhaler for relief of symptoms is not required.	Budesonide 160mcg, Formoterol 4.5mcg.	60 & 120	Symbicord Turbuhaler	DPI	Budesonide 320mcg Formoterol 9mcg	60	Symbicord Turbuhaler	DPI	Budesonide 80mcg, Formoterol 4.5mcg	120	Vannair	MDI	VANNAIR is taken as a regular maintenance treatment. Patients should be advised to always have their separate rapid-acting bronchodilator available for rescue use. Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy	Budesonide 160mcg, Formoterol 4.5mcg	120	Vannair	MDI	Mometasone furoate 50 mcg, formoterol fumarate dihydrate 5 mcg.	120	Dulera	MDI	Mometasone furoate 100 mcg, formoterol	120	Dulera	MDI
ICS/Formoterol combination product	Pack size	Trade name	Device	SAHPRA approved PI recommendations for the management of acute attacks/reliever therapy																																	
Budesonide 80mcg, Formoterol 4.5mcg.	60	Symbicord Turbuhaler	DPI	SYMBICORD is taken as an anti-inflammatory reliever therapy, and in addition, patients take a daily maintenance dose of SYMBICORD. The as-needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have SYMBICORD TURBUHALER available to relieve symptoms at all times. A separate inhaler for relief of symptoms is not required.																																	
Budesonide 160mcg, Formoterol 4.5mcg.	60 & 120	Symbicord Turbuhaler	DPI																																		
Budesonide 320mcg Formoterol 9mcg	60	Symbicord Turbuhaler	DPI																																		
Budesonide 80mcg, Formoterol 4.5mcg	120	Vannair	MDI	VANNAIR is taken as a regular maintenance treatment. Patients should be advised to always have their separate rapid-acting bronchodilator available for rescue use. Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy																																	
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Mometasone furoate 50 mcg, formoterol fumarate dihydrate 5 mcg.	120	Dulera	MDI																																		
Mometasone furoate 100 mcg, formoterol	120	Dulera	MDI																																		

		<table><tr><td>fumarate dihydrate 5 mcg.</td><td></td><td></td><td></td><td rowspan="2">If symptoms arise between doses, an inhaled short-acting beta2-agonist should be used for immediate relief.</td></tr><tr><td>Mometasone furoate 200 mcg, formoterol fumarate dihydrate 5 mcg.</td><td>120</td><td>Dulera</td><td>MDI</td></tr><tr><td>Beclometasone dipropionate 100 mcg, Formoterol fumarate dihydrate 6 mcg</td><td>120 & 180</td><td>Innuvair</td><td>MDI</td><td>INNUVAIR Inhaler is not appropriate for the treatment of acute asthma attacks</td></tr></table>	fumarate dihydrate 5 mcg.				If symptoms arise between doses, an inhaled short-acting beta2-agonist should be used for immediate relief.	Mometasone furoate 200 mcg, formoterol fumarate dihydrate 5 mcg.	120	Dulera	MDI	Beclometasone dipropionate 100 mcg, Formoterol fumarate dihydrate 6 mcg	120 & 180	Innuvair	MDI	INNUVAIR Inhaler is not appropriate for the treatment of acute asthma attacks
fumarate dihydrate 5 mcg.				If symptoms arise between doses, an inhaled short-acting beta2-agonist should be used for immediate relief.												
Mometasone furoate 200 mcg, formoterol fumarate dihydrate 5 mcg.	120	Dulera	MDI													
Beclometasone dipropionate 100 mcg, Formoterol fumarate dihydrate 6 mcg	120 & 180	Innuvair	MDI	INNUVAIR Inhaler is not appropriate for the treatment of acute asthma attacks												
FEASIBILITY	Is the implementation of this recommendation feasible? Yes No Uncertain ☒ ☐ ☐	Budesonide/formoterol 160/4.5mcg is listed on the public sector tender and is already an EML item; this is an additional indication of its use. Despite the paucity of evidence comparing ICS/LABA to ICS/SABA amongst adults and adolescents with asthma symptoms <twice a week, pragmatic considerations include: • Patient preference is for a combination inhaler of ICS/LABA over two separate inhalers of mono-components. See Appendix 7. • Combination therapy with fixed-dose formoterol/ICS simplifies treatment and promotes adherence (Murphy, 2009). • Patients may or may not use their ICS with the SABA reliever as needed, as they are separate inhalers. • Safety concerns and the increased risk of exacerbations associated with SABA-only therapy. • Streamlining therapy for asthmatics across the different spectrums of disease severity allows for programmatic ease and simplified patient care. • Modelling ICS as the mainstay of asthma control from the outset is believed to reinforce the focus on maintenance therapy and discourage the overuse of SABA-only reliever therapy. • Patient training for DPI use is easier than MDI use • Reduced environmental impact with DPI vs. MDI use Additional considerations: The committee noted concerns regarding affordability and potential drug scheduling issues in the private sector of ICS/formoterol combination inhalers vs. SABA inhalers.														

RESOURCE USE	How large are the resource requirements? More intensive Less intensive Uncertain ☐ ☒ ☐	Refer to the associated pharmacoeconomic evaluation for detailed information.
VALUES, PREFERENCES, ACCEPTABILITY	Is there important uncertainty or variability about how much people value the options? Minor Major Uncertain ☒ ☐ ☐ Is the option acceptable to key stakeholders? Yes No Uncertain ☒ ☐ ☐	The available evidence of patient preferences when comparing combined ICS/LABA to ICS/SABA is lacking. However, one study demonstrated patient preferences for a combination ICS/LABA inhaler rather than for the separate components of ICS and LABA, simplifying treatment and promoting adherence (Murphy, 2009). In addition, another two studies showed greater health-related quality of life (HRQoL) with combined ICS/LABA using the Asthma Quality of Life Questionnaire (AQLQ[S]) compared to the separate ICS and LABA mono-components (Chervinsky, 2008; Bateman, 2004).
EQUITY	Would there be an impact on health inequity? Yes No Uncertain ☐ ☐ ☒	Improved access to intervention in the public sector.

PICO 2

Key findings

- *The current standard of care for mild persistent asthma in the South African standard treatment guidelines is a regular inhaled corticosteroid (ICS) with a short-acting beta₂-agonist (SABA) reliever.*
- *A rapid review was conducted to evaluate the efficacy and safety of the combination inhaler formoterol [long-acting beta₂-agonist (LABA)] and budesonide [inhaled corticosteroid (ICS)], taken as needed, compared to daily low-dose ICS and a SABA reliever in adults and adolescents aged 12 years and older with mild persistent asthma.*
- *Several asthma guidelines were initially considered, most of which refer to the Global Initiative for Asthma (GINA) guideline. However, although the GINA guideline is well-used globally, we could not appraise the underlying evidence synthesis (it was not available), so we proceeded with our independent review.*
- *We searched PubMed (20 October 2023) and Epistemonikos (23 October 2023) databases for systematic reviews (SRs) of randomised controlled trials (RCTs). We identified two relevant SRs that both included the same four RCTs: Novel START (Beasley, 2019a), PRACTICAL (Hardy, 2019), SYGMA 1 (O'Byrne, 2018) and SYGMA 2 (Bateman, 2018). All four trials compared the combination of budesonide 200 µg and formoterol 6 µg with regular budesonide 200 µg twice daily. The as-needed beta₂-agonist given with the regular budesonide was salbutamol (200 µg) in Novel START (Beasley, 2019a) and terbutaline (500 µg) in the other three studies (Bateman, 2018; Hardy, 2019; O'Byrne, 2018).*
- *Formoterol plus ICS as-needed compared to daily low-dose ICS plus SABA reliever (follow-up duration of 52 weeks):*
 - *Likely results in little to no difference in acute severe exacerbations requiring systemic steroids*
 - *Risk Ratio (RR) 0.81 (95% CI 0.61 to 1.07)*
 - *4 studies, n = 8,065*
 - *Moderate certainty evidence*
 - *15 fewer cases per 1,000 (32 fewer to 6 more)*
 - *NNT 67*
 - *Results in a slight reduction in asthma-related visits to the emergency room*
 - *RR 0.65 (95% CI 0.46 to 0.93)*
 - *4 studies, n = 8,065*
 - *High certainty evidence*
 - *7 fewer cases per 1,000 (10 fewer to 1 fewer)*
 - *NNT 143*
 - *Results in little to no difference in asthma-related hospital admissions*
 - *RR 0.88 (95% CI 0.50 to 1.53)*
 - *3 studies, n = 7,620*
 - *High certainty evidence*
 - *1 fewer case per 1,000 (4 fewer to 4 more)*
 - *NNT 1,000*
 - *Probably results in little to no difference in serious adverse events (SAEs)*
 - *RR 1.13 (95% CI 0.83 to 1.55)*
 - *4 studies, n = 8,065*
 - *Moderate certainty evidence*
 - *4 more cases per 1,000 (6 fewer to 18 more)*
 - *NNH 250*

- *Probably results in little to no difference in adverse events*
 - *RR 0.98 (95% CI 0.92 to 1.06)*
 - *4 studies, n = 8,065*
 - *Moderate certainty evidence*
 - *10 fewer cases per 1,000 (39 fewer to 30 more)*
 - *NNT 100*
- *Probably results in little to no difference in mortality*
 - *RR 0.63 (95% CI 0.12 to 3.26)*
 - *4 studies, n = 8,065*
 - *Moderate certainty evidence*
 - *4 fewer cases per 10,000 (9 fewer to 22 more)*
 - *NNT 2,500*
- *The formulation of formoterol with budesonide available in South Africa is a combination of formoterol 4.5 µg with budesonide 160 µg as a dry powder inhaler. This is equivalent to the 6-µg formoterol with 200 µg budesonide used in the studies examined in this evidence review, as the delivered dose is noted to be the same (4.5 µg formoterol and 160 µg budesonide).*

Search results

We proceeded to search for relevant SRs as described above. The search produced 594 records and 41 reports, of which two SRs (Crossingham, 2021; Hatter, 2021) were included in the final review (Figure 6).

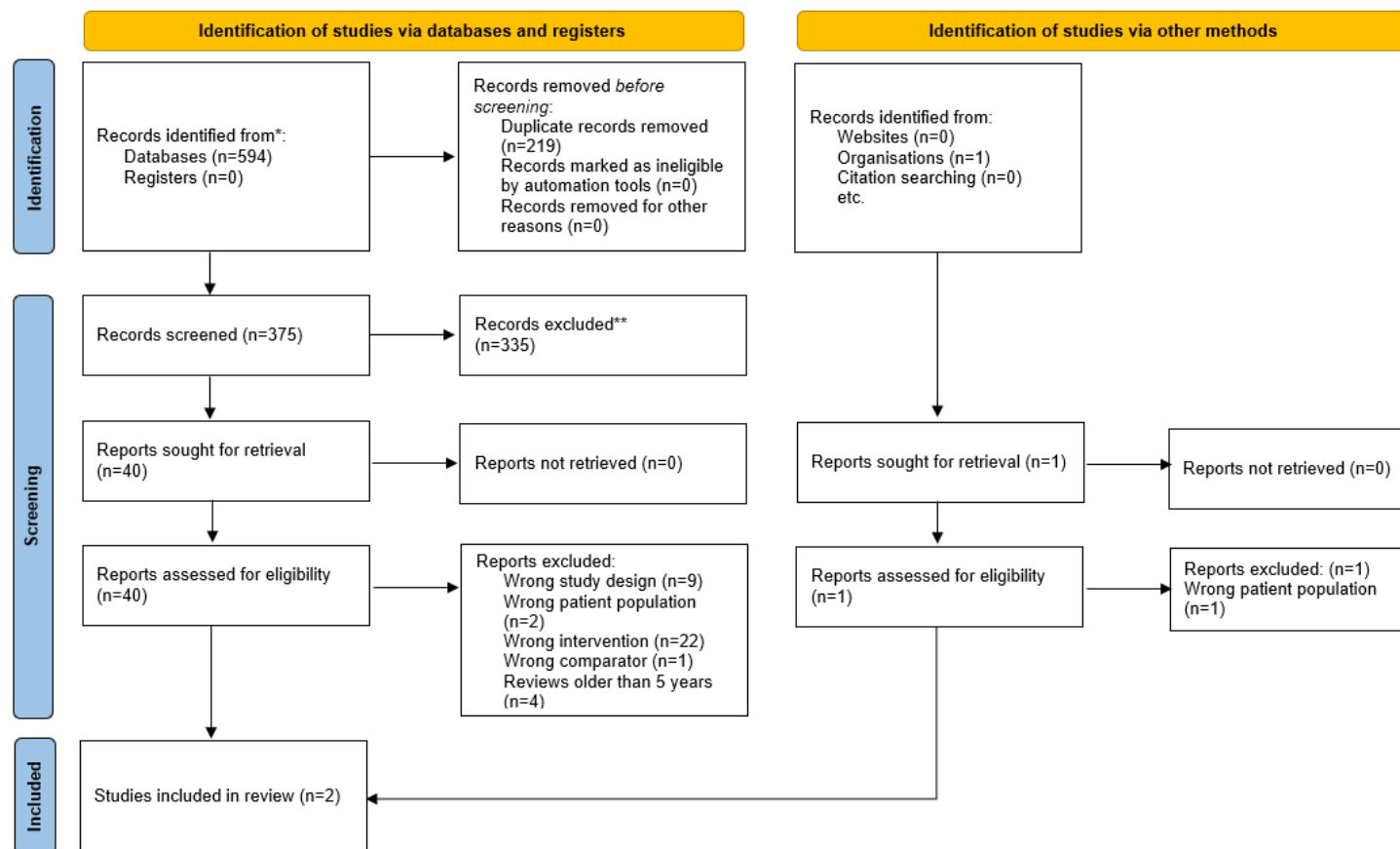


Figure 6: PRISMA flow diagram for review, PICO 2

Excluded studies:

Four studies (Agarwal, 2009; Cates, 2013; Kew, 2013; Wang, 2017) published between 2009 and 2017 were considered outdated for the current review and thus excluded. Other studies excluded and reasons for exclusion are provided in (Appendix 3: Characteristics of excluded studies).

Evidence synthesis

Description of included studies

Appendix 4: Characteristics of included SRs has a detailed description of both included SRs (Crossingham, 2021; Hatter, 2021).

Systematic Reviews

Crossingham *et al.* (Crossingham, 2021) was found to be the most relevant, trustworthy, and up-to-date review and included GRADE certainty of evidence judgments. Crossingham *et al.* (Crossingham, 2021) aimed to assess the efficacy and safety of a single combined (fast-onset beta₂-agonist [FABA] plus an inhaled corticosteroid [ICS]) inhaler only used as needed in people with mild asthma. The definition of mild asthma in this review used the GINA definition (GINA, 2019), corresponding with steps 1 and 2 of management. In this review, FABA agents included salbutamol (albuterol), terbutaline, and formoterol. Primary outcomes reported were exacerbations requiring systemic steroids, hospital admissions/emergency department or urgent care visits for asthma, and measures of asthma control.

- They included four RCTs (Beasley, 2019a; Hardy, 2019; O’Byrne, 2018; Bateman, 2018) (see Table 5: Characteristics of Included Trials) with 8,065 participants. The trials, Novel START (Beasley, 2019a), PRACTICAL (Hardy, 2019), SYGMA 1 (O’Byrne, 2018), and SYGMA 2 (Bateman, 2018), were large studies from the same research group. Two studies, SYGMA 1 (O’Byrne, 2018) and SYGMA 2 (Bateman, 2018), included adolescents aged 12 years and over and adults. Novel START (Beasley, 2019a) and PRACTICAL (Hardy, 2019) included adults only (≥18 years).
- Four studies compared an as-needed FABA/ICS combination inhaler versus a regular inhaled corticosteroid plus an as-needed beta₂-agonist. Novel START (Beasley, 2019a), PRACTICAL (Hardy, 2019), SYGMA 1 (O’Byrne, 2018), and SYGMA 2 (Bateman, 2018) all compared the combination of budesonide 200 µg and formoterol 6 µg with regular budesonide 200 µg twice daily. The as-needed beta₂-agonist given with the regular budesonide was salbutamol (200 µg) in Novel START (Beasley, 2019a) and terbutaline (500 µg) in the other three studies (Bateman, 2018; Hardy, 2019; O’Byrne, 2018). Risk of Bias (ROB) of the included studies was assessed using the Cochrane ROB 1.0 tool (Higgins, 2008). GRADE certainty of evidence for outcomes reported in the Crossingham *et al.* SR ranged from high to low across outcomes (Crossingham, 2021).

Hatter *et al.* (Hatter, 2021) aimed to compare the efficacy and safety of as-needed budesonide-formoterol with maintenance ICS plus SABA reliever in adults and children with mild to moderate asthma. The primary outcome was time to first severe exacerbation. “Secondary outcomes included *rate ratio* (RR) of severe exacerbation; risk of at least one severe exacerbation, emergency department (ED) visit, hospital admission, combined ED visit or hospital admission, serious adverse events (SAE) and death; mean daily ICS dose; Asthma (ACQ)-5 scores; and forced expiratory volume in 1 s (FEV1)” (Hatter, 2021, p. 2).

- They included the same four RCTs as in the Crossingham *et al.* (Crossingham, 2021) SR: (Novel START, PRACTICAL, SYGMA 1, and SYGMA 2) with a total of 8,065 participants that compared as needed Budesonide-formoterol (4,023 participants) with maintenance ICS plus SABA reliever (4,042 participants). Risk of Bias (ROB) was assessed in the included studies using the Cochrane ROB 2.0 tool (Higgins, 2023; Sterne, 2019). GRADE certainty of evidence for outcomes reported in the Hatter *et al.* SR ranged from high to very low across outcomes (Hatter, 2021).

Table 5: Characteristics of included RCTs (Hatter, 2021)

Study, first author (year)	Design	Duration	Sites	Population	Participants (intervention versus control) # n	Primary outcome (analysis)	Intervention	Control
SYGMA 1 O'BYRNE (2018)	RCT, parallel-group, double-blind placebo-controlled	52 weeks	261 sites, 18 countries	Adults and adolescents (≥ 12 years)	2559 (1277 <i>versus</i> 1282)	Mean percentage of electronically recorded weeks with well-controlled asthma per patient (noninferiority) [¶]	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed plus twice-daily placebo	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500 µg (Turbuhaler) as needed
SYGMA 2 BATEMAN (2018)	RCT, parallel-group, double-blind placebo-controlled	52 weeks	350 sites, 25 countries	Adults and adolescents (≥ 12 years)	4176 (2089 <i>versus</i> 2087)	Annualised rate of severe exacerbations (non-inferiority) ⁺	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed plus twice-daily placebo	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500 µg (Turbuhaler) as needed
Novel start BEASLEY (2019)	RCT, parallel-group, open-label, real-world	52 weeks	16 sites, 4 countries	Adults (≥ 18 years)	445 (220 <i>versus</i> 225)	Annualised rate of asthma exacerbations (superiority)	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus albuterol 100 µg (Ventolin pMDI) two inhalations as needed
PRACTICAL HARDY (2019)	RCT, parallel-group, open-label, real-world	52 weeks	15 sites, 1 country	Adults and adolescents (≥ 18 years)	885 (437 <i>versus</i> 448)	Number of severe exacerbations per patient per year (superiority)	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 250 µg (Bricanyl Turbuhaler, AstraZeneca) two inhalations as needed

This table does not include details of additional trial arms present in the SYGMA 1 and Novel START studies. All information is derived from published trial protocols (including trial registries), manuscripts, and supplementary material. RCT: randomised controlled trial; pMDI: pressurised metered-dose inhaler. #: Intervention refers to as-needed budesonide-formoterol; control refers to maintenance budesonide plus short-acting β_2 -agonist (SABA) reliever. Participant numbers refer to as-needed inhaled corticosteroid (ICS)-formoterol and maintenance ICS plus SABA arms only; numbers for SABA-only arms in SYGMA 1 and Novel START not included; ¶: superiority analysis for as-needed budesonide-formoterol *versus* SABA (primary), and noninferiority analysis for as-needed budesonide-formoterol *versus* maintenance budesonide plus SABA (secondary); +: initially superiority.

Evidence quality

Appraisal of Guidelines and SRs

The GINA 2023 guideline (GINA, 2023) was appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (Brouwers, 2010). The overall assessment score was 67% (recommended with modifications). Both appraisers' scores and judgment comments can be found in (Appendix 5: AGREE II appraisal of GINA guideline).

AMSTAR II assessment (Shea, 2017) of the two SRs (Crossingham, 2021; Hatter, 2021) ranged from moderate quality to low quality (Appendix 6: AMSTAR II appraisal of included studies). To avoid duplication of synthesis, we used the most recent SR that was of the highest quality and most applicable to our PICO. Crossingham *et al.* (Crossingham, 2021) had the highest AMSTAR II overall score (moderate quality review) and was the most recent SR that included the most recent trials and used GRADE in reporting the findings.

Risk of Bias (RoB) of included trials in SR

Using the Cochrane RoB 2.0 tool, we found the RoB to be low across the four included trials, as reported by Hatter *et al.* (2021) (Hatter, 2021) in Figure 7. Assessment of RoB in the Hatter *et al.* SR (2021) (Hatter, 2021) used the Cochrane RoB 2.0 tool, which is an updated tool and recommended for use in Cochrane Reviews (Higgins, 2023; Sterne, 2009). Crossingham *et al.* (2021) (Crossingham, 2021), using the older Cochrane RoB 1.0 tool (Higgins, 2008) reported a high risk of bias in two [Novel START (Beasley, 2019a) and PRACTICAL (Hardy, 2019)] RCTs and two RCTs [SYGMA 1 (O'Byrne, 2018) and SYGMA 2 (Bateman, 2018)] were judged to have a low risk of bias. The authors noted that the revised RoB 2.0 tool (Higgins, 2023; Sterne, 2009) was not widely used when their protocol was written (Crossingham, 2021). Hence, the older RoB 1.0 tool was used in that review (Crossingham, 2021).

	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
SYGMA 1						
SYGMA 2						
Novel START						
PRACTICAL						

Figure 7: Risk of bias of included RCTs (Hatter, 2021), PICO 2

Effects of the intervention

The GRADE Evidence Profile in Table 6 and Summary of Findings in Table 7 summarise the effects of the intervention for each of the following outcomes. We sought data from the included studies on adverse reactions, but this was not available.

1. Acute severe exacerbations requiring systemic steroids (Crossingham, 2021)

Formoterol plus ICS as needed compared to daily low-dose ICS plus SABA reliever likely results in little to no difference in acute severe exacerbations requiring systemic steroids (52 weeks), Risk Ratio (RR) 0.81 (95% CI 0.61 to 1.07), 4 studies, $n = 8,065$, moderate certainty evidence. That is an absolute effect of 15 fewer cases per 1,000 (ranging from 32 fewer to 6 more). Four studies, Novel START, PRACTICAL, SYGMA 1, and SYGMA 2, had available event/total group data to evaluate this outcome. Figure 8 shows the forest plot for this comparison.

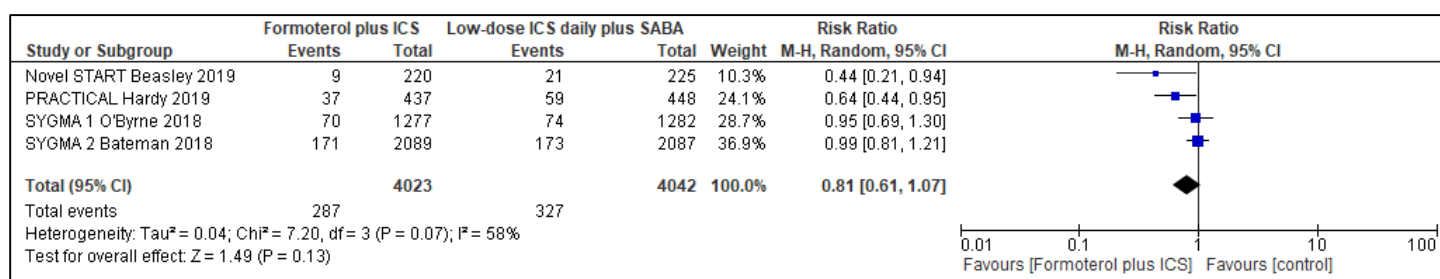


Figure 8: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: acute severe exacerbations requiring systemic steroid

2. Asthma-related visits to the emergency room

Formoterol plus ICS as needed compared to daily low-dose ICS plus SABA reliever results in a slight reduction in asthma-related visits to the emergency room (52 weeks), RR 0.65 (95% CI 0.46 to 0.93), 4 studies, $n = 8,065$, high certainty evidence. That is an absolute effect of 7 fewer cases per 1,000 (ranging from 10 fewer to 1 fewer). Four studies, Novel START, PRACTICAL, SYGMA 1, and SYGMA 2, had available event/total group data to evaluate this outcome. Figure 9 shows the forest plot for this comparison.

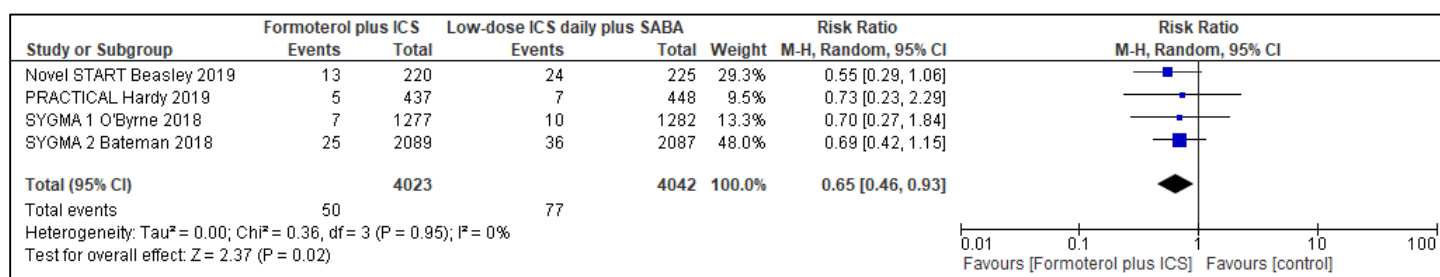


Figure 9: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: asthma-related visits to the emergency room

3. Asthma-related hospital admissions

Formoterol plus ICS as needed compared to daily low-dose ICS plus SABA reliever results in little to no difference in asthma-related hospital admissions (52 weeks), RR 0.88 (95% CI 0.50 to 1.53), 3 studies, n = 7,620, high certainty evidence. That is an absolute effect of 1 fewer case per 1,000 (ranging from 4 fewer to 4 more). Three studies, PRACTICAL, SYGMA 1, and SYGMA 2, had available event/total group data to evaluate this outcome. Figure 10 shows the forest plot for this comparison.

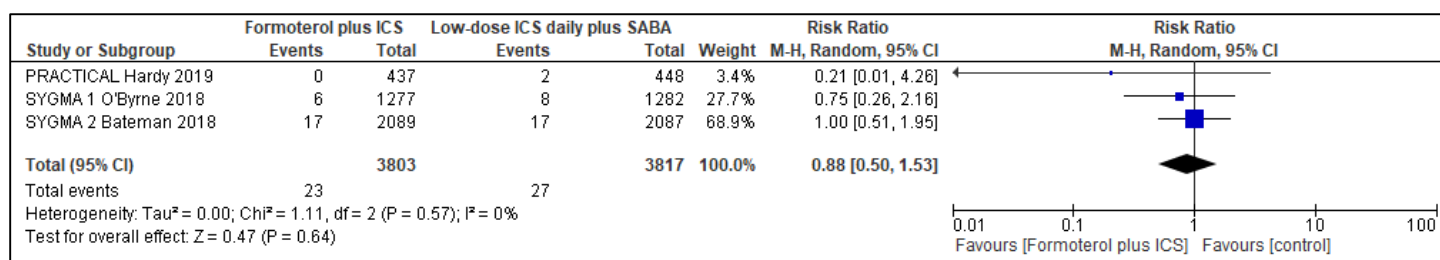


Figure 10: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: asthma-related hospital admissions

4. Total systemic corticosteroid dose (Crossingham 2021)

There was similar total systemic steroid exposure in the Formoterol plus ICS as needed and daily low-dose ICS plus SABA reliever groups (52 weeks), Mean Difference (MD) -7.00 mg prednisolone (95% CI -13.97 to -0.03), 2 studies, n = 1,330, high certainty evidence. Two studies, Novel START and PRACTICAL, had available data to evaluate this outcome. Figure 11 shows the forest plot for this comparison.

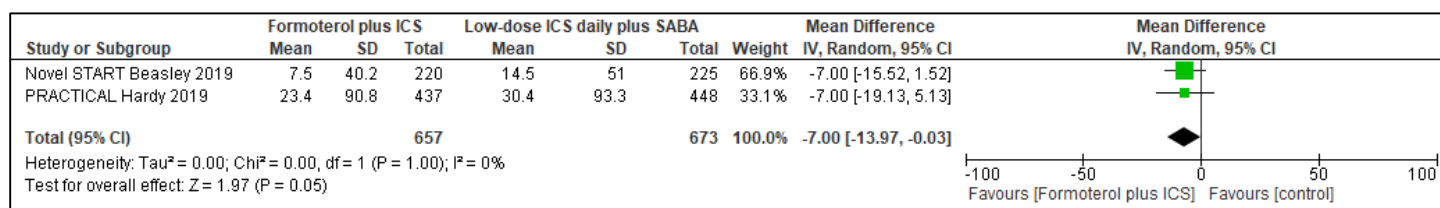


Figure 11: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: total systemic corticosteroid dose

There were numerically fewer total days on systemic steroids in the Formoterol plus ICS as needed group compared with the daily low-dose ICS plus SABA reliever group in SYGMA 1 (465 versus 500 days) (4, 23). SYGMA 2 reported that those in the Formoterol plus ICS as needed and the daily low-dose ICS plus SABA reliever groups had the same median number of days on systemic steroids (six days) (Crossingham, 2021; Bateman, 2018).

5. Serious adverse events (SAEs)

Formoterol plus ICS as needed compared to daily low-dose ICS plus SABA reliever probably results in little to no difference in SAEs (52 weeks), Risk Ratio (RR) 1.13 (95% CI 0.83 to 1.55), 4 studies, n = 8,065, moderate certainty evidence. That is an absolute effect of 4 more cases per 1,000 (ranging from 6 fewer to 18 more). Four studies, Novel START, PRACTICAL, SYGMA 1, and SYGMA 2, had available event/total group data to evaluate this outcome. Figure 12 shows the forest plot for this comparison.

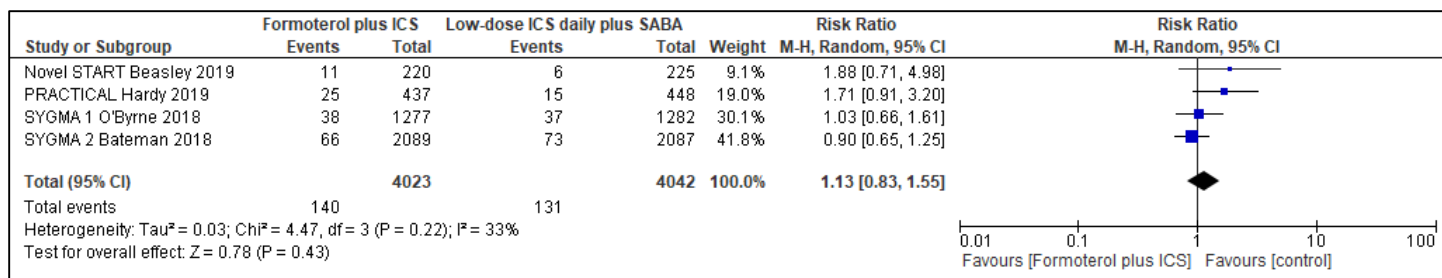


Figure 12: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: serious adverse events

6. All adverse events

Formoterol plus ICS as needed compared to daily low-dose ICS plus SABA reliever probably results in little to no difference in adverse events (52 weeks), Risk Ratio (RR) 0.98 (95% CI 0.92 to 1.06), 4 studies, $n = 8,065$, moderate certainty evidence. That is an absolute effect of 10 fewer cases per 1,000 (ranging from 39 fewer to 30 more). Four studies, Novel START, PRACTICAL, SYGMA 1, and SYGMA 2, had available event/total group data to evaluate this outcome. Figure 13 shows the forest plot for this comparison.

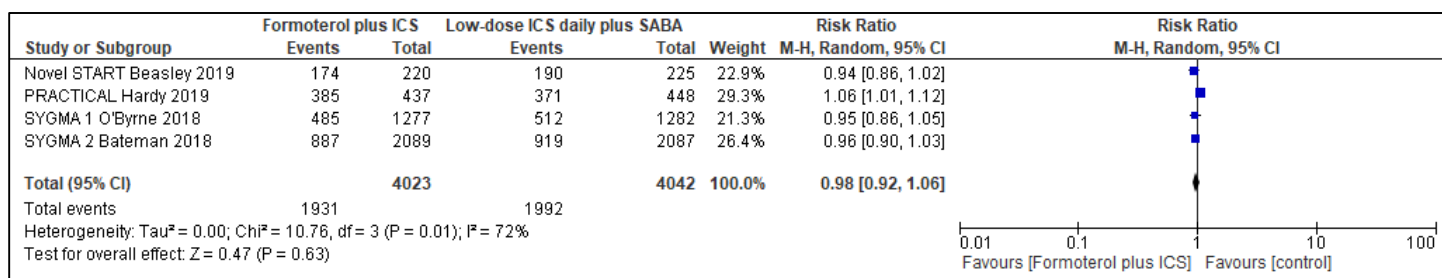


Figure 13: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: all adverse events

7. Mortality

Formoterol plus ICS as needed compared to daily low-dose ICS plus SABA reliever probably results in little to no difference in mortality (52 weeks), Risk Ratio (RR) 0.63 (95% CI 0.12 to 3.26), 4 studies, $n = 8,065$, moderate certainty evidence. That is an absolute effect of 4 fewer cases per 10,000 (ranging from 9 fewer to 22 more). This analysis is based on a small number of events with a broad 95% CI. Four studies, Novel START, PRACTICAL, SYGMA 1, and SYGMA 2, had available event/total group data to evaluate this outcome. Figure 14 shows the forest plot for this comparison.

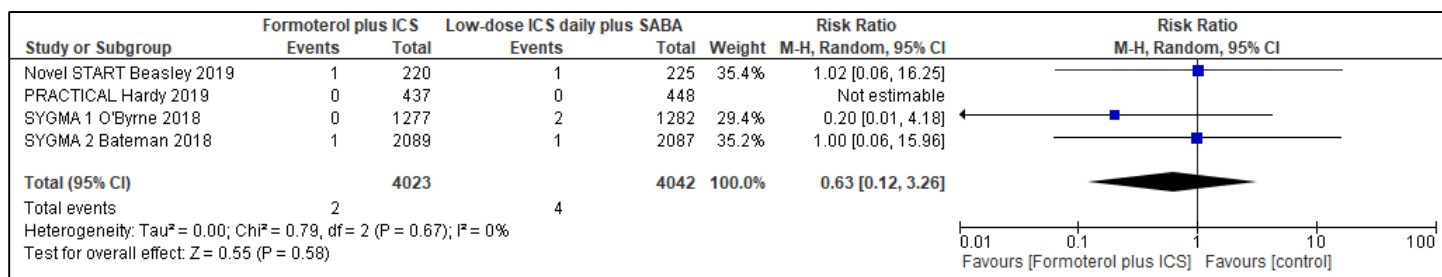


Figure 14: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: mortality

Table 6: GRADE evidence profile

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Formoterol plus ICS as needed	Daily low-dose ICS plus SABA reliever	Relative (95% CI)	Absolute (95% CI)	
Acute severe exacerbations requiring systemic steroid											
4	randomised trials	not serious	not serious	not serious ^a	serious ^b	none	287/4023 (7.1%)	327/4042 (8.1%)	RR 0.81 (0.61 to 1.07)	15 fewer per 1,000 (from 32 fewer to 6 more)	⊕⊕⊕○ Moderate
Asthma-related visits to the emergency room											
4	randomised trials	not serious	not serious	not serious ^a	not serious ^c	none	50/4023 (1.2%)	77/4042 (1.9%)	RR 0.65 (0.46 to 0.93)	7 fewer per 1,000 (from 10 fewer to 1 fewer)	⊕⊕⊕⊕ High
Asthma-related hospital admissions											
3	randomised trials	not serious	not serious	not serious ^a	not serious ^c	none	23/3803 (0.6%)	27/3817 (0.7%)	RR 0.88 (0.50 to 1.53)	1 fewer per 1,000 (from 4 fewer to 4 more)	⊕⊕⊕⊕ High
Total systemic corticosteroid dose											
2	randomised trials	not serious	not serious	not serious ^a	not serious	none	657	673	-	MD 7 mg prednisolone lower (13.97 lower to 0.03 lower)	⊕⊕⊕⊕ High
Serious adverse events											
4	randomised trials	not serious	not serious	not serious ^a	serious ^d	none	140/4023 (3.5%)	131/4042 (3.2%)	RR 1.13 (0.83 to 1.55)	4 more per 1,000 (from 6 fewer to 18 more)	⊕⊕⊕○ Moderate
All adverse events											
4	randomised trials	not serious	not serious	not serious ^a	serious ^e	none	1931/4023 (48.0%)	1992/4042 (49.3%)	RR 0.98 (0.92 to 1.06)	10 fewer per 1,000 (from 39 fewer to 30 more)	⊕⊕⊕○ Moderate
Mortality											
4	randomised trials	not serious	not serious	not serious ^a	serious ^f	none	2/4023 (0.0%)	4/4042 (0.1%)	RR 0.63 (0.12 to 3.26)	4 fewer per 10,000 (from 9 fewer to 22 more)	⊕⊕⊕○ Moderate

CI: confidence interval; MD: mean difference; RR: risk ratio

Table 7: Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Daily low-dose ICS plus SABA reliever	Risk with Formoterol plus ICS as needed				
Acute severe exacerbations requiring systemic steroid: follow-up 52 weeks	81 per 1,000	66 per 1,000 (49 to 87)	RR 0.81 (0.61 to 1.07)	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,b}	Formoterol plus ICS likely results in little to no difference in acute severe exacerbations requiring systemic steroids
Asthma-related visits to the emergency room: follow-up 52 weeks	19 per 1,000	12 per 1,000 (9 to 18)	RR 0.65 (0.46 to 0.93)	8065 (4 RCTs)	⊕⊕⊕⊕ High ^{a,c}	Formoterol plus ICS results in a slight reduction in asthma-related visits to the emergency room
Asthma-related hospital admissions: follow-up 52 weeks	7 per 1,000	6 per 1,000 (4 to 11)	RR 0.88 (0.50 to 1.53)	7620 (3 RCTs)	⊕⊕⊕⊕ High ^{a,c}	Formoterol plus ICS results in little to no difference in asthma-related hospitalisation
Total systemic corticosteroid dose: follow-up 52 weeks	The mean total systemic corticosteroid dose was 20.97 mg prednisolone (4)	MD 7 mg prednisolone lower (13.97 lower to 0.03 lower)	-	1330 (2 RCTs)	⊕⊕⊕⊕ High ^a	Total systemic corticosteroid exposure was similar and low in both groups (4)
Serious adverse events: follow-up 52 weeks	32 per 1,000	37 per 1,000 (27 to 50)	RR 1.13 (0.83 to 1.55)	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,d}	Formoterol plus ICS probably results in little to no difference in SAEs
All adverse events: follow-up 52 weeks	493 per 1,000	483 per 1,000 (453 to 522)	RR 0.98 (0.92 to 1.06)	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,e}	Formoterol plus ICS probably results in little to no difference in adverse events
Mortality: follow-up 52 weeks	10 per 10,000	6 per 10,000 (1 to 32)	RR 0.63 (0.12 to 3.26)	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,f}	Formoterol plus ICS probably results in little to no difference in mortality

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the effect estimate.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to differ substantially from the estimate of effect.

Explanations

a. The Novel START trial was conducted in Australia, New Zealand, the United Kingdom, and Italy, and the PRACTICAL trial was in New Zealand; trial participants may differ from those in our setting regarding ethnicity, comorbidity, and genotypic profile.

b. Downgraded by one level for imprecision: wide absolute 95% confidence interval ranging from -3.2% to 0.6%, i.e. the absolute 95% CI ranges from important benefit to unimportant harm.

c. With a low event rate and an adequate sample size, rating down for imprecision becomes inappropriate.

d. Downgraded by one level for imprecision: wide absolute 95% confidence interval ranging from -0.6% to 1.8%, i.e. the absolute 95% CI ranges from unimportant benefit to potentially important harm.

e. Downgraded by one level for imprecision: wide absolute 95% confidence interval ranging from -3.9% to 3.0%, i.e. the absolute 95% CI ranges from important benefit to important harm.

f. Downgraded by one level for imprecision: wide absolute 95% confidence interval ranging from -0.09% to 0.22%, i.e. the absolute 95% CI ranges from unimportant benefit to potentially important harm.

Evidence to decision framework: PICO 2

QUESTION	
Should formoterol/ICS as needed versus low-dose ICS daily plus SABA, as needed, be used for symptom relief in adults and adolescents aged 12 years and older with mild persistent asthma [asthma symptoms twice monthly or more requiring reliever therapy (although less than 4-5 days per week)]?	
POPULATION	Patients with mild persistent asthma [asthma symptoms twice monthly or more requiring reliever therapy (although less than 4-5 days per week)], aged 12 years and older
INTERVENTION	Formoterol plus ICS as needed for symptom relief
COMPARISON	Low-dose ICS daily plus SABA as needed for symptom relief
OUTCOMES	Acute exacerbations, asthma visits to the emergency room, asthma admissions, courses of systemic steroids, mortality, adverse events, and adverse reactions
SETTING	Public sector, South Africa
PERSPECTIVE	Public health/population

Recommendation PICO 2:

The ASC recommends that the ICS/formoterol combination be used for symptom relief in adults and adolescents aged 12 years and older with mild persistent asthma (*strong recommendation, moderate certainty evidence*).

JUDGEMENT		RESEARCH EVIDENCE & ADDITIONAL CONSIDERATIONS					
QUALITY OF EVIDENCE OF BENEFIT	What is the certainty/quality of evidence? High ☐ Moderate ☒ Low ☐ Very low ☐ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect						
EVIDENCE OF BENEFIT	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☐ Small ☒ None ☐	There is a small but clinically relevant benefit of a formoterol plus ICS combination taken as needed in adolescents and adults aged 12 years and older with mild persistent asthma. Additional Considerations: - Poor adherence to regular ICS is likely to occur with greater frequency outside of a study setting and, in practice, may result in even greater effectiveness of a formoterol-ICS combination used as needed. - It must be noted that the SYGMA studies were randomised, double-blinded, controlled trials, whereas the PRACTICAL and Novel START studies were open-label. It must be noted that open-label studies are likely more representative of real-world situations, and we may see a greater impact on adherence to these studies					

QUALITY OF EVIDENCE OF HARM	What is the certainty/quality of evidence? High ☐ Moderate ☒ Low ☐ Very low ☐ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect	<table border="1"> <tr> <th rowspan="2">Outcomes</th> <th rowspan="2">No of participants</th> <th rowspan="2">Certainty of the evidence (GRADE)</th> <th rowspan="2">Relative effect (95% CI)</th> <th colspan="2">Anticipated absolute effects</th> </tr> <tr> <th>Risk with Low-dose ICS daily plus SABA as-needed</th> <th>Risk difference with Formoterol plus ICS as-needed</th> </tr> <tr> <td>Serious adverse events</td> <td>8065 (4 RCTs)</td> <td>⊕⊕⊕○ Moderate^{a,d}</td> <td>RR 1.13 (0.83 to 1.55)</td> <td>32 per 1,000</td> <td>4 more per 1,000 (6 fewer to 18 more): NNT 250</td> </tr> <tr> <td>All adverse events</td> <td>8065 (4 RCTs)</td> <td>⊕⊕⊕○ Moderate^{a,e}</td> <td>RR 0.98 (0.92 to 1.06)</td> <td>493 per 1,000</td> <td>10 fewer per 1,000 (39 fewer to 30 more): NNT 100</td> </tr> <tr> <td>Mortality</td> <td>8065 (4 RCTs)</td> <td>⊕⊕⊕○ Moderate^{a,f}</td> <td>RR 0.63 (0.12 to 3.26)</td> <td>10 per 10,000</td> <td>4 fewer per 10,000 (9 fewer to 22 more): NNT 2,500</td> </tr> </table>					Outcomes	No of participants	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Risk with Low-dose ICS daily plus SABA as-needed	Risk difference with Formoterol plus ICS as-needed	Serious adverse events	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,d}	RR 1.13 (0.83 to 1.55)	32 per 1,000	4 more per 1,000 (6 fewer to 18 more): NNT 250	All adverse events	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,e}	RR 0.98 (0.92 to 1.06)	493 per 1,000	10 fewer per 1,000 (39 fewer to 30 more): NNT 100	Mortality	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,f}	RR 0.63 (0.12 to 3.26)	10 per 10,000	4 fewer per 10,000 (9 fewer to 22 more): NNT 2,500
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EVIDENCE OF HARMS	What is the size of the effect for harmful outcomes? Large ☐ Moderate ☐ Small ☐ None ☒	There is probably little to no difference in the undesirable effects.																														
BENEFITS & HARMS	Do the desirable effects outweigh the undesirable harms? Favours intervention ☒ Favours control ☐ Intervention = Control or Uncertain ☐	The decision is based on the above criteria: - Small benefits - No difference in harms - Moderate certainty of the evidence - Values and preferences: Minor																														
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☒ No ☐	There are currently no therapeutic alternatives on the EML as salmeterol has a slower onset of action and is, therefore, not a therapeutic equivalent for formoterol. The following ICS/formoterol combination inhalers are SAHPRA-approved. Only Symbicord® DPI is approved for use as MART. <table border="1"> <tr> <th>ICS/Formoterol combination product</th> <th>Pack size</th> <th>Trade name</th> <th>Device</th> <th>SAHPRA approved PI recommendations for the management of acute attacks/reliever therapy</th> </tr> <tr> <td>Budesonide 80mcg, Formoterol 4.5mcg.</td> <td>60</td> <td>Symbicord Turbuhaler</td> <td>DPI</td> <td rowspan="2">SYMBICORD is taken as an anti-inflammatory reliever therapy, and in addition, patients take a daily maintenance dose of SYMBICORD. The as-needed</td> </tr> <tr> <td>Budesonide 160mcg, Formoterol 4.5mcg.</td> <td>60 & 120</td> <td>Symbicord Turbuhaler</td> <td>DPI</td> </tr> </table>					ICS/Formoterol combination product	Pack size	Trade name	Device	SAHPRA approved PI recommendations for the management of acute attacks/reliever therapy	Budesonide 80mcg, Formoterol 4.5mcg.	60	Symbicord Turbuhaler	DPI	SYMBICORD is taken as an anti-inflammatory reliever therapy, and in addition, patients take a daily maintenance dose of SYMBICORD. The as-needed	Budesonide 160mcg, Formoterol 4.5mcg.	60 & 120	Symbicord Turbuhaler	DPI												
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Budesonide 160mcg, Formoterol 4.5mcg.	60 & 120	Symbicord Turbuhaler	DPI																													

		Budesonide 320mcg Formoterol 9mcg	60	Symbicord Turbuhaler	DPI	inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have SYMBICORD TURBUHALER available to relieve symptoms at all times. A separate inhaler for relief of symptoms is not required.
		Budesonide 80mcg, Formoterol 4.5mcg	120	Vannair	MDI	VANNAIR is taken as a regular maintenance treatment. Patients should be advised to always have their separate rapid-acting bronchodilator available for rescue use. Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy
		Budesonide 160mcg, Formoterol 4.5mcg	120	Vannair	MDI	
		Mometasone furoate 50 mcg, formoterol fumarate dihydrate 5 mcg.	120	Dulera	MDI	
		Mometasone furoate 100 mcg, formoterol fumarate dihydrate 5 mcg.	120	Dulera	MDI	If symptoms arise between doses, an inhaled short-acting beta2-agonist should be used for immediate relief.
		Mometasone furoate 200 mcg, formoterol fumarate dihydrate 5 mcg.	120	Dulera	MDI	
		Beclometasone dipropionate 100 mcg, Formoterol fumarate dihydrate 6 mcg	120 & 180	Innuvair	MDI	INNUVAIR Inhaler is not appropriate for the treatment of acute asthma attacks
FEASIBILITY	Is the implementation of this recommendation feasible?		- The LABA/ICS combinations containing Budesonide 160mcg, formoterol 4.5mcg (non-EML) and Budesonide, 320mcg, formoterol 9mcg (EML for COPD and severe asthma) are currently available on the tender. A sustainable supply of this combination inhaler would need to be assured. Additional considerations by the committee members: - The strategy is more straightforward for patients as only one device is needed, i.e. a fixed-dose combination inhaler. - Taking medication is driven by symptoms on an as-needed basis, so compliance with preventer therapies is less of a concern. - Patient preference is for a combination inhaler of ICS/LABA over two separate inhalers of mono-components. - Combination therapy with fixed-dose formoterol/ICS simplifies treatment and promotes adherence.			
	Yes ☒ No ☐ Uncertain ☐					

		- Streamlining therapy for asthmatics across the different spectrums of disease severity allows for programmatic ease and simplified patient care. - Additional programmatic barriers to implementation that would need to be managed include training requirements for inhaler technique (MDI versus DPI) and addressing diagnostic challenges with the differential diagnosis between COPD and asthma, particularly at the PHC level of care.
RESOU RCE USE	How large are the resource requirements? More intensive Less intensive Uncertain ☐ ☒ ☐	Refer to the associated pharmacoeconomic evaluation for detailed information.
VALUES, PREFERENCES, ACCEPTABILITY	Is there important uncertainty or variability about how much people value the options? Minor Major Uncertain ☒ ☐ ☐ Is the option acceptable to key stakeholders? Yes No Uncertain ☒ ☐ ☐	The available evidence of patient preferences when comparing combined ICS/LABA to ICS/SABA is lacking. However, one study demonstrated patient preferences for a combination ICS/LABA inhaler rather than for the separate components of ICS and LABA, simplifying treatment and promoting adherence (Murphy, 2009). In addition, another two studies showed greater health-related quality of life (HRQoL) with combined ICS/LABA using the Asthma Quality of Life Questionnaire (AQLQ[S]) compared to the separate ICS and LABA mono-components (Chervinsky, 2008; Bateman, 2004).
EQUITY	Would there be an impact on health inequity? Yes No Uncertain ☐ ☐ ☒	Improved access to the intervention in the public sector.

PICO 3

Key findings

- *The current standard of care for patients with asthma symptoms almost daily or waking due to asthma at least once a week, according to the South African Primary Healthcare Standard Treatment Guidelines (2020), is a combination inhaler of long-acting beta₂-agonist (LABA) and a corticosteroid as maintenance therapy with a short-acting beta₂-agonist (SABA) as needed.*
- *A rapid review was conducted to evaluate the efficacy and safety of inhaled corticosteroid (ICS) with formoterol (LABA) fixed-dose combination (FDC) taken daily and as needed, compared to ICS/LABA FDC daily maintenance therapy and as needed SABA for symptom relief in adults and adolescents aged 12 years and older with moderate asthma.*
- *The intention was to compare a LABA with a rapid onset of action that would allow for use as asthma reliever therapy. Formoterol is currently the only LABA registered locally for this indication.*
- *Several asthma guidelines were initially considered, most of which refer to the Global Initiative for Asthma (GINA, 2023; GINA, 2024) guideline. However, although the GINA guideline is well-used globally, we could not appraise the underlying evidence synthesis (as it was unavailable), so we proceeded with our independent review.*
- *We searched the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases for trials on 14 and 15 May 2024, respectively. We identified 11 trials for inclusion.*
 - *Six RCTs: (Atienza, 2013; O'Byrne, 2005; Patel, 2013; Rabe, 2006; Stållberg, 2008; Takeyama, 2014) investigated the safety and efficacy of Budesonide/Formoterol maintenance and reliever therapy compared to Budesonide/Formoterol maintenance and a SABA (terbutaline or salbutamol) reliever therapy, in adolescents and adults aged 12 years and older*
 - *(Papi, 2013) investigated the safety and efficacy of Beclometasone/Formoterol maintenance and reliever therapy compared to Beclometasone/Formoterol maintenance and a SABA (salbutamol) reliever therapy in adults aged 18 years and older*
 - *Three trials (Bousquet, 2007; Hozawa, 2014; Vogelmeier, 2005) investigated the safety and efficacy of Budesonide/Formoterol maintenance and reliever therapy compared to Fluticasone/Salmeterol maintenance and a SABA (terbutaline, procaterol or salbutamol) reliever therapy, in adolescents and adults aged 12 years and older*
 - *The (Kuna, 2007) trial had three study arms and investigated the safety and efficacy of Budesonide/Formoterol maintenance and reliever therapy compared to Budesonide/Formoterol maintenance and a SABA (terbutaline) reliever therapy, and Fluticasone/Salmeterol maintenance and a SABA (terbutaline) reliever therapy in adolescents and adults aged 12 years and older*
- *ICS/Formoterol maintenance and reliever versus ICS/LABA maintenance and a SABA reliever (follow-up duration of 52 weeks):*
 - *Results in a reduction in severe asthma exacerbations (a composite outcome defined as a deterioration in asthma resulting in hospitalisation or emergency room (ER) treatment or the need for oral steroids for $\pm$ 3 days)*
 - *Risk Ratio (RR) 0.71 (95% CI 0.65 to 0.77)*
 - *10 studies, n = 17,376*
 - *High certainty evidence*
 - *43 fewer cases per 1,000 (ranging from 52 fewer to 34 fewer)*
 - *NNT 24*
 - *Results in a reduction in systemic corticosteroid use*

- *RR 0.69 (95% CI 0.60 to 0.80)*
- *4 studies, n = 9,436*
- *High certainty evidence*
- *41 fewer cases per 1,000 (ranging from 54 fewer to 27 fewer)*
- *NNT 25*
- *Results in a slight reduction in asthma-related visits to the emergency room (ER) and/or hospital admissions*
 - *RR 0.70 (95% CI 0.62 to 0.80)*
 - *7 studies, n = 14,136*
 - *High certainty evidence*
 - *22 fewer cases per 1,000 (ranging from 28 fewer to 15 fewer)*
 - *NNT 46*
- *Likely results in a reduction in asthma-related visits to the ER*
 - *RR 0.74 (95% CI 0.59 to 0.93)*
 - *1 study, n = 2,091*
 - *Moderate certainty evidence*
 - *38 fewer cases per 1,000 (ranging from 59 fewer to 10 fewer)*
 - *NNT 27*
- *Likely results in a slight reduction in asthma-related hospital admissions*
 - *RR 0.39 (95% CI 0.18 to 0.85)*
 - *2 studies, n = 2,394*
 - *Moderate certainty evidence*
 - *18 fewer cases per 1,000 (ranging from 24 fewer to 4 fewer)*
 - *NNT 56*
- *Results in little to no difference in mortality*
 - *RR 0.77 (95% CI 0.25 to 2.33)*
 - *7 studies, n = 14,136*
 - *High certainty evidence*
 - *0 fewer cases per 1,000 (ranging from 1 fewer to 1 more)*
 - *NNT 0*
- *Likely results in little to no difference in serious adverse events (SAEs)*
 - *RR 0.85 (95% CI 0.72 to 1.00)*
 - *8 studies, n = 15,970*
 - *Moderate certainty evidence*
 - *8 fewer cases per 1,000 (ranging from 15 fewer to 0 fewer)*
 - *NNT 125*
- *Results in little to no difference in adverse events (AEs)*
 - *RR 1.00 (95% CI 0.96 to 1.05)*
 - *5 studies, n = 7,965*
 - *High certainty evidence*
 - *0 fewer cases per 1,000 (ranging from 19 fewer to 24 more)*
 - *NNT 0*

Search results

An electronic search of the databases, with no language or publication date restrictions, retrieved 1,045 records, of which 1,037 were RCTs. Following deduplication and identification of ineligible records by automation tools, 680 records were screened, and 23 were identified for full-text screening. Twelve studies were excluded for having the incorrect comparator and/or intervention and/or study design or because they were ongoing clinical trials (See Figure 15). See Appendix 10 for the characteristics of the included studies table.

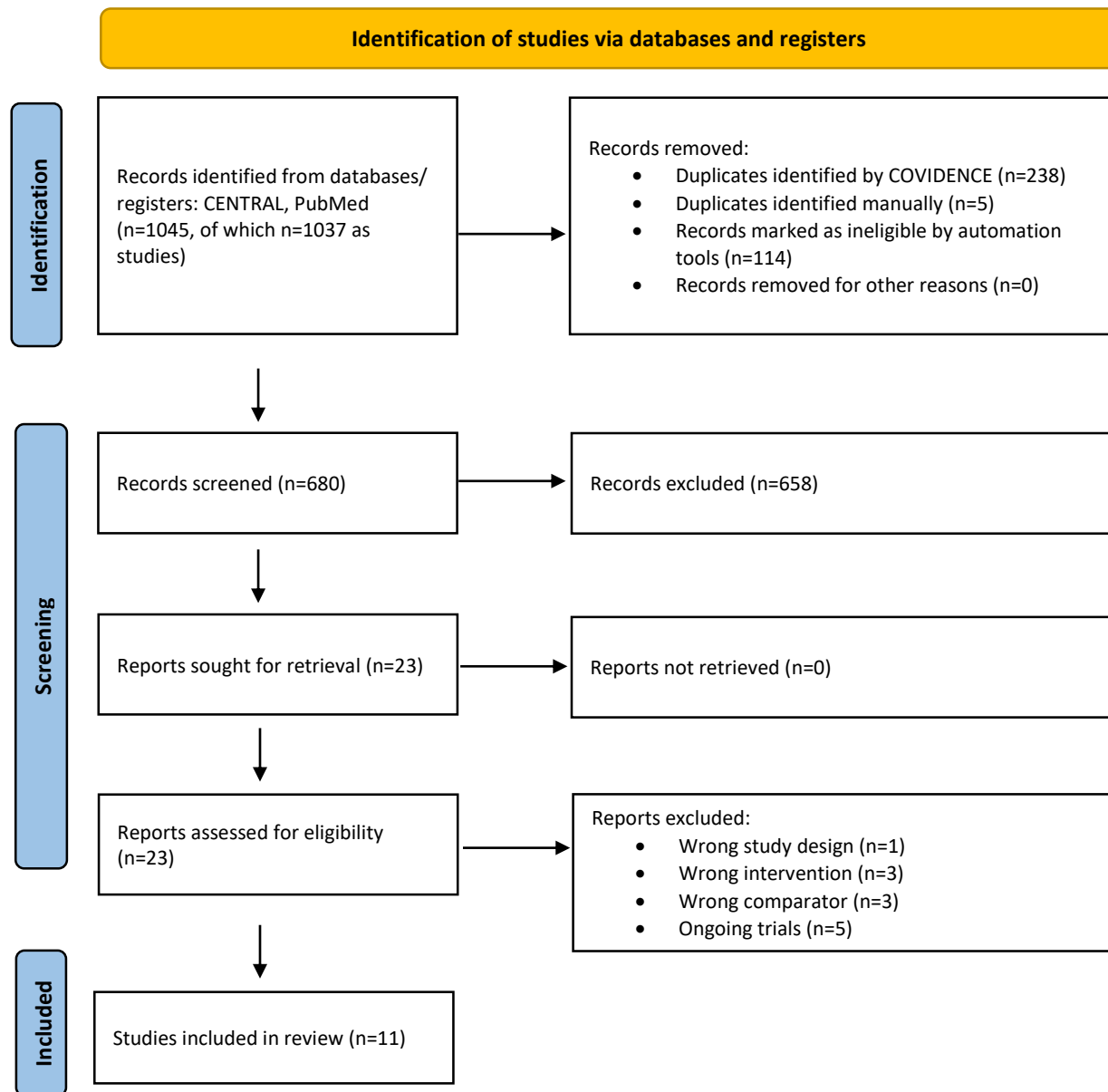


Figure 15: PRISMA flow diagram for review, PICO 3

Excluded and ongoing studies:

Seven RCTs were excluded as they were not eligible and are listed with the reasons for exclusion in Appendix 8: Characteristics of excluded studies. The details of five ongoing RCTs are described in Appendix 9: Characteristics of planned or ongoing studies. One trial, NCT03924635 (AstraZeneca, 2023), was a randomised, open-label, parallel-group, multicentre phase IV exploratory study to “characterise changes in airway inflammation, symptoms, lung function, and reliever use in asthma patients” using a SABA (salbutamol) or anti-inflammatory reliever (SYMBICORT® [budesonide/formoterol 100/6 µg or 200/6 µg, × 2 inhalations twice daily]) as reliever medication in addition to SYMBICORT as daily asthma controller. Preliminary results published on the website (AstraZeneca, 2023) of 42 participants reported that 11.1% (2/18) participants in the SYMBICORT as maintenance and reliever treatment experienced a severe asthma exacerbation vs 29.2% (7/24) in the SYMBICORT as maintenance, salbutamol as the reliever treatment group. One patient (4.2%) in the SYMBICORT as maintenance, salbutamol as the reliever treatment group experienced a serious adverse event, with no SAEs reported in the SYMBICORT as maintenance and reliever treatment group. No other AEs were reported in either group. The findings from this small trial (AstraZeneca, 2023) are similar to those reported below, and adding the results from this trial is unlikely to change the findings substantively.

Evidence synthesis

Description of included studies

There were six RCTs: three were multicentre trials (Atienza, 2013; O’Byrne, 2005; Rabe, 2006) and others were conducted in New Zealand (Patel, 2013), Sweden (Ställberg, 2008) and Japan (Takeyama, 2014); they investigated the safety, and efficacy of Budesonide/Formoterol maintenance and reliever therapy compared to Budesonide/Formoterol maintenance and a SABA (terbutaline or salbutamol) reliever therapy, in adolescents and adults aged 12 years and older. Papi *et al.* (Papi, 2013) investigated the safety and efficacy of Beclometasone/Formoterol maintenance and reliever therapy compared to Beclometasone/Formoterol maintenance and a SABA (salbutamol) reliever therapy in adults aged 18 years and older. The follow-up duration ranged from 24 to 52 weeks. The analytic sample sizes ranged from n = 63–3,394, and ages ranged from 4 to 80 years. O’Byrne *et al.* (O’Byrne, 2005) evaluated children aged 4–11 years and those aged 12 years and older).

Two multicentre trials (Bousquet, 2007; Vogelmeier, 2005) and one conducted in Japan (Hozawa, 2014) investigated the safety and efficacy of Budesonide/Formoterol maintenance and reliever therapy compared to Fluticasone/Salmeterol maintenance and a SABA (terbutaline, procaterol or salbutamol) reliever therapy, in adolescents and adults aged 12 years and older. The analytic sample sizes ranged from n = 30–2,309.

Kuna *et al.* (Kuna, 2007) conducted a multicentre trial in which three study arms investigated the safety and efficacy of Budesonide/Formoterol maintenance and reliever therapy compared to Budesonide/Formoterol maintenance and a SABA (terbutaline) reliever therapy, and Fluticasone/Salmeterol maintenance and a SABA (terbutaline) reliever therapy in adolescents and adults aged 12 years and older. The analytic sample size in this study was 3,335 participants.

Outcomes assessed in the included studies were i) severe asthma exacerbation (Atienza, 2013; Kuna, 2007; O’Byrne, 2005; Papi, 2013; Patel, 2013; Rabe, 2006; Ställberg, 2008; Takeyama 2014; Bousquet, 2007; Vogelmeier, 2005); ii) systemic corticosteroid use (Atienza, 2013; Kuna, 2007; Papi, 2013; Bousquet, 2007); iii) asthma-related visits to the emergency room (ER) and/or hospital admissions (Atienza, 2013; Kuna, 2007; O’Byrne, 2005; Papi, 2013; Patel, 2013; Rabe, 2006; Bousquet, 2007; Vogelmeier, 2005); iv) asthma-related visits to the ER (Atienza, 2013); asthma-related hospital admissions (Atienza, 2013; Patel, 2013); mortality (Atienza, 2013; Kuna, 2007; Papi, 2013; Patel, 2013; Rabe, 2006; Bousquet, 2007; Vogelmeier, 2005); severe adverse events (SAEs) (Atienza, 2013; Kuna, 2007; O’Byrne 2005; Papi, 2013; Patel, 2013; Rabe,

2006; Bousquet, 2007; Vogelmeier, 2005); other adverse events (AEs) (Atienza, 2013; O'Byrne, 2005; Papi, 2013; Bousquet, 2007; Hozawa, 2014); and adverse drug reactions (ADRs) (Papi, 2013; Rabe, 2006). Appendix 10 provides a detailed description of these studies.

Qualitative assessment

Two of the eligible studies reported on health-related quality of life (HrQoL) using the standardised version of the Asthma Quality of Life Questionnaire (AQLQ(S)), consisting of 32 questions (Kuna, 2007; Vogelmeier, 2005), scored on a scale of 1–7, where 7 represented the least impairment. A change in AQLQ(S) overall scores of ≥ 0.5 from baseline was considered clinically relevant. In both studies, the overall AQLQ(S) improved from baseline to a similar extent in the intervention and comparator groups. We did not collect data on patients' preferences or prescribers' perspectives, as these were not reported in the included studies. However, a study by Murphy *et al.* (Murphy, 2009) reported that patients highly valued the rapid onset of action of fixed-dose inhaled controller LABA/ICS combinations due to the rapid onset of action and anti-inflammatory activity. Furthermore, they reported that a 12-member consensus of community healthcare professionals agreed that it was clinically relevant and meaningful to decision-making that patients could feel the immediate effect of their medication, which would contribute to patient adherence. A network meta-analysis (Maneechotesuwan, 2022) comparing fixed-dose salmeterol/fluticasone to other ICS/LABA and MART regimens amongst patients with moderate-to-severe asthma showed that HRQoL is responsive to treatment and strongly associated with asthma control.

Equity assessment

PROGRESS-PLUS variables include research setting, described as the place of residence and socio-economic status, personal characteristics associated with discrimination, features of relationships, and time-dependent relationships. Four multicentre RCTs included research sites from LMIC countries (Atienza, 2013; Papi, 2013; Rabe, 2006; Bousquet, 2007), four RCTs took place in high-income countries (Hozawa, 2014; Patel, 2013; Ställberg, 2008; Takeyama, 2014) and the published reports of three multicentre RCTs did not specify the country study sites (Kuna, 2007; O'Byrne, 2005; Vogelmeier, 2005). Study sites were mainly in Europe and Asia, but two RCTs included South African sites (Rabe, 2006; Bousquet, 2007).

The ages of participants in the included RCTs ranged from 4 to 89 years. No adults older than 60 years were included. All RCTs were conducted amongst adults, but one RCT also included children 4 to 11 years (~13% of study participants) and adolescents (number not reported) (O'Byrne, 2005), and four RCTs included adolescents (Kuna, 2007; Rabe, 2006; Ställberg, 2008; Bousquet, 2007; Vogelmeier, 2005). Trial participants mainly were females (~55 to 60%). No RCT reported on the type of occupation, but one RCT reported that approximately 50% of study participants were unemployed (Bousquet, 2007).

Across RCTs, study participants' socioeconomic and lifestyle status was not provided, but the smoking status of study participants, a risk factor for asthma, was reported in five RCTs. Of these, one RCT only included non-smokers (Hozawa, 2014), whilst three RCTs (Atienza, 2013; Kuna, 2007; Bousquet, 2007) mainly included non-smokers (~80 to 85%), some ex-smokers (~11 to 15%) and few smokers (~3 to 5%). Another RCT conducted in New Zealand included more smokers (~20%) and ex-smokers (~30%) (Patel, 2013). Tobacco use contributes to social inequalities (Davy, 2007), and a study of 14 European countries showed a difference in life expectancy between high and low socioeconomic groups attributed to smoking (Gregoraci, 2017). Smoking risk is associated with cumulative socio-economic and health-related disadvantages (Leventhal, 2019). Additionally, a USA report suggested that smokers with low socioeconomic status experience more smoking-related illnesses compared to affluent smokers (National Center for Chronic Disease Prevention and Health Promotion [NCCDPHP], 2014). More research is required to understand the socio-economic and lifestyle impact on asthmatic patients.

All RCTs, except one (Hozawa, 2014), reported unscheduled emergency room visits and/or hospital admissions due to severe asthma exacerbations and poor asthma control. These would require an absence of leave from work. We did not collect data on other PROGRESS-PLUS variables such as religion, education, social capital, disability, and features of relationships. These were not reported within the included studies. Two of the included studies (Takeyama, 2014; Hozawa, 2014) were judged as having some concerns of bias in the randomisation process - poor randomisation may speak to baseline imbalance across PROGRESS-PLUS factors.

Evidence quality

Risk of Bias Assessment of RCTs

For the outcomes of severe asthma exacerbation, asthma-related ER visits and/or asthma-related hospital admissions, systemic corticosteroid use, mortality, SAEs, AEs, and ADRs, most trials (Atienza, 2013; Kuna, 2007; O'Byrne, 2005; Papi, 2013; Patel, 2013; Ställberg, 2008; Bousquet, 2007) were judged as having a low risk of bias. Two trials (Takeyama, 2014; Hozawa, 2014) were assessed as having 'some concerns' in Domain 1 (Randomisation process) due to insufficient information on randomisation and allocation concealment of the study medication. One trial (Takeyama, 2014) was assessed as having 'some concerns' in Domain 2 (Deviations from the intended interventions) due to insufficient information on blinding. Three trials (Rabe, 2006; Takeyama, 2014; Vogelmeier, 2005) were assessed as having 'some concerns' as study protocols were not available to determine the risk of bias in Domain 5 (Selection of the reported result). Please see Appendix 11.

Effects of the intervention

The GRADE Evidence Profile in Table 8 and Summary of Findings in Table 9 summarise the effects of the intervention for each of the following outcomes. Appendix 12 summarises the SAEs, AEs, and ADRs as reported by the studies.

ICS/Formoterol maintenance and reliever versus ICS/LABA maintenance and a SABA reliever

1. Severe asthma exacerbations

ICS/Formoterol maintenance and reliever therapy compared to an ICS/LABA maintenance and a SABA reliever results in a reduction in severe asthma exacerbations (52 weeks), Risk Ratio (RR) 0.71 (95% CI 0.65 to 0.77), 10 studies, n = 17,376, high certainty evidence. That is an absolute effect of 43 fewer cases per 1,000 (ranging from 52 fewer to 34 fewer). Ten studies (Atienza, 2013; Bousquet, 2007; Kuna, 2007; O'Byrne, 2005; Papi, 2013; Patel, 2013; Rabe, 2006; Ställberg, 2008; Takeyama, 2014; Vogelmeier, 2005) had available event/total group data to evaluate this outcome. Figure 16 shows the forest plot for this comparison.

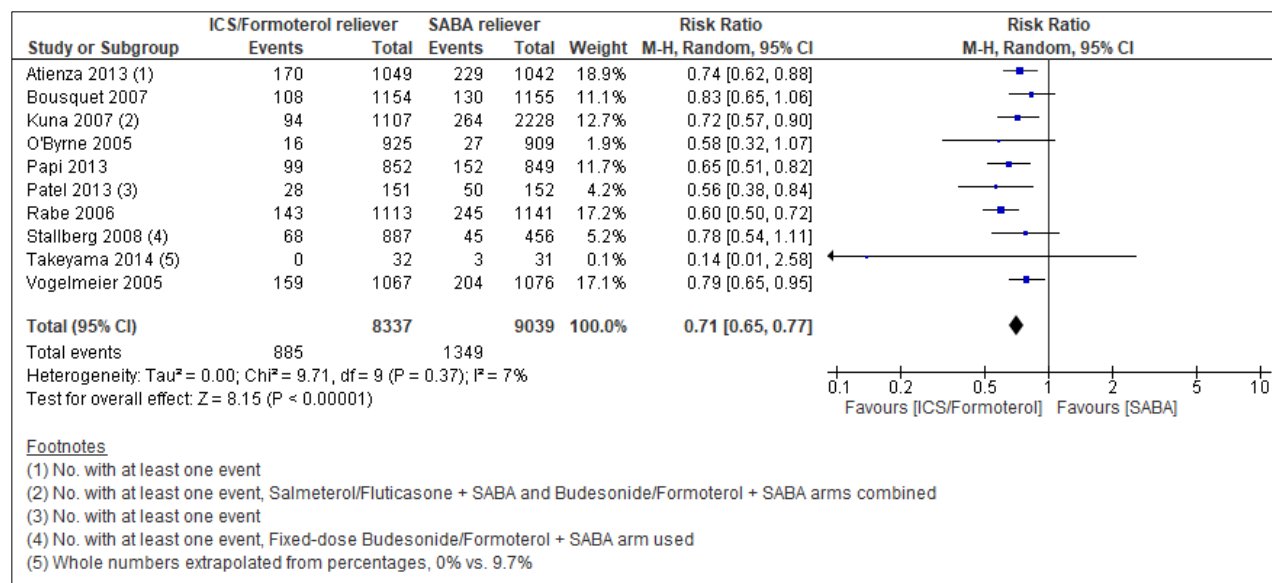


Figure 16: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Severe asthma exacerbation

2. Systemic corticosteroid use

ICS/Formoterol maintenance and reliever therapy compared to an ICS/LABA maintenance and a SABA reliever results in a reduction in systemic corticosteroid use (52 weeks), Risk Ratio (RR) 0.69 (95% CI 0.60 to 0.80), 4 studies, n = 9,436, high certainty evidence. That is an absolute effect of 41 fewer cases per 1,000 (ranging from 54 fewer to 27 fewer). Four studies (Atienza, 2013; Bousquet, 2007; Kuna, 2007; Papi, 2013) had available event/total group data to evaluate this outcome. Figure 17 shows the forest plot for this comparison.

O'Byrne *et al.* (O'Byrne, 2005) reported that participants who used Budesonide/Formoterol as maintenance and reliever therapy also had fewer courses of oral steroids, 0.19 courses per year among patients aged 12 to 80 years compared with participants who received Budesonide/Formoterol plus SABA (0.42 courses per year for patients aged 12–80). Oral corticosteroid dose (mg prednisone) and standard deviation (SD) was 77.5mg (240.5mg) in the Budesonide/Formoterol as maintenance and reliever therapy group and 126.6mg (382.1mg) in the comparator Budesonide/Formoterol plus SABA group (Patel, 2013). Ställberg *et al.* (Ställberg, 2008) reported that the use of oral steroids was similar in the three treatment groups. Vogelmeier *et al.* (Vogelmeier, 2005) reported that there was a 34% reduction in oral steroid days due to severe exacerbations (1,980 in the Budesonide/Formoterol maintenance and reliever group versus 2,978 in the Fluticasone/Salmeterol maintenance and a SABA reliever group).

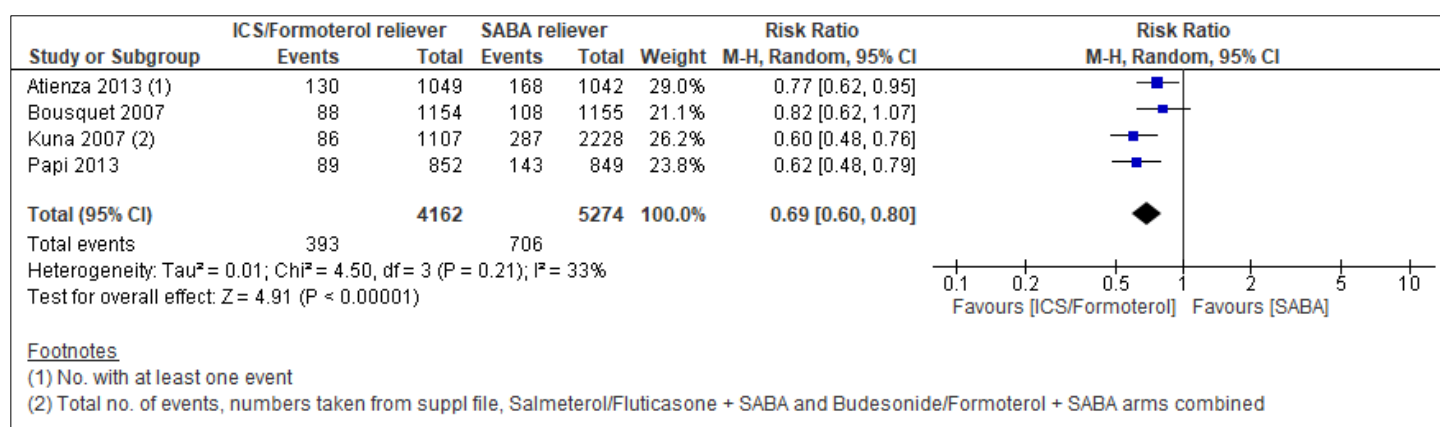


Figure 17: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Systemic corticosteroid use

3. Asthma-related visits to the emergency room (ER) and/or hospital admissions

ICS/Formoterol maintenance and reliever therapy compared to an ICS/LABA maintenance and a SABA reliever results in a slight reduction in asthma-related visits to the emergency room (ER) and/or hospital admissions (52 weeks), Risk Ratio (RR) of 0.70 (95% CI 0.62 to 0.80), 7 studies, $n = 14,136$, high certainty evidence. That is an absolute effect of 22 fewer cases per 1,000 (ranging from 28 fewer to 15 fewer). Seven studies (Atienza, 2013; Bousquet, 2007; Kuna, 2007; Papi, 2013; Patel, 2013; Rabe, 2006; Vogelmeier, 2005) had available event/total group data to evaluate this outcome. Figure 18 shows the forest plot for this comparison.

In a study comparing Budesonide/Formoterol maintenance and reliever therapy to Budesonide/Formoterol maintenance and a SABA reliever (O'Byrne, 2005), severe exacerbations resulting in medical intervention were reported as 1.2% (11/925) vs. 2.3% (21/909) on the respective groups. No further information was provided about what constituted medical intervention in this study (O'Byrne, 2005). Hence, results for this outcome are reported narratively. Ställberg *et al.* (Ställberg, 2008) reported that the percentage of hospitalisations/ER visits was similar in the three treatment groups.

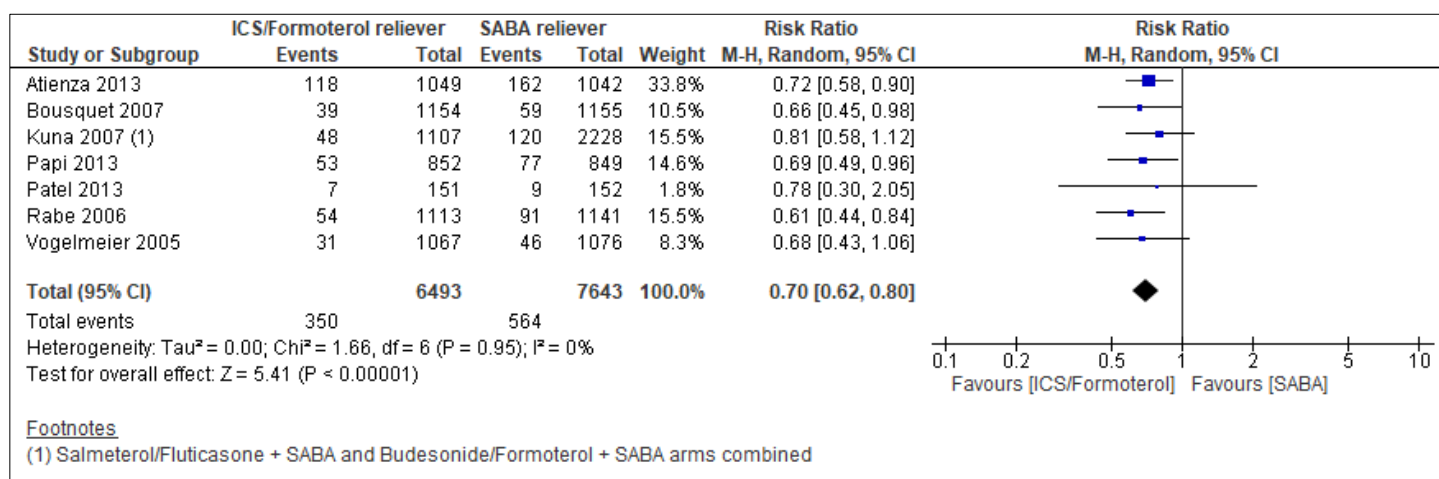


Figure 18: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related visits to the emergency room (ER) and/or hospital admissions

4. Asthma-related visits to the emergency room (ER)

ICS/Formoterol maintenance and reliever therapy compared to an ICS/Formoterol maintenance and a SABA reliever likely results in a reduction in asthma-related visits to the ER (52 weeks), Risk Ratio (RR) 0.74 (95% CI 0.59 to 0.93), 1 study, $n = 2,091$, moderate certainty evidence. That is an absolute effect of 38 fewer cases per 1,000 (ranging from 59 fewer to 10 fewer). Only one study (Atienza, 2013) reported this outcome.

5. Asthma-related hospital admissions

ICS/Formoterol maintenance and reliever therapy compared to an ICS/Formoterol maintenance and a SABA reliever likely results in a slight reduction in asthma-related hospital admissions (52 weeks), Risk Ratio (RR) 0.39 (95% CI 0.18 to 0.85), 2 studies, $n = 2,394$, moderate certainty evidence. That is an absolute effect of 18 fewer cases per 1,000

(ranging from 24 fewer to 4 fewer). Two studies (Atienza, 2013; Patel, 2013) had available event/total group data to evaluate this outcome. Figure 19 shows the forest plot for this comparison.

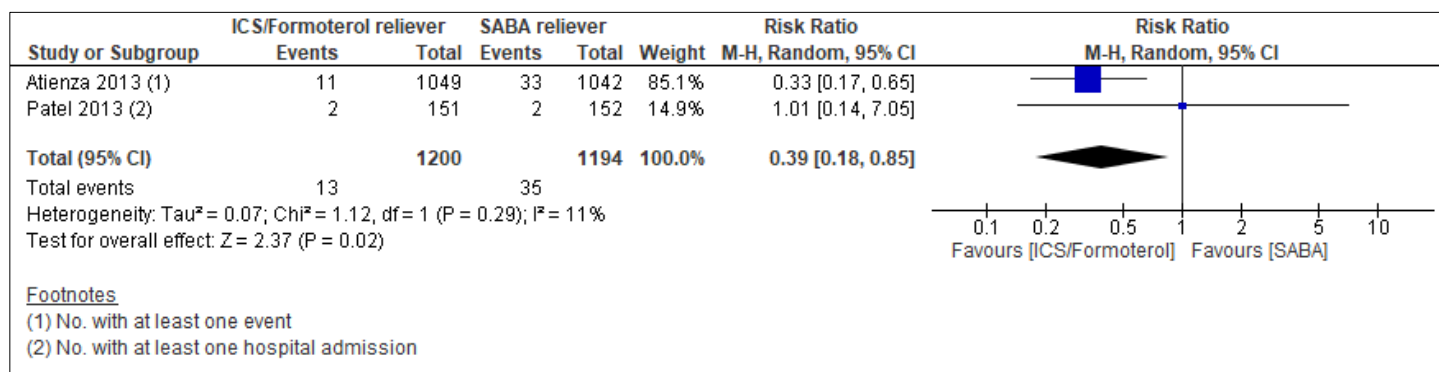


Figure 19: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related hospital admissions

6. Mortality

ICS/Formoterol maintenance and reliever therapy compared to an ICS/LABA maintenance and a SABA reliever results in little to no difference in mortality (52 weeks), Risk Ratio (RR) 0.77 (95% CI 0.25 to 2.33), 7 studies, $n = 14,136$, high certainty evidence. That is an absolute effect of 0 fewer cases per 1,000 (ranging from 1 fewer to 1 more). Seven studies (Atienza, 2013; Bousquet, 2007; Kuna, 2007; Papi, 2013; Patel, 2013; Rabe, 2006; Vogelmeier, 2005) had available event/total group data to evaluate this outcome. Figure 20 shows the forest plot for this comparison.

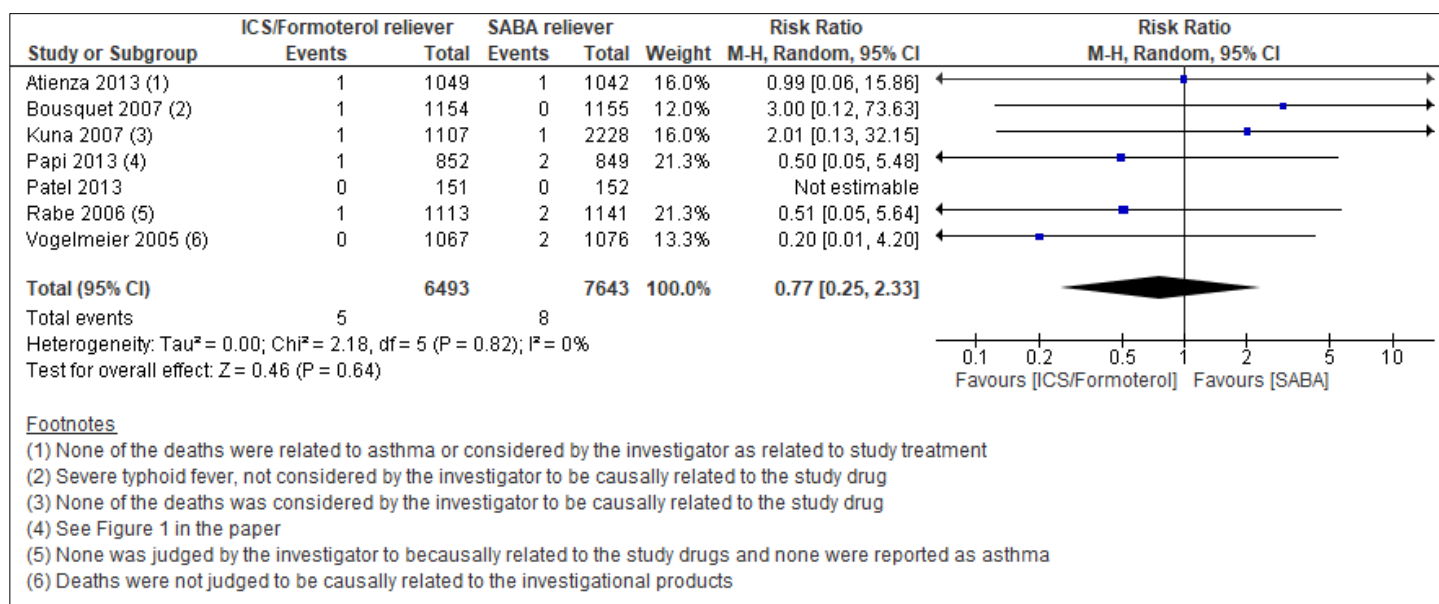


Figure 20: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Mortality

7. Serious adverse events (SAEs)

ICS/Formoterol maintenance and reliever therapy compared to an ICS/LABA maintenance and a SABA reliever likely results in little to no difference in SAEs (52 weeks), Risk Ratio (RR) 0.85 (95% CI 0.72 to 1.00), 8 studies, $n = 15,970$, moderate certainty evidence. That is an absolute effect of 8 fewer cases per 1,000 (ranging from 15 fewer to 0 fewer). Eight studies (Atienza, 2013; Bousquet, 2007; Kuna, 2007; O'Byrne, 2005; Papi, 2013; Patel, 2013; Rabe, 2006; Vogelmeier, 2005) had available event/total group data to evaluate this outcome. Figure 21 shows the forest plot for

this comparison. Ställberg *et al.* (Ställberg, 2008) reported that the number and type of SAEs were low (66 SAEs in total) and similar between the treatment groups; no clinically important differences were observed.

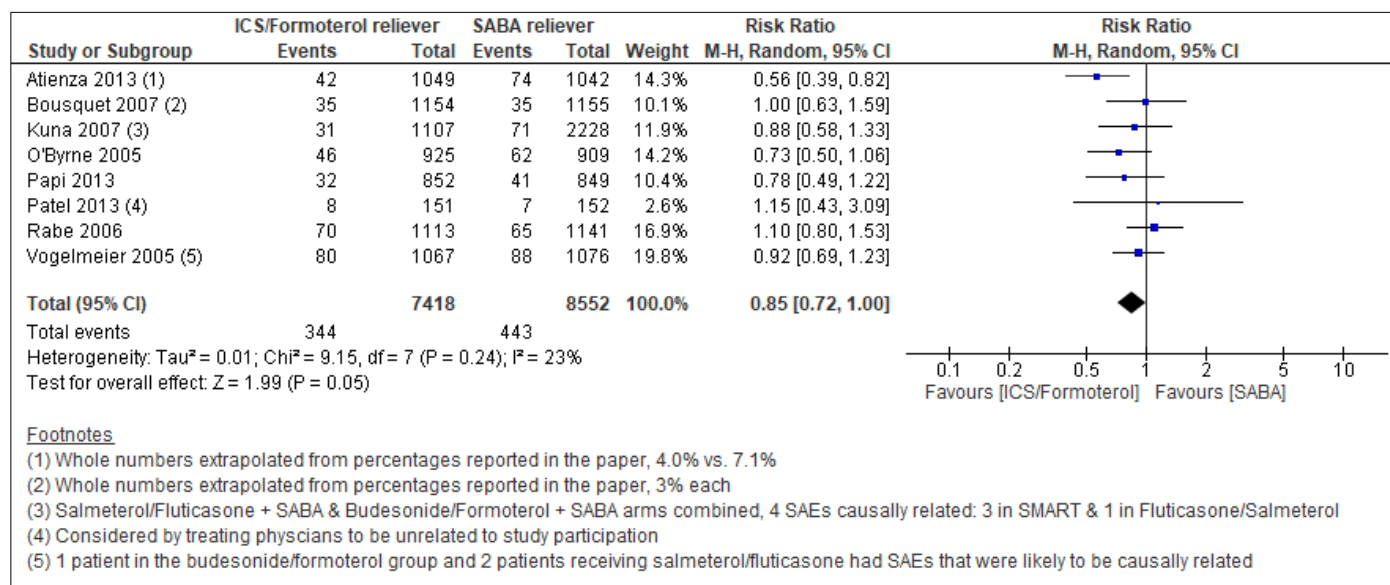


Figure 21: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Serious adverse events

8. Adverse events (AEs)

ICS/Formoterol maintenance and reliever therapy compared to an ICS/LABA maintenance and a SABA reliever results in little to no difference in AEs (52 weeks), Risk Ratio (RR) 1.00 (95% CI 0.96 to 1.05), 5 studies, n = 7,965, high certainty evidence. That is an absolute effect of 0 fewer cases per 1,000 (ranging from 19 fewer to 24 more). Five studies (Atienza, 2013; Bousquet, 2007; Hozawa, 2014; O'Byrne, 2005; Papi, 2013) had available event/total group data to evaluate this outcome. Figure 22 shows the forest plot for this comparison.

Kuna *et al.* (Kuna, 2007) reported that the most frequently reported AEs in their study were upper respiratory tract infection, pharyngitis and nasopharyngitis; there were no notable between-group differences in the number of AEs. The number of AEs was similar between treatment groups, with the most frequently occurring AEs being upper respiratory tract infection (66 [44%] participants in the Budesonide/Formoterol maintenance and reliever therapy group and 65 [43%] in the Budesonide/Formoterol maintenance and a SABA reliever group), injury, trauma, or musculoskeletal ailment (27 [18%] and 17 [11%], respectively), and adverse taste (19 [13%] and 19 [13%], respectively) (Patel, 2013).

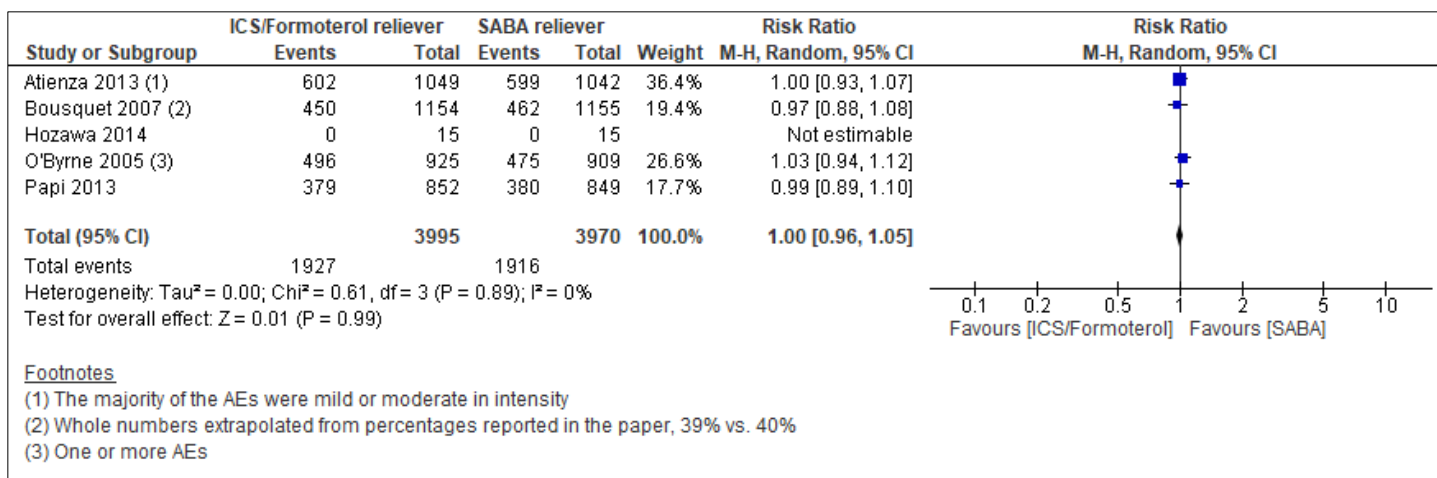


Figure 22: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Adverse events

Pharmacologically predictable AEs: Three studies reported this outcome (O'Byrne, 2005; Papi, 2013; Rabe, 2006). Pharmacologically predictable AEs when ICS/Formoterol maintenance and reliever therapy is used compared to an ICS/Formoterol maintenance and a SABA reliever: RR 1.53; 95% CI 0.94 to 2.51; I² = 66%; 5,789 participants; as shown in Figure 23. Kuna *et al.* (Kuna, 2007) reported that the incidence of pharmacologically predictable adverse events related to ICS and LABA use was low and comparable in all treatment groups.

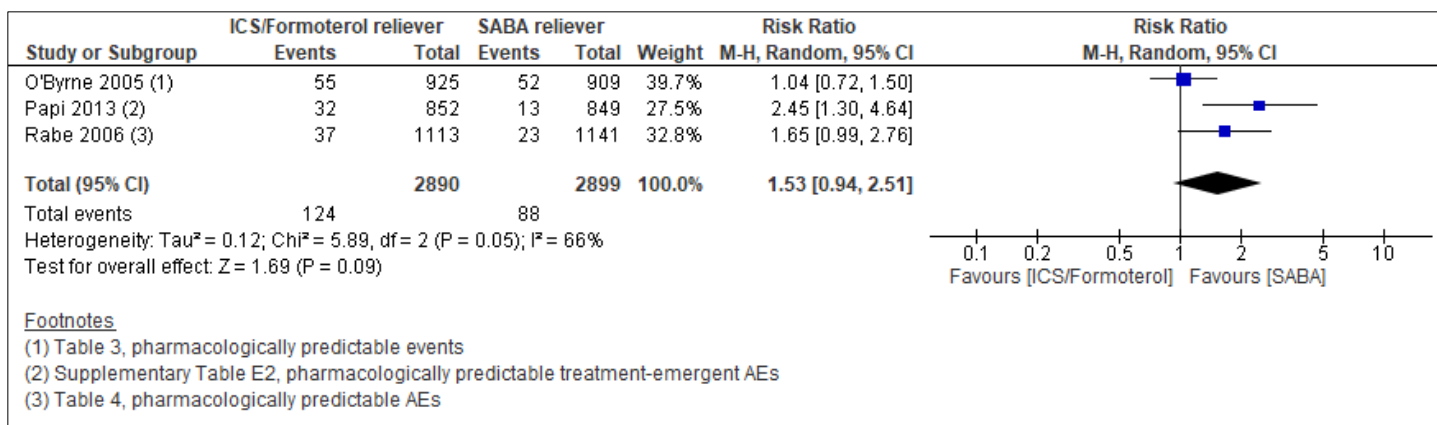


Figure 23: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Pharmacologically predictable AEs

9. Adverse drug reactions (ADRs)

Papi *et al.* (Papi, 2013) reported that adverse drug reactions were significantly (p=0.01) higher in the beclometasone–formoterol group for maintenance and reliever treatment (4.5%, 38/852) compared to beclometasone–formoterol maintenance and as-needed salbutamol reliever group (2.2%, 19/849). They did not provide further details on the ADRs reported.

Subgroup and sensitivity analyses for PICO 3

Post-hoc subgroup analyses by daily ICS dose (low and medium-high subgroups), see Table 1, were conducted. In the study by Kuna *et al.* (Kuna, 2007), study arms comparing low daily ICS doses were included, i.e. (Budesonide/formoterol 160/4.5mcg bd + budesonide/formoterol as needed vs Salmeterol/fluticasone 25/125mcg bd + terbutaline as needed), and the study arm with data from the medium daily ICS dose (Budesonide/formoterol

320/9mcg bd + terbutaline as needed) were excluded. We did not include data from one study (Bousquet, 2007) in the subgroup analyses as daily ICS doses in each study arm were not comparable, i.e. medium (Budesonide/formoterol 160/4.5mcg, 2 inhalations bd + budesonide/formoterol as needed) vs. high (Salmeterol/fluticasone 50/500mcg bd + terbutaline as needed).

Similarly, for sensitivity analyses, we removed the following two studies (Bousquet, 2007; Kuna, 2007) where the background maintenance ICS dose differed between groups, as noted above. We further excluded the study by Vogelmeier *et al.* (Vogelmeier, 2005) in the sensitivity analysis as participants in both study arms received varying doses of daily maintenance ICS therapy (either medium or high doses) depending on their individual symptom control.

The subgroup and sensitivity analyses showed that the overall relative effect sizes and their 95% CIs do not substantially change despite changes in the ICS doses. Hence, we report the original forest plots, associated effect sizes, and 95% CIs. The findings from the subgroup and sensitivity analyses can be found in Appendix 13.

Table 8: GRADE evidence profile

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Formoterol maintenance therapy and as-needed reliever therapy	ICS/LABA maintenance therapy and as-needed SABA reliever therapy	Relative (95% CI)	Absolute (95% CI)	
Severe Asthma Exacerbation											
10	randomised trials	not serious	not serious	not serious ^a	not serious	none	885/8337 (10.6%)	1349/9039 (14.9%)	RR 0.71 (0.65 to 0.77)	43 fewer per 1,000 (from 52 fewer to 34 fewer)	⊕⊕⊕⊕ High
Systemic Corticosteroid Use											
4	randomised trials	not serious	not serious	not serious ^b	not serious	none	393/4162 (9.4%)	706/5274 (13.4%)	RR 0.69 (0.60 to 0.80)	41 fewer per 1,000 (from 54 fewer to 27 fewer)	⊕⊕⊕⊕ High
Asthma-related visits to the ER and/or hospital admissions											
7	randomised trials	not serious	not serious	not serious ^b	not serious	none	350/6493 (5.4%)	564/7643 (7.4%)	RR 0.70 (0.62 to 0.80)	22 fewer per 1,000 (from 28 fewer to 15 fewer)	⊕⊕⊕⊕ High
Asthma-related visits to the ER											
1	randomised trials	not serious	not serious	not serious ^b	serious ^c	none	112/1049 (10.7%)	151/1042 (14.5%)	RR 0.74 (0.59 to 0.93)	38 fewer per 1,000 (from 59 fewer to 10 fewer)	⊕⊕⊕○ Moderate
Asthma-related hospital admissions											
2	randomised trials	not serious	not serious	not serious ^b	serious ^c	none	13/1200 (1.1%)	35/1194 (2.9%)	RR 0.39 (0.18 to 0.85)	18 fewer per 1,000 (from 24 fewer to 4 fewer)	⊕⊕⊕○ Moderate
Mortality											

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Formoterol maintenance therapy and as-needed reliever therapy	ICS/LABA maintenance therapy and as-needed SABA reliever therapy	Relative (95% CI)	Absolute (95% CI)	
7	randomised trials	not serious	not serious	not serious ^b	not serious ^d	none	5/6493 (0.1%)	8/7643 (0.1%)	RR 0.77 (0.25 to 2.33)	0 fewer per 1,000 (from 1 fewer to 1 more)	⊕⊕⊕⊕ High
Serious Adverse Events											
8	randomised trials	not serious	not serious	not serious ^b	serious ^e	none	344/7418 (4.6%)	443/8552 (5.2%)	RR 0.85 (0.72 to 1.00)	8 fewer per 1,000 (from 15 fewer to 0 fewer)	⊕⊕⊕○ Moderate
Adverse Events											
5	randomised trials	not serious	not serious	not serious ^b	not serious ^f	none	1927/3995 (48.2%)	1916/3970 (48.3%)	RR 1.00 (0.96 to 1.05)	0 fewer per 1,000 (from 19 fewer to 24 more)	⊕⊕⊕⊕ High

CI: confidence interval; RR: risk ratio

Explanations

- a. O'Byrne trial included children aged 4-11 years; approximately 12% of trial participants. The effects across studies are consistent despite differing doses or specific medicines; we have not downgraded for indirectness
- b. The effects across studies are consistent despite differing doses or specific medicines; we have not downgraded for indirectness
- c. Downgraded by one level for imprecision: wide absolute 95% confidence interval ranging from an important to a trivial reduction
- d. Not downgraded for imprecision: Despite the low event rate, this is a rare event with a narrow absolute 95% CI, and we are confident that there is no effect between the intervention and the comparator
- e. Downgraded by one level for imprecision: wide absolute 95% confidence interval ranging from a trivial reduction to no reduction
- f. Not downgraded for imprecision: the absolute 95% CI ranges from a trivial reduction to a trivial increase

Table 9: Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with ICS/LABA maintenance therapy and as-needed SABA reliever therapy	Risk with ICS/Formoterol maintenance therapy and as-needed reliever therapy			
Severe Asthma Exacerbation	149 per 1,000	106 per 1,000 (97 to 115)	RR 0.71 (0.65 to 0.77)	17376 (10 RCTs)	⊕⊕⊕⊕ High ^a
Systemic Corticosteroid Use	134 per 1,000	92 per 1,000 (80 to 107)	RR 0.69 (0.60 to 0.80)	9436 (4 RCTs)	⊕⊕⊕⊕ High ^b
Asthma-related visits to the ER and/or hospital admissions	74 per 1,000	52 per 1,000 (46 to 59)	RR 0.70 (0.62 to 0.80)	14136 (7 RCTs)	⊕⊕⊕⊕ High ^b
Asthma-related visits to the ER	145 per 1,000	107 per 1,000 (85 to 135)	RR 0.74 (0.59 to 0.93)	2091 (1 RCT)	⊕⊕⊕○ Moderate ^{b,c}
Asthma-related hospital admissions	29 per 1,000	11 per 1,000 (5 to 25)	RR 0.39 (0.18 to 0.85)	2394 (2 RCTs)	⊕⊕⊕○ Moderate ^{b,c}
Mortality	1 per 1,000	1 per 1,000 (0 to 2)	RR 0.77 (0.25 to 2.33)	14136 (7 RCTs)	⊕⊕⊕⊕ High ^{b,d}
Serious Adverse Events	52 per 1,000	44 per 1,000 (37 to 52)	RR 0.85 (0.72 to 1.00)	15970 (8 RCTs)	⊕⊕⊕○ Moderate ^{b,e}
Adverse Events	483 per 1,000	483 per 1,000 (463 to 507)	RR 1.00 (0.96 to 1.05)	7965 (5 RCTs)	⊕⊕⊕⊕ High ^{b,f}
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio					
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the effect estimate. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to differ substantially from the estimate of effect.					

Evidence to decision framework: PICO 3

QUESTION	
Should formoterol/ICS as maintenance and as-needed reliever therapy versus LABA plus ICS fixed-dose combination (FDC) maintenance therapy and as-needed SABA reliever be used in adults and adolescents aged 12 years and older with moderate to severe persistent asthma	
POPULATION	Patients with asthma using daily inhaled LABA plus ICS fixed-dose combination (FDC), aged 12 years and older
INTERVENTION	Daily maintenance ICS/LABA combination + Formoterol/ICS combination as needed for symptom relief
COMPARISON	Daily maintenance ICS/LABA combination + SABA as needed for symptom relief
OUTCOMES	Acute severe exacerbations, asthma visits to the emergency room, asthma admissions, courses of systemic steroids, mortality, serious adverse events, adverse events and adverse reactions
SETTING	Public sector, South Africa
PERSPECTIVE	Public health/population

Recommendation PICO 3:

The ASC recommends that the ICS/formoterol combination be used as a maintenance and reliever therapy in adults and adolescents aged 12 years and older with moderate to severe persistent asthma (*strong recommendation, moderate certainty evidence*).

JUDGEMENT		RESEARCH EVIDENCE & ADDITIONAL CONSIDERATIONS					
QUALITY OF EVIDENCE OF BENEFIT	What is the certainty/quality of evidence? High ☐ Moderate ☒ Low ☐ Very low ☐ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect						
EVIDENCE OF BENEFIT	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	Moderate benefit.					

QUALITY OF EVIDENCE OF HARM	What is the certainty/quality of evidence? High ☐ Moderate ☒ Low ☐ Very low ☐ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect	<table border="1"> <tr> <th rowspan="2">Outcomes</th> <th rowspan="2">№ of participants</th> <th rowspan="2">Certainty of the evidence (GRADE)</th> <th rowspan="2">Relative effect (95% CI)</th> <th colspan="2">Anticipated absolute effects</th> </tr> <tr> <th>Risk with ICS/LABA maintenance therapy and as needed SABA reliever therapy</th> <th>Risk difference with ICS/Formoterol maintenance therapy and as needed reliever therapy</th> </tr> <tr> <td>Mortality</td> <td>14136 (7 RCTs)</td> <td>⊕⊕⊕⊕ High^{b,d}</td> <td>RR 0.77 (0.25 to 2.33)</td> <td>1 per 1,000</td> <td>0 fewer per 1,000 (1 fewer to 1 more): NNT 0</td> </tr> <tr> <td>Serious Adverse Events</td> <td>15970 (8 RCTs)</td> <td>⊕⊕⊕○ Moderate^{b,e}</td> <td>RR 0.85 (0.72 to 1.00)</td> <td>52 per 1,000</td> <td>8 fewer per 1,000 (15 fewer to 0 fewer): NNT 125</td> </tr> <tr> <td>Adverse Events</td> <td>7965 (5 RCTs)</td> <td>⊕⊕⊕⊕ High^{b,f}</td> <td>RR 1.00 (0.96 to 1.05)</td> <td>483 per 1,000</td> <td>0 fewer per 1,000 (19 fewer to 24 more): NNT 0</td> </tr> </table>					Outcomes	№ of participants	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Risk with ICS/LABA maintenance therapy and as needed SABA reliever therapy	Risk difference with ICS/Formoterol maintenance therapy and as needed reliever therapy	Mortality	14136 (7 RCTs)	⊕⊕⊕⊕ High ^{b,d}	RR 0.77 (0.25 to 2.33)	1 per 1,000	0 fewer per 1,000 (1 fewer to 1 more): NNT 0	Serious Adverse Events	15970 (8 RCTs)	⊕⊕⊕○ Moderate ^{b,e}	RR 0.85 (0.72 to 1.00)	52 per 1,000	8 fewer per 1,000 (15 fewer to 0 fewer): NNT 125	Adverse Events	7965 (5 RCTs)	⊕⊕⊕⊕ High ^{b,f}	RR 1.00 (0.96 to 1.05)	483 per 1,000	0 fewer per 1,000 (19 fewer to 24 more): NNT 0
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EVIDENCE OF HARMS	What is the size of the effect for harmful outcomes? Large ☐ Moderate ☐ Small ☐ None ☒	There is probably little to no difference in the undesirable effects.																														
BENEFITS & HARMS	Do the desirable effects outweigh the undesirable harms? Favours intervention ☒ Favours control ☐ Intervention = Control or Uncertain ☐	The decision is based on the above criteria: - Moderate benefits - No difference in harms - Moderate certainty of the evidence - Values and preferences: Minor																														
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☒ No ☐	There are currently no therapeutic alternatives on the EML as salmeterol has a slower onset of action and is, therefore, not a therapeutic equivalent for formoterol. The following ICS/formoterol combination inhalers are SAHPRA-approved. Only Symbicord® DPI is approved for use as MART. <table border="1"> <tr> <td>ICS/Formoterol combination product</td> <td>Pack size</td> <td>Trade name</td> <td>Device</td> <td>SAHPRA approved PI recommendations for the</td> </tr> </table>					ICS/Formoterol combination product	Pack size	Trade name	Device	SAHPRA approved PI recommendations for the																					
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		• Patient preference is for a combination inhaler of ICS/LABA over two separate inhalers of mono-components. • Combination therapy with fixed-dose formoterol/ICS simplifies treatment and promotes adherence. • Streamlining therapy for asthmatics across the different spectrums of disease severity allows for programmatic ease and simplified patient care. • Additional programmatic barriers to implementation that would need to be managed include training requirements for inhaler technique (MDI versus DPI) and addressing diagnostic challenges with the differential diagnosis between COPD and asthma, particularly at the PHC level of care.
RESOURCE USE	How large are the resource requirements? More intensive Less intensive Uncertain ☐ ☒ ☐	Refer to the associated pharmacoeconomic evaluation for detailed information.
VALUES, PREFERENCES, ACCEPTABILITY	Is there important uncertainty or variability about how much people value the options? Minor Major Uncertain ☒ ☐ ☐ Is the option acceptable to key stakeholders? Yes No Uncertain ☒ ☐ ☐	The available evidence of patient preferences when comparing combined ICS/LABA to ICS/SABA is lacking. However, one study demonstrated patient preferences for a combination ICS/LABA inhaler rather than for the separate components of ICS and LABA, simplifying treatment and promoting adherence (Murphy, 2009). In addition, another two studies showed greater health-related quality of life (HRQoL) with combined ICS/LABA using the Asthma Quality of Life Questionnaire (AQLQ[S]) compared to the separate ICS and LABA mono-components (Chervinsky, 2008; Bateman, 2004).
EQUITY	Would there be an impact on health inequity? Yes No Uncertain ☐ ☐ ☒	Improved access to the intervention in the public sector.

CONCLUSIONS

PICO 1

There is a lack of direct RCT evidence for as-needed ICS/formoterol compared to ICS with SABA in asthmatic patients aged ≥ 12 years, with symptoms occurring less than twice per month. The current Adult Hospital Level STGs and EML (NDoH, 2019) are aligned with GINA guidelines (GINA, 2024) Track 2, step 1, of as-needed SABA administered with ICS (as a combination or separate inhalers) based on the limited evidence and safety concerns of mortality and severe asthma exacerbations associated with SABA monotherapy. Track 1, step 1, is the preferred approach of low-dose ICS/formoterol as the reliever, as it reduces the risk of severe exacerbations compared with SABA alone as the reliever (with/without a maintenance controller). However, in the absence of direct evidence to evaluate this PICO, the evidence is likely to be of very low certainty.

PICO 2

The available evidence included in this review demonstrates that an ICS/formoterol combination taken as needed:

- Probably results in little to no difference in acute severe exacerbations requiring systemic steroids, serious adverse events (SAEs), adverse events (AEs) and mortality; moderate certainty evidence
- Results in a slight reduction in asthma-related visits to the emergency room; high certainty evidence
- Results in little to no difference in asthma-related hospital admissions; high certainty evidence

PICO 3

The available evidence included in this review demonstrates that an ICS/formoterol combination taken as maintenance and reliever therapy:

- Results in a reduction in severe asthma exacerbations and systemic corticosteroid use, high certainty evidence
- Results in a slight reduction in asthma-related visits to the emergency room (ER) and/or hospital admissions; high certainty evidence
- Likely results in a reduction in asthma-related visits to the ER; moderate certainty evidence
- Likely results in a slight reduction in asthma-related hospital admissions; moderate certainty evidence
- Likely results in little to no difference in SAEs, moderate certainty evidence
- Results in little to no difference in AEs and mortality; high certainty evidence

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APPENDICES

Appendix 1: Search Strategy

PICOs 1 and 3

Title: Formoterol plus inhaled corticosteroid (ICS) fixed-dose combination for symptom relief in chronic asthma management

Database: PubMed

Date: 14 May 2024

Search	Query	Results
#11	Search: #9 AND #10	501
#10	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	5,287,551
#9	Search: #4 AND #8	562
#8	Search: #5 OR #6 OR #7	20,233
#7	Search: terbutaline[mh] OR terbutalin*[tiab]	4,304
#6	Search: albuterol[mh] OR albuterol[tiab] OR salbutamol[tiab] OR ventolin[tiab] OR sultanol[tiab] OR proventil[tiab]	14,486
#5	Search: short-acting beta*[tiab] OR short-acting agonist*[tiab] OR SABA[tiab] OR SABAs[tiab]	2,684
#4	Search: #1 AND #2 AND #3	1,281
#3	Search: Adrenal cortex hormones[mh] OR adrenal cortex hormone*[tiab] OR fluticasone*[tiab] OR beclomethasone*[tiab] OR ciclesonide*[tiab] OR flunisolide*[tiab] OR mometasone*[tiab] OR budesonide[tiab] OR (inhal*[tiab] AND (corticosteroid*[tiab] OR corticoid*[tiab] OR steroid*[tiab] OR glucocorticoid*[tiab]))	327,117
#2	Search: Formoterol Fumarate [Mesh] OR BD 40A[tiab] OR Formoterol [tiab] OR Eformoterol [tiab] OR Oxis [tiab] OR Arformoterol [tiab] OR Foradil [tiab]	3,135
#1	Search: Asthma [Mesh] OR asthma* [tiab] OR Bronchial spasm [Mesh] OR Bronchial Spasm* [tiab] OR bronchospasm* [tiab] OR Bronchoconstriction [Mesh] OR Bronchoconstriction*[tiab] OR broncho constriction*[tiab] OR Bronchial constriction*[tiab] OR Respiratory sound [Mesh] OR Wheez* [tiab] OR rhonchi [tiab] OR lung sound*[tiab] OR breathing sound* [tiab] OR Respiratory Hypersensitivity [Mesh] OR Airway Hyper Responsiveness [tiab] OR Bronchial Hyperreactivity [Mesh] OR Bronchial Hyperreactiv*[tiab] OR Bronchial Hyper reactiv*[tiab]	258,148

Date: 15 May 2024

ID	Search	Hits
#1	[mh Asthma] or asthma*:ti,ab,kw or [mh "Bronchial spasm"] or ("Bronchial" NEXT Spasm*):ti,ab,kw or bronchospasm*:ti,ab,kw or [mh Bronchoconstriction] or Bronchoconstriction*:ti,ab,kw or ("broncho" NEXT constriction*):ti,ab,kw or ("Bronchial" NEXT constriction*):ti,ab,kw or [mh "Respiratory sound"] or Wheez*:ti,ab,kw or rhonchi:ti,ab,kw or ("lung" NEXT sound*):ti,ab,kw or ("breathing" NEXT sound*):ti,ab,kw or [mh "Respiratory Hypersensitivity"] or "Airway Hyper Responsiveness":ti,ab,kw or [mh "Bronchial Hyperreactivity"] or ("Bronchial" NEXT Hyperreactiv*):ti,ab,kw or ("Bronchial Hyper" NEXT reactiv*):ti,ab,kw (Word variations have been searched)	45275
#2	[mh "Formoterol Fumarate"] or "BD 40A":ti,ab,kw or Formoterol:ti,ab,kw or Eformoterol:ti,ab,kw or Oxis:ti,ab,kw or Arformoterol:ti,ab,kw or Foradil:ti,ab,kw (Word variations have been searched)	4190
#3	[mh "Adrenal cortex hormones"] or ("adrenal cortex" NEXT hormone*):ti,ab,kw or fluticasone*:ti,ab,kw or beclomethasone*:ti,ab,kw or ciclesonide*:ti,ab,kw or flunisolide*:ti,ab,kw or mometasone*:ti,ab,kw or budesonide:ti,ab,kw or (inhal*:ti,ab,kw AND (corticosteroid*:ti,ab,kw or corticoid*:ti,ab,kw or steroid*:ti,ab,kw or glucocorticoid*:ti,ab,kw)) (Word variations have been searched)	35507
#4	#1 and #2 and #3	1634
#5	("short-acting" NEXT beta*):ti,ab,kw or ("short-acting" NEXT agonist*):ti,ab,kw or SABA:ti,ab,kw or SABAs:ti,ab,kw (Word variations have been searched)	958
#6	[mh albuterol] or albuterol:ti,ab,kw or salbutamol:ti,ab,kw or ventolin:ti,ab,kw or sultanol:ti,ab,kw or proventil:ti,ab,kw (Word variations have been searched)	7859
#7	[mh terbutaline] or terbutalin*:ti,ab,kw (Word variations have been searched)	1554
#8	#5 or #6 or #7	9769
#9	#4 and #8 in Trials	544

PICO 2

Title: Formoterol plus inhaled corticosteroid (ICS) fixed-dose combination for symptom relief in chronic asthma management

Database: PubMed

Date: 20 October 2023

Search	Query	Results
#11	Search: #1 AND #8 Filters: Meta-Analysis, Systematic Review	254
#10	Search: #1 AND #8 Filters: Systematic Review	196
#9	Search: #1 AND #8	5,908
#8	Search: #2 OR #3 OR #4 OR #5 OR #6 OR #7	11,047
#7	Search: Vilanterol [supplementary concept] OR Vilanterol[tiab] OR Breo ellipta [tiab]	532
#6	Search: Indacaterol [supplementary concept] OR indacaterol[tiab] OR arcapta neohaler [tiab] OR Onbrez [tiab] OR QAB 149 [tiab]	578
#5	Search: Salmeterol xinafoate [Mesh] OR Salmeterol [tiab] OR Serevent [tiab]	3,202

Search	Query	Results
#4	Search: Formoterol Fumarate [Mesh] OR BD 40A[tiab] OR Formoterol [tiab] OR Eformoterol [tiab] OR Oxis [tiab] OR Arformoterol [tiab] OR Foradil [tiab]	3,049
#3	Search: Procaterol [Mesh] OR OPC2009 [tiab] OR OPC-2009[tiab] OR Pro Air[tiab] OR ProAir [tiab] OR Procaterol [tiab] OR CI 888 [tiab]	526
#2	Search: Long-acting beta-2 agonist* [tiab] OR LABA [tiab] OR long-acting beta agonist*[tiab] OR long-acting β 2-agonist*[tiab] OR long-acting beta2 agonist*[tiab] OR adrenergic beta-2 receptor agonists [Mesh]	6,908
#1	Search: Asthma [Mesh] OR asthma* [tiab] OR Bronchial spasm [Mesh] OR Bronchial Spasm* [tiab] OR bronchospasm* [tiab] OR Bronchoconstriction [Mesh] OR Bronchoconstriction*[tiab] OR broncho constriction*[tiab] OR Bronchial constriction*[tiab] OR Respiratory sound [Mesh] OR Wheez* [tiab] OR rhonchi [tiab] OR lung sound*[tiab] OR breathing sound* [tiab] OR Respiratory Hypersensitivity [Mesh] OR Airway Hyper Responsiveness [tiab] OR Bronchial Hyperreactivity [Mesh] OR Bronchial Hyperreactiv*[tiab] OR Bronchial Hyper reactiv*[tiab]	253,367

Database: EPISTEMONIKOS

Date: 23 October 2023

Search	Query	Results
#7	#1 AND #5 (Limited to Systematic Reviews)	206
#6	#1 AND #5	801
#5	(title:("Long-acting beta-2" OR "Long acting beta" OR "Long acting beta-2" OR LABA) OR abstract:("Long-acting beta-2" OR "Long acting beta" OR "Long acting beta-2" OR LABA)) OR (title:("long-acting beta-agonist" OR "long-acting beta-agonists") OR abstract:("long-acting beta-agonist" OR "long-acting beta-agonists")) OR (title:("long-acting β 2-agonist" OR "long-acting β 2-agonists" OR "long acting β 2 agonist" OR "long acting β 2 agonists") OR abstract:("long-acting β 2-agonist" OR "long-acting β 2-agonists" OR "long acting β 2 agonist" OR "long acting β 2 agonists")) OR (title:("adrenergic beta-2 receptor" OR "adrenergic beta 2 receptor") OR abstract:("adrenergic beta-2 receptor" OR "adrenergic beta 2 receptor")) – 1220	1,220
#4	#2 AND #3 (Limited to Systematic Reviews)	134
#3	#2 AND #3	1,235

Search	Query	Results
#2	(title:(Procaterol OR OPC2009 OR OPC-2009 OR "OPC 2009" OR "Pro Air" OR ProAir OR Procaterol OR "CI 888") OR abstract:(Procaterol OR OPC2009 OR OPC-2009 OR "OPC 2009" OR "Pro Air" OR ProAir OR Procaterol OR "CI 888")) OR (title:(Formoterol OR "BD 40A" OR Eformoterol OR Oxis OR Arformoterol OR Foradil) OR abstract:(Formoterol OR "BD 40A" OR Eformoterol OR Oxis OR Arformoterol OR Foradil)) OR (title:(Salmeterol OR Serevent) OR abstract:(Salmeterol OR Serevent)) OR (title:(Indacaterol OR arcapta neohaler OR Onbrez OR "QAB 149") OR abstract:(Indacaterol OR arcapta neohaler OR Onbrez OR "QAB 149")) OR (title:(Vilanterol OR Breo ellipta) OR abstract:(Vilanterol OR Breo ellipta))	3,034
#1	(title:(asthma* OR bronchial spasm* OR bronchospasm* OR bronchoconstriction* OR broncho constriction* OR respiratory sound* OR wheez*) OR abstract:(asthma* OR bronchial spasm* OR bronchospasm* OR bronchoconstriction* OR broncho constriction* OR respiratory sound* OR wheez*)) OR (title:(rhonchi OR lung sound* OR breathing sound* OR respiratory hypersensitivity) OR abstract:(rhonchi OR lung sound* OR breathing sound* OR respiratory hypersensitivity)) OR (title:(airway hyper responsiveness OR bronchial hyperreactiv* OR bronchial hyper reactiv*) OR abstract:(airway hyper responsiveness OR bronchial hyperreactiv* OR bronchial hyper reactiv*))	194,027

Appendix 2: Characteristics of excluded studies for PICO 1

STUDY CITATION	REASON FOR EXCLUSION
Papi A, et al; AIFASMA Study Group. Regular versus as needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. <i>Lancet Respir Med</i> . 2015 Feb;3(2):109-119.	Wrong comparator
Rabe KF, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. <i>Chest</i> . 2006 Feb;129(2):246-256.	Wrong comparator
Scicchitano R, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. <i>Curr Med Res Opin</i> . 2004 Sep;20(9):1403-18.	Wrong comparator
EudraCT 2018-003467-64: Variability in airway inflammation, symptoms, lung function and reliever use in asthma: anti-inflammatory reliever hypothesis and STIFLE study design	Wrong intervention
Clinical trial registry number, jRCT2031210576: A Randomized, Double-Blind, Parallel Group, Multicenter 24 Week Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler Relative to Budesonide Metered Dose Inhaler and Open-Label Symbicort-R Turbuhaler-R in Participants with Inadequately Controlled Asthma	Wrong intervention
Clinical trial registry number, ChiCTR2300070550: The Rescue Intervention Strategy for Asthma Under Air Pollution Exposure (RISAPE) Trial	Wrong intervention
Clinical trial registry number, ACTRN12620001010987: The Anti-Inflammatory Reliever (AIR) Algorithm Study: a protocol for a single-group study of an AIR stepwise approach to the treatment of adult asthma	Wrong intervention
Atienza T, et al. Budesonide/formoterol maintenance and reliever therapy via Turbuhaler versus fixed-dose budesonide/formoterol plus terbutaline in patients with asthma: Phase III study results. <i>Respirology</i> . 2013 Feb;18(2):354-63.	Wrong intervention
Kuna P, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. <i>International Journal of Clinical Practice</i> . 2007 May;61(5):725-36.	Wrong intervention
O'Byrne PM, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. <i>American Journal of Respiratory and Critical Care Medicine</i> . 2005 Jan 15;171(2):129-36.	Wrong intervention
Papi A, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. <i>The Lancet Respiratory Medicine</i> . 2013 Mar 1;1(1):23-31.	Wrong intervention
Patel M, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. <i>The Lancet Respiratory Medicine</i> . 2013 Mar 1;1(1):32-42.	Wrong intervention
Rabe KF, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. <i>The Lancet</i> . 2006 Aug 26;368(9537):744-53	Wrong intervention
Ställberg B, et al, SHARE trial group. A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. <i>Respiratory medicine</i> . 2008 Oct 1;102(10):1360-70.	Wrong intervention
Takeyama K, et al. Budesonide/formoterol maintenance and reliever therapy in moderate-to-severe asthma: effects on eosinophilic airway inflammation. <i>Allergy & Asthma Proceedings</i> 2014 Mar 1 (Vol. 35, No. 2).	Wrong intervention
Bousquet J, et al. Budesonide/ formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/ fluticasone. <i>Respir Med</i> . 2007 Dec;101(12):2437-46.	Wrong intervention
Hozawa S, et al. Comparison of the effects of budesonide/formoterol maintenance and reliever therapy with fluticasone/salmeterol fixed-dose treatment on airway inflammation and small airway impairment in patients who need to step-up from inhaled corticosteroid monotherapy. <i>Pulm Pharmacol Ther</i> . 2014 Apr;27(2):190-6.	Wrong intervention
Vogelmeier C, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? <i>Eur Respir J</i> . 2005 Nov;26(5):819-28.	Wrong intervention
Saito T, et al. Safety and tolerability of high-dose budesonide/formoterol via Turbuhaler® in Japanese patients with asthma: a randomized, double-blind, crossover, active comparator-controlled, phase III study. <i>Clin Drug Investig</i> . 2012 Jan 1;32(1):51-61.	Wrong intervention
Balanag VM, et al. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. <i>Pulm Pharmacol Ther</i> . 2006;19(2):139-47.	Wrong intervention
Huang SG et al. As needed formoterol (F) in asthma: an analysis of the East-Asian subgroup of the RELIEF study. <i>ERJ</i> . Sep 2014;44 (Suppl 58):P2425	Wrong intervention
Bruce SA, et al. Maintenance and symptom relief with budesonide plus formoterol reduced severe asthma exacerbations (Commentary). <i>EBN</i> July 2005;8:78	Wrong study design

Appendix 3: Characteristics of excluded studies for PICO 2

NO.	CITATION	TYPE OF STUDY	REASON FOR EXCLUSION
1	Agarwal R, Khan A, Aggarwal AN, Gupta D. Is the SMART approach better than other treatment approaches for prevention of asthma exacerbations? A meta-analysis. Monaldi Archives for Chest Disease. 2009;71 (4). Available from: https://doi.org/10.4081/monaldi.2009.348	Systematic review	Outdated review
2	Ahmad S, Kew KM, Normansell R. Stopping long-acting beta 2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. Cochrane Database of Systematic Reviews. 2015; (6). Available from: https://doi.org/10.1002/14651858.CD011306.pub2	Systematic review	Wrong intervention
3	Bateman ED, Harrison TW, Quirce S, Reddel HK, Buhl R, Humbert M, Jenkins CR, Peterson S, Östlund O, O'Byrne PM, Sears MR. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. Respiratory Research. 2011; 12:1-1. Available from: https://doi.org/10.1186/1465-9921-12-38	Post-hoc analysis	Wrong study design
4	Beasley R, Harper J, Bird G, Dunphy H, Semprini A, Pavord ID, Papi A, Weatherall M. Dose-response relationship of ICS/fast-onset LABA as reliever therapy in asthma. BMC Pulmonary Medicine. 2019;19 (1): 1-8. Available from: https://doi.org/10.1186/s12890-019-1014-4	Non-systematic review	Wrong study design
5	Beasley R, Harrison T, Peterson S, Gustafson P, Hamblin A, Bengtsson T, Fagerås M. Evaluation of budesonide-formoterol for maintenance and reliever therapy among patients with poorly controlled asthma: a systematic review and meta-analysis. JAMA Network Open. 2022; 5(3): e220615. Available from: https://doi.org/10.1001/jamanetworkopen.2022.0615	Systematic review	Wrong patient population
6	Canadian Agency for Drugs and Technologies in Health (CADTH). Long-acting beta2-agonist and inhaled corticosteroid combination therapy for adult persistent asthma: systematic review of clinical outcomes and economic evaluation. CADTH Technology Overviews. 2010; 1 (3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411155/	Systematic review	Wrong intervention
7	Castro-Rodriguez JA, Rodrigo GJ. A Systematic Review of Long-Acting β 2-Agonists Versus Higher Doses of Inhaled Corticosteroids in Asthma. Pediatrics. 2012;130 (3): e650-7. Available from: https://doi.org/10.1542/peds.2012-0162	Systematic review	Wrong patient population
8	Castro-Rodriguez JA, Rodrigo GJ, Rodriguez-Martinez CE. Principal findings of systematic reviews for chronic treatment in childhood asthma. Journal of Asthma. 2015;52 (4): 407-16. Available from: https://doi.org/10.3109/02770903.2014.971968	Overview of reviews	Wrong study design
9	Cates CJ, Lasserson TJ. Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2009; Issue 1. Art. No.: CD007085. Available from: https://doi.org/10.1002/14651858.CD007085.pub2	Systematic review	Wrong comparator
10	Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews 2009; Issue 2. Art. No.: CD006924. Available from: https://doi.org/10.1002/14651858.CD006924.pub2	Systematic review	Wrong intervention
11	Cates CJ, Oleszczuk M, Stovold E, Wieland LS. Safety of regular formoterol or salmeterol in children with asthma: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2012; Issue 10. Art. No.: CD010005. Available from: https://doi.org/10.1002/14651858.CD010005.pub2	Overview of reviews	Wrong study design
12	Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database of Systematic Reviews. 2013; (4). Available from: https://doi.org/10.1002/14651858.CD007313.pub3	Systematic review	Outdated review
13	Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2014; Issue 2. Art. No.: CD010314. Available from: https://doi.org/10.1002/14651858.CD010314.pub2	Overview of reviews	Wrong study design
14	Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database of Systematic Reviews 2010; Issue 4. Art. No.: CD005533. Available from: https://doi.org/10.1002/14651858.CD005533.pub2	Systematic review	Wrong intervention
15	Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2010; Issue 5. Art. No.: CD005535. Available from: https://doi.org/10.1002/14651858.CD005535.pub2	Systematic review	Wrong intervention
16	Edwards SJ, Gruffydd-Jones K, Ryan DP. Systematic review and meta-analysis of budesonide/formoterol in a single inhaler. Current medical research and opinion. 2007;23 (8): 1809-20. Available from: https://doi.org/10.1185/030079907X210697	Systematic review	Wrong intervention

17	Edwards SJ, Von Maltzahn R, Naya IP, Harrison T. Budesonide/formoterol for maintenance and reliever therapy of asthma: a meta analysis of randomised controlled trials. International journal of clinical practice. 2010;64 (5): 619-27. Available from: https://doi.org/10.1111/j.1742-1241.2009.02320.x	Non-systematic review	Wrong study design
18	Gibson PG, Powell H, Ducharme FM. Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2005; Issue 4. Art. No.: CD005076. Available from: https://doi.org/10.1002/14651858.CD005076.pub2	Systematic review	Wrong intervention
19	Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting β -agonist and inhaled corticosteroid on asthma control and asthma exacerbations. Journal of allergy and clinical immunology. 2007;119(2): 344-50. Available from: https://doi.org/10.1016/j.jaci.2006.10.043	Overview of reviews	Wrong study design
20	Greenstone IIG, Ni Chroinin M, Lasserson TJ, Ducharme F. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. Cochrane Database of Systematic Reviews 2005; Issue 4. Art. No.: CD005533. Available from: https://doi.org/10.1002/14651858.CD005533	Systematic review	Wrong intervention
21	Jaeschke R, O'Byrne PM, Mejza F, Nair P, Lesniak W, Brozek J, Thabane L, Cheng J, Schünemann HJ, Sears MR, Guyatt G. The safety of long-acting β -agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis. American journal of respiratory and critical care medicine. 2008;178 (10): 1009-16. Available from: https://doi.org/10.1164/rccm.200804-494OC	Systematic review	Wrong intervention
22	Jaeschke R, O'Byrne PM, Nair P, Mejza F, Leśniak W, Brożek J, Thabane L, Cheng J, Bała M, Schünemann HJ, Sears MR. The safety of formoterol among patients with asthma using inhaled corticosteroids: systematic review and meta-analysis. Polskie Archiwum Medycyny Wewnętrznej= Polish Archives of Internal Medicine. 2008; 118 (11). Available from: https://ruj.uj.edu.pl/xmlui/bitstream/handle/item/173112/mejza_et-al_the_safety_of_formoterol_among_2008.pdf?sequence=1&isAllowed=y	Systematic review	Wrong intervention
23	Janjua S, Schmidt S, Ferrer M, Cates CJ. Inhaled steroids with and without regular formoterol for asthma: serious adverse events. Cochrane Database of Systematic Reviews 2019; Issue 9. Art. No.: CD006924. Available from: https://doi.org/10.1002/14651858.CD006924.pub4	Systematic review	Wrong intervention
24	Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database of Systematic Reviews. 2013; (12). Available from: https://doi.org/10.1002/14651858.CD009019.pub2	Systematic review	Outdated review
25	Ni Chroinin M, Greenstone IIG, Ducharme F. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naïve adults. Cochrane Database of Systematic Reviews 2004; Issue 4. Art. No.: CD005307. Available from: https://doi.org/10.1002/14651858.CD005307	Systematic review	Wrong intervention
26	Ni Chroinin M, Greenstone IIG, Ducharme F, Masse V, Danish A. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database of Systematic Reviews 2005; Issue 4. Art. No.: CD005535. Available from: https://doi.org/10.1002/14651858.CD005535	Systematic review	Wrong intervention
27	Park HJ, Huh JY, Lee JS, Lee JS, Oh YM, Lee SW. Comparative efficacy of inhalers in mild-to-moderate asthma: systematic review and network meta-analysis. Scientific Reports. 2022; 12 (1): 5949. Available from: https://doi.org/10.1038/s41598-022-09941-z	Systematic review and network meta-analysis	Wrong study design
28	Rodrigo GJ, Moral VP, Marcos LG, Castro-Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. Pulmonary Pharmacology & Therapeutics. 2009;22 (1): 9-19. Available from: https://doi.org/10.1016/j.pupt.2008.10.008	Systematic review	Wrong intervention
29	Rodrigo GJ, Neffen H, Colodenco FD, Castro-Rodriguez JA. Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis. Annals of Allergy, Asthma & Immunology. 2010; 104 (3): 247-52. Available from: https://doi.org/10.1016/j.anai.2009.11.064	Systematic review	Wrong intervention
30	Rogliani P, Ritondo BL, Ora J, Cazzola M, Calzetta L. SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis. European Respiratory Journal. 2020; 56 (3). Available from: https://doi.org/10.1183/13993003.00625-2020	Systematic review and network meta-analysis	Wrong study design
31	Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting β -agonists on severe asthma exacerbations and asthma-related deaths. Annals of Internal Medicine. 2006; 144 (12): 904-12. Available from: https://doi.org/10.7326/0003-4819-144-12-200606200-00126	Systematic review	Wrong intervention

32	Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. The American Journal of Medicine. 2010;123 (4): 322-8. Available from: https://doi.org/10.1016/j.amjmed.2009.07.035	Systematic review	Wrong intervention
33	Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE, Baker WL. Association of inhaled corticosteroids and long-acting β -agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. JAMA. 2018; 319 (14): 1485-96. Available from: https://doi.org/10.1001/jama.2018.2769	Systematic review	Wrong patient population
34	Venkitakrishnan, MD, dnb R, Thomas, MD PK, Bansal, MD, dnb A, Ghosh, MD I, Augustine, dtcd, dnb J, Divya, md R, Cleetus, dtcd, dnb M. Fluticasone/formoterol compared with other ICS/LABAs in asthma: a systematic review. Journal of Asthma. 2022; 59 (6): 1221-30. Available from: https://doi.org/10.1080/02770903.2021.1900864	Systematic review	Wrong intervention
35	Walters EH, Walters JAE, Gibson PG. Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma. Cochrane Database of Systematic Reviews 2002; Issue 3. Art. No.: CD003901. Available from: https://doi.org/10.1002/14651858.CD003901 .	Systematic review	Wrong intervention
36	Walters EH, Walters JAE, Gibson MDP, Gibson PG. Long-acting beta2-agonists for stable chronic asthma. Cochrane Database of Systematic Reviews 2003; Issue 3. Art. No.: CD001385. Available from: https://doi.org/10.1002/14651858.CD001385	Systematic review	Wrong intervention
37	Walters EH, Gibson PG, Lasserson TJ, Walters JAE. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database of Systematic Reviews 2007; Issue 1. Art. No.: CD001385. Available from: https://doi.org/10.1002/14651858.CD001385.pub2	Systematic review	Wrong intervention
38	Wang G, Zhang X, Zhang HP, Wang L, Kang DY, Barnes PJ, Wang G. Corticosteroid plus β 2-agonist in a single inhaler as reliever therapy in intermittent and mild asthma: a proof-of-concept systematic review and meta-analysis. Respiratory Research. 2017; 18: 1-8. Available from: https://doi.org/10.1186/s12931-017-0687-6	Systematic review	Outdated review
39	Welsh EJ, Cates CJ. Formoterol versus short-acting beta-agonists as relief medication for adults and children with asthma. Cochrane Database of Systematic Reviews 2010; Issue 9. Art. No.: CD008418. Available from: https://doi.org/10.1002/14651858.CD008418.pub2 .	Systematic review	Wrong intervention

Appendix 4: Characteristics of included SRs for PICO 2

CITATION	STUDY DESIGN	POPULATION	TREATMENT	MAIN FINDINGS	COMMENTS
Crossingham_I, Turner_S, Ramakrishnan_S, Fries_A, Gowell_M, Yasmin_F, Richardson_R, Webb_P, O'Boyle_E, Hinks_TSC. Combination fixed-dose beta-agonist and steroid inhaler as required for adults or children with mild asthma. <i>Cochrane Database of Systematic Reviews</i> 2021, Issue 5. Art. No.: CD013518. DOI: 10.1002/14651858.CD013518.pub2.	Systematic review and meta-analysis	4 studies: RCTs N=8,065	Interventions: As-required FAB/ICS SYGMA 1, SYGMA 2, Novel START and PRACTICAL: combination of budesonide 200 µg and formoterol 6 µg Control: Regular ICS Regular budesonide 200 µg twice daily. The as-required beta-agonist given with the regular budesonide was salbutamol (200 µg) in Novel START and terbutaline (500 µg) in the other three	Primary outcomes Exacerbations requiring systemic steroids The odds of an asthma exacerbation requiring systemic steroids were reduced in participants treated with as-required FAB/ICS compared with regular ICS, but confidence intervals include no difference (OR 0.79, 95% CI 0.59 to 1.07; participants = 8065, low-certainty evidence. In the control group, 81 people out of 1000 had exacerbations requiring systemic steroids over 52 weeks, compared to 65 (95% CI 49 to 86) out of 1000 for the active treatment group. Hospital admissions/emergency department or urgent care visits for asthma There were fewer exacerbations of asthma requiring either hospital admission or a visit to an emergency department or urgent care clinic in participants taking as-required FAB/ICS compared with regular ICS (OR 0.63, 95% CI 0.44 to 0.91; participants = 8065, low certainty evidence. Measures of asthma control Two studies (Novel START and PRACTICAL) reported ACQ-5 at the last trial visit and two studies (SYGMA 1 and SYGMA 2) reported a change in ACQ-5 from baseline. We found that analyses of these data showed a statistical advantage to regular ICS compared with as-required FAB/ICS but the absolute differences were small and probably not clinically significant (MD 0.12, 95% CI 0.09 to 0.15; participants = 7382). The MCID in ACQ-5 is around 0.5 points. Measures of lung function Two studies (PRACTICAL and Novel START) reported (probably prebronchodilator) FEV1 at 52 weeks. We found no difference between as-required FAB/ICS and regular ICS for this outcome (MD -0.01 L 95% CIs -0.11 to 0.09, participants = 1199, Analysis 2.5). SYGMA 1 and SYGMA 2 reported the change in FEV1 from baseline. FEV1 was 38 mL lower in the as-required FAB/ICS group compared with regular ICS (MD -37.68 mL, 95% CIs -68.19 to -7.17; participants = 6287, Analysis 2.6). This finding is below the MCID in FEV1 of around 100 mL. SYGMA 1 found that morning and evening PEFR increased slightly in the regular ICS group compared with baseline and fell slightly compared with baseline in the as-required FAB/ICS group. The absolute differences between as-required FAB/ICS and regular ICS in change in peak flow from baseline were small, less than 10 L/minute. The other studies did not report PEFR data. Two studies (PRACTICAL and Novel START) reported data on FeNO. Both studies reported the ratio of geometric means due to skew in this outcome, which indicated that mean FeNO levels at 52 weeks were 13%	2 of the 4 RCTs had a high risk of bias and 2 RCTs were judged to have a low risk of bias. Assessment of ROB was done using Cochrane RoB 1.0 tool

				higher in the as-required FAB/ICS arm compared to the regular ICS arm (OR 1.13, 95% CI 1.06 to 1.20; participants = 1197, Analysis 2.7). Quality of life measures Both SYGMA 1 and SYGMA 2 collected data on AQLQ but the findings were only available in graphical form. AQLQ scores were generally higher in the regular ICS arms compared with as-required FAB/ICS but by less than the minimal clinically important difference of 0.5 points. PRACTICAL did not report quality of life measures. Adverse events Serious adverse events occurred at similar rates in the as-required FAB/ICS and regular ICS arms across four trials, although confidence intervals are wide (OR 1.14, 95% CI 0.82 to 1.57; participants = 8072. We found similar odds of experiencing any adverse event in the two groups (OR 0.96, 95% CIs 0.82 to 1.14; participants = 8072, moderate-certainty evidence. Total inhaled steroid dose We found that participants randomised to as-required FAB/ICS received about 150 µg less ICS (beclomethasone equivalent) per day than those on regular ICS (MD -154.51 µg/day, 95% CI -207.94 to -101.09; participants = 7180; moderate-certainty evidence. Total systemic corticosteroid dose Using data from two studies (PRACTICAL; Novel START), we found similar total systemic steroid exposure in the as-required FAB/ICS and regular ICS groups (MD -7.00 mg prednisolone, 95% CI -13.97 to -0.03; participants = 1330, moderate-certainty evidence. The other three studies did not report systemic steroid doses. There were numerically fewer total days on systemic steroids in the as-required FAB/ICS group compared with regular ICS in SYGMA 1 (465 versus 500 days). SYGMA 2 reported that those in the as-required FAB/ICS and the regular ICS groups had the same median number of days on systemic steroids (six days). Mortality There was no clear difference in the risk of death between as-required FAB/ICS and regular ICS in four studies (OR 0.63, 95% CI 0.12 to 3.25; participants = 8070. This analysis is based on a small number of events and consequently has a very broad confidence interval.	
CITATION	STUDY DESIGN	POPULATION	TREATMENT	MAIN FINDINGS	COMMENTS
Hatter L, Bruce P, Braithwaite I, Holliday M, Fingleton J, Weatherall M, Beasley R. ICS-formoterol reliever versus ICS and short-acting β2-agonist reliever in asthma: a systematic review and meta-	Systematic review and meta-analysis	4 studies: RCTs N=8,065	Interventions: As-required FAB/ICS SYGMA 1, SYGMA 2, Novel START and PRACTICAL:	Primary outcomes - As-needed budesonide-formoterol was associated with a prolonged time to first severe exacerbation (HR 0.85, 95% CI 0.73–1.00; p=0.048) - As-needed budesonide-formoterol reduced the rate ratio of severe exacerbations (RR 0.85, 95% CI 0.72–1.00) and the risk of at least	All studies were deemed to be at low RoB. Assessment of ROB was done using Cochrane RoB 2.0 tool

analysis. ERJ Open Research. 2021 Jan 1;7(1). DOI: 10.1183/23120541.00701-2020			combination of budesonide 200 µg and formoterol 6 µg Control: Regular ICS Regular budesonide 200 µg twice daily. The as-required beta-agonist given with the regular budesonide was salbutamol (200 µg) in Novel START and terbutaline (500 µg) in the other three	one severe exacerbation (OR 0.86, 95% CI 0.73–1.01). Quantitative heterogeneity was evident in these analyses with the two larger studies showing less of a difference between the two treatment groups. • There were fewer ED visits in the as-needed budesonide-formoterol group (POR 0.65, 95% CI 0.43–0.98). There was no difference in hospitalisations (POR 0.85, 95% CI 0.49–1.49) or the combination of ED visits or hospitalisations (POR 0.73, 0.52–1.04). The datasets contributing to these variables had few or no events • There was no difference between the two groups in the number of participants experiencing at least one SAE (OR 1.07, 95% CI 0.84–1.36) or deaths (POR 0.52, 95% CI 0.10–2.57). Of the six reported deaths, one was asthma-related and occurred in the maintenance ICS group. • The ICS dose taken was lower in the as-needed budesonide-formoterol group across all four studies (mean difference –177.3 µg, 95% CI –182.2–172.4 µg), with evidence of heterogeneity (I² 98.8). • The number of formoterol-adjusted β₂-agonist-containing actuations per day was higher in the as-needed budesonide-formoterol group across all four studies (mean difference 0.08, 95% CI 0.05–0.10), with evidence of heterogeneity (I² 94.2) • The ACQ-5 score was higher in the as-needed budesonide-formoterol group (mean difference 0.12, 95% CI 0.09–0.14). The FEV₁ was lower in the as-needed budesonide-formoterol group (mean difference –27.4 mL, 95% CI –40.7–14.1 mL). There was evidence of heterogeneity (I² 74.8) with the two SYGMA studies having a larger and negative effect on FEV₁, favouring ICS maintenance	
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**A critical group appraisal of:
Global Strategy for Asthma Management and
Prevention 2023 Update
using the AGREE II Instrument**

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Date: 18 January 2024

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URL of this appraisal: <http://www.agreetrust.org/group-appraisal/20518>

Guideline URL: <https://ginasthma.org/2023-gina-main-report/>

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
72%	78%	64%	81%	71%	75%	67%	Yes - 1, Yes with modifications - 1, No - 0

<i>Domain 1. Scope and Purpose</i>		
	Appraiser 1	Appraiser 2
Item 1	5	6
Item 2	5	5
Item 3	5	6
<i>Domain 2. Stakeholder Involvement</i>		
	Appraiser 1	Appraiser 2
Item 4	5	5
Item 5	6	5
Item 6	6	7
<i>Domain 3. Rigour of Development</i>		
	Appraiser 1	Appraiser 2
Item 7	3	4
Item 8	4	6
Item 9	3	3
Item 10	5	7
Item 11	5	5
Item 12	4	5
Item 13	6	6
Item 14	5	6
<i>Domain 4. Clarity of Presentation</i>		
	Appraiser 1	Appraiser 2
Item 15	6	6
Item 16	6	6
Item 17	6	5
<i>Domain 5. Applicability</i>		
	Appraiser 1	Appraiser 2
Item 18	5	5
Item 19	5	7
Item 20	5	5
Item 21	4	6
<i>Domain 6. Editorial Independence</i>		
	Appraiser 1	Appraiser 2
Item 22	4	5
Item 23	7	6
<i>Overall Assessment</i>		
	Appraiser 1	Appraiser 2
OA1	4	6

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Appendix 6: AMSTAR II appraisal of included studies for PICO 2

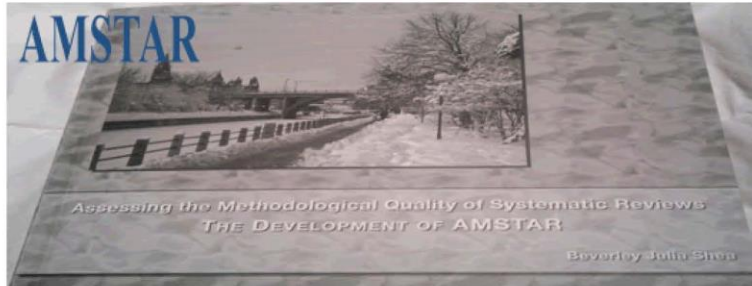
I. Crossingham 2021 (Reviewer 1: SE)

11/23/23, 11:33 AM

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AMSTAR 2 Results

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Article Name:

Crossingham 2021

Crossingham 2021 is a Moderate quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?

Yes
Yes
Yes
Yes
Yes

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

YesYesYesYesYesYesYesYes

3. Did the review authors explain their selection of the study designs for inclusion in the review?

No

4. Did the review authors use a comprehensive literature search strategy?

Yes

Yes
Yes
Yes
Yes
Yes

5. Did the review authors perform study selection in duplicate?

Yes

https://amstar.ca/mascripts/Calc_Checklist.php

1/3

6. Did the review authors perform data extraction in duplicate? Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions? Yes

Yes

8. Did the review authors describe the included studies in adequate detail? Yes

Yes

Yes

Yes

Yes

Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCT Yes

NRSI

Yes

Yes

10. Did the review authors report on the sources of funding for the studies included in the review? Yes

Yes

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCT Yes

NRSI

Yes

Yes

Yes

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Yes

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? Yes

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
	Yes

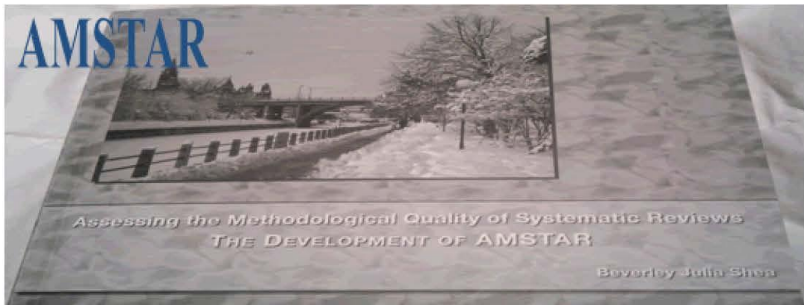
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
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16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Article Name:
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Combination fixed-dose beta agonist and steroid inhaler as required for adu is a Moderate quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?

Yes
Yes
Yes
Yes
Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

YesYesYesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?

No
4. Did the review authors use a comprehensive literature search strategy?

Yes
Yes
Yes
Yes
Yes
Yes

	Yes
	Yes
5. Did the review authors perform study selection in duplicate?	Yes
	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
	Yes
	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	Yes
NRSI	0
	Yes
	Yes
	Yes
	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	Yes
NRSI	
	Yes
	Yes
	Yes

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

No

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

Yes

Yes

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Yes

Yes

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Yes

Yes

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Yes

Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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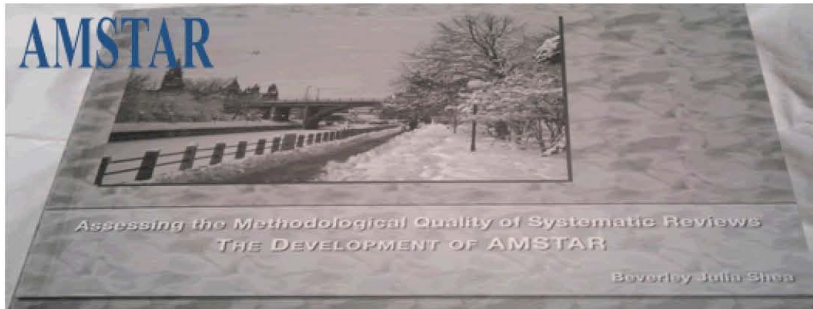
III. Hatter 2021 (Reviewer 1: SE)

11/24/23, 12:47 PM

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Article Name:

Hatter 2021

Hatter 2021 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?

Yes
Yes
Yes
Yes

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

YesYesYesYesYesYesYes

3. Did the review authors explain their selection of the study designs for inclusion in the review?

No

4. Did the review authors use a comprehensive literature search strategy?

Partial Yes
Yes
Yes
Yes
Yes
Yes
Yes

5. Did the review authors perform study selection in duplicate?

Yes

https://amstar.ca/mascripts/Calc_Checklist.php

1/3

6. Did the review authors perform data extraction in duplicate? Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions? No

8. Did the review authors describe the included studies in adequate detail? Yes

Yes
Yes
Yes
Yes
Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
RCT

Yes

NRSI

10. Did the review authors report on the sources of funding for the studies included in the review? Yes

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
RCT

Yes

NRSI

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Yes

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? Yes

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Yes

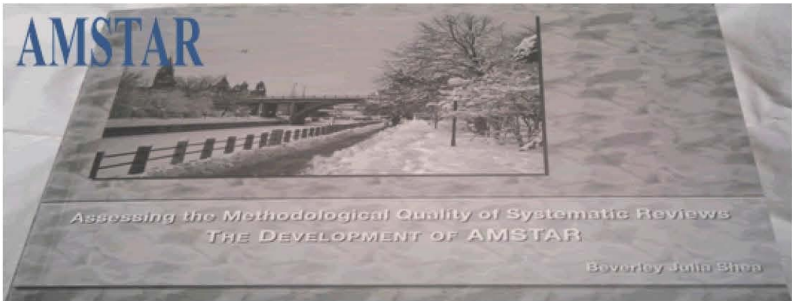
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Yes

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Article Name:

Hatter et al

Hatter et al is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?

Yes
Yes
Yes
Yes
Yes

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

YesYesYesYesYesYesYesYes

3. Did the review authors explain their selection of the study designs for inclusion in the review?

No

4. Did the review authors use a comprehensive literature search strategy?

Yes
Yes
Yes
Yes
Yes

Yes

5. Did the review authors perform study selection in duplicate?	Yes
	Yes

6. Did the review authors perform data extraction in duplicate?	Yes
	Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
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8. Did the review authors describe the included studies in adequate detail?	Yes
--	-----

Yes
Yes
Yes
Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	Yes

NRSI

10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
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11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	Yes

NRSI

Yes
Yes
Yes

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
---	-----

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
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14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
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15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
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16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
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To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Appendix 7: Qualitative criteria

Mild to moderate asthma

The PRACTICAL study (Hardy, 2019) was a randomised controlled trial that compared symptom-driven budesonide–formoterol with maintenance budesonide plus as-needed terbutaline. A subgroup of participants in the PRACTICAL study completed a survey on treatment preferences, satisfaction, beliefs, and experience at their final study visit¹. 75% (306/407) of the eligible participants completed the survey². Combination preventer and reliever as-needed therapy was preferred by 90% (135/150; 95% CI 85.2–94.8%) who were randomised to as-needed budesonide–formoterol, and by 40% (63/156; 95% CI 32.7– 48.1%) who were randomised to maintenance budesonide².

Moderate to Severe Asthma

An observational study by Albsoul-Younes *et al.* examined changes in the quality of life for paediatric asthma patients who switched to a single-metered dose inhaler (MDI) of budesonide/formoterol³. Thirty children, aged 6 to 15 years, with moderate to severe chronic asthma using inhaled beclomethasone disproportionate (≥ 400 mcg daily) with as-needed salbutamol metered-dose inhaler (MDI) were switched to a single MDI of budesonide/formoterol (one inhalation, twice a day) after a one-month baseline period. Health-related quality of life (HRQoL) was assessed at baseline, and each follow-up visit was made monthly for two months³. The study authors noted a significant improvement in quality of life, in line with an improvement in pulmonary function tests³. The overall quality of life score dropped from 1.75 ± 0.04 to 0.80 ± 0.07 , $p < 0.001$ (0 = excellent; 2 = very bad HRQoL)³. Of note, there was a significant improvement in the quality of sleep and the children's ability to engage in sporting activities.

A review of patient perspectives on and preferences for controller medication and adherence to therapy by Murphy *et al.* showed adherence is higher with a combined ICS/LABA than when components are administered separately and that patients prefer a single inhaler⁴. Patients are more likely to adhere when an effective reliever with quick onset and long duration of action is prescribed. Using a single MDI also simplifies the treatment regimen and promotes adherence⁴.

A double-blind, placebo-controlled, multicentre RCT comparing budesonide/formoterol in a single MDI with budesonide MDI, or formoterol DPI, or budesonide MDI plus formoterol DPI, or placebo in 596 patients aged 12 years or older, with moderate to severe asthma used several elements to assess patient-reported outcomes⁵. The standardised 32-item Asthma Quality of Life Questionnaire (AQLQ[S]) was used to evaluate patient perceptions of HRQoL at baseline and each clinic visit; the 12-item Medical Outcomes Study (MOS) Sleep Scale was used to determine sleep quantity and quality at baseline and at each subsequent visit; the 23-item Patient Satisfaction With Asthma Medication (PSAM) questionnaire to assess patient satisfaction with their treatment; and patient and physician global assessments of asthma were assessed at the end of treatment⁵. The study found that patient-reported outcomes (PROs) were improved in those using the budesonide/formoterol pressurised MDI (pMDI) compared to placebo and significantly improved compared to the individual mono-components⁵. Patients in the budesonide/formoterol pMDI group also showed greater improvements from baseline in AQLQ(S) scores and asthma control variables (apart from waking up at night), as well as better outcomes for the PSAM questionnaire and physician-assessed global health compared to those receiving formoterol DPI or budesonide pMDI⁵. The greatest improvement in HRQoL appeared to be in those with moderate to severe asthma, supported by another trial – the Gaining Optimal Asthma Control (GOAL) study. However, this study examined the use of a salmeterol/fluticasone combination MDI instead of budesonide/formoterol MDI⁶.

- ¹Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, Corin A, Sparks J, Hall D, Sabbagh D, Mane S. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *The Lancet*. 2019 Sep 14;394(10202):919-28.
- ²Baggott C, Reddel HK, Hardy J, Sparks J, Holliday M, Corin A, Montgomery B, Reid J, Sheahan D, Hancox RJ, Weatherall M. Patient preferences for symptom-driven or regular preventer treatment in mild to moderate asthma: findings from the PRACTICAL study, a randomised clinical trial. *European Respiratory Journal*. 2020 Apr 1;55(4).
- ³Albsoul-Younes AM, Al-Doghim IA, Al-Safi SA, Najada AS. Improving the quality of life in asthmatic children. *Indian J Pediatr*. 2004;71:1075-8. DOI: 10.1007/BF02829817
- ⁴Murphy KR, Bender BG. Treatment of moderate to severe asthma: patient perspectives on combination inhaler therapy and implications for adherence. *J Asthma Allergy*. 2009; 2:63-72. DOI: 10.2147/jaa.s4214
- ⁵Chervinsky P, Baker J, Bensch G, Parasuraman B, Boggs R, Martin P, et al. Patient-reported outcomes in adults with moderate to severe asthma after the use of budesonide and formoterol administered via one pressurised metered-dose inhaler. *Ann Allergy Asthma Immunol*. 2008;101:463-73. DOI: 10.1016/S1081-1206(10)60284-0
- ⁶Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004 Oct 15;170(8):836-44. Doi: 10.1164/rccm.200401-033OC. Epub 2004 Jul 15. PMID: 15256389.

Appendix 8: Characteristics of excluded studies for PICO 3

STUDY CITATION	REASON FOR EXCLUSION
Papi A, et al.; AIFASMA Study Group. Regular versus as needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. <i>Lancet Respir Med</i> . 2015 Feb;3(2):109-119.	Wrong comparator
Rabe KF, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. <i>Chest</i> . 2006 Feb;129(2):246-256.	Wrong comparator
Scicchitano R, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. <i>Curr Med Res Opin</i> . 2004 Sep;20(9):1403-18.	Wrong comparator
Saito T, et al. Safety and tolerability of high-dose budesonide/formoterol via Turbuhaler® in Japanese patients with asthma: a randomized, double-blind, crossover, active comparator-controlled, phase III study. <i>Clin Drug Investig</i> . 2012 Jan 1;32(1):51-61.	Wrong intervention
Balanag VM, et al. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. <i>Pulm Pharmacol Ther</i> . 2006;19(2):139-47.	Wrong intervention
Huang SG et al. As needed formoterol (F) in asthma: an analysis of the East-Asian subgroup of the RELIEF study. <i>ERJ</i> . Sep 2014;44 (Suppl 58): P2425	Wrong intervention
Bruce SA, et al. Maintenance and symptom relief with budesonide plus formoterol reduced severe asthma exacerbations (Commentary). <i>EBN</i> July 2005;8:78	Wrong study design

Appendix 9: Characteristics of planned and ongoing studies for PICO 3

TREATMENT (PER ARM)	SAMPLE SIZE	SEVERITY AT ENROLLMENT	SPONSOR	REGISTRATION NUMBER	FULL-TEXT LINK	SOURCE
Maintenance budesonide/formoterol (100/6µg or 200/6µg, two inhalations twice daily) with either as-needed budesonide/formoterol (same dose as maintenance) or salbutamol (100µg) as a reliever for 24 weeks.	60-80	STIFLE is a phase IV, randomised, active-comparator, open-label, parallel-group, multicenter, exploratory, 24-week study in adult asthma patients (≥18 years of age) receiving Global Initiative for Asthma 2018 step 3 or step 4 treatment (low- or medium-dose ICS/LABA only)	AstraZeneca	EudraCT identifier number 2018-003467-64	https://doi.org/10.1183/23120541.00333-2019 and https://www.atsjournals.org/doi/10.1164/ajrcm-conference.2019.199.1.MeetingAbstracts.A1308	CENTRAL (15 May 2024)
Budesonide and Formoterol Fumarate Metered Dose Inhaler vs. Budesonide Metered Dose Inhaler and Open-Label Symbicort-R Turbuhaler-R	Recruiting, sample size not reported	Participants who have been regularly using a stable daily ICS or an ICS/LABA regimen (including a stable ICS dose), with the ICS doses, for at least 8 weeks prior to Visit 1	AstraZeneca	JRCT2031210576	https://rctportal.niph.go.jp/s/detail/um?trial_id=jRCT2031210576 and https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-jRCT2031210576 and https://jrct.niph.go.jp/en/latest-detail/jRCT2031210576	CENTRAL (15 May 2024)
Rescue intervention strategy (RIS): If the air quality index (AQI) issued by the monitoring station closest to the participant's residence exceeds 150 between 20:00 of the previous day and 07:00 of the current day, the participants in RIS group are required to add one inhalation of budesonide/formoterol (160/4.5) to their baseline asthma treatment; control group: the baseline asthma treatment will be continued, and budesonide/formoterol or SABA as needed for symptom relief are allowed	Recruitment status pending; sample size not reported	Established diagnosis of asthma by physicians according to Guidelines for Asthma Prevention and Management in China (2020 edition)	Beijing Municipal Science & Technology Commission No.Z221100007422040; National High-Level Hospital Clinical Research Funding (Multi-center Clinical Research Project of Peking University First Hospital)	ChiCTR2300070550	https://www.chictr.org.cn/showproj.html?proj=194088 and https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2300070550	CENTRAL (15 May 2024)
Participants will be allocated to budesonide-formoterol 200/6 µg, one actuation as needed (Step 1), one actuation twice daily and as needed (Step 2), or two actuations twice daily and one as needed (Step 3)	100	Adults aged 18 to 75 years with mild, moderate and moderate-severe asthma	AstraZeneca	ACTRN12620001010987	https://doi.org/10.1183/23120541.00239-2023	PUBMED (14 May 2024)
SYMBICORT as maintenance and reliever treatment: Patients on ICS (low dose)/LABA prior to study entry will receive SYMBICORT (budesonide/formoterol 100/6 µg) ×	42, trial completed, preliminary	Adults aged 18 to 100 years	AstraZeneca	NCT03924635	https://clinicaltrials.gov/study/NCT03924635	CENTRAL (15 May 2024)

TREATMENT (PER ARM)	SAMPLE SIZE	SEVERITY AT ENROLLMENT	SPONSOR	REGISTRATION NUMBER	FULL-TEXT LINK	SOURCE
2 inhalations twice a day (BID) for maintenance and as needed (PRN) for relief and patients on ICS (medium dose)/LABA prior to study entry will receive SYMBICORT (budesonide/formoterol 200/6 µg) × 2 inhalations BID for maintenance and PRN for relief vs. SYMBICORT as maintenance, salbutamol as reliever treatment: Patients on ICS (low dose)/LABA prior to study entry will receive SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief and patients on ICS (medium dose)/LABA prior to study entry will receive SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.	results available					

Appendix 10: Characteristics of included studies for PICO 3

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
A: Comparator – ICS (Budesonide or Beclomethasone)/Formoterol maintenance and a SABA reliever				
Atienza T, Aquino T, Fernandez M, Boonsawat W, Kawai M, Kudo T, Ekelund J, Ivanov S, Carlsson LG. Budesonide /formoterol maintenance and reliever therapy via Turbuhaler versus fixed-dose budesonide /formoterol plus terbutaline in patients with asthma: Phase III study results. <i>Respirology</i> . 2013 Feb;18(2):3 54-63.	<u>Design</u> Double-blind, parallel-group, randomised clinical trial <u>Setting</u> 148 centres across 13 countries <u>Follow-up duration (weeks)</u> 52 <u>Funding</u> Astra Zeneca <u>Declarations</u> Listed in the paper <u>Informed Consent</u> "All patients provided written informed consent prior to enrolment".	Patients aged ≥16 years <u>Sample size</u> N=3,209 participants were randomly assigned (1,049 patients assigned to Budesonide/formoterol maintenance + reliever and 1,042 to Budesonide/formoterol maintenance + terbutaline for 12 months) <u>Asthma severity</u> Persistent asthmatics on maintenance ICS for ≥3 months before study entry and at a constant dose for ≥4 weeks before study entry, and having at least one asthma exacerbation in the 12 months before the study entry; were eligible. To be randomised, patients had to have used their as-needed medication on at least 5 of the last 7 days of the run-in phase.	<u>Intervention</u> Budesonide/formoterol 160/4.5µg one inhalation twice daily plus budesonide/formoterol 160/4.5mg as needed <u>Comparator/s</u> Budesonide/formoterol 160/4.5µg one inhalation twice daily plus terbutaline 0.4mg as needed	<u>Primary Outcomes</u> Time to first severe asthma exacerbation, defined as deterioration in asthma leading to oral corticosteroid treatment for at least 3 days, or hospitalisation or emergency room treatment due to asthma <u>Secondary Outcomes</u> - Morning and evening peak expiratory flow, FEV1 - Diary card variables: use of as-needed medication, asthma symptom score, night-time awakening, symptom-free days, as-needed medication-free days, asthma control days, time to first mild asthma exacerbation, number of mild asthma exacerbation days - Asthma control questionnaire (ACQ) - Safety evaluations included reporting adverse events (AE), monitoring clinical laboratory variables, 12-lead electrocardiograms, and vital signs. <u>Results</u> 170 (16%) receiving budesonide/formoterol maintenance and reliever therapy experienced 259 severe exacerbations versus 229 patients (22%) receiving budesonide/formoterol plus terbutaline who experienced 363 severe exacerbations - Budesonide/formoterol maintenance and reliever therapy prolonged the time to the first severe exacerbation versus budesonide/formoterol plus terbutaline (P =0.0007) and reduced the instantaneous risk of an exacerbation by 30% (hazard ratio 0.70, 95% confidence interval 0.57–0.85, P = 0.0003). - Oral steroid use (number of participants with at least one event): 130/1,049 vs 168/1,042 for budesonide/formoterol maintenance and reliever therapy and budesonide/formoterol plus terbutaline cohorts, respectively. - Emergency room treatment (number of participants with at least one event): 112/ 1049 vs 151/1042 for budesonide/formoterol maintenance and reliever therapy and budesonide/formoterol plus terbutaline cohorts, respectively. - Hospitalization (number of participants with at least one event): 11/1,049 vs 33/1,042 for budesonide/formoterol maintenance and reliever therapy and budesonide/formoterol plus terbutaline cohorts, respectively. - Composite endpoint of hospitalisation or emergency room treatment: 118/1,049 vs 162/1,042 for budesonide/formoterol maintenance and reliever therapy and budesonide/formoterol plus terbutaline cohorts, respectively - Safety: - AEs: 602 budesonide/formoterol maintenance and reliever therapy patients (57.4%) and 599 (57.5%) budesonide/formoterol plus terbutaline

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
				patients experienced at least one AE, the majority of AEs were mild or moderate in intensity - One death was reported in each treatment group (budesonide/formoterol maintenance and reliever therapy: septic shock; budesonide/formoterol plus terbutaline: none of the deaths were related to asthma or considered by the investigator as related to study treatment - SAEs other than death occurred in 4.0% and 7.1% of patients in the budesonide/formoterol maintenance and reliever therapy and budesonide/formoterol plus terbutaline groups, respectively
Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, Buhl R. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. International Journal of Clinical Practice. 2007 May;61(5):725-36.	<u>Design</u> Double-blind, double-dummy, parallel-group study <u>Setting</u> Multicentre, across sixteen countries <u>Follow-up duration (weeks)</u> 24 <u>Funding</u> Astra Zeneca <u>Declarations</u> Listed in paper <u>Informed Consent</u> "All patients and parents/guardians of adolescents gave written informed consent".	Outpatients aged ≥ 12 years <u>Sample size</u> N=3,335 participants were randomly assigned (1,107 patients assigned to Budesonide/formoterol maintenance + reliever [SMART], 1,105 to Budesonide/formoterol maintenance + terbutaline, and 1,123 to Salmeterol/fluticasone + terbutaline for 6 months) <u>Asthma severity</u> Those with a diagnosis of asthma [as defined by the American Thoracic Society] for ≥ 6 months and using ICS for ≥ 3 months [≥ 500 lg/day of budesonide or fluticasone (or ≥ 1000 lg/day of another ICS) for ≥ 1 month].	<u>Intervention</u> Budesonide/formoterol 160/4.5µg one inhalation twice daily plus budesonide/formoterol 160/4.5mg as needed (SMART) <u>Comparator/s</u> - Budesonide/ formoterol 320/9.0µg one inhalation twice daily plus terbutaline as needed - Salmeterol/fluticasone 25/125µg, two inhalations twice daily + terbutaline as needed	<u>Primary Outcomes</u> Time to first severe asthma exacerbation: Severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room (ER) treatment or the need for oral steroids for ≥ 3 days. <u>Secondary Outcomes</u> - Total number of severe exacerbations - Inhalations of as-needed medication - Change in morning and evening peak expiratory flow (PEF), FEV1 - Asthma symptom score - Nights with awakenings caused by asthma - Symptom-free days - As-needed-free days - Asthma-control days - Number of mild exacerbations <u>Results</u> - Budesonide/formoterol for maintenance and relief prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs fixed-dose salmeterol/fluticasone and budesonide/formoterol (p = 0.0034 and p = 0.023 respectively; log-rank test) - Exacerbation rates were 19, 16, and 12 events/100 patients/6 months for salmeterol/fluticasone, fixed-dose budesonide/formoterol, and budesonide/formoterol for maintenance and relief, respectively, [rate reduction vs. fixed-dose salmeterol/fluticasone (0.61; 95% CI 0.49–0.76, p < 0.001) and vs. fixed-dose budesonide/formoterol (0.72; 95% CI 0.57–0.90, p = 0.0048)] - Budesonide/formoterol maintenance and relief patients used less inhaled corticosteroid vs salmeterol/fluticasone and fixed-dose budesonide/formoterol patients - Oral steroid use (total number of events/group): 86/1,107 vs 139/1,105 vs 148/1,123 for budesonide/formoterol maintenance and reliever therapy, budesonide/formoterol plus terbutaline and salmeterol/fluticasone plus terbutaline groups, respectively - Safety:

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
		Patients using reliever medication on $\pm$ 5 of the last 7 days of the 2-week run-in were randomised.		- All three treatments were well tolerated, and there were no notable between-group differences in the number or severity of adverse events - SAEs were uncommon, and their incidence was comparable across all three treatment groups: 32 patients (3%) in the salmeterol/fluticasone group, 39 patients (4%) in the fixed-dose budesonide/formoterol group, and 31 patients (3%) in the SMART group - Two deaths occurred during the study, one in the SMART group (respiratory failure) and one in the salmeterol/fluticasone group (cardiac failure). The investigator considered neither death to be causally related to the study drug
O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekström T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. American Journal of Respiratory and Critical Care Medicine. 2005 Jan 15;171(2):129-36.	<u>Design</u> Double-blind, randomised, parallel-group study. <u>Setting</u> 246 centers in 22 countries <u>Follow-up duration (weeks)</u> 52 <u>Funding</u> Astra Zeneca <u>Declarations</u> Listed in paper <u>Informed Consent</u> "All patients gave written informed consent".	Outpatients aged 4 to 80 years <u>Sample size</u> N=2,760 participants were randomly assigned (925 patients assigned to Budesonide/formoterol maintenance + reliever, 909 to Budesonide/formoterol maintenance + terbutaline, and 926 to Budesonide + terbutaline for 12 months) <u>Asthma severity</u> Persistent asthma on ICS (400 to 1000µg/day) with LABA for $\geq$3 months pre-study and $\geq$ one asthma exacerbation in 12 months pre-study	<u>Intervention</u> Budesonide/formoterol 80/4.5µg one inhalation twice daily plus budesonide/formoterol 80/4.5mg as needed (bud/form maintenance + relief) <u>Comparator/s</u> - Budesonide/formoterol 80/4.5µg one inhalation twice daily plus terbutaline 0.4mg as needed (bud/form + SABA) - Budesonide 320µg twice a day plus terbutaline 0.4mg as needed (bud + SABA)	<u>Primary Outcomes</u> Time to first severe exacerbation, severe asthma exacerbations were defined as a deterioration in asthma resulting in hospitalisation/emergency room treatment, oral steroid treatment (or an increase in ICS [via a separate inhaler] and/or other additional treatment for children aged 4–11 years), or morning peak expiratory flow (PEF) of 70% or less of baseline on two consecutive days <u>Secondary Outcomes</u> - Mild exacerbations were defined as two consecutive days with either a morning PEF of 80% or less of baseline, as needed use of two or more inhalations per day above baseline, or awakenings caused by asthma - AEs, electrocardiogram, morning plasma cortisol, and vital signs assessed safety. <u>Results</u> - Bud/form maintenance + relief prolonged time to first severe exacerbation ($p < 0.001$; primary endpoint), resulting in a 45–47% lower exacerbation risk versus bud/form + SABA (hazard ratio, 0.55; 95% confidence interval, 0.44, 0.67) or bud + SABA (hazard ratio, 0.53; 95% confidence interval 0.43, 0.65) - Bud/form maintenance + relief also prolonged the time to the first, second, and third exacerbation requiring medical intervention ($p < 0.001$), reduced severe exacerbation rate, and improved symptoms, awakenings, and lung function compared with both fixed dosing regimens - Safety - All treatments were well tolerated, and AEs were generally mild to moderate in intensity - The total number of patients with one or more AE was 528 (57%) with bud + SABA, 475 (52%) with bud/form + SABA, and 496 (54%) with bud/form for maintenance + relief - The number of patients with one or more SAE was similar in each of the treatment groups: 5% (48/925) for bud + SABA, 7%

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
				(62/906) for bud/form + SABA, and 5% (46/922) for bud/form maintenance + relief
Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, Fabbri LM, Rabe KF. Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. The Lancet Respiratory Medicine. 2013 Mar 1;1(1):23-31.	<u>Design</u> Double-blind, randomised, parallel-group study <u>Setting</u> 183 centres in 14 European countries <u>Follow-up duration (weeks)</u> 48 <u>Funding</u> Chiesi Farmaceutici <u>Declarations</u> Listed in paper <u>Informed Consent</u>	Patients aged 18 years or older <u>Sample size</u> N=1,174 participants were randomly assigned (857 patients assigned to Beclometasone /formoterol maintenance + reliever, and 857 to Beclometasone /formoterol maintenance + salbutamol reliever) <u>Asthma severity</u> Persistent asthma (diagnosed last 6 months) with a history of at least one severe exacerbation in	<u>Intervention</u> Beclometasone 100µg and formoterol 6µg in a single inhaler, one inhalation twice daily, plus an as-needed reliever <u>Comparator/s</u> Beclometasone 100µg and formoterol 6µg in a single inhaler, one inhalation twice daily, plus salbutamol 100µg through a pressurised metered-dose inhaler (pMDI) as needed	<u>Primary Outcomes</u> Time to first severe asthma exacerbation, defined as deterioration in asthma resulting in admission to hospital or visit to the emergency department, or requiring systemic steroids for at least 3 days <u>Secondary Outcomes</u> - Number of severe exacerbations (events per 100 patients per year), time to first, and number of mild exacerbations. A mild exacerbation was defined as the occurrence of one of the following: use of two or more inhalations of as-needed reliever in addition to the baseline in 24 h; morning PEF less than the baseline by at least 20%; or a night awakening due to asthma - Additional exacerbation variables (different ways of expressing exacerbations), lung function, symptom scores, and asthma control <u>Results</u> 251 patients reported 326 severe exacerbations during the study, and 99 versus 152 patients had at least one exacerbation during the 48 weeks, respectively - Compared with beclometasone–formoterol plus salbutamol as needed, beclometasone–formoterol for both maintenance and reliever treatment significantly increased the time to first exacerbation (209 days vs 134 days) by 75 days, with a 36% reduction in risk (hazard ratio 0.64 [95% CI 0.49 to 0.82]; p=0.0005)

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	"All patients provided written informed consent".	12 months pre-study or Persistent asthma on regular ICS (beclomethasone ≥ 500 to $\geq 1000\mu\text{g/day}$ or equivalent) with LABA for 2 months pre-study. Note: ICS dose at study entry $>500\mu\text{g}$ was 1420; Beclomethasone/formoterol maintenance + reliever $n=711$ Beclomethasone/formoterol maintenance + salbutamol $n=709$		- Visit to the emergency department or admission to hospital due to asthma (<i>intervention vs comparator</i>): 53/852 (6%) vs 77/849 (9%) - Systemic corticosteroid for more than 3 days for asthma (<i>intervention vs comparator</i>): 89/852 (10%) vs 143/849 (17%) - Safety: All treatments were well tolerated. Similar numbers of patients in the as-needed beclomethasone-formoterol and salbutamol groups had SAEs (32 [4%] and 41 [5%], respectively)
Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, Harwood M, Black P, Weatherall M, Beasley R. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. The	<u>Design</u> Open-label, parallel-group, randomised, controlled trial <u>Setting</u> Four primary healthcare practices and one hospital in New Zealand <u>Follow-up duration (weeks)</u> 24 <u>Funding</u> "This study was funded by the Health Research Council of	Patients aged 16–65 years <u>Sample size</u> $N=303$ participants were randomly assigned (151 patients assigned to Budesonide/formoterol maintenance + reliever [SMART group], and 152 to Budesonide/formoterol maintenance + salbutamol reliever [Standard group]) <u>Asthma severity</u> Persistent asthma (diagnosed last 6 months) on routine ICS and	<u>Intervention</u> Budesonide $200\mu\text{g}$ and formoterol $6\mu\text{g}$ in a single inhaler, two actuations twice daily plus one extra actuation as needed reliever, delivered by use of a combination metered dose inhaler (MDI) <u>Comparator/s</u> Budesonide $200\mu\text{g}$ and formoterol $6\mu\text{g}$ in a single inhaler, two actuations twice daily, delivered by MDI plus salbutamol $100\mu\text{g}$ one to two actuations of salbutamol ($100\mu\text{g}$ per actuation) as needed by use of MDI	<u>Primary Outcomes</u> The proportion of participants with at least one high use (high-use episode) of β agonist during the study. For the SMART group, a high-use episode was defined as more than eight actuations of budesonide-formoterol in addition to the four maintenance doses (i.e., total >12 actuations) per 24 h; and for the standard group, it was more than 16 actuations of salbutamol per 24 h <u>Secondary Outcomes</u> - Medication use - Corticosteroid load* - Efficacy* - Adverse events* <i>*See definitions in paper, pages 34-35</i> <u>Results</u> - No significant difference was noted between the SMART and standard groups in the proportion of participants with at least one high-use episode of β agonist (84 [56%] vs 68 [45%], respectively, relative risk 1.24 [95% CI 0.99–1.56]; $p=0.058$) - There were fewer days of high use in the SMART group (mean 5.1 days [SD 14.3] vs 8.9 days [20.9], relative rate 0.58 [0.39–0.88]; $p=0.01$) - The SMART regimen resulted in higher inhaled corticosteroid exposure (943.5μg budesonide per day [1502.5] vs 684.3μg budesonide per day [390.5], respectively; ratio of means 1.22 [1.06–1.41]; $p=0.006$), but reduced oral corticosteroid exposure

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Lancet Respiratory Medicine. 2013 Mar 1;1(1):32-42.	New Zealand (reference 09/108B), a government funding organisation. The Medical Research Institute of New Zealand has received research funding from AstraZeneca for the unrelated study (ACTRN12610000666022)". <u>Declarations</u> Listed in paper <u>Informed Consent</u> "All participants provided written informed consent".	with a history of at least one severe exacerbation in 12 months pre-study		(77.5 mg prednisone [240.5] vs 126.6 mg prednisone [382.1], respectively; $p=0.011$), with no significant difference in composite systemic corticosteroid exposure (793.7 mg prednisone equivalent per year [893.1] vs 772.1 mg prednisone equivalent per year [1062.7], respectively; 1.03 [0.86–1.22]; $p=0.76$) - Participants in the SMART group had fewer severe asthma exacerbations (35 [weighted mean rate per year 0.53] vs 66 [0.97]; relative rate 0.54 [0.36–0.82]; $p=0.004$) - Safety: - The adverse events were similar between treatment groups - All serious adverse events, eight in the SMART group and seven in the standard group were considered by the treating physicians to be unrelated to study participation

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Laloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. The Lancet. 2006 Aug 26;368(9537):744-53.	<u>Design</u> Double-blind, randomised parallel-group study <u>Setting</u> 289 centres in 20 countries: Belgium (21 centres), Bulgaria (11), China (6), Czech Republic (34), Germany (26), Greece (9), Hungary (20), Indonesia (6), Italy (6), Malaysia (3), The Netherlands (30), Norway (17), the Philippines (11), Poland (18), Romania (12), Russia (11), Slovakia (12), South Africa (30), South Korea (4), and Vietnam (2) <u>Follow-up duration (weeks)</u> 52 <u>Funding</u> AstraZeneca	Outpatients aged 12 years or older <u>Sample size</u> N=3,394 participants were randomly assigned (1,113 patients assigned to Budesonide/formoterol maintenance + reliever, 1,141 to Budesonide/formoterol maintenance + terbutaline reliever, and 1,140 to Budesonide/formoterol maintenance + as needed formoterol) <u>Asthma severity</u> Persistent asthma (diagnosed for at least 6 months). All patients had used ICS for at least 3 months and at a constant dose for ≥4 weeks immediately before entry and with a history of at least one severe exacerbation in the 12 months pre-study. Eligible for randomisation if reliever used ≥ 5 days (not >10 inhalations/day) for last 7 days of run-in	<u>Intervention</u> Budesonide/formoterol 160/4.5µg one inhalation twice daily plus budesonide/formoterol 160/4.5mg as needed <u>Comparator/s</u> - Budesonide/formoterol 160/4.5µg one inhalation twice daily plus additional inhalations of terbutaline 0.4mg as needed - Budesonide/formoterol 160/4.5µg one inhalation twice daily plus additional inhalations of formoterol 4.5µg as needed	<u>Primary Outcomes</u> Time to first severe exacerbation. The total number of severe exacerbations, number of days with hospitalisation, emergency room treatment, or both, and days with oral steroids because of exacerbations were recorded. A severe exacerbation was defined as deterioration in asthma resulting in emergency treatment or hospitalisation or the need for oral steroids for 3 days or more (as judged by the investigator) <u>Secondary Outcomes</u> - Total number of severe exacerbations - Time to the first and total number of emergency treatments or hospitalisations - Asthma symptom scores—asthma control questionnaire (five-item symptom and activity version; ACQ-5) score - Mild exacerbations - FEV1, morning and evening peak expiratory flow (PEF) - Reliever medication use <u>Results</u> - Time to first severe exacerbation was longer with as-needed budesonide-formoterol versus formoterol ($p=0.0048$; log-rank test) and with as-needed formoterol versus terbutaline ($p=0.0051$) - The rate of severe exacerbations was 37, 29, and 19 per 100 patients per year with as-needed terbutaline, formoterol, and budesonide-formoterol, respectively (rate ratios budesonide-formoterol versus formoterol 0.67 [95% CI 0.56–0.80; $p<0.0001$]; budesonide-formoterol versus terbutaline 0.52 [0.44–0.62; $p<0.0001$]; formoterol versus terbutaline 0.78 [0.67–0.91; $p=0.0012$]) - Safety: - Non-fatal SAEs were comparable across groups: 70 (6.3%), 55 (4.8%), and 65 (5.7%) for the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively - SAEs reported as asthma occurred in 16, 23, and 26 patients in the budesonide-formoterol, formoterol, and terbutaline groups, respectively - There were four deaths during the study (one in the as-needed budesonide-formoterol group, one in the formoterol group, and two in the terbutaline group), but the investigator judged none to be causally related to the study drugs, and none were reported as asthma

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	<u>Declarations</u> Listed in paper <u>Informed Consent</u> “All patients and parents or guardians of underage children gave written informed consent”.			
Ställberg B, Ekström T, Neij F, Olsson P, Skoogh BE, Wennergren G, Löfdahl CG, SHARE trial group. A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. Respiratory medicine. 2008 Oct 1;102(10):1360-70.	<u>Design</u> Randomised, open-label, parallel-group study <u>Setting</u> Primary care setting in Sweden <u>Follow-up duration (weeks)</u> 52 <u>Funding</u> AstraZeneca <u>Declarations</u> Listed in paper <u>Informed Consent</u>	Outpatients aged ≥12 years <u>Sample size</u> N=1,776 participants were randomly assigned (887 patients assigned to Budesonide/formoterol maintenance + reliever, 433 to free adjustable Budesonide/formoterol maintenance + terbutaline reliever, and 456 to fixed-dose Budesonide/formoterol maintenance + as-needed terbutaline) <u>Asthma severity</u> Persistent asthma	<u>Intervention</u> Budesonide/formoterol (160/4.5µg or 80/4.5µg, one inhalation twice daily or two inhalations once daily) for maintenance plus additional inhalations as needed. Doses depended on previous inhaled corticosteroid doses. <u>Comparator/s</u> - Free adjustable combination of budesonide (100–400µg/inhalation) and formoterol (4.5 or 9µg/inhalation) via separate inhalers plus terbutaline as needed (0.25 or 0.5 mg/inhalation). Budesonide and formoterol doses could be adjusted up or down within the approved dose range throughout the study at the discretion of the investigator - Budesonide/formoterol (160/4.5µg or 80/4.5µg, depending on previous ICS therapy, two inhalations twice daily) plus terbutaline	<u>Primary Outcomes</u> For direct asthma-related healthcare costs, the measure to determine clinical effectiveness in the cost-effectiveness analysis was the number of patients suffering at least one exacerbation during 1 year. An exacerbation was defined as deterioration in asthma resulting in a hospitalisation/emergency room visit or the use of oral corticosteroids due to asthma. <u>Secondary Outcomes</u> - Serious adverse events (SAEs) - Discontinuations due to an adverse event (DAEs) <u>Results</u> - Statistically significant reductions in annual direct costs per patient were observed with budesonide/formoterol maintenance and reliever therapy compared with the free adjustable combination of budesonide and formoterol (-13%, P<0.001) and fixed-dose budesonide/formoterol plus terbutaline (-20%, P<0.001) - Time to first severe exacerbation did not differ significantly across treatment groups, with a mean reduction of 28% versus the free adjustable combination of budesonide and formoterol (P=0.076) - Patients receiving budesonide/formoterol maintenance and reliever therapy used a significantly lower daily dose of budesonide compared with the conventional (P<0.001) - Safety:

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	“All patients gave written informed consent”.	(diagnosed last 30 days or more) on daily maintenance treatment with a free combination of an ICS ($\geq 400\mu\text{g}$) and a LABA, or to be symptomatic despite regular use of an ICS alone	as needed (0.25 or 0.5 mg/inhalation)	All study treatments were well tolerated. The number and type of SAEs and DAEs were low (66 SAEs and 71 DAEs in total) and similar between the treatment groups, and no clinically important differences were observed.
Takeyama K, Kondo M, Tagaya E, Kirishi S, Ishii M, Ochiai K, Isono K, Tamaoki J. Budesonide/formoterol maintenance and reliever therapy in moderate-to-severe asthma: effects on eosinophilic airway inflammation. Allergy & Asthma Proceedings 2014 Mar 1 (Vol. 35, No. 2).	<u>Design</u> Randomised, parallel-group study <u>Setting</u> Japan <u>Follow-up duration (weeks)</u> 52 <u>Funding</u> “Funded in part by Grant-in-Aid 23591127 from the Ministry of Education, Culture, Sports, Science and Technology, Japan”.	Outpatients aged 16–80 years <u>Sample size</u> N=63 participants were randomly assigned (32 patients assigned to Budesonide/formoterol maintenance + reliever, and 31 to Budesonide/formoterol maintenance + salbutamol reliever) <u>Asthma severity</u> Persistent asthma on a constant dose of ICS (daily budesonide 320–640μg or fluticasone,	<u>Intervention</u> Budesonide/formoterol 160/4.5μg, one inhalation twice daily for maintenance plus additional inhalations as needed. <u>Comparator/s</u> Budesonide/formoterol 160/4.5μg two inhalations twice daily plus salbutamol 100μg as needed	<u>Primary Outcomes</u> Time to first asthma exacerbations and the cumulative number of severe and mild exacerbations. Severe asthma exacerbations were defined as emergency department visits, systemic steroid use, or hospitalisation. Mild exacerbations were defined as unscheduled outpatient visits or reliever use more than four times a day. <u>Secondary Outcomes</u> • Mean use of as-needed medication • Peak expiratory flow (PEF), FEV1 • Symptom scores (ACT) • Airway inflammation <u>Results</u> • The time to first asthma exacerbation was significantly prolonged with as-needed budesonide/formoterol compared with salbutamol (log-rank test; $p = 0.0342$) • There was a 66% reduction in the hazard ratio for a first exacerbation with as-needed budesonide/formoterol ($p = 0.0334$) • The frequencies of both mild and severe exacerbations and reliever use were consistently less with budesonide/formoterol than with salbutamol • As needed, budesonide/formoterol significantly improved lung function and symptom scores compared with salbutamol

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	<u>Declarations</u> "The authors have no conflicts of interest to declare about this article". <u>Informed Consent</u> "All patients gave written informed consent".	200–500µg) ≥3 months plus LABA with a history of ≥1 severe exacerbation in 12 months pre-study, asthma control test (ACT) score of ≤20 points, and reliever use ≥5 times per week		

B: Comparator – Fluticasone/Salmeterol maintenance and a SABA reliever

Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quirarte J, Martinez-Aguilar NE, Carlsheimer A. Budesonide / formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/ fluticasone. Respir Med. 2007 Dec;101(12):2437-46.	<u>Design</u> Randomised, double-blind, parallel-group, multinational study <u>Setting</u> Multicentre, across 184 centres in 17 countries <u>Follow-up duration (weeks)</u> 26 <u>Funding</u> Astra Zeneca <u>Declarations</u> Listed in paper	Outpatients aged 12 years or older <u>Sample size</u> N=2,309 participants were randomly assigned (1,154 patients assigned to Budesonide/formoterol maintenance + reliever, and 1,155 to Salmeterol/fluticasone maintenance + terbutaline) <u>Asthma severity</u> Those with persistent asthma who had been treated with ICS alone (800–1600 mg/day) or ICS (400–1000 mg/day)	<u>Intervention</u> Budesonide/formoterol 160/4.5µg two inhalations twice daily plus budesonide/formoterol 160/4.5mg as needed <u>Comparator/s</u> Salmeterol/fluticasone 50/500µg, one inhalation twice daily + terbutaline 0.4mg as needed	<u>Primary Outcomes</u> Time to first severe exacerbation, defined as deterioration in asthma leading to hospitalisation/ emergency room (ER) treatment and/or oral corticosteroid treatment for at least 3 days <u>Secondary Outcomes</u> - Rate of severe exacerbations (as the same composite), the time to first hospitalisation/ER treatment and the rate of hospitalisation/ER treatments - Measures of daily asthma control, including peak expiratory flow, reliever use, asthma symptoms and nights with awakenings due to asthma symptoms, were recorded by patients in daily asthma diaries - Total use of as-needed inhalations recorded in patient diaries was also used to evaluate the mean daily dose of ICS with budesonide/formoterol maintenance and reliever therapy in delivered budesonide and beclomethasone dipropionate (BDP)-equivalent doses <u>Results</u> - Time to first severe exacerbation was not significantly prolonged (risk ratio 0.82; 95% confidence interval 0.63, 1.05) - Budesonide/formoterol maintenance and reliever therapy reduced total exacerbations from 31 to 25 events/100 patients/year (P = 0.039) and exacerbations requiring hospitalisation/emergency room (ER) treatment from 13 to 9 events/100 patients/year (P = 0.046).
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CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	<u>Informed Consent</u> "Written consent was obtained from all patients and parents or guardians of adolescents".	in combination with LABA for at least 3 months before study entry. To be eligible for randomisation at the end of the run-in, patients had to have used as-needed terbutaline on ≥ 5 of the previous 7 days, with no more than eight inhalations in any single day.		- The treatments showed no difference in measures of lung function or asthma symptoms - The mean dose of ICS received was lower using budesonide/formoterol maintenance and reliever therapy (792 mg/day budesonide [1238μg/day beclomethasone dipropionate (BDP) equivalent] versus 1000μg/day fluticasone [2000μg/day BDP equivalent] with salmeterol/fluticasone therapy; $P < 0.0001$). - Safety: - Both treatments were well tolerated: the number of patients reporting AEs (39% with budesonide/formoterol, 40% with salmeterol/fluticasone) - SAEs (3% with budesonide/formoterol, 3% with salmeterol/fluticasone) - One death occurred during the study (in the budesonide/formoterol group; severe typhoid fever) but was not considered by the investigator to be causally related to the study drug
Hozawa S, Terada M, Hozawa M. Comparison of the effects of budesonide/formoterol maintenance and reliever therapy with fluticasone/salmeterol fixed-dose treatment on airway inflammation and small airway impairment in patients who need to step up from inhaled corticosteroid monotherapy. Pulm Pharmacol Ther. 2014 Apr;27(2):190-6.	<u>Design</u> Single-center, randomised, open-label study <u>Setting</u> Single-center, Japan <u>Follow-up duration (weeks)</u> 8 <u>Funding</u> Astra Zeneca <u>Declarations</u> Listed in paper <u>Informed Consent</u> "All subjects provided written informed consent before	Outpatients ≥ 20 years of age <u>Sample size</u> N=30 participants were randomly assigned (15 patients assigned to Budesonide/formoterol maintenance + reliever, and 15 to Fluticasone propionate/salmeterol maintenance + procaterol) <u>Asthma severity</u> Prior treatment for ≥ 12 consecutive weeks with a medium dose of ICS (BUD, 800 mg/day; or FP and mometasone furoate, 400 mg/day) without	<u>Intervention</u> Budesonide/formoterol 160/4.5 μ g two inhalations twice daily plus budesonide/formoterol 160/4.5mg, one inhalation as needed (SMART) <u>Comparator/s</u> Fluticasone propionate/salmeterol 250/50 μ g, one inhalation twice daily + procaterol 10 μ g two inhalations as needed (FP/SM group)	<u>Primary Outcomes</u> The change in fractional exhaled nitric oxide (FeNO) values from baseline to after 8 weeks of treatment <u>Secondary Outcomes</u> - ACQ5 scores, spirometry parameters, and impulse oscillometry (IOS) parameters <u>Results</u> - Both groups showed significant improvement in airway inflammation, pulmonary functions, and symptoms from baseline - The SMART group showed significant improvement in the fraction of nitric oxide, ACQ score, rescue medication use, and small airway parameter R5eR20 measured by impulse oscillometry compared with the FP/SM group - Safety: No adverse event was reported in either group

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	participating in this study".	another controller or concomitant asthma medication except for SABA; Asthma Control Questionnaire (ACQ5; five-item Japanese version) score >0.75; SABA use 2-6 times per week		
Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, Naya I, Price D. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J. 2005 Nov;26(5):819-28.	<u>Design</u> Randomised, open-label, parallel-group study <u>Setting</u> 246 centres in 16 countries <u>Follow-up duration (weeks)</u> 52 <u>Funding</u> Astra Zeneca <u>Declarations</u> Listed under Acknowledgements in the paper <u>Informed Consent</u> "All patients gave written	Outpatients aged ≥12 years <u>Sample size</u> N=2,143 participants were randomly assigned (1,067 patients assigned to Budesonide/formoterol maintenance + reliever, and 1,076 to Salmeterol/fluticasone maintenance + salbutamol) <u>Asthma severity</u> Those with a diagnosis of asthma (as defined by the American Thoracic Society) for ≥6 months were eligible for inclusion in the study (0691) if they had used ≥500µg/day of budesonide or fluticasone (or	<u>Intervention</u> Budesonide/formoterol 160/4.5µg, 2 to 4 inhalations twice daily for maintenance plus additional inhalations as needed <u>Comparator/s</u> Salmeterol/fluticasone 50/250µg or 50/100µg or 50/500µg two inhalations twice daily plus salbutamol 100µg as needed	<u>Primary Outcomes</u> Time to first severe exacerbation: A severe exacerbation was defined as a deterioration in asthma, resulting in hospitalisation/emergency room (ER) treatment, oral steroids for ≥3 days, or an unscheduled visit (i.e. patient-initiated) leading to treatment change <u>Secondary Outcomes</u> - Severe exacerbations excluding unscheduled patient-initiated visits not resulting in hospitalisation/ER treatment or oral steroid therapy - Hospitalisation/ER treatment alone - The total number of severe exacerbations - Number of days with exacerbations - Days with oral steroids due to exacerbations were recorded - FEV1 - Asthma Control Questionnaire (five-item version ACQ-5) - Adverse events (AEs) <u>Results</u> - Maintenance plus as-needed budesonide/formoterol prolonged the time to the first severe exacerbation versus salmeterol/fluticasone (25% risk reduction) - The total number of severe exacerbations was significantly reduced in the budesonide/formoterol group (255 versus 329) - Both regimens provided sustained improvements in symptoms, as-needed use, quality of life, and FEV1, with differences in favour of the budesonide/formoterol group for as-needed use (0.58 versus 0.93 inhalations/day) and FEV1 (post-β2-agonist values) - Mean ICS dose during treatment was similar in both groups (653µg budesonide/day (maintenance plus as needed) versus 583µg fluticasone/day) - Safety:

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	informed consent".	≥1,000µg of another ICS) for at least 1 month before study entry and had at least one severe exacerbation >2 weeks but ≤12 months before study entry. Patients must have used as-needed medication on ≥4 of the last 7 days of run-in to be eligible for randomisation.		○ Both treatments were well tolerated, and there were no notable differences between the groups in the number or severity of AEs ○ There were 168 SAEs (80 versus 88 for budesonide/formoterol versus salmeterol/fluticasone patients, respectively); of these, one patient in the budesonide/formoterol group and two patients receiving salmeterol/fluticasone had SAEs that the investigator considered to be causally related to study medication ○ Two deaths occurred during the treatment period in the salmeterol/fluticasone group, but these were not judged to be causally related to the investigational products

Appendix 11: Risk of Bias Assessment for PICO 3

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall	
Alenza 2013	Bud/form maintenance + reliever	Bud/form + terbutaline	Severe asthma exacerbations	+	+	+	+	+	+	Low risk
Alenza 2013	Bud/form maintenance + reliever	Bud/form + terbutaline	Emergency room treatments	+	+	+	+	+	+	Some concerns
Alenza 2013	Bud/form maintenance + reliever	Bud/form + terbutaline	Asthma hospital admissions	+	+	+	+	+	+	High risk
Alenza 2013	Bud/form maintenance + reliever	Bud/form + terbutaline	Systemic corticosteroid course	+	+	+	+	+	+	
Alenza 2013	Bud/form maintenance + reliever	Bud/form + terbutaline	Mortality	+	+	+	+	+	+	D1 Randomisation process
Alenza 2013	Bud/form maintenance + reliever	Bud/form + terbutaline	Adverse events	+	+	+	+	+	+	D2 Deviations from the intended interventions
Alenza 2013	Bud/form maintenance + reliever	Bud/form + terbutaline	SAEs	+	+	+	+	+	+	D3 Missing outcome data
Kuna 2007	Bud/form maintenance + reliever	Bud/form double dose + terbutaline OR Flu/salm + terbutaline	Severe asthma exacerbations	+	+	+	+	+	+	D4 Measurement of the outcome
Kuna 2007	Bud/form maintenance + reliever	Bud/form double dose + terbutaline OR Flu/salm + terbutaline	Emergency room treatments/ hospitalisations	+	+	+	+	+	+	D5 Selection of the reported result
Kuna 2007	Bud/form maintenance + reliever	Bud/form double dose + terbutaline OR Flu/salm + terbutaline	Systemic corticosteroid course	+	+	+	+	+	+	
Kuna 2007	Bud/form maintenance + reliever	Bud/form double dose + terbutaline OR Flu/salm + terbutaline	Mortality	+	+	+	+	+	+	
Kuna 2007	Bud/form maintenance + reliever	Bud/form double dose + terbutaline OR Flu/salm + terbutaline	Adverse events	+	+	+	+	+	+	
Kuna 2007	Bud/form maintenance + reliever	Bud/form double dose + terbutaline OR Flu/salm + terbutaline	SAEs	+	+	+	+	+	+	
O'Byrne 2005	Bud/form maintenance + reliever	Bud/form + terbutaline	Severe asthma exacerbations	+	+	+	+	+	+	
O'Byrne 2005	Bud/form maintenance + reliever	Bud/form + terbutaline	Systemic corticosteroid course	+	+	+	+	+	+	
O'Byrne 2005	Bud/form maintenance + reliever	Bud/form + terbutaline	Adverse events	+	+	+	+	+	+	
O'Byrne 2005	Bud/form maintenance + reliever	Bud/form + terbutaline	SAEs	+	+	+	+	+	+	
Papi 2013	Beco/form maintenance + reliever	Beco/form + salbutamol	Severe asthma exacerbations	+	+	+	+	+	+	
Papi 2013	Beco/form maintenance + reliever	Beco/form + salbutamol	Emergency room treatments/ hospitalisations	+	+	+	+	+	+	
Papi 2013	Beco/form maintenance + reliever	Beco/form + salbutamol	Systemic corticosteroid course	+	+	+	+	+	+	
Papi 2013	Beco/form maintenance + reliever	Beco/form + salbutamol	Mortality	+	+	+	+	+	+	
Papi 2013	Beco/form maintenance + reliever	Beco/form + salbutamol	Adverse events	+	+	+	+	+	+	
Papi 2013	Beco/form maintenance + reliever	Beco/form + salbutamol	SAEs	+	+	+	+	+	+	
Papi 2013	Beco/form maintenance + reliever	Beco/form + salbutamol	ADRs	+	+	+	+	+	+	
Patel 2013	Bud/form maintenance + reliever	Bud/form + salbutamol	Severe asthma exacerbations	+	+	+	+	+	+	
Patel 2013	Bud/form maintenance + reliever	Bud/form + salbutamol	Emergency room treatments/ hospitalisations	+	+	+	+	+	+	
Patel 2013	Bud/form maintenance + reliever	Bud/form + salbutamol	Systemic corticosteroid course	+	+	+	+	+	+	
Patel 2013	Bud/form maintenance + reliever	Bud/form + salbutamol	Mortality	+	+	+	+	+	+	
Patel 2013	Bud/form maintenance + reliever	Bud/form + salbutamol	Adverse events	+	+	+	+	+	+	
Patel 2013	Bud/form maintenance + reliever	Bud/form + salbutamol	SAEs	+	+	+	+	+	+	
Rabe 2006	Bud/form maintenance + reliever	Bud/form + terbutaline	Severe asthma exacerbations	+	+	+	+	!	!	
Rabe 2006	Bud/form maintenance + reliever	Bud/form + terbutaline	Emergency room treatments/ hospitalisations	+	+	+	+	!	!	
Rabe 2006	Bud/form maintenance + reliever	Bud/form + terbutaline	Mortality	+	+	+	+	!	!	
Rabe 2006	Bud/form maintenance + reliever	Bud/form + terbutaline	Adverse events	+	+	+	+	!	!	
Rabe 2006	Bud/form maintenance + reliever	Bud/form + terbutaline	SAEs	+	+	+	+	!	!	
Rabe 2006	Bud/form maintenance + reliever	Bud/form + terbutaline	ADRs	+	+	+	+	!	!	
Stalberg 2008	Bud/form maintenance + reliever	Bud/form + terbutaline	Severe asthma exacerbations	+	+	+	+	+	+	
Stalberg 2008	Bud/form maintenance + reliever	Bud/form + terbutaline	Adverse events	+	+	+	+	+	+	
Stalberg 2008	Bud/form maintenance + reliever	Bud/form + terbutaline	SAEs	+	+	+	+	+	+	
Takeyama 2014	Bud/form maintenance + reliever	Bud/form + salbutamol	Severe asthma exacerbations	!	!	+	+	!	!	
Bousquet 2007	Bud/form maintenance + formoterol	Flu/salm + salbutamol	Severe asthma exacerbations	+	+	+	+	+	+	
Bousquet 2007	Bud/form maintenance + formoterol	Flu/salm + salbutamol	Emergency room treatments/ hospitalisations	+	+	+	+	+	+	
Bousquet 2007	Bud/form maintenance + formoterol	Flu/salm + salbutamol	Systemic corticosteroid course	+	+	+	+	+	+	
Bousquet 2007	Bud/form maintenance + formoterol	Flu/salm + salbutamol	Mortality	+	+	+	+	+	+	
Bousquet 2007	Bud/form maintenance + formoterol	Flu/salm + salbutamol	Adverse events	+	+	+	+	+	+	
Bousquet 2007	Bud/form maintenance + formoterol	Flu/salm + salbutamol	SAEs	+	+	+	+	+	+	
Hozawa 2014	Bud/form maintenance + reliever	Flu/salm + procaterol	Adverse events	!	+	+	+	+	!	
Vogelmeier 2005	Bud/form maintenance + reliever	Flu/salm + salbutamol	Severe asthma exacerbations	+	+	+	+	!	!	
Vogelmeier 2005	Bud/form maintenance + reliever	Flu/salm + salbutamol	Emergency room treatments/ hospitalisations	+	+	+	+	!	!	
Vogelmeier 2005	Bud/form maintenance + reliever	Flu/salm + salbutamol	Systemic corticosteroid course	+	+	+	+	!	!	
Vogelmeier 2005	Bud/form maintenance + reliever	Flu/salm + salbutamol	Mortality	+	+	+	+	!	!	
Vogelmeier 2005	Bud/form maintenance + reliever	Flu/salm + salbutamol	Adverse events	+	+	+	+	!	!	
Vogelmeier 2005	Bud/form maintenance + reliever	Flu/salm + salbutamol	SAEs	+	+	+	+	!	!	

Risk of bias assessment – review authors' judgments for each reported outcome per the included study

We assessed the following domains of risk of bias using the Cochrane ROB2 tool for outcomes reported in the eligible RCTs:

- *Bias arising from the randomisation process:* We judged most trials as low risk of bias for this domain, as randomisation was performed using computer-generated lists and there was adequate allocation concealment. Two trials reported insufficient information to determine if the allocation sequence was adequately randomised and concealed (Takeyama, 2014; Hozawa, 2014).
- *Bias arising from deviation from the intended interventions:* One trial did not provide information on whether the study was blinded or open-label (Takeyama, 2014). The remaining studies were either blinded or open-label, and appropriate intention-to-treat analyses were performed to estimate the effect of assignment to intervention in all the trials.
- *Bias due to missing outcome data:* Outcome data was available for all or nearly all study participants who underwent randomisation.
- *Bias in measurement of the outcome:* We judged all trials as low risk of bias for all outcomes for this domain.
- *Bias due to selection of the reported result:* Published protocols detailing pre-specified outcome(s) and statistical analysis plans were unavailable for three trials (Rabe, 2006; Takeyama, 2014; Volgmeier, 2005). Study investigators have been contacted.

Appendix 12: Summary of serious adverse events, adverse events and adverse drug reactions for PICO 3

Study ID	Serious Adverse Events	Adverse Events	Adverse Drug Reactions
Atienza 2013	- SAEs other than death occurred in 4.0% and 7.1% of patients in the budesonide/formoterol maintenance and reliever therapy and budesonide/ formoterol plus terbutaline groups, respectively - Asthma recorded as an SAE occurred less frequently in budesonide/formoterol maintenance and reliever therapy patients than those receiving budesonide/formoterol plus terbutaline (0.5% vs 3.0%)	- These are reported in Supporting Table S2 - Most AEs were mild or moderate in intensity - The most frequently reported AEs were nasopharyngitis, bronchitis, and viral upper respiratory tract infection (URTI) - Asthma recorded as an AE occurred less frequently among budesonide/ formoterol maintenance and reliever therapy patients than budesonide/formoterol plus terbutaline patients (4.7% [49/1,049] vs 7.2% [75/1,042]) - AEs were related to study treatment for 3.9% of budesonide/formoterol maintenance and reliever therapy patients and 3.5% of budesonide/formoterol plus terbutaline patients 11 patients receiving budesonide/ formoterol maintenance and reliever therapy, and 12 receiving budesonide/formoterol plus terbutaline discontinued due to an AE	NR
Bousquet 2007	The number of patients reporting SAEs (3% with budesonide/formoterol, 3% with salmeterol/fluticasone) was similar in both treatment groups	- The number of patients reporting AEs (39% with budesonide/formoterol, 40% with salmeterol/fluticasone) was similar in both treatment groups - Discontinuations were rare in both treatment groups; there were 31 in total (11/1154 [1.0%] with budesonide/formoterol, 20/1155 [1.7%] with salmeterol/fluticasone) - Discontinuations in the salmeterol/fluticasone group included eight reports of events associated with the class effects of ICS or β_2-agonists (dysphonia, oral candidiasis, oral fungal infection, tremor, tachycardia and palpitations), compared with only one such report in the budesonide/ formoterol group (headache)	NR
Hozawa 2014	NR	No adverse event was reported in either group	NR
Kuna 2007	- SAEs were uncommon, and their incidence was comparable across all three treatment groups: 32 patients (3%) in the salmeterol/fluticasone group, 39 patients (4%) in the fixed-dose budesonide/formoterol group, and 31 patients (3%) in the SMART group experienced such events - Asthma reported as an SAE occurred in 15 patients (1.3%) in the salmeterol/fluticasone group, 12 patients (1.1%) in the fixed-dose budesonide/ formoterol group, and seven patients (0.6%) in the SMART group (Supplementary file) - The investigator considered four SAEs to be causally related to the study drug: three in the SMART group (pneumonia, gastritis and asthma) and one in the salmeterol/fluticasone group (asthma)	- The most frequently reported AEs were URIs, pharyngitis, and nasopharyngitis - ten patients (0.1%) receiving salmeterol/fluticasone therapy, 13 (1.2%) receiving fixed-dose budesonide/formoterol therapy, and 11 (1.0%) receiving SMART therapy discontinued due to an AE (Supplementary file) - The incidence of pharmacologically predictable adverse events related to ICS and LABA use was low and comparable in all treatment groups	NR

Study ID	Serious Adverse Events	Adverse Events	Adverse Drug Reactions
O'Byrne 2005	The number of patients with one or more SAEs was similar in each treatment group: 7% (62/906) for bud/form + SABA and 5% (46/922) for bud/form maintenance + relief.	• AEs were generally mild to moderate in intensity • There were no notable differences between the three groups for AEs • The total number of patients with one or more AEs was 475 (52%) with bud/form + SABA and 496 (54%) with bud/form for maintenance + relief • There were 7 and 15 discontinuations because of respiratory events in the bud/form maintenance + relief and bud/form +SABA respectively. Of these, aggravated asthma (worsening asthma) occurred in 2 patients in the bud/form maintenance + relief group compared with 13 patients in the bud/form + SABA group • There were no notable differences between the groups for AEs related to treatment with β2-agonists or ICS (Table 3): 55/925 (5.9%) vs 52/909 (5.7%) in the bud/form for maintenance + relief and bud/form + SABA, respectively	NR
Papi 2013	• Similar numbers of patients in the as-needed beclometasone–formoterol and salbutamol groups had serious adverse events (32/852 [4%] and 41/849 [5%], respectively; paper appendix p 14 • Serious adverse events reported as asthma occurred in 8/852 (0.9%) patients treated with as-needed beclomethasone/formoterol and 19/849 (2.2%) patients treated with as-needed salbutamol	• Treatments were well tolerated with no difference in the incidence of adverse events between groups (Supplementary Table E2) • Discontinuations due to asthma were less common in the as-needed beclomethasone/formoterol group (one patient [0.1%] discontinued) compared with the as-needed salbutamol group (11 patients [1.3%] discontinued) • The occurrence of pharmacologically predictable adverse events related to treatment with inhaled corticosteroids or β2 agonists were low in both treatment groups	Adverse drug reactions were significantly ($p=0.01$) higher in the beclometasone–formoterol group for maintenance and reliever treatment (4.5%, 38/852) compared to beclometasone–formoterol maintenance and as-needed salbutamol reliever group (2.2%, 19/849); (paper appendix pp 14–15). No further details were reported on these ADRs
Patel 2013	All SAEs, 8/151 (5.3%) in the SMART group and 7/152 (4.6%) in the standard (SABA reliever) group, were considered by the treating physicians to be unrelated to study participation (paper appendix pp 18–21)	• The AEs were similar between treatment groups • The most frequently occurring adverse events were URTI (66 [44%] participants in the SMART group and 65 [43%] in the standard group), injury, trauma, or musculoskeletal ailment (27 [18%] and 17 [11%], respectively), and adverse taste (19 [13%] and 19 [13%], respectively) • The most frequently occurring AE leading to discontinuation was palpitations (one [$<1\%$] participant in the SMART group and two [1%] in the standard group)	NR

Rabe 2006	- The number of patients with non-fatal SAEs was comparable across groups: 70 (6.3%) and 65 (5.7%) for the as-needed budesonide-formoterol and terbutaline groups, respectively - SAEs reported as asthma occurred in 16/1113 (1.4%) and 26/1141 (2.3%) of patients in the budesonide-formoterol and terbutaline groups, respectively (table 4)	- Discontinuations due to asthma were less common in the as-needed budesonide-formoterol group compared with the formoterol and terbutaline groups (1 patient (0.09%) versus ten patients, respectively) - The incidence of pharmacologically predictable adverse events related to treatment with inhaled corticosteroids or β_2 agonists were rare and comparable across all treatment groups (table 4)	NR
Study ID	Serious Adverse Events	Adverse Events	Adverse Drug Reactions
Ställberg 2008	The number and type of SAEs and DAEs were low (66 SAEs and 71 DAEs in total) and similar between the treatment groups, and no clinically important differences were observed	NR	NR
Takeyama 2014	NR	NR	NR
Vogelmeier 2005	- There were 168 serious AEs (80/1067 [7.5%] versus 88/1076 [8.2%] for budesonide/formoterol versus salmeterol/fluticasone patients, respectively) - Overall, one patient in the budesonide/formoterol group and two patients receiving salmeterol/fluticasone had serious AEs that the investigator considered to be causally related to the study medication	Although a comparable number of patients discontinued the study due to AEs (27/1067 [2.5%] budesonide/formoterol patients versus 28/1076 [2.6%] salmeterol/fluticasone patients), a greater number of salmeterol/fluticasone patients withdrew owing to asthma versus budesonide/ formoterol patients (11 versus three patients, respectively)	NR

Appendix 13: Subgroup and sensitivity analyses for PICO 3

Post-hoc subgroup analyses by daily ICS dose (low and medium-high subgroups) were conducted (see Excel embedded file below). Study arms comparing low daily ICS doses were included, i.e. (Bud/form 160/4.5mcg bd + bud/form as needed vs. Salm/fluticasone 25/125mcg bd + terbutaline as needed), and the study arm with data from the medium daily ICS dose (Bud/form 320/9mcg bd + terbutaline as needed) were excluded (Kuna, 2007). We did not include data from one study (Bousquet, 2007) in the subgroup analyses as daily ICS doses in each study arm were not comparable i.e. medium vs. high.

Similarly, for sensitivity analyses, we removed studies (Bousquet, 2007; Kuna, 2007) where the background maintenance ICS dose differed between groups, as noted above. We further excluded the study by Vogelmeier *et al.* (Vogelmeier, 2005) in the sensitivity analysis as participants in both study arms received varying doses of daily maintenance ICS therapy (either medium or high doses) depending on their individual symptom control.

Both subgroup and sensitivity analyses did not substantially affect the overall relative effect sizes and their 95% CIs. Hence, we report the original forest plots and associated effect sizes and 95% CIs, and the findings from the subgroup and sensitivity analyses can be found in Appendix 13.

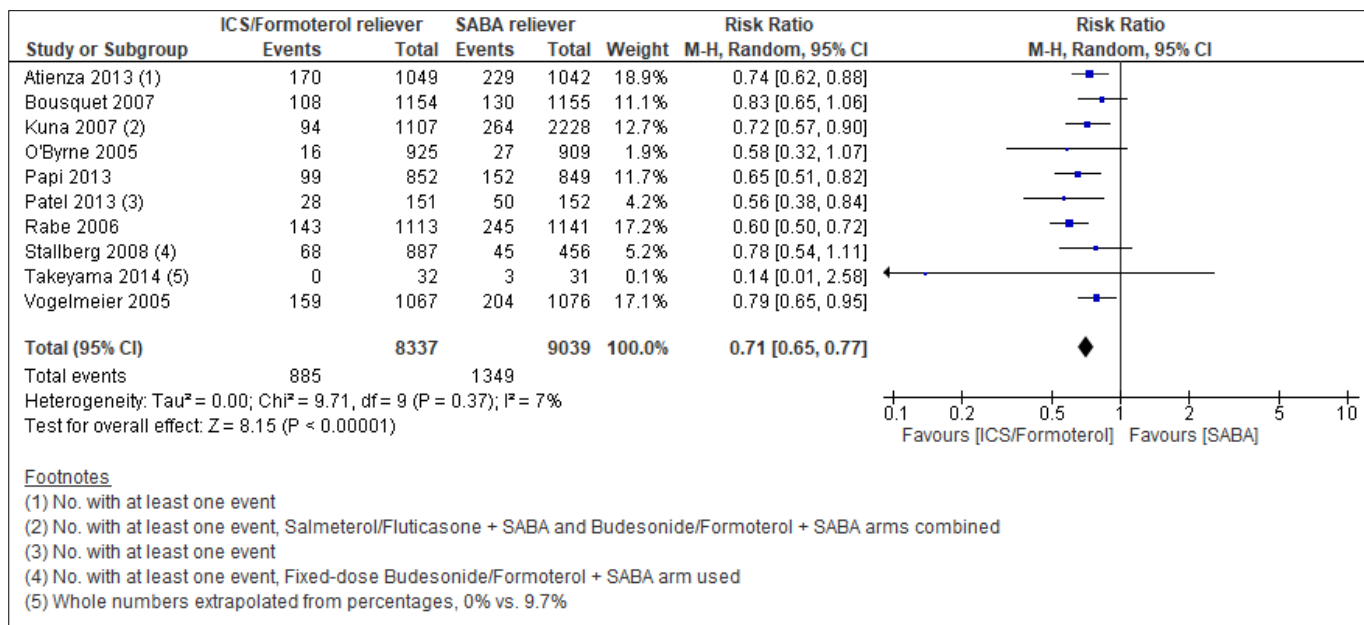


PICO 3_Doses
across studies_v3.xls

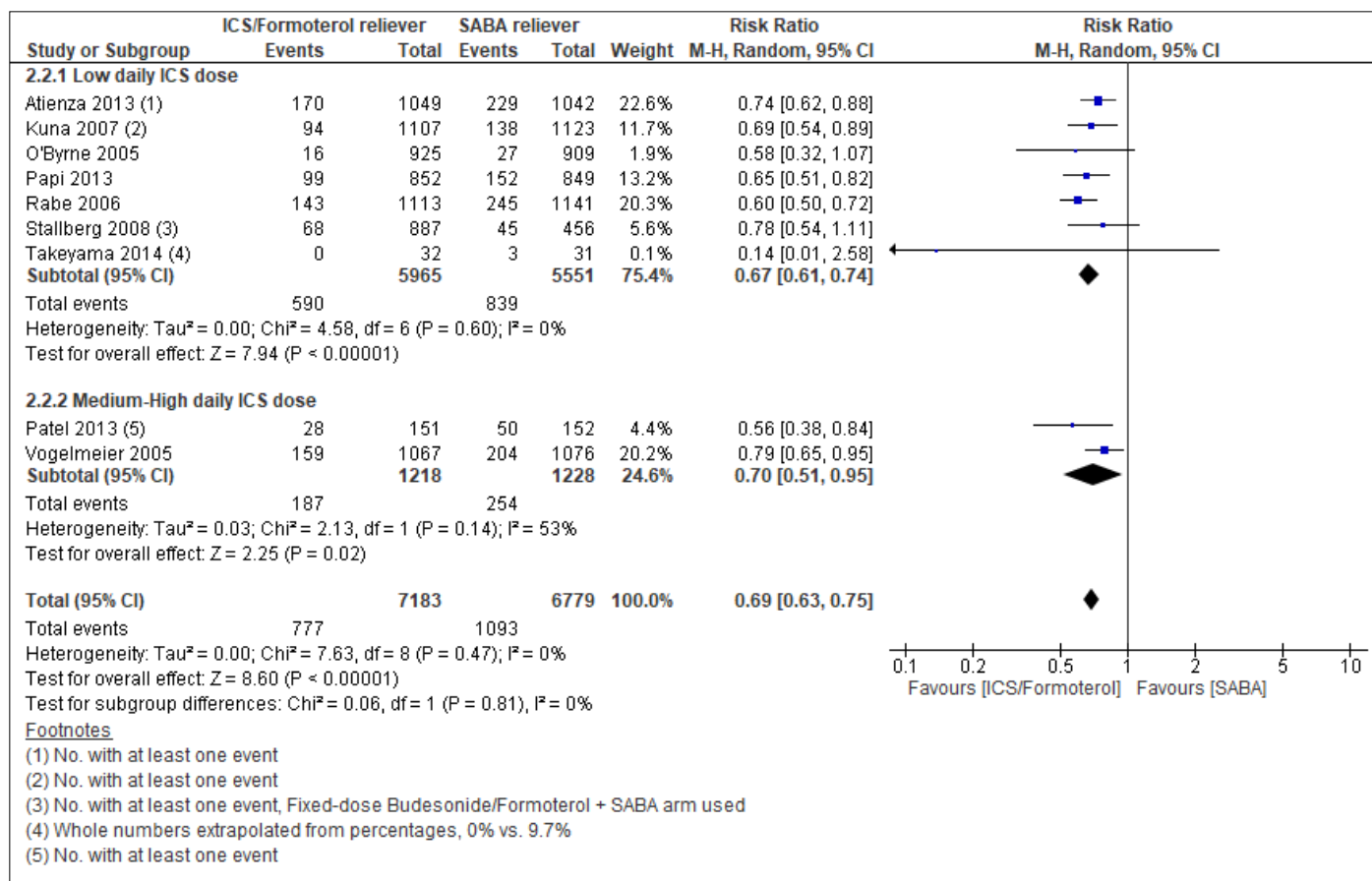
Effects of the intervention

ICS/Formoterol maintenance and reliever versus ICS/LABA maintenance and a SABA reliever

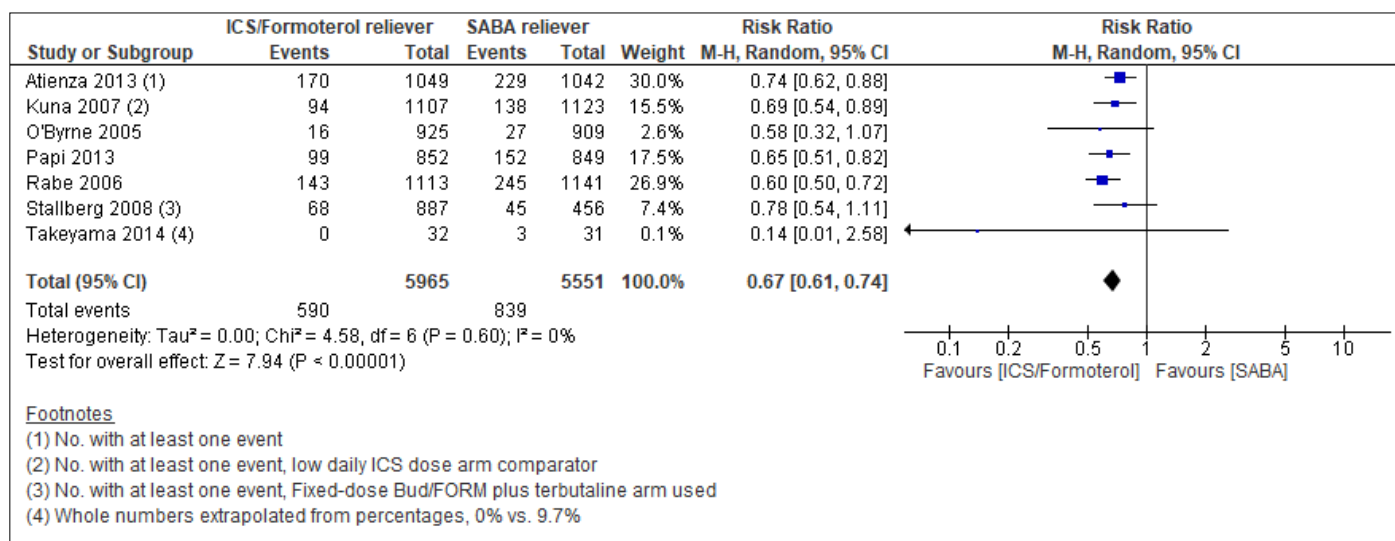
1. Severe asthma exacerbations



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Severe asthma exacerbation (Original)

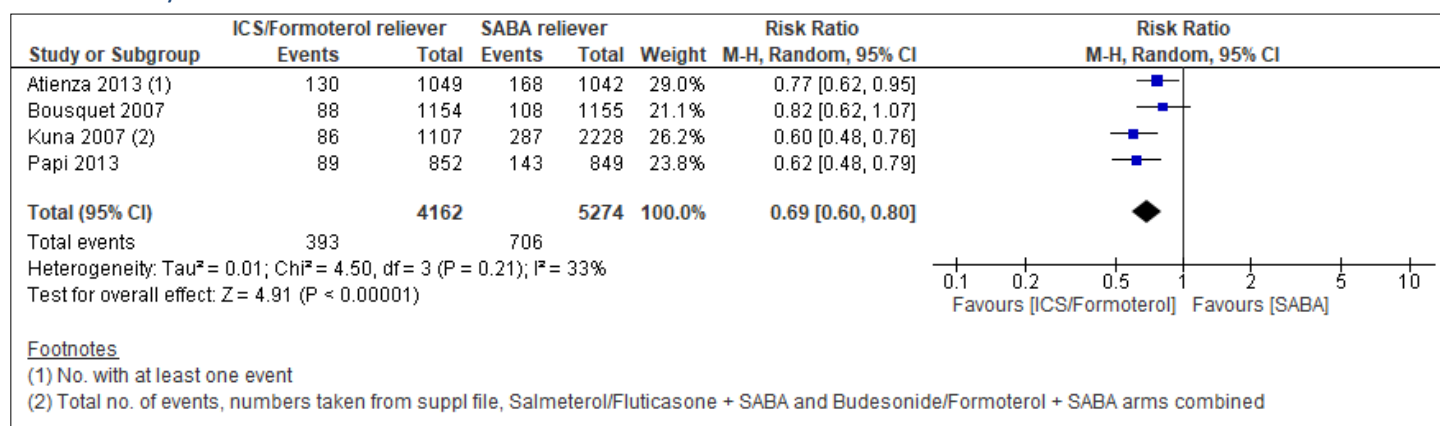


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Severe asthma exacerbation (Subgroup analyses)

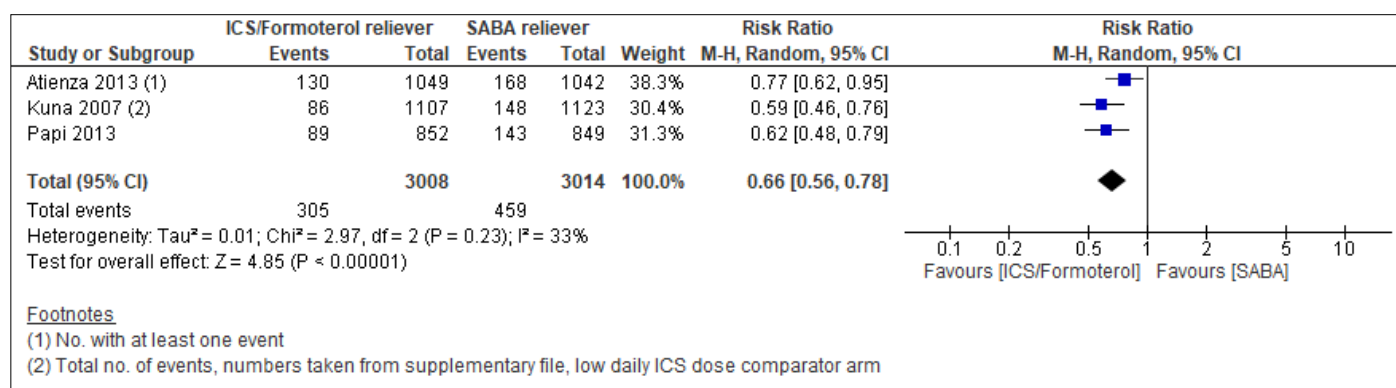


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Severe asthma exacerbation (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

2. Systemic corticosteroid use*



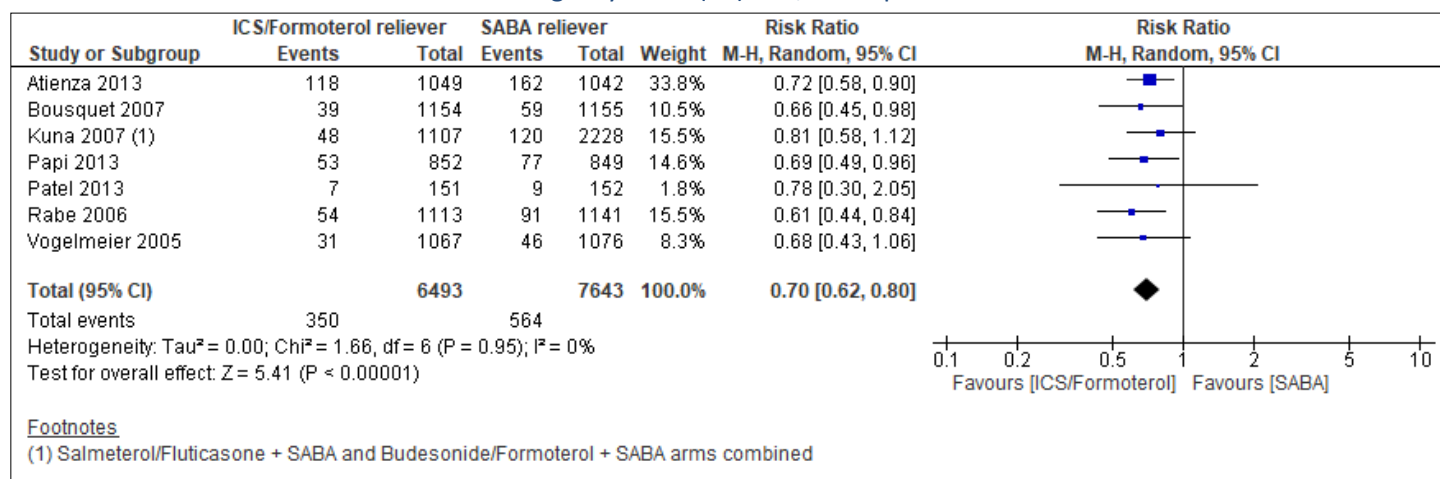
Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Systemic corticosteroid use (Original)



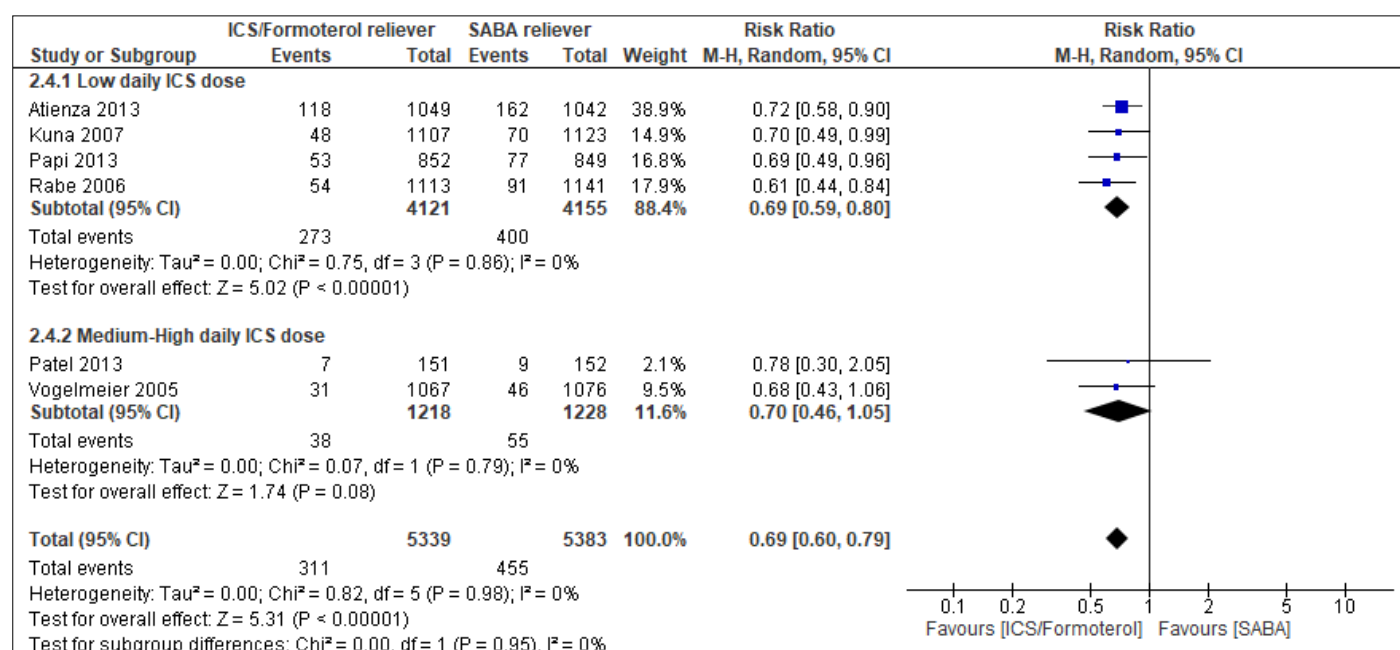
Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Systemic corticosteroid use (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

*No subgroup analyses were conducted as the studies (Atienza, 2013; Kuna, 2007; Papi, 2013) compared low daily ICS maintenance doses in both arms. We did not include data from one study (Bousquet, 2007) in the subgroup analyses as daily ICS doses in each study arm were not comparable i.e. medium vs. high.

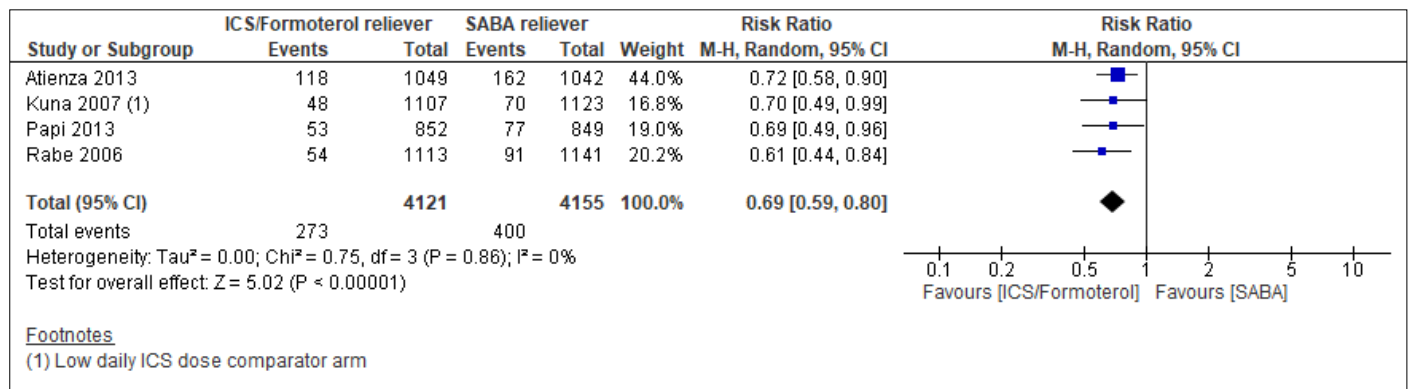
3. Asthma-related visits to the emergency room (ER) and/or hospital admissions



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related visits to the emergency room (ER) and/or hospital admissions (Original)

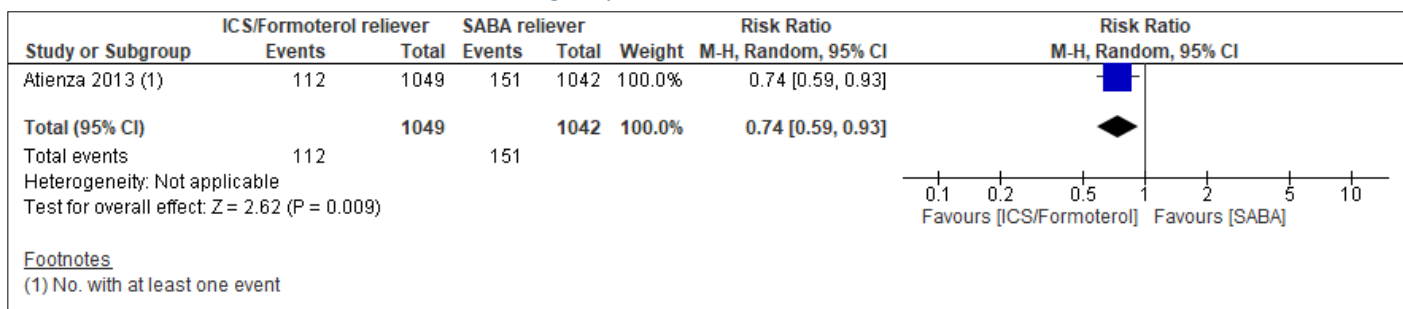


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related visits to the emergency room (ER) and/or hospital admissions (Subgroup analyses)



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related visits to the emergency room (ER) and/or hospital admissions (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

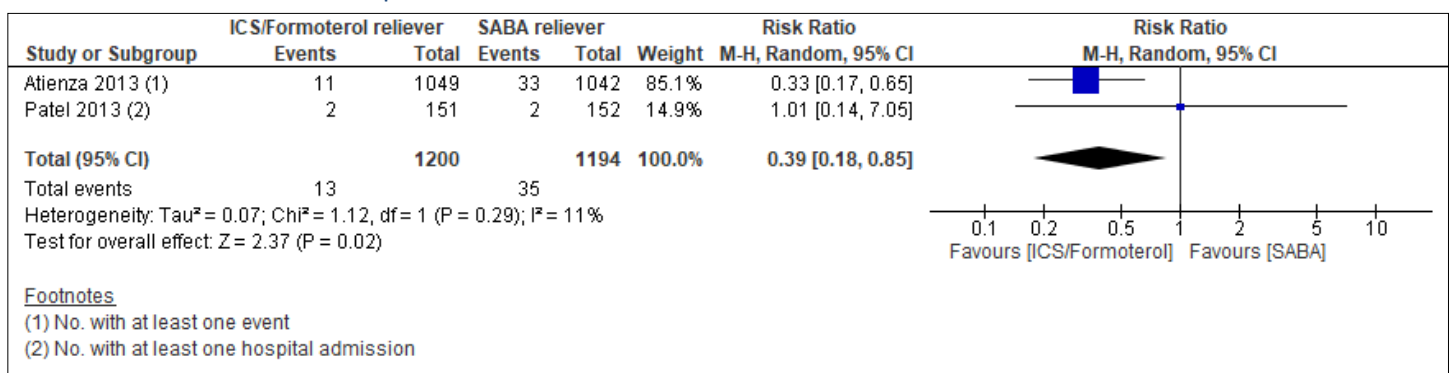
4. Asthma-related visits to the emergency room (ER)**



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related visits to the ER (Original)

**Only one study was included in the meta-analysis; thus, no subgroup or sensitivity analyses were done

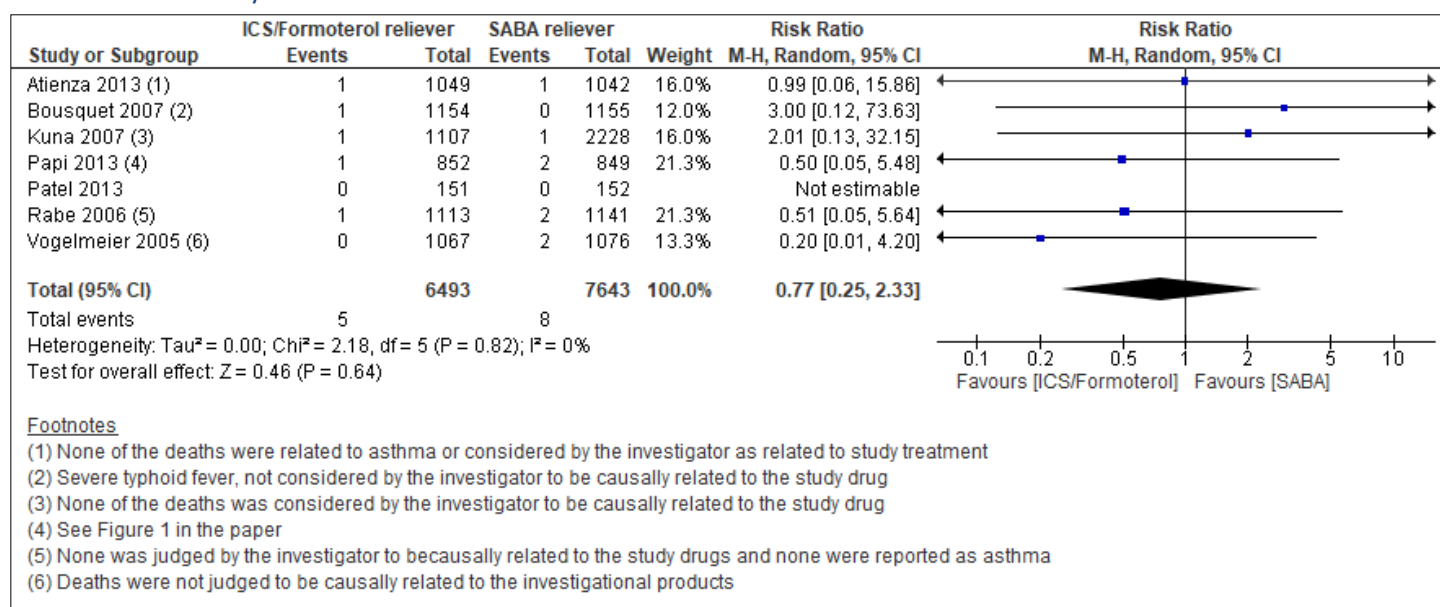
5. Asthma-related hospital admissions***



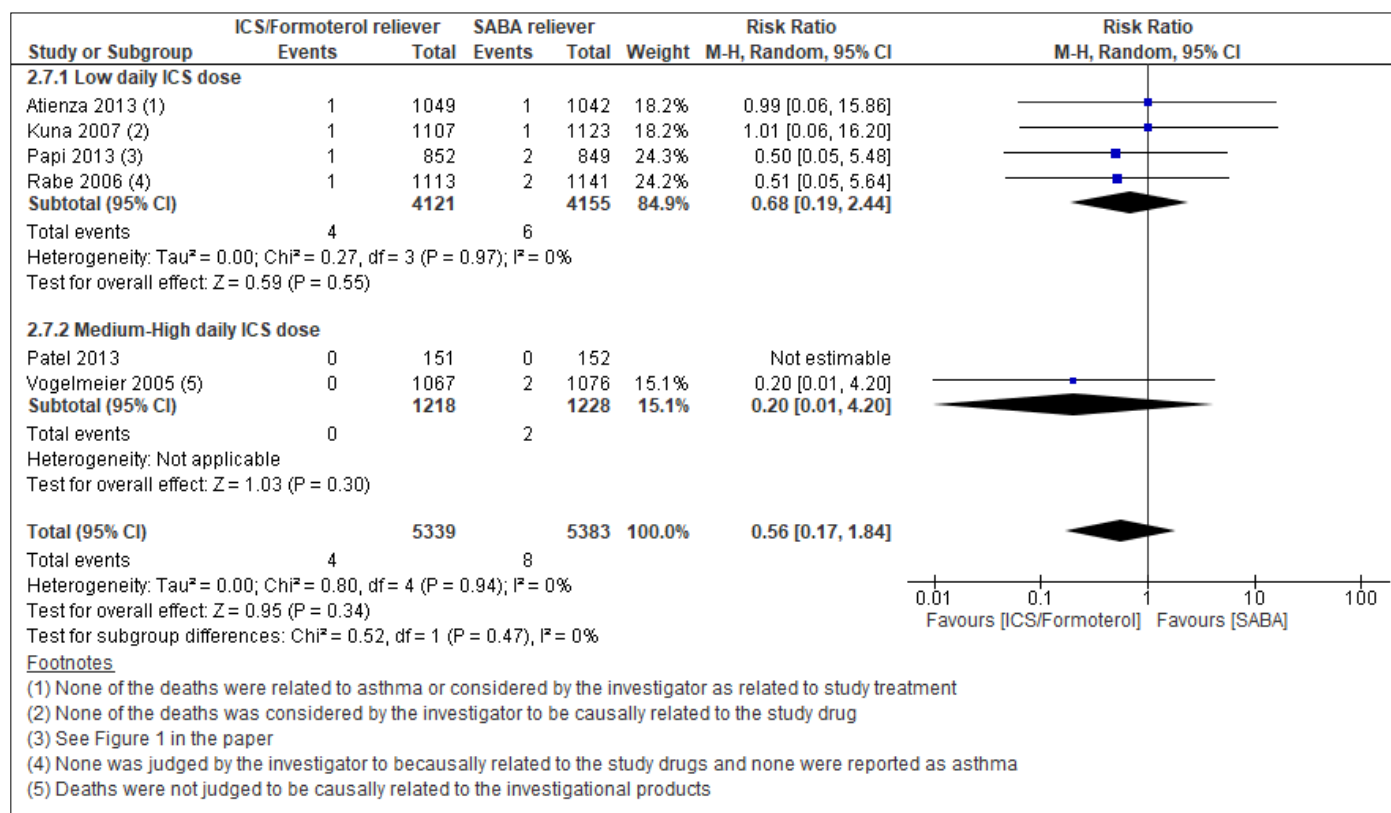
Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related hospital admissions (Original)

***Only two studies were included in the meta-analysis; thus, no subgroup or sensitivity analyses were done

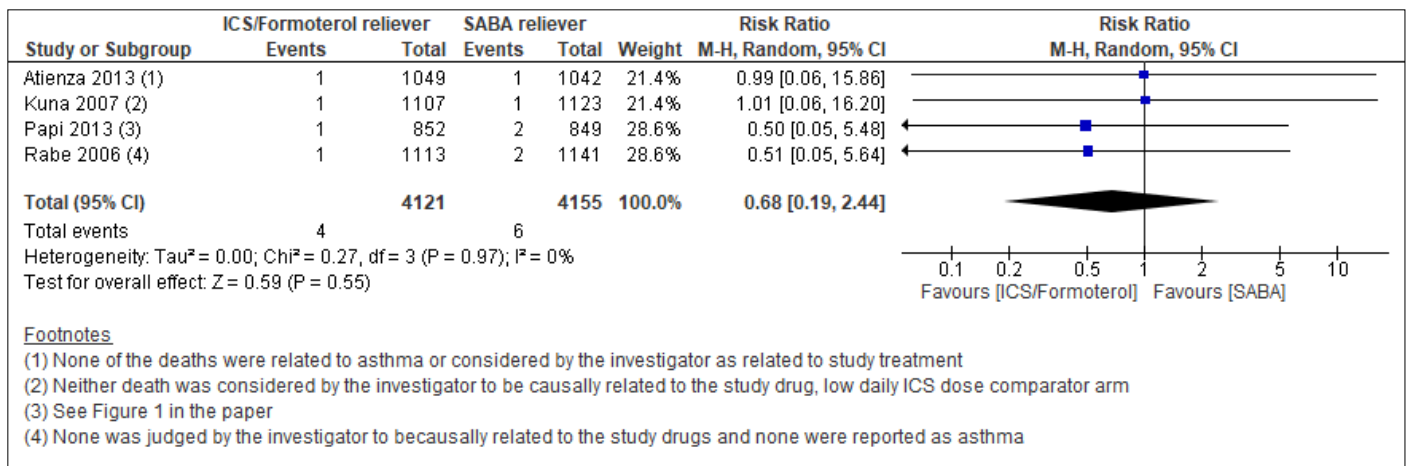
6. Mortality



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Mortality (Original)

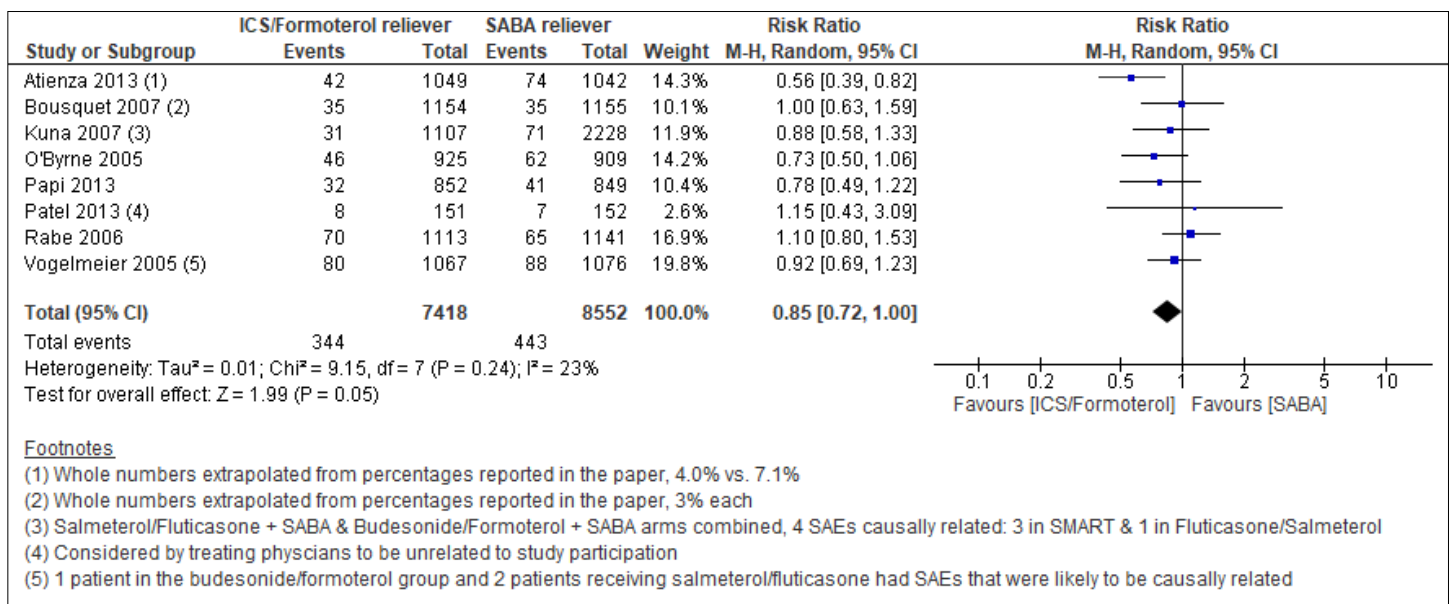


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Mortality (Subgroup analyses)

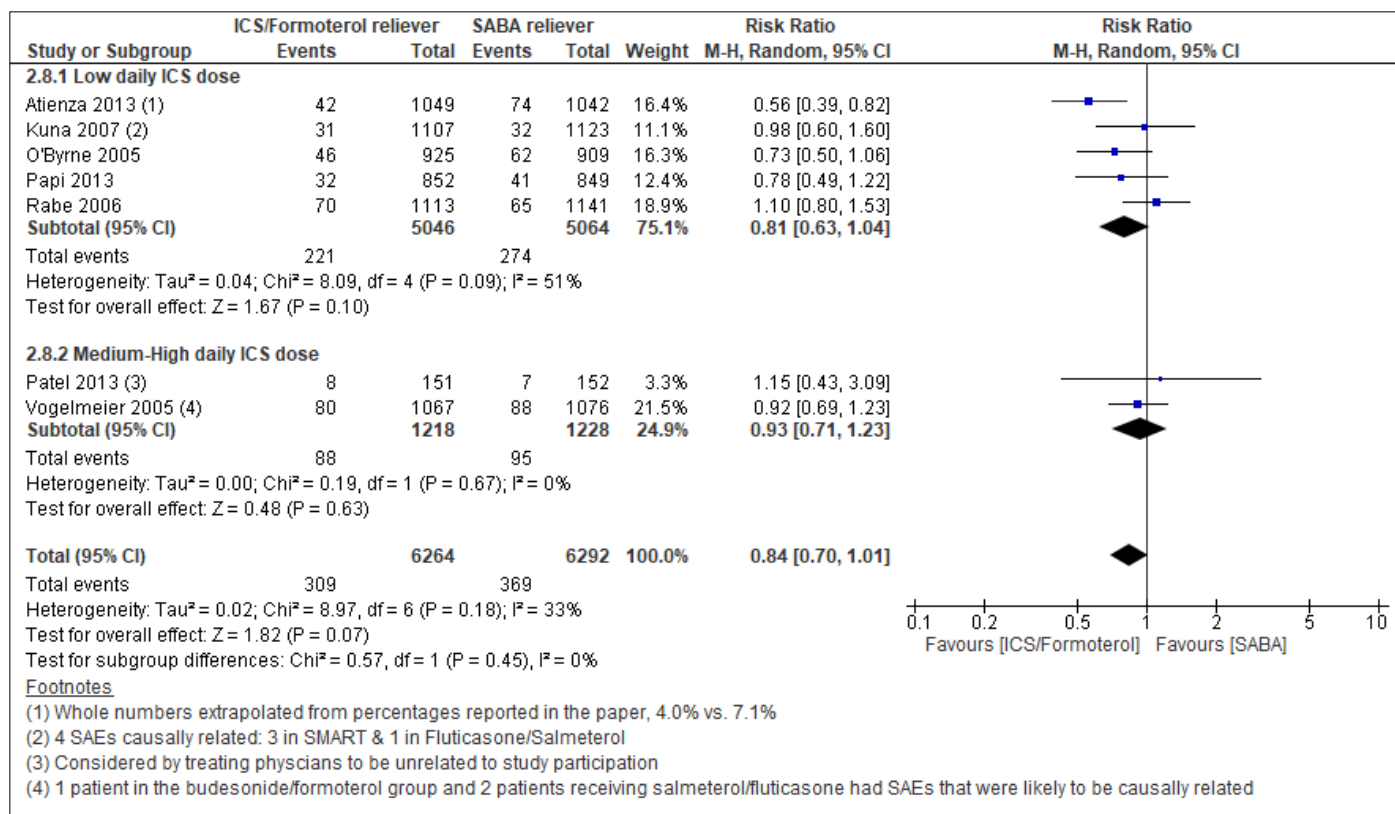


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Mortality
(Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

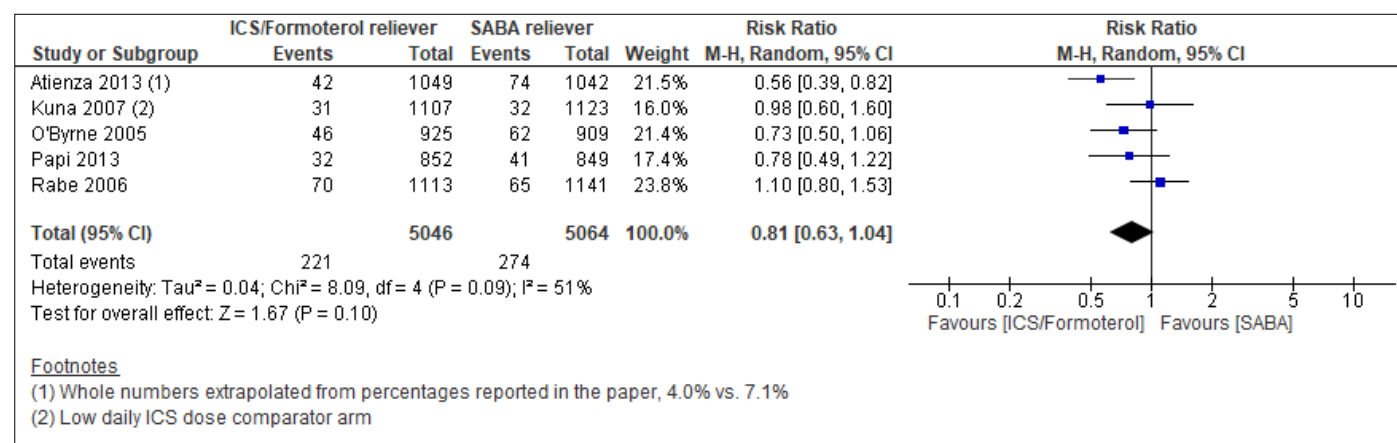
7. Serious adverse events (SAEs)



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Serious adverse events
(Original)

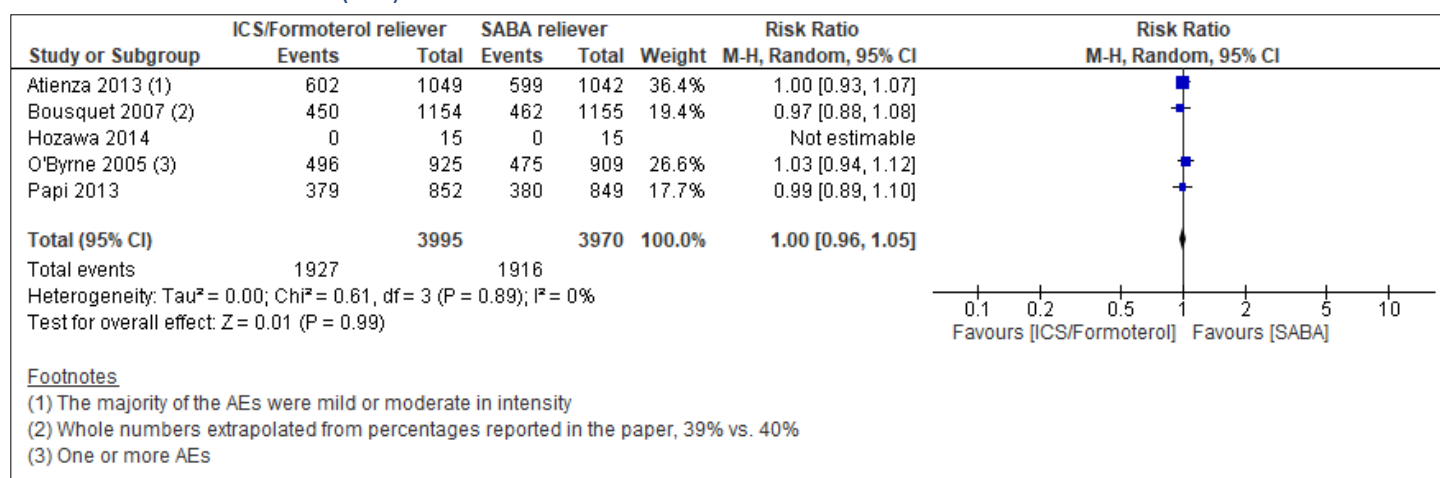


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Serious adverse events (Subgroup analyses)

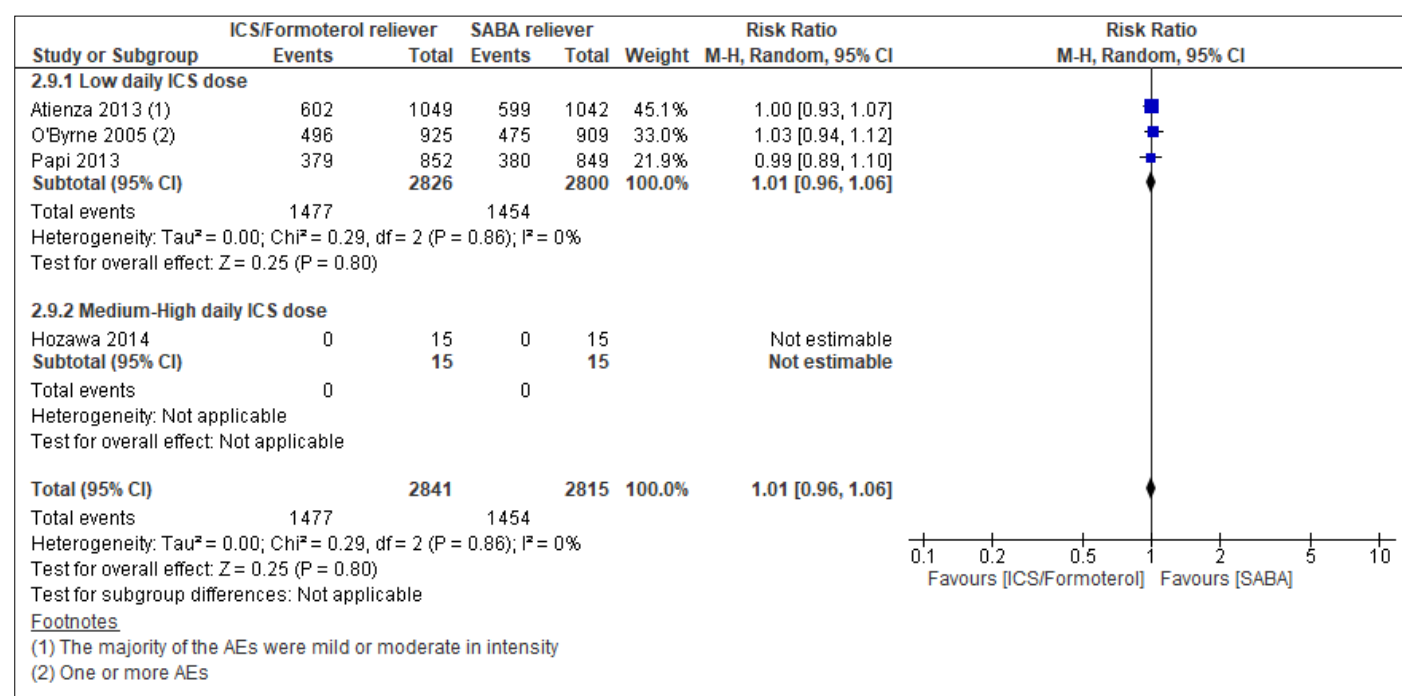


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Serious adverse events (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

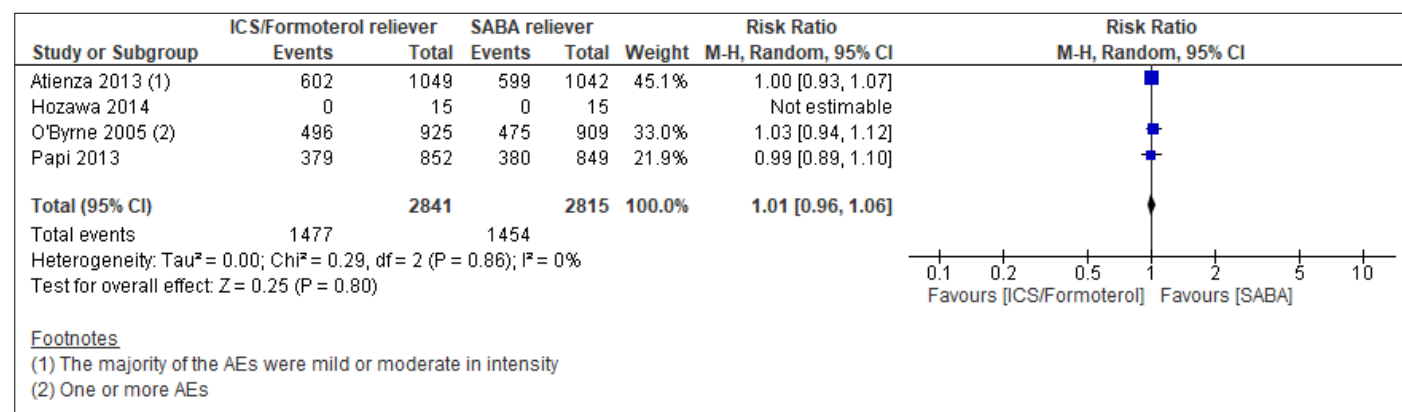
8. Adverse events (AEs)



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Adverse events (Original)



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Adverse events (Subgroup analyses)



Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Adverse events (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

Budget impact analysis of inhaled corticosteroid plus formoterol fixed-dose combination for symptom relief and maintenance therapy in chronic asthma management

27 March 2025

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CONFLICT OF INTEREST DETAILS

Declarations of interest: The reviewers and motivators have no interests related to the reviewed interventions to declare.

Funding: SE, TDL and MM are partly supported by the Research, Evidence, and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies. ZA is a consultant for the Clinton Health Access Initiative (CHAI).

ACKNOWLEDGEMENTS

- Andy Parrish and Renee de Waal, Co-Chairs of the National Essential Medicines List Committee, Jacqui Miot from the Health Economics and Epidemiology Research Office (HE²RO) of the University of the Witwatersrand and Geetesh Solanki from the Health Systems Research Unit, South African Medical Research Council provided technical support.
- Joy Oliver from the Health Systems Research Unit, South African Medical Research Council, provided support with the search strategy
- Yusentha Balikrishna from the South African Medical Research Council provided statistical support.
- Support to access utilisation data was provided by Maropeng Rapetsoa: Essential Drugs Programme, National Department of Health, Andre de Beer: USAID Global Health Supply Chain Program – Technical Assistance, Maggie Munsamy: Central Chronic Medicines Dispensing and Distribution Programme, and Mariette Smith: Provincial Health Data Centre - Western Cape Department of Health and Wellness.
- HE²RO shared unpublished data on hospital costs during the COVID-19 pandemic.

KEY FINDINGS

- We conducted a budget impact analysis to compare standard of care treatment to an inhaled corticosteroid (ICS)/formoterol combination inhaler for symptom relief in adults and adolescents aged ≥ 12 years with intermittent asthma (symptoms less than twice per month) and mild persistent asthma (symptoms ≥ 2 times per month, but < 4 -5 days per week); and ICS/formoterol as maintenance-and-reliever therapy (MART) for those with moderate asthma (symptoms almost daily or waking due to asthma $\geq$ once a week), within the South African public sector, assuming current asthma prevalence and treatment coverage ('status quo').
- We estimated that implementing ICS/formoterol combination inhaler therapy would reduce pharmaceutical costs by R937,613 per annum. Estimated overall pharmaceutical cost for the current standard of care across all asthma severities was R202.76 million, compared to R201.82 million for the ICS/formoterol strategy.
 - Pharmaceutical costs were higher for ICS/formoterol than the standard of care for moderate asthma only.
- We estimated that implementing ICS/formoterol would increase total healthcare costs (pharmaceutical and non-pharmaceutical) by R31.9 million per annum. Estimated total healthcare cost for the standard of care in the status quo scenario was R471.1 million, compared to R502.96 million for the ICS/formoterol strategy
 - For mild intermittent asthma, ICS/formoterol increases total costs, largely driven by our assumption of three visits per year to a healthcare facility for ICS/formoterol, compared to two visits per year for standard of care.
 - For mild persistent asthma, ICS/formoterol reduces both pharmaceutical and healthcare utilisation costs, resulting in net savings.
 - For moderate asthma, pharmaceutical costs are higher for ICS/formoterol, but these are offset by lower healthcare utilisation, leading to a net saving.
- A rapid transition to the ICS/formoterol from current standard of care (20% uptake per year) appears more cost-efficient from a pharmaceutical budget perspective. By Year 5, the total pharmaceutical net cost saving across all asthma severities amounts to R988,498. In contrast, slow adoption (10% uptake per year) leads to total pharmaceutical net cost saving across all asthma severities of R494,249.

Policy and practical implications

- The findings support policy shifts towards ICS/formoterol therapy to improve asthma outcomes and reduce pharmaceutical costs.
- The proposed strategy could optimise resource allocation in the national health budget for the public sector.
- Improving local epidemiological data through a national asthma registry and strengthening health information systems are essential to achieve efficient and equitable evidence-informed decision-making.

EXECUTIVE SUMMARY

Medicine (Intervention): Inhaled corticosteroid/formoterol

Medicine (ATC): R03AK07 (formoterol and budesonide), R03AK08 (formoterol and mometasone) R03AK11 (formoterol and fluticasone).

Note that this BIA focuses on the ICS budesonide in combination with formoterol. Other ICS/formoterol options are included in the therapeutic interchange database.

Indication: Intermittent mild asthma, persistent mild asthma, moderate asthma (J45.0-1/J45.8-9)

Research questions:

PICO 1: Among adults and adolescents ≥ 12 years with mild intermittent asthma (symptoms $<$ twice per month), is inhaled ICS/formoterol affordable compared to inhaled short-acting beta2 agonist (SABA) combined with inhaled corticosteroid (ICS) administered as needed for symptom relief?

PICO 2: Among adults and adolescents ≥ 12 years with mild persistent asthma (symptoms $\geq$ twice a month), is inhaled ICS/formoterol taken as reliever therapy affordable, compared with daily low-dose ICS and a SABA as needed for symptom relief?

PICO 3: Among adults and adolescent ≥ 12 years with moderate asthma (symptoms almost daily or waking due to asthma $\geq$ once a week), is inhaled ICS/formoterol taken daily and as reliever therapy, affordable compared to daily long-acting beta2 agonist (LABA)/ ICS controller and a SABA as needed for symptom relief?

Patient population: Adolescents (≥ 12 years) and adults with asthma

Level of Care: Primary Healthcare and adult hospital level

Prescriber level: Nurse prescriber (mild asthma)/ Medical officer initiated (moderate asthma)

Current Standard of Care/ Comparator(s) per PICO:

PICO 1: SABA inhaler plus ICS inhaler administered as needed for symptom relief

PICO 2: Daily low-dose ICS inhaler and as-needed SABA inhaler

PICO 3: Daily combination ICS/LABA inhaler and as-needed SABA inhaler

Intervention(s) per PICO:

PICO 1: ICS/formoterol as needed for symptom relief

PICO 2: ICS/formoterol as needed for symptom relief

PICO 3: ICS/formoterol as maintenance and as-needed reliever therapy (MART)

Outcomes

Pharmaceutical and healthcare costs

Background

Asthma burden in South Africa is significant with 331.3 DALYs per 100,000 and a mortality rate of 9.09 per 100,000.

The current standard of care for symptom relief amongst adolescents/adults with mild intermittent and mild persistent asthma in the South African public sector is an as-needed inhaled corticosteroid (ICS) and a SABA (administered as separate inhalers). The NEMLC conducted evidence reviews, to evaluate the efficacy and safety of ICS/formoterol (a long acting β_2 -agonist, LABA) combination therapy compared to ICS plus SABA (standard of care) for symptom relief in mild intermittent (PICO 1) and mild persistent (PICO 2) asthma, and ICS/formoterol for symptom relief and maintenance therapy (maintenance-and-reliever therapy, MART) for moderate (PICO 3) asthma. Randomised clinical trial evidence demonstrated that for mild persistent asthma, as-needed ICS/formoterol likely results in little to no difference in acute severe exacerbations requiring systemic corticosteroids, asthma-related hospital admissions, mortality, adverse events (AEs) and serious adverse events (SAEs), but a slight reduction in asthma-related emergency room visits compared to standard of care (moderate

to high certainty evidence). Amongst adults/adolescents with moderate asthma, compared to standard of care, ICS/formoterol as MART showed a reduction in severe asthma exacerbations, systemic corticosteroid use, asthma-related emergency room visits or hospitalisations, with little to no difference in mortality, SAEs and AEs (moderate to high certainty evidence). There is a paucity of evidence directly comparing as-needed ICS/SABA to ICS/formoterol for mild intermittent asthma; however, expert opinion suggests comparable efficacy and safety.

We conducted a pharmacoeconomic analysis to determine the budget impact of implementing the ICS/formoterol strategy for adolescents/adults with asthma in the South African public healthcare sector.

Methods

We built budget impact, decision-analytic models using 12-month scenarios comparing costs of current standard treatment guidelines ('standard of care') with the implementation of an ICS/formoterol strategy in adults and adolescents aged 12 and over with asthma in South Africa, assuming current asthma prevalence and treatment coverage ('status quo') (see Section II Budget analysis: Models). The status quo was determined using national procurement data, which was triangulated with estimates from public sector tenders, dispensing data from the Western Cape public sector, and data from the Central Chronic Medicine Dispensing and Distribution (CCMDD) program.

Due to limited local prevalence data, available data were supplemented with utilisation data and expert opinion. The rates of exacerbations, adverse effects, and use of reliever therapy were sourced from randomised controlled trial data in the rapid evidence syntheses. In the absence of direct comparison evidence, we used a conservative estimate of similar efficacy of ICS/formoterol and standard of care for mild intermittent asthma. Direct medical costs, including the costs of asthma medications and treating exacerbations, were obtained from public sector pharmaceutical tenders and the NDoH Uniform Patient Fee Schedule, and hospitalisation costs were extrapolated from data collected by HE2RO during the COVID-19 pandemic. Population data were obtained from StatsSA. Assumptions regarding the number of inhalers needed for mild intermittent asthma, severe asthma prevalence in adults, referrals from primary healthcare (PHC), ICU and general ward admission rates, and length of stay were based on a combination of expert opinion and published studies (see Sensitivity analyses section and Table 14). We conducted scenario analyses from a payer perspective and deterministic sensitivity analyses. An ethics waiver was obtained from the SAMRC Human Research Ethics Committee for the collection of delinked anonymised secondary data from the Western Cape Department of Health and aggregated utilisation data from the NDoH.

Rapid vs slow uptake rate: Besides the status quo scenario, we modelled slow (10%) and rapid (20%) uptake scenarios, within the current budget, factoring in an annual population growth of 1.3%.

Results

We estimated a target population of 10.958 million uninsured adolescents/adults with asthma, based on local epidemiological data, public-sector utilisation data, and expert opinion. South Africa's public-sector coverage was estimated to be 606,000 (6%) overall, with approximately 46% with mild intermittent, 46% mild persistent, and 8% moderate to severe asthma (see Table 8). In PICO 1, pharmaceutical costs decreased from R51.15 million in the standard of care scenario to R49.78 million in the ICS/formoterol scenario, reflecting a reduction of R1.37 million. However, non-pharmaceutical costs increased by R63.89 million, leading to a higher total cost for ICS/formoterol. In PICO 2, pharmaceutical costs decreased from R110.71 million for standard of care to R99.91 million for ICS/formoterol, a reduction of R10.81 million. Additionally, non-pharmaceutical costs declined by R10.36 million, resulting in an overall cost saving of R21.16 million. This scenario presents the most substantial cost reduction among the three asthma severity groups. In PICO 3, pharmaceutical costs increased from R40.89 million in the standard of care to R52.13 million with ICS/formoterol, an increase of R11.24 million. However, non-pharmaceutical costs decreased by R20.73 million, leading to an overall total cost saving of R9.49 million. Estimated total healthcare costs (pharmaceutical and non-pharmaceutical) for the standard of care scenario is R471.1 million, compared to R502.96 million for the ICS/formoterol strategy (an increase of R31.9 million).

The increase in total healthcare costs is largely driven by our estimate of three visits per year to a healthcare facility for medication supply for ICS/formoterol (60-dose inhaler), for adults/adolescents with mild intermittent asthma compared to two visits for standard of care (SABA and ICS: 200-dose inhalers each). The overall national health budget for 2024 was R62.2 billion.

A rapid transition to the ICS/formoterol strategy appears more cost-efficient from a pharmaceutical budget perspective, yielding overall savings compared to maintaining the current standard of care. By year 5, the total pharmaceutical net cost saving amounts to R988,498. In contrast, slow adoption leads to total pharmaceutical net cost savings of R494,249. Sensitivity analysis indicates uncertainty surrounding the costs of emergency room visits, hospitalisations and ICU admissions, and the proportion of people with asthma referred from PHC for hospitalisation. This introduces uncertainty around the total budget impact but does not change the overall conclusion of likely cost savings with ICS/formoterol. Significant uncertainty remains around the effectiveness of SABA with ICS in comparison to ICS/formoterol in mild intermittent asthma. There is further uncertainty regarding the utilisation patterns of inhalers for the standard of care, which could contribute to higher treatment costs in the standard of care arm. Furthermore, there is high uncertainty around the proportion of adults with severe asthma, which significantly impacts the total budget impact for managing asthma.

Conclusion

The budget impact analysis indicates that adopting ICS/formoterol therapy for asthma in adults and children ≥ 12 years could generate cost savings for the South African public health sector for the currently treated population. Reduced healthcare utilisation costs (particularly fewer hospitalisations and emergency visits) with ICS/formoterol compared to standard of care offset pharmaceutical costs in most scenarios, leading to net savings. Successful implementation will require investment in procurement, provider training, and patient education to ensure adherence. Given data limitations, further research is needed to refine cost estimates. Price monitoring and negotiations could enhance affordability and expand access, thus supporting sustainable asthma management and efficient resource allocation.

Introduction

Current evidence favours maintenance and reliever therapy (MART) with inhaled corticosteroid (ICS)/formoterol over South Africa's current standard of care for asthma. NEMLC recommended that a budget impact analysis of ICS/formoterol for chronic asthma care in South Africa be conducted¹.

The current standard of care for chronic asthma therapy, in the Adult Hospital and Primary Healthcare STGs and EMLs, Respiratory chapters (2024) are for:

- *Infrequent asthma symptoms < twice a month (mild intermittent asthma)*: short-acting beta2 agonist (SABA) + ICS as needed (separate inhalers).
- *Asthma symptoms ≥ twice a month (mild persistent asthma)*: daily low dose ICS as controller therapy, and SABA as needed; and
- *Asthma symptoms almost daily or waking due to asthma ≥ once a week (moderate asthma)*: daily medium dose ICS/LABA as controller therapy, and SABA as needed.

The 2024 GINA guidelines recommend ICS/formoterol across the entire asthma disease spectrum, as shown in Track 1 (“controller and preferred reliever”) in Figure 1, below.

Note: GINA does not recommend concomitant use of salmeterol and formoterol-containing formulations due to lack of evidence.

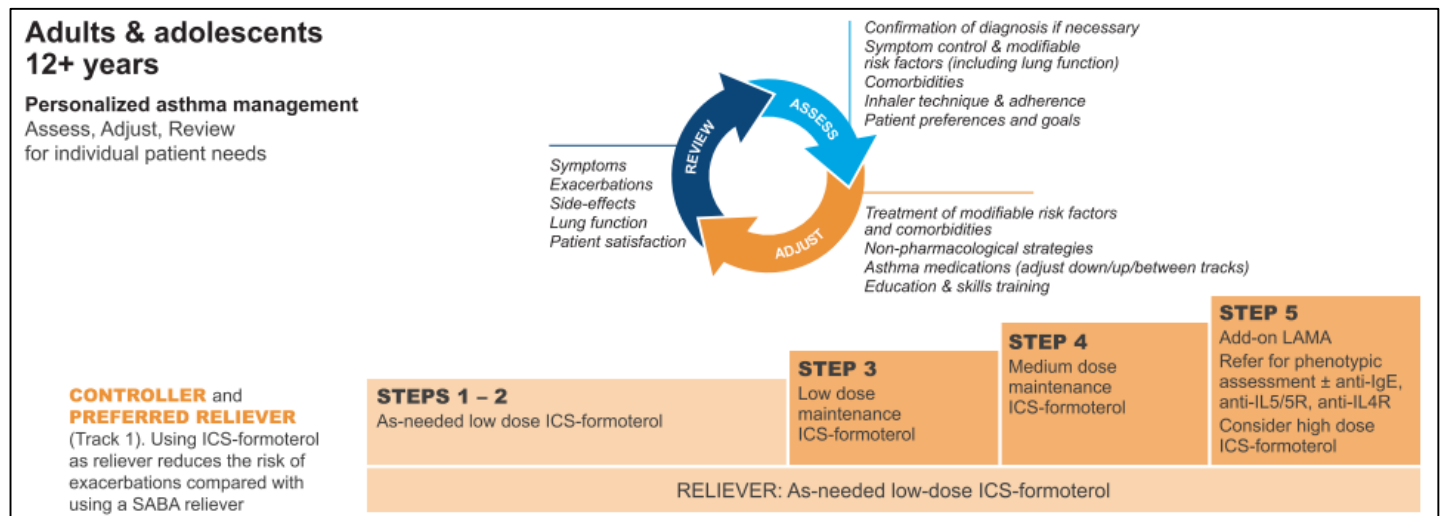


Figure 1: Personalized management for adults and adolescents to control symptoms and minimize risk

ICS = inhaled corticosteroid; LABA = long-acting β 2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β 2-agonist

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This budget impact analysis (BIA), conducted from the payer’s perspective, evaluates the affordability of adopting ICS/formoterol for adolescents and adults with asthma in the South African public sector, compared to the current standard of care.

¹ Minutes of the NEMLC meeting of 29 August 2024

Technology under review

Table 1: Health technology being assessed

		Source
Acquisition cost (ZAR)		
• Formoterol/ budesonide 160/4.5 mcg inhaler (60 doses)	ZAR 59.47	Contract circular HP07-2023DAI
Method of administration	Inhalation	2024 GINA guidelines
Dosage	1 inhalation as needed	2024 GINA guidelines
Average length of a course of treatment	As needed	2024 GINA guidelines
Anticipated average interval between courses of treatments	Long-term treatment	
Anticipated number of repeat treatments	Long-term treatment	
Dose adjustments	n/a not modelled	

Table adapted from the NICE budget impact analysis template

This study includes:

- I. A secondary data analysis to estimate South African prevalence of asthma and Chronic Obstructive Pulmonary Disease (COPD), as well as utilisation of ICS/LABA, ICS and SABA inhalers in the South African public sector to establish the status quo situation in terms of treatment coverage.
- II. An incremental budget impact analysis.

The SAMRC Human Research Ethics Committee waived the requirement for informed consent for this analysis, which utilised secondary data sources, including delinked, anonymised records from the Western Cape Department of Health and aggregated utilisation data from the National Department of Health. Permission to use anonymised data was also granted by the Western Cape Provincial Health Data Centre.

Prevalence and utilisation data analysis

Methods

We sourced overall asthma, severe asthma and chronic obstructive pulmonary disease (COPD) prevalence estimates in South Africa from available published literature. This information was triangulated where possible and compared with expert opinion. We sourced disaggregated prevalence estimates for children, adolescents and adults, where relevant. However, due to the lack of patient registries for asthma and national electronic health records, there is a paucity of local prevalence estimates for mild persistent and mild intermittent asthma. Prevalence estimates were thus extrapolated from utilisation data sourced from national utilisation/procurement data, and national public-sector tender estimates, and triangulated against utilisation data from the Central Chronic Medicines Dispensing and Distribution (CCMDD) and Western Cape Central Dispensing Unit (CDU).

Assumptions

The following assumptions were made to estimate current utilisation:

1. All prescribers, dispensers and patients comply with the STGs and EML which guide asthma management for paediatrics, adolescents and adults in the South African public sector.
2. No stockouts requiring substitution.
3. SABA inhaler use for the management of acute asthma attacks is assumed to be negligible noting paucity of data to determine usage in this setting.
4. Proportion of patients on moderate-high dose and low-dose LABA/ICS sourced from the national utilisation data (estimated as 60.5% and 39.5% respectively)
5. Number as inhalers as per the standard of care arm in the BIA (see Table 4)
6. Severe asthma prevalence for adults was assumed to be 4% guided by expert opinion.

Current inhaler utilisation for moderate asthma was estimated by modelling chronic use of ICS/LABA inhalers as controller therapy for asthma, less the estimated proportion of these inhalers used for COPD (based on prevalence estimates of COPD as outlined below). For mild persistent asthma, current inhaler consumption was derived from regular use of ICS inhalers. For the mild intermittent asthma scenario, the utilisation of SABA inhalers was modelled by subtracting the estimated use for COPD, moderate adult asthma, and paediatric asthma.

Given the uncertainty surrounding these variables, sensitivity analyses were conducted.

Results

a: Prevalence of asthma and COPD

Asthma

There is limited data on the current prevalence of asthma among adults in South Africa (Lion-Cachet, 2021). The 2012 World Health Survey reported that 6.09% of South Africans aged 18-45 years reported clinically diagnosed asthma with symptoms, while the rate of doctor-diagnosed asthma was 5.92% (To, 2012). Subsequently, there have been no further population studies in South Africa. However, a systematic review in the African region indicated a self-reported wheezing rate of 13.25% (95% CI 10.5 to 16.5) among individuals aged 5 to 69 years and a physician-diagnosed asthma rate of 11.3% (9.0 to 14.1) (Song, 2022).

The self-reported symptoms of asthma among adolescents rose from 16.0% in the 1995 ISAAC Phase 1 study (Zar, 2007) to 21.3% in the 2017 GAN Phase 1 study (Baard, 2021). Similarly, diagnosed asthma prevalence increased from 13.1% (Zar, 2007) to 16.6% over the same period (Baard, 2021). There is a paucity of data on severe asthma prevalence in South African adults. Importantly, South Africa had the third highest age-standardized asthma mortality rates globally for 2011-2015 (Global Asthma Report, 2022).

Notably, the definitions for asthma and methodology to estimate asthma are variable across countries and globally definitions and denominators need standardisation (Quint, 2024).

COPD

ICS/LABA, LABA, and SABA inhalers are also indicated for chronic obstructive pulmonary disease (COPD), and two systematic reviews (Adeloye, 2022; Awokola, 2022) reported South African prevalence rates of 8%, largely based on the BOLD study (Buist, 2007). Studies suggest that the age onset of COPD is ≥ 40 years (Buist, 2007; Jarhyan, 2022). From the COPD Gene cohort study, we estimated that the proportion of COPD patients who may be eligible for an ICS/LABA in our setting is 26.7%, translating to a prevalence of 2.14 % (Criner, 2019; Ramkrishan, 2024) (see Table 2)

Table 2: Asthma and COPD prevalence estimates for the BIA models

Population group		Lower	Base-model	Upper	References
<i>Children</i>	Overall asthma	9%	11.20%	13%	Wichman 2007
	Severe asthma	4%	5.70%	8%	Wichman 2007
<i>Adolescents</i>	Overall asthma	17%	22%	27%	Baard 2020; Mphahlele 2023
	Severe asthma (% of study sample)	6%	8%	10%	Baard 2020; Mphahlele 2023; Asher 2021; Chung 2014
	Severe asthma (% of current asthma)		55%		Baard 2020
	Severe asthma (% of current asthma)		66%		Mphahlele 2023
<i>Adults</i>	Overall asthma	6%	10%	14%	To 2012; Zar 2013; Song 2022
	Severe asthma	1%	4%	7%	Expert opinion
	COPD	6%	8%	11%	Adeloye 2022; Awokola 2022; Buist 2007
	COPD Group E blood eosinophils $\geq 300/\mu\text{L}$	1.60%	2.14%	2.94%	Ramkrishan 2024; Criner 2019

See Appendix A for a summary of available prevalence studies.

b: Eligible population and current proportion accessing treatment (treatment coverage)

Eligible population

Approximately 85.88% of the uninsured adolescent and adult asthmatic population in South Africa, use public sector services (StatsSA 2004; CMS 2022/3). Although routine clinical management for all people with asthma is ideal, only a proportion of people access treatment.

Proportion of people with asthma who currently access treatment (treatment coverage)

The South African target adolescent/adult population for mild intermittent to severe asthma for 2024 was estimated to be 10.958 million people, and those accessing public-sector care were estimated to be 606,000. The estimated disaggregated target population and status quo treatment coverage estimates for mild intermittent asthma (PICO 1) were 4,576,000 and 279,000; mild persistent asthma (PICO 2) were 4,576,000 and 280,000; and moderate asthma (PICO 3) were 1,806,000 and 47,000, respectively (see Table 3). See Appendix B for the comparative analysis of the different utilisation datasets.

The estimated treatment coverage for the status quo scenario (modelled using the National Department of Health National Surveillance data (procurement data) for 1 June 2023 to 31 July 2024 and available asthma prevalence rates) and for the target population are described in Table 3).

Table 3: Treatment coverage for 1) status quo (based on utilisation data); 2) ideal treatment coverage (100% of estimated population with asthma)

STATUS QUO & IDEAL TREATMENT COVERAGE				Uninsured total population	Adolescents	2961809
					Adults	39235760
PICO 1						
	<i>Uptake rate</i>	<i>Prevalence</i>	<i>Currently treated population (n)</i>	<i>Rounded up/ down</i>	<i>Population (100%)</i>	<i>Rounded up/ down</i>
Adolescents	6,35%	22%	41405	41000	651598	652000
Adults	6,07%	10%	238152	238000	3923576	3924000
Total				279000		4576000
PICO 2						
	<i>Uptake rate</i>	<i>Prevalence</i>	<i>Currently treated population (n)</i>	<i>Rounded up/ down</i>	<i>Population (100%)</i>	<i>Rounded up/ down</i>
Adolescents	6,11%	22%	39821	40000	651598	652000
Adults	6,11%	10%	239779	240000	3923576	3924000
Total				280000		4576000
PICO 3						
	<i>Uptake rate</i>	<i>Prevalence</i>	<i>Currently treated population (n)</i>	<i>Rounded up/ down</i>	<i>Population (100%)</i>	<i>Rounded up/ down</i>
Adolescents	2,61%	8%	6180	6000	236945	237000
Adults	2,61%	4%	40935	41000	1569430	1569000
Total				47000		1806000
TOTAL POPULATION FOR PICOS 1,2,3:						
<i>Model (PICOs 1,2,3)</i>			<i>Status quo (PICOs 1,2,3)</i>	606000	<i>100% Uptake (PICOs 1,2,3)</i>	10958000

Budget impact analysis

Methods

Analytic framework, time horizon and perspective

The National Department of Health Technology Assessment Methods Guide (NDoH, 2023), the NEMLC-approved scoping report and ISPOR guidance for BIA (Sullivan, 2014) guided the static BIA modelling frameworks. The BIAs were conducted from the national public sector payer's perspective and considered 2024 pharmaceutical and healthcare costs.

Intervention(s) and comparator(s)

The intervention under review is budesonide/formoterol 160/4.5 mcg per inhalation, a 60-dose dry powder turbuhaler device, used as needed and, in moderate asthma used daily as part of the MART strategy. The agent is listed on the public sector contract (Contract circular HP07-2023DAI, 2023). Dosing was aligned with respective trial data, sourced from systematic reviews and where this was lacking, guided by expert opinion.

The comparator/s listed for PICO 1, 2 and 3 were aligned with the current standard of care, as described in the PICO summary, clinical trial data and drug utilisation data which was confirmed by experts.

Eligible populations and uptake

The **status quo scenario** was based on the estimated adolescent/adult asthmatic population accessing treatment in the public sector (treatment coverage) using current utilisation and prevalence estimates sourced from the published literature, as per the analysis above.

Implementation scenarios were costed for both **slow- and rapid-adoption scenarios**. The slow-adoption scenario assumes limited prescribing and uptake of ICS/formoterol therapy (10% transition to ICS/formoterol strategy per year). This may be due to training required for both the patient and healthcare professionals. The rapid-adoption scenario (20% transition per year) assumes that there are few or no delays in supply and that eligible patients will access the medicine/s where indicated. Guidance was sought from clinical pulmonology experts to estimate the uptake rates for the two implementation scenarios, with assumptions described and referenced.

Resources

As per the HTA Methods Guide (NDoH, 2023), only direct health costs from the payer's perspective with an expected difference between the proposed medicine/s and comparator/s, and direct health care utilisation costs were presented. Costs assumed to be the same for the interventions and comparator were not presented as they will not affect the decision to include/exclude the medicine from the EML.

Medicine costs were sourced from public sector pharmaceutical contract prices. Estimates of as-needed reliever therapy as either ICS/formoterol or SABA were costed for the BIA model - sourcing the cumulative doses of formoterol/ICS or SABA reliever therapy from the available evidence.

Inpatient day estimates for hospital costs were sourced from secondary data rather than derived from an ingredients approach.

Costs were adjusted for inflation to current 2024 costs, where required.

Assumptions

1. Wastage factor for salbutamol 0.5% 20 ml inhalation solution for acute asthma attacks was estimated as 25%.
2. Administration sets, syringes and other consumables have not been costed, as this was assumed to have little potential effect on the model.
3. Patients with moderate asthma in the ICS/formoterol arm of the model are assumed to be controlled on formoterol/budesonide 160/4.5 or 320/9 mcg inhalation twice a day (currently the cheapest ICS/LABA formulation on public sector tender).
4. During emergency transport from the clinic to the hospital for severe asthma exacerbation, only basic life support has been costed. Distance from the clinic to the hospital emergency room is assumed to be less than 50 km.
5. Cost for PHC clinic visit has been extrapolated from Uniform Patient Fee Schedule port health and travel clinic fee, and assuming 10% (5% to 15%) of people with asthma who present at the PHC level would require referral to a hospital for management, and 90% would be controlled through PHC services.
6. For mild intermittent asthma, systemic corticosteroids for severe exacerbation would require a clinic visit.
7. There is a paucity of effectiveness and safety data comparing inhaled ICS/SABA to ICS/formoterol in mild intermittent asthma, and experts recommended comparable efficacy and safety between these two agents in this clinical setting. Efficacy data was extrapolated from the ICS/formoterol group in the PICO 1 evidence review.
8. In the standard of care arm, inhaled corticosteroids as controller therapy dosed as 200 mcg (beclomethasone/budesonide) 12 hourly was assumed to be the standard dosing amongst adolescents/adults, with 3x budesonide 200 mcg (300 doses) and 4x beclomethasone 200 mcg (200 doses) inhalers used per annum – assuming that 85.5% on beclomethasone and 14.5% on budesonide extrapolated from national utilisation data.
9. For moderate asthma, it was assumed that 60.5% of patients use budesonide/formoterol 160/4.5 mcg and 39.5% use budesonide/formoterol 320/9 mcg extrapolated from national utilisation data.
10. Hospital costs were extrapolated from unpublished data collected by HE2RO, shared in confidence and awaiting publication (at the time of undertaking this analysis).
11. The rate of ICU admission for adults/adolescents with moderate asthma was assumed to be 3% (2%, 4%) based on expert opinion (noting that the ICU admission rate amongst children, reported in a recent thesis was 1.2%), with a length of ICU stay of three days, extrapolated from Manyeruke et al (Manyeruke, 2023). For mild persistent asthma, no patients were assumed to be admitted to ICU.
12. For adults and adolescents with mild intermittent asthma, 10% (5%-15%) of patients visiting the emergency room were assumed to require a hospital stay.
13. Length of hospital stay in the general ward was assumed to be two days extrapolated from Manyeruke et al (Manyeruke, 2023).
14. For moderate asthma, all deaths occur in the ICU.
15. Among adolescents and adults, a spacer was not included in the cost analysis.
16. Stats SA population growth of 1.3% was applied to years 2-5 for patients receiving treatment.
17. Discount rate of 3% was applied to future costs from years 2-5.
18. For the BIA model of 1000 patients, we assumed the health states to be as outlined in the PICO summary above, and assumed all patients were adult males weighing 70 kg.

Number of inhalers

The number of inhalers required per annum was estimated using effectiveness trial data and the STGs and EML with pragmatic consideration of Chronic Medicines Dispensing data CCMDD and WC CDU (see Appendix C), confirmed by expert opinion. Of note is that a single fixed-dose combination inhaler of ICS with SABA is currently not available on the South African market and therefore, one SABA inhaler plus one ICS inhaler was assumed to be dispensed per prescription for PICO 1 (mild intermittent asthma). For mild intermittent asthma (PICO 1), wastage could not be quantified. In PICO 2, wastage estimates were applied to beclometasone (38%), budesonide (45%), salbutamol (40%), and budesonide/formoterol 160/4.5 mcg (32%) based on CDU data and expert opinion. In PICO 3, wastage was assumed to be 0% for budesonide/formoterol maintenance inhalers and 40% for salbutamol. The numbers of inhalers used in the models are summarised in Table 4.

Table 4: Number of inhalers per annum used in the BIA models for each PICO.

Population	Intervention inhalers per annum	Comparator inhalers per annum	Evidence
Mild intermittent asthma (step 1)	- ICS/formoterol as needed - Bud/form 160/4.5mcg: 3	- ICS as needed - Bud 200mcg (300 doses): 2 - Beclo 200mcg (200 doses): 2 - SABA as needed: 2	Expert opinion
Mild persistent asthma (step 2)	- ICS/formoterol as needed - Bud/form 160/4.5mcg: 6	- ICS maintenance - Bud 200mcg (300doses): 4 - Beclo 200mcg (200 doses): 3 - SABA as needed: 6	Hatter et al (2021). Western Cape Chronic Dispensing Unit data
Moderate asthma (steps 3-4)	- ICS/formoterol maintenance - Bud/form 160/4.5 mcg: 12 OR - Bud/form 320/9 mcg: 12 PLUS - ICS/FABA as needed - Bud/form 160/4.5mcg: 6	- ICS/LABA maintenance - Bud/form 160/4.5 mcg: 12 OR - Bud/form 320/9 mcg: 12 PLUS - SABA as needed: 6	As needed reliever therapy estimates extracted from RCTs included in the PICO 3 rapid review. Western Cape Chronic Dispensing Unit data
Abbreviations: Beclo=beclomethasone (metered-dose inhaler); Bud=budesonide (metered dose inhaler); Bud/form=budesonide/formoterol (60 doses, dry powder inhaler); ICS=inhaled corticosteroid; FABA=fast-acting- β 2-agonists; MART=maintenance-and-reliever therapy; SABA=short-acting- β 2-agonist (salbutamol 100mcg, 200 doses, metered dose inhaler).			

Sensitivity analyses

As local epidemiological data is limited, uncertainties in this static BIA analysis were addressed with sensitivity analyses, varying the value of variables included in the baseline BIA analysis, as appropriate for each asthma severity group. These include the medicine price of ICS/formoterol, as-needed SABA use for PICO 2 and 3, the number of inhalers (for ICS/formoterol and standard of care) for PICO 1, PHC visits and hospitalisation costs, the proportion of patients requiring upward referrals from PHC facilities, estimates and uptake rates in the public sector (using the various implementation scenarios, described above). We also estimated a threshold price for budesonide/ formoterol 160/4.5 mcg, by determining price parity between the intervention and standard of care.

Models

A static probabilistic decision model was used to estimate the incremental budget impact for a cohort of 1000 patients. TreeAge Pro® 2024 software was used to compute the BIA model.

PICO 1: mild intermittent asthma

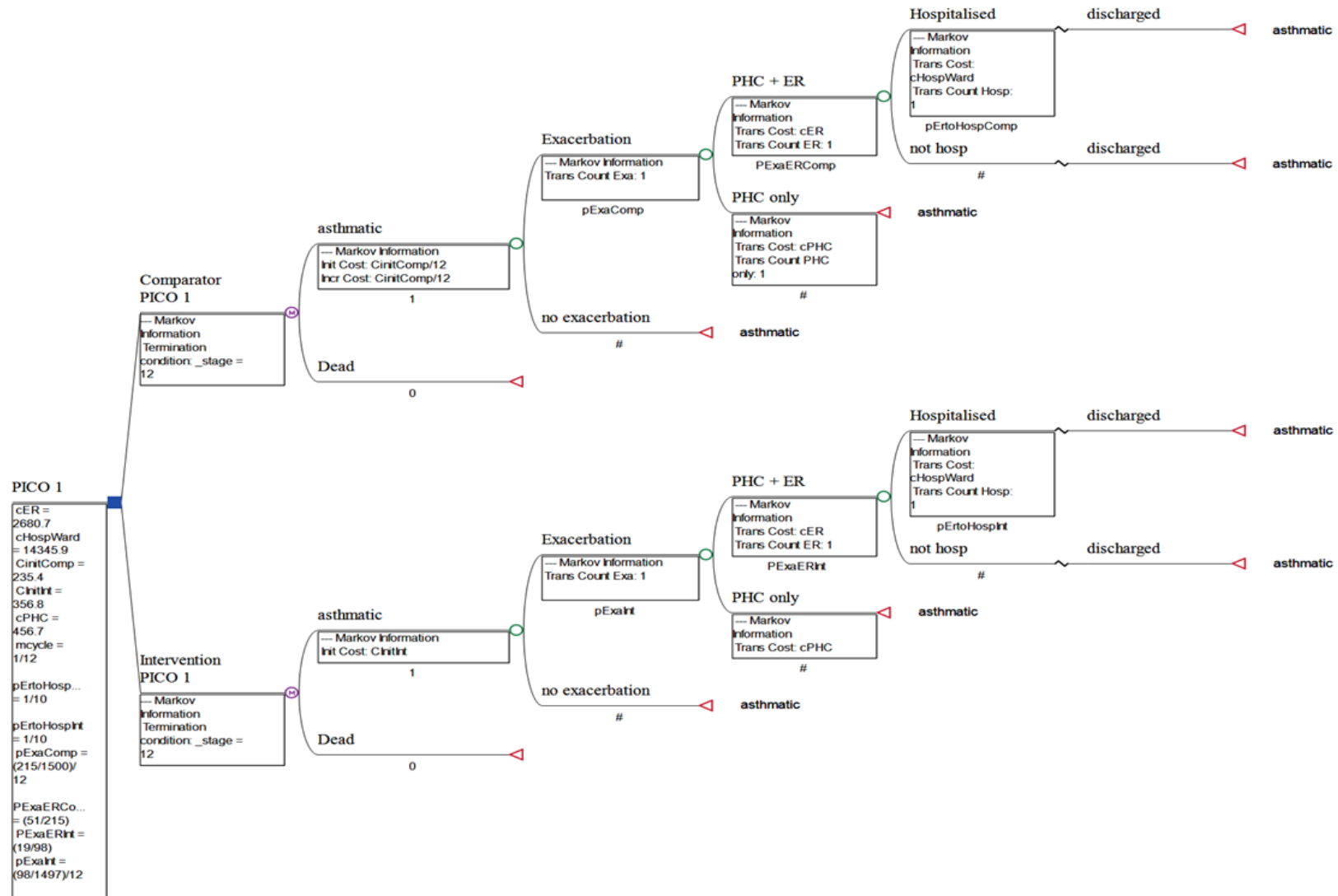


Figure 2: BIA model for mild intermittent asthma

PICO 2: mild persistent asthma

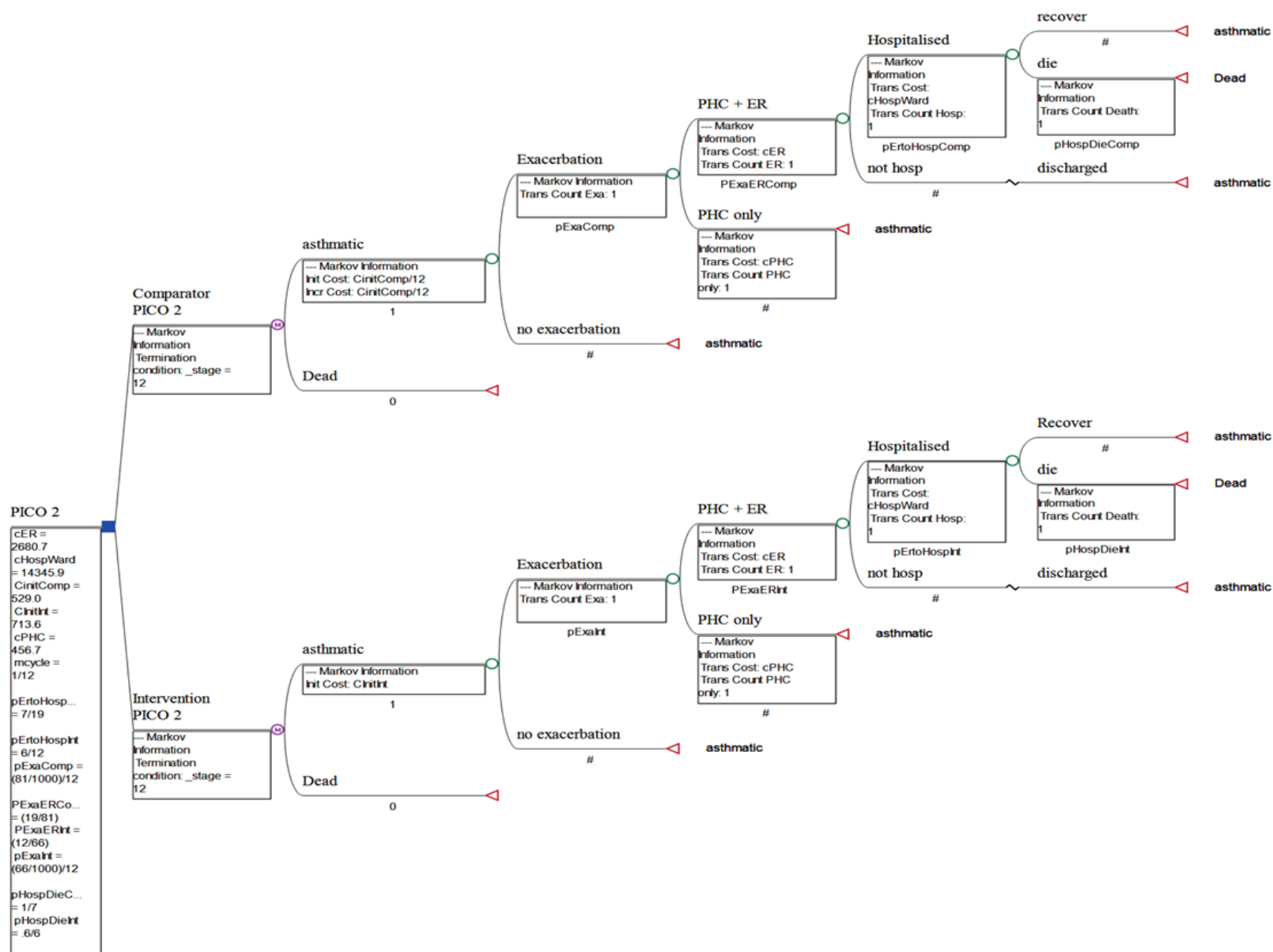


Figure 3: BIA model for mild persistent asthma

PICO 3: moderate persistent asthma

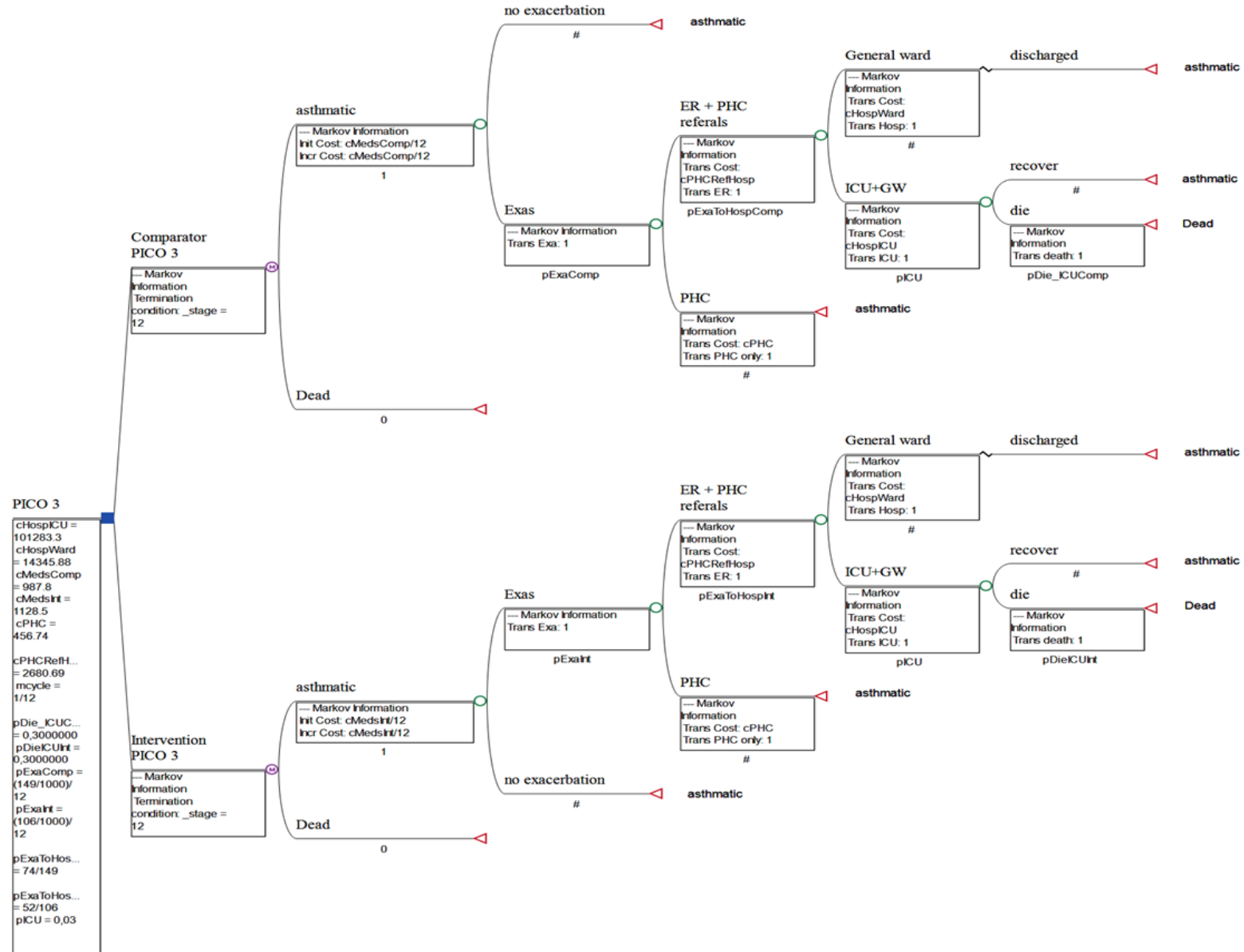


Figure 4: BIA for moderate asthma

Resources

Healthcare resources

Healthcare resources associated with the use of ICS/formoterol inhalers (aligned with 2024 GINA guidelines) include staff costs, diagnostic and monitoring costs, facility costs and referral transport costs. These resources would also apply to current clinical practice. An ingredient approach was used to estimate the costs for primary healthcare clinic visits (sourced from public sector tenders, National Department of Health, Uniform Patient Fee Schedule 2024, and buy-out price on file at NDoH for non-tender medicine prices); whilst hospitalisation cost data was extrapolated from data collected by HE²RO on hospital costs during COVID-19 (HE²RO, 2019), inflated to 2024 ZAR. Table 5 presents the unit costs for 12 months.

Table 5: Unit costs for ICS/formoterol and standard of care

Cost type	Cost (ZAR)	Unit
ICS/formoterol		
Acquisition costs		Per person per course of treatment per year (ZAR)
<i>PICO 1:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x3	@59.47	178.41
<i>PICO 2:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x6	@59.47	356.82
<i>PICO 3:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x18, OR	@59.47	1070.46
• Budesonide/formoterol 320/9mcg (60 doses) x12 PLUS	@67.64	1168.50
• Budesonide/formoterol 160/4.5mcg (60 doses) x6	@59.47	
Healthcare resource use		Per person per event
• Primary healthcare clinic visit		429.72 (411.13, 475.28)
• Primary healthcare clinic visit, with referral to hospital		2441.72 (2396.18, 2487.30)
• Hospital emergency room visit		2436.52 (2037.68, 3982.19)
• General ward hospital admission		7172.94 (6953.76, 7399.39)
• ICU admission		28979.13 (28063.74, 30087.49)
Standard of Care		
Acquisition costs		Per person per course of treatment per year
<i>PICO 1:</i>		
• Beclomethasone 200mcg (200 doses) x2	@72.01	Beclomethasone 200mcg + SABA: 183.26*
• Budesonide 200 mcg (300 doses) x2	@72.22	Budesonide 200 mcg + SABA: 183.68*
• Salbutamol 100mcg (200 doses)** x2	@19.62	
<i>PICO 2:</i>		
• Beclomethasone 200mcg (200 doses) x4	@72.01	Beclomethasone 200mcg + SABA: 405.76
• Budesonide 200 mcg (300 doses) x3	@72.22	Budesonide 200 mcg + SABA: 334.38
• Salbutamol 100mcg (200 doses)** x6	@19.62	
<i>PICO 3:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x12	@59.47	Low-dose ICS/LABA + SABA as needed: 831.36
• Budesonide/formoterol 320/9mcg (60 doses) x12	@67.64	High-dose ICS/LABA + SABA as needed: 929.40
• Salbutamol 100mcg (200 doses)** x6	@19.62	

Healthcare resource use		Per person per event
• Primary healthcare clinic visit		429.72 (411.13, 475.28)
• Primary healthcare clinic visit, with referral to hospital		2441.72 (2396.18, 2487.30)
• Hospital emergency room visit		2436.52 (2037.68, 3982.19)
• General ward hospital admission		7172.94 (6953.76, 7399.39)
• ICU admission		28979.13 (28063.74, 30087.49)

*ICS/SABA combination inhaler is not available on the South African market, thus 1x SABA inhaler + 1x ICS inhaler per prescription was costed.

**Salbutamol 100mcg (200 doses) = SABA

Adverse events

The adverse events reported in the studies were similar between the formoterol/ICS inhaler (the intervention) and the standard of care (the control). For patients with mild persistent asthma, asthma-related events and deaths were among the reported adverse events. However, these were also assessed as separate outcomes, so they were not included in the overall adverse event count.

Efficacy: i.e. events avoided

Anticipated savings (or events avoided) associated with ICS/formoterol relate to severe exacerbations, emergency room visits, and hospitalisation compared to standard of care (see Table 6).

Table 6: Efficacy estimates of ICS/formoterol compared with standard of care treatment

1. PICO 1 (Refer to the medicine review for PICO 1 for detailed information)						
Note: 1) There is a paucity of data for the efficacy and safety of ICS+SABA compared to ICS/formoterol for mild intermittent asthma. Based on expert opinion, it was assumed that the efficacy and safety of ICS+SABA were comparable to ICS/formoterol. Evidence: Expert opinion; <i>very low certainty evidence</i>						
2. PICO 2 (Refer to the medicine review for PICO 2 for detailed information)						
Outcomes	Anticipated absolute effects* (95% CI)		NNT	Relative effect (95% CI)	n (studies)	Certainty of the evidence (GRADE)
	Risk with daily low-dose ICS +SABA reliever	Risk with formoterol + ICS as needed				
Acute severe exacerbations requiring systemic steroid: follow-up 52 weeks	81 per 1,000	66 per 1,000 (49 to 87)	67	RR 0.81 (0.61 to 1.07)	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,b}
Asthma-related visits to the emergency room: follow-up 52 weeks	19 per 1,000	12 per 1,000 (9 to 18)	143	RR 0.65 (0.46 to 0.93)	8065 (4 RCTs)	⊕⊕⊕⊕ High ^{a,c}
Asthma-related hospital admissions: follow-up 52 weeks	7 per 1,000	6 per 1,000 (4 to 11)	1000	RR 0.88 (0.50 to 1.53)	7620 (3 RCTs)	⊕⊕⊕⊕ High ^{a,c}
Evidence: PICO 2 rapid review; <i>moderate certainty evidence</i>						

3. PICO 3

(Refer to the medicine review for PICO 3 for detailed information)

Outcomes	Anticipated absolute effects* (95% CI)		NNT	Relative effect (95% CI)	n (studies)	Certainty of the evidence (GRADE)
	Risk with ICS/LABA maintenance therapy + as needed SABA reliever therapy	Risk with ICS/formoterol maintenance therapy + as needed reliever therapy				
Severe Asthma Exacerbation	149 per 1,000	106 per 1,000 (97 to 115)	24	RR 0.71 (0.65 to 0.77)	17376 (10 RCTs)	⊕⊕⊕⊕ High ^a
Systemic Corticosteroid Use	134 per 1,000	92 per 1,000 (80 to 107)	25	RR 0.69 (0.60 to 0.80)	9436 (4 RCTs)	⊕⊕⊕⊕ High ^b
Asthma-related visits to the ER and/or hospital admissions	74 per 1,000	52 per 1,000 (46 to 59)	46	RR 0.70 (0.62 to 0.80)	14136 (7 RCTs)	⊕⊕⊕⊕ High ^b
Asthma-related visits to the ER	145 per 1,000	107 per 1,000 (85 to 135)	27	RR 0.74 (0.59 to 0.93)	2091 (1 RCT)	⊕⊕⊕○ Moderate ^{b,c}
Asthma-related hospital admissions	29 per 1,000	11 per 1,000 (5 to 25)	56	RR 0.39 (0.18 to 0.85)	2394 (2 RCTs)	⊕⊕⊕○ Moderate ^{b,c}
Mortality	1 per 1,000	1 per 1,000 (0 to 2)	0	RR 0.77 (0.25 to 2.33)	14136 (7 RCTs)	⊕⊕⊕⊕ High ^{b,d}

Evidence: PICO 3 rapid review; *moderate certainty evidence*

Abbreviations: BIA=budget impact analysis, ICS=inhaled corticosteroid, LABA=long-acting b2 agonist, n=number of study participants, NNT=number needed to treat, RCT=randomised controlled trial, SABA=short-acting b2 agonist

Results

Estimates of annual incremental budget impact

The target adolescent/asthma population with mild to moderate asthma to be treated with the ICS/formoterol strategy was estimated to be 10.958 million, while coverage with the current standard of care in the South African public sector was estimated to be 606,000 (status quo).

Total annual costs (pharmaceutical and non-pharmaceutical costs), from the payer perspective, were estimated to be R10,155,093,096 for the current status quo population receiving standard of care scenario compared to R10,469,994,035 for ICS/formoterol. This will result in an additional cost of R314,900,939 over 1 year (see Table 10).

This total budget impact of implementing ICS/formoterol over standard of care includes increased pharmaceutical costs (R232,754,939) and non-pharmaceutical costs (R82,146,000). Pharmaceutical costs were higher for ICS/formoterol for PICO 3, but lower for PICOs 1 and 2. In addition, healthcare resource use costs (mostly hospitalisation) were significantly lower for ICS/formoterol for PICO 3. The disaggregated estimates for mild intermittent (PICO 1), mild persistent (PICO 2) and moderate asthma (PICO 3) are described in Tables 7, 8 and 9.

PICO 1: mild intermittent asthma

Table 7: Estimated budget impact for mild intermittent asthma

Comparator vs Intervention:	Model	Full Eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	4,576,000	279,000					
A: RAPID ADOPTION (20% per annum)								
Rapid implementation scenario (comparator)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	183,000	838,876,438	51,146,531	40,917,225	31,096,068	21,006,430	10,642,908	-
Healthcare resource use costs	533,000	2,439,008,000	148,707,000	118,965,600	90,410,882	61,075,564	30,943,935	-
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	716,000	3,277,884,438	199,853,531	159,882,825	121,506,950	82,081,995	41,586,843	-
Rapid adoption implementation scenario (intervention)	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	178,000	816,404,160	49,776,390	9,955,278	20,175,366	30,665,548	41,431,200	52,477,794
Healthcare resource use costs	762,000	3,486,912,000	212,598,000	42,519,600	86,170,221	130,974,428	176,955,184	224,135,860
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	940,000	4,303,316,160	262,374,390	52,474,878	106,345,588	161,639,976	218,386,384	276,613,653
NET & incremental BUDGET IMPACT (future - current treatment pathway costs)	[224,000]	[1,025,431,722]	[62,520,859]	212,357,703	227,852,538	243,721,971	259,973,226	276,613,653
B: SLOW ADOPTION (10% per annum)								
Slow implementation scenario (comparator)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	183,000	838,876,438	51,146,531	46,031,878	41,461,424	36,761,253	31,928,724	26,961,147
Healthcare resource use costs	533,000	2,439,008,000	148,707,000	133,836,300	120,547,842	106,882,238	92,831,804	78,388,723
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	716,000	3,277,884,438	199,853,531	179,868,178	162,009,266	143,643,491	124,760,528	105,349,869
Slow implementation scenario (intervention)	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	178,000	816,404,160	49,776,390	4,977,639	10,087,683	15,332,774	20,715,600	26,238,897
Healthcare resource use costs	762,000	3,486,912,000	212,598,000	21,259,800	43,085,111	65,487,214	88,477,592	112,067,930
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	940,000	4,303,316,160	262,374,390	26,237,439	53,172,794	80,819,988	109,193,192	138,306,827
NET BUDGET IMPACT (future - current treatment pathway costs)	[224,000]	[1,025,431,722]	[62,520,859]	206,105,617	215,182,060	224,463,479	233,953,720	243,656,696

Note: Costs are provided as South African Rands (ZAR).

PICO 2: mild persistent asthma

Table 8: Estimated budget impact for mild persistent asthma

Comparator vs Intervention:	Model	Full eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	4,576,000	280,000					
A: RAPID ADOPTION (20% per annum)								
Rapid implementation scenario (comparator)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	395,000	1,809,395,702	110,714,772	88,571,818	67,312,367	45,471,748	23,038,261	-
Healthcare resource use costs	178,000	814,528,000	49,840,000	39,872,000	30,301,723	20,469,824	10,371,036	-
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	573,000	2,623,923,702	160,554,772	128,443,818	97,614,090	65,941,572	33,409,297	-
Rapid adoption implementation scenario (intervention)	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	357,000	1,632,808,320	99,909,600	19,981,920	40,495,359	61,550,921	83,159,398	105,331,772
Healthcare resource use costs	141,000	645,216,000	39,480,000	7,896,000	16,002,034	24,322,291	32,861,037	41,622,610
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	498,000	2,278,024,320	139,389,600	27,877,920	56,497,393	85,873,212	116,020,434	146,954,383
NET & incremental BUDGET IMPACT (future - current treatment pathway costs)	[-75,000]	[-345,899,382]	[21,165,172]	156,321,738	154,111,483	151,814,784	149,429,732	146,954,383
B: SLOW ADOPTION (10% per annum)								
Slow implementation scenario (comparator)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	395,000	1,809,395,702	110,714,772	99,643,295	89,749,823	79,575,558	69,114,783	58,361,675
Healthcare resource use costs	178,000	814,528,000	49,840,000	44,856,000	40,402,298	35,822,192	31,113,109	26,272,428
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	573,000	2,623,923,702	160,554,772	144,499,295	130,152,120	115,397,751	100,227,892	84,634,103
Slow implementation scenario (intervention)	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	357,000	1,632,808,320	99,909,600	9,990,960	20,247,680	30,775,461	41,579,699	52,665,886
Healthcare resource use costs	141,000	645,216,000	39,480,000	3,948,000	8,001,017	12,161,145	16,430,518	20,811,305
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	498,000	2,278,024,320	139,389,600	13,938,960	28,248,696	42,936,606	58,010,217	73,477,191
NET BUDGET IMPACT (future - current treatment pathway costs)	[-75,000]	[-345,899,382]	[21,165,172]	158,438,255	158,400,817	158,334,357	158,238,109	158,111,294

Note: Costs are provided as South African Rands (ZAR).

PICO 3: moderate persistent asthma

Table 9: Estimated budget impact for moderate asthma

Comparator vs Intervention:	Model	Full eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	1,806,000	47,000					
A: RAPID ADOPTION (20% per annum)								
Rapid implementation scenario (comparator)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	870,000	1,571,374,955	40,894,033	32,715,226	24,862,754	16,795,619	8,509,500	-
Healthcare resource use costs	1,485,000	2,681,910,000	69,795,000	55,836,000	42,433,964	28,665,557	14,523,405	-
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,130,000	110,689,033	88,551,226	67,296,718	45,461,176	23,032,905	-
Rapid adoption implementation scenario (intervention)	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	1,109,000	2,003,189,555	52,131,733	10,426,347	21,130,034	32,116,595	43,391,661	54,960,962
Healthcare resource use costs	1,044,000	1,885,464,000	49,068,000	9,813,600	19,888,242	30,229,133	40,841,574	51,730,959
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	2,153,000	3,888,653,555	101,199,733	20,239,947	41,018,276	62,345,728	84,233,235	106,691,921
NET & incremental BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400]	[-9,489,300]	108,791,173	108,314,994	107,806,904	107,266,140	106,691,921
B: SLOW ADOPTION (10% per annum)								
Slow implementation scenario (comparator)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	870,000	1,571,374,955	40,894,033	36,804,629	33,150,339	29,392,333	25,528,501	21,556,692
Healthcare resource use costs	1,485,000	2,681,910,000	69,795,000	62,815,500	56,578,619	50,164,725	43,570,214	36,791,415
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,130,000	110,689,033	99,620,129	89,728,957	79,557,058	69,098,715	58,348,106
Slow implementation scenario (intervention)	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	1,109,000	2,003,189,555	52,131,733	5,213,173	10,565,017	16,058,297	21,695,830	27,480,481
Healthcare resource use costs	1,044,000	1,885,464,000	49,068,000	4,906,800	9,944,121	15,114,567	20,420,787	25,865,479
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	2,153,000	3,888,653,555	101,199,733	10,119,973	20,509,138	31,172,864	42,116,617	53,345,961
NET BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400]	[-9,489,300]	109,740,103	110,238,095	110,729,922	111,215,332	111,694,067

Note: Costs are provided as South African Rands (ZAR).

Table 10: Total costs for the eligible target population (PICO 1, 2 &3)

COMPARATOR	
• Total pharmaceutical costs	4,219,647,096
• Total healthcare resource use costs	5,935,446,000
Total costs	10,155,093,096
INTERVENTION	
• Total pharmaceutical costs	4,452,402,035
• Total healthcare resource use costs	6,017,592,000
Total costs	10,469,994,035
NET ADDITIONAL COST	
[314,900,939]	

The estimated budget impact for the BIA model with 1,000 patients was a net cost-saving of R53,401 but once implemented for patients currently accessing care (status quo) and for the total eligible population, additional cost is incurred, as shown in Table 11.

Table 11: Estimates of total annual incremental budget impact (PICO 1, 2, 3)

Population/ PICO	Costs	Model (1000)	Status quo	Total target population (100%)
Mild intermittent asthma / PICO 1	Net Pharmaceutical costs	-4,911	-1,370,141	-22,472,278
	Net-health care use costs	229,000	63,891,000	1,047,904,000
	NET BUDGET IMPACT	224,089	62,520,859	1,025,431,722
Mild persistent asthma/ PICO 2	Net Pharmaceutical costs	-38,590	-10,805,172	-176,587,382
	Net-health care use costs	-37,000	-10,360,000	-169,312,000
	NET BUDGET IMPACT	-75,590	-21,165,172	-345,899,382
Moderate asthma/ PICO 3	Net Pharmaceutical costs	239,100	11,237,700	431,814,600
	Net-health care use costs	-441,000	-20,727,000	-796,446,000
	NET BUDGET IMPACT	-201,900	-9,489,300	-364,631,400
TOTAL ADOLESCENT/ ADULT POPULATION (GINA steps 1-4)	Net Pharmaceutical costs	195,599	-937,613	232,754,939
	Net-health care use costs	-249,000	32,804,000	82,146,000
	NET BUDGET IMPACT TOTAL	(53,401)	31,866,387	314,900,939

Table 12 summarises the annual cost per person comparisons of ICS/formoterol compared to standard of care across the various asthma severities

Table 12: Overview of the annual per-patient cost comparisons of ICS/formoterol vs standard of care across asthma severities

Intervention	Total intervention cost (pharmaceutical + healthcare use)	Comparator	Total comparator cost (pharmaceutical + healthcare use)
PICO 1: Mild intermittent asthma			
ICS/formoterol (budesonide/formoterol 160/4.5mcg) as needed	R940 (R178 + R7625)	ICS (budesonide/ beclometasone 200mcg) as needed + SABA as needed	R716 (R183 + R533)
PICO 2: Mild persistent asthma			
ICS/formoterol (budesonide/formoterol 160/4.5mcg) as needed	R498 (R357 + R141)	ICS (budesonide/ beclometasone 200mcg) 12 hourly + SABA as needed	R573 (R395 + R178)
PICO 3: Moderate asthma			
ICS/formoterol (budesonide/formoterol 160/4.5mcg or 320/9mcg) 12 hourly as controller therapy + ICS/FABA (budesonide/formoterol 160/4.5mcg) as needed	R2153 (R1109 + R1044)	ICS/LABA (budesonide/ formoterol 160/4.5mcg or 320/9mcg) 12-hourly as controller therapy + SABA as needed	R2355 (R870 + R1485)

SABA = salbutamol 100mcg inhaler, 200 doses, dosed as 200mcg as needed to a maximum daily dose of 800 mcg.

Budgetary implications of rapid compared to slow adoption scenarios

The analysis highlights the budgetary implications of transitioning patients from the current standard of treatment to the new treatment regimen under two adoption scenarios: rapid and slow. In the rapid adoption scenario, 20% of patients transition annually to the ICS/formoterol strategy, resulting in full adoption by Year 5. In contrast, the slow adoption scenario transitions 10% of patients annually, with 50% remaining on the current standard of treatment by the end of Year 5. In both scenarios, net costs are assessed relative to maintaining all patients on the current standard of care.

This analysis accounts for annual population growth, resulting in an incremental increase in the treatment population each year. However, it does not assume improvements in programmatic coverage to reach the full eligible population living with asthma. As a result, the budgetary implications reflect costs for patients currently on treatment, without expanding coverage to untreated individuals who may benefit from the intervention.

Rapid adoption scenario

In the rapid adoption scenario, pharmaceutical costs exhibit varying trends across the three PICO groups. For PICO 1, pharmaceutical costs initially decrease compared to the standard of care scenario, with a net saving of R274,028 in Year 1, increasing to R1.44 million by Year 5. However, total healthcare costs increase significantly over time. PICO 2 follows a similar trend, with pharmaceutical costs decreasing by R2.16 million in Year 1 and accumulating to R11.39 million in savings by Year 5. Additionally, healthcare costs decline, suggesting overall cost savings in this group. Conversely, PICO 3 experiences increased pharmaceutical spending, with costs rising by R2.25 million in Year 1 and reaching R11.85 million by Year 5, though healthcare costs decline.

When aggregated, the net pharmaceutical cost difference across all groups shows an initial reduction of R187,523 in Year 1, increasing to R988,498 by Year 5 in favour of ICS/formoterol. However, this is offset by healthcare cost increases, particularly in PICO 1.

Slow adoption scenario

Under the slow adoption scenario, pharmaceutical cost reductions are more gradual. In PICO 1, savings start at R137,014 in Year 1 and grow to R722,250 by Year 5. PICO 2 also experiences pharmaceutical cost reductions, saving R1.08 million in Year 1 and accumulating R5.70 million by Year 5. In contrast, PICO 3 sees an increase in pharmaceutical spending, similar to the rapid adoption scenario, with costs rising by R1.12 million in Year 1 and reaching R5.92 million by Year 5.

The overall net pharmaceutical cost savings under the slow adoption scenario is R93,761 in Year 1, increasing to R494,249 by Year 5, which is smaller than the savings observed under the rapid adoption approach.

Key insights

- PICO 1 and PICO 2 show pharmaceutical cost savings in both adoption scenarios, but PICO 3 leads to increased pharmaceutical costs under both strategies.
- Healthcare costs increase in PICO 1 under rapid adoption, which offsets pharmaceutical savings, whereas PICO 2 sees both pharmaceutical and healthcare savings, making it the most cost-effective shift.
- The rapid adoption scenario results in greater overall pharmaceutical cost savings (R988,498 by Year 5) compared to the slow adoption scenario (R494,249 by Year 5).

Table 13: Difference in costs for the rapid compared to slow adoption scenarios

Rapid adoption scenario: SoC/ICS/formoterol use	100%/0%	80%/20%	60%/40%	40%/60%	20%/80%	0%/100%
	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
PICO 1 Total Pharmaceutical Costs Rapid Uptake	R51,146,531	R50,872,503	R51,271,434	R51,671,979	R52,074,108	R52,477,794
PICO 1 Total Healthcare Costs Rapid Uptake	R148,707,000	R161,485,200	R176,581,103	R192,049,992	R207,899,118	R224,135,860
PICO 1 Total Pharmaceutical Costs Maintaining SoC	R51,146,531	R51,146,531	R51,826,780	R52,516,076	R53,214,540	R53,922,293
PICO 1 Pharmaceutical NET Cost Difference	R0	-R274,028	-R555,346	-R844,098	-R1,140,432	-R1,444,500
PICO 2 Total Pharmaceutical Costs Rapid Uptake	R110,714,772	R108,553,738	R107,807,726	R107,022,669	R106,197,659	R105,331,772
PICO 2 Total Healthcare Costs Rapid Uptake	R49,840,000	R47,768,000	R46,303,757	R44,792,115	R43,232,073	R41,622,610
PICO 2 Total Pharmaceutical Costs Maintaining SoC	R110,714,772	R110,714,772	R112,187,278	R113,679,369	R115,191,305	R116,723,349
PICO 2 Pharmaceutical NET Cost Difference	R0	-R2,161,034	-R4,379,552	-R6,656,701	-R8,993,646	-R11,391,577
PICO 3 Total Pharmaceutical Costs Rapid Uptake	R40,894,033	R43,141,573	R45,992,788	R48,912,214	R51,901,161	R54,960,962
PICO 3 Total Healthcare Costs Rapid Uptake	R69,795,000	R65,649,600	R62,322,206	R58,894,690	R55,364,979	R51,730,959
PICO 3 Total Pharmaceutical Costs Maintaining SoC	40894032.6	40894032.6	41437923.23	41989047.61	42547501.95	43113383.72
PICO 3 Pharmaceutical NET Cost Difference	R0	R2,247,540	R4,554,865	R6,923,166	R9,353,659	R11,847,579
TOTAL PHARMACEUTICAL COST NET DIFFERENCE OVERALL	R0	-R187,523	-R380,033	-R577,632	-R780,419	-R988,498
Slow Adoption Scenario						
PICO 1 Total Pharmaceutical Costs Slow Uptake	51,146,531	51,009,517	51,549,107	52,094,027	52,644,324	53,200,043
PICO 1 Total Healthcare Costs Slow Uptake	148,707,000	21,259,800	43,085,111	65,487,214	88,477,592	112,067,930
PICO 1 Total Pharmaceutical Costs Maintaining SoC	51,146,531	51,146,531	51,826,780	52,516,076	53,214,540	53,922,293
PICO 1 Pharmaceutical NET Cost Difference	-	-R137,014	-R277,673	-R422,049	-R570,216	-R722,250
PICO 2 Total Pharmaceutical Costs Slow Uptake	110,714,772	109,634,255	109,997,502	110,351,019	110,694,482	111,027,561
PICO 2 Total Healthcare Costs Slow Uptake	49,840,000	48,804,000	48,403,314	47,983,338	47,543,627	47,083,733
PICO 2 Total Pharmaceutical Costs Maintaining SoC	110,714,772	110,714,772	112,187,278	113,679,369	115,191,305	116,723,349
PICO 2 Pharmaceutical NET Cost Difference	-	-R1,080,517	-R2,189,776	-R3,328,350	-R4,496,823	-R5,695,789
PICO 3 Total Pharmaceutical Costs Slow Uptake	40,894,033	42,017,803	43,715,356	45,450,631	47,224,332	49,037,173
PICO 3 Total Healthcare Costs Slow Uptake	69,795,000	67,722,300	66,522,740	65,279,292	63,991,001	62,656,894
PICO 3 Total Pharmaceutical Costs Maintaining SoC	40,894,033	40,894,033	41,437,923	41,989,048	42,547,502	43,113,384
PICO 3 Pharmaceutical NET Cost Difference	-	1,123,770	2,277,432	3,461,583	4,676,830	5,923,789
TOTAL PHARMACEUTICAL COST NET DIFFERENCE OVERALL	-	-R93,761	-R190,017	-R288,816	-R390,209	-R494,249

Sensitivity analyses

The variables for the sensitivity analysis included rates of PHC referral, hospitalisation and ICU admission rates, and severe asthma prevalence based on expert opinion. For SABA usage, the base case annual number of inhalers was derived from Western Cape utilisation data and the upper limit from CCMDD dispensing data from other Provinces. An upper sensitivity analysis was also applied for PICO 1 based on expert consensus. No additional sensitivity analysis was applied to medicine use for PICO 2 and 3 outside of SABA use for the standard of care, given the time constraints to conduct the BIAs. For general ward and ICU length of stay, base case values were derived from the study by Manyureke et al (Manyureke,2023) with upper and lower estimates informed by expert opinion. See Table 14. Univariate sensitivity analysis was applied to the hospitalisation rate for PICO 1, ICU admission rate for PICO 3, PICO 1 SABA, budesonide and beclometasone usage, PICO 2/3 SABA use and severe asthma adult rates. Multivariate sensitivity analysis was undertaken for emergency room, general ward and ICU costs accounting for uncertainty around general ward and ICU length of stay, and PHC referral rates to the emergency room.

Table 14: Variables for the sensitivity analysis

PICO	Variable	Lower limit	Base	Upper limit	Reference
1-3	PHC referrals	5%	10%	15%	Expert opinion
1	Hospitalisation	5%	10%	15%	Expert opinion
3	ICU admission rate	2%	3%	4%	Manyeruke, 2023; Salie, 2023, Expert opinion
1	Salbutamol; 100mcg; Inhaler; 200 Doses	-	2	4	Expert opinion
1	Budesonide; 200mcg; Inhaler; 300 Doses	-	2	4	Expert opinion
1	Beclometasone; 200mcg; Inhaler; 200 Doses	-	2	4	Expert opinion
1	Budesonide/Formoterol; 160/4.5 mcg, Inhaler; 60 Doses	-	3	6	Expert opinion
2-3	SABA usage	-	6	12	Western Cape CDU/pharmacy data; other Provinces CCMDD data
3	ICU LOS	1	3	5	Manyeruke, 2023; Expert opinion
1-3	GW LOS	1	2	3	Manyeruke, 2023; Expert opinion
3	Severe asthma prevalence	1	4	7	Expert opinion
1-3	PHC cost	429.72	411.13	475.28	Contract circulars HP07-2023DAI, HP09-2023SD, NDoH: UPFS 2024, Annexure A2; NDoH price on file for hydrocortisone 100mg/ml injection
1-3	ER costs w/ PHC referral (ZAR)	2157.50	2680.70	4355.30	HE ² RO costing data on file
1-3	GW cost & LOS (ZAR)	6953.80	14345.90	22198.20	HE ² RO costing data on file
3	GW + ICU cost & LOS (ZAR)	35017.50	101283.30	172635.60	HE ² RO costing data on file

CDU=Chronic Dispensary Unit, CCMDD=Central Chronic Medicines Dispensing and Distribution, ER=emergency room, GW=General ward, ICU=intensive care unit, LL=lower limit, LOS=length of hospitalisation stay, NDoH=National Department of Health, SABA=short-acting β_2 agonist, UL=upper limit, UPFS=Uniform Patient Fee Schedule, ZAR=South African Rand

Sensitivity analysis was undertaken for the various asthma severities, mild intermittent asthma (PICO 1), mild persistent asthma (PICO 2), and moderate asthma (PICO 3).

For tornado graphics below (PICO 1, 2, & 3), the expected value (EV) vertical line represents the expected total treatment cost (per individual patient) assuming all base case values for input parameters. The horizontal bars represent the variation in total treatment cost after applying the lower and upper estimates around input parameters.

PICO 1

The cost of treatment for mild intermittent asthma is primarily influenced by the number of inhalers used by individuals both for the standard of care or ICS/formoterol. Inappropriate use of inhalers could translate to a doubling in the cost of medication for both treatment arms.

Uncertainty around costs of PHC, ER and general ward admissions could affect the total treatment costs, but equally across both arms. Furthermore, uncertainty around the proportions of patients requiring further upward referrals to the hospital level may also increase costs. As needed ICS/formoterol is not more cost-effective than the current standard of care (ICS/SABA as needed) despite reduced medication costs, given that healthcare resource use is higher in the intervention arms due to additional PHC visits required to pick up inhalers. (Refer to the tornado diagram in Figure 5).

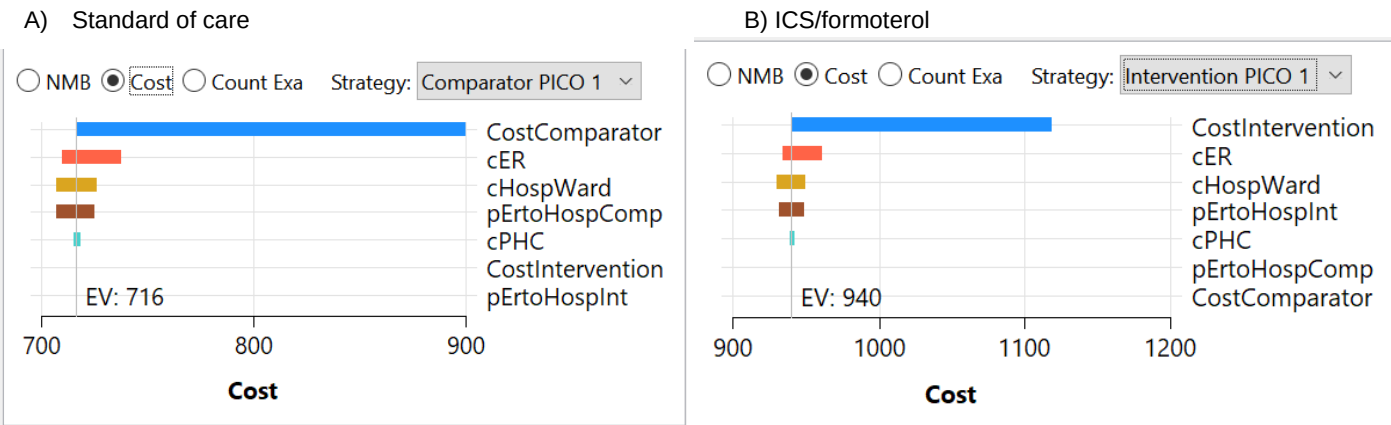


Figure 5: Tornado diagrams for A) Standard of care and B) ICS/formoterol for mild intermittent asthma (PICO 1)

Abbreviations: CostComparator =Annual per patient cost of standard of care; CostIntervention=Annual per patient cost of ICS/formoterol; cER=Cost of emergency room visit; CHospWard=Cost of stay in a general ward; cPHC=Cost of PHC care; pERtoHospComp=Probability of hospitalisation following Emergency room visit for standard of care; pERtoHospInt=Probability of hospitalisation following Emergency room visit for intervention; EV=expected value

PICO 2

For mild persistent asthma, the sensitivity analysis revealed that the budget impact of the new intervention is primarily influenced by the cost of the standard of care. Furthermore, variation in general ward admission costs, influenced by length of stay and uncertainty around the costs had a notable impact on the budget, while the costs of ER admission and PHC care had a smaller influence on budget impact. (Refer to the tornado diagram in Figure 6).

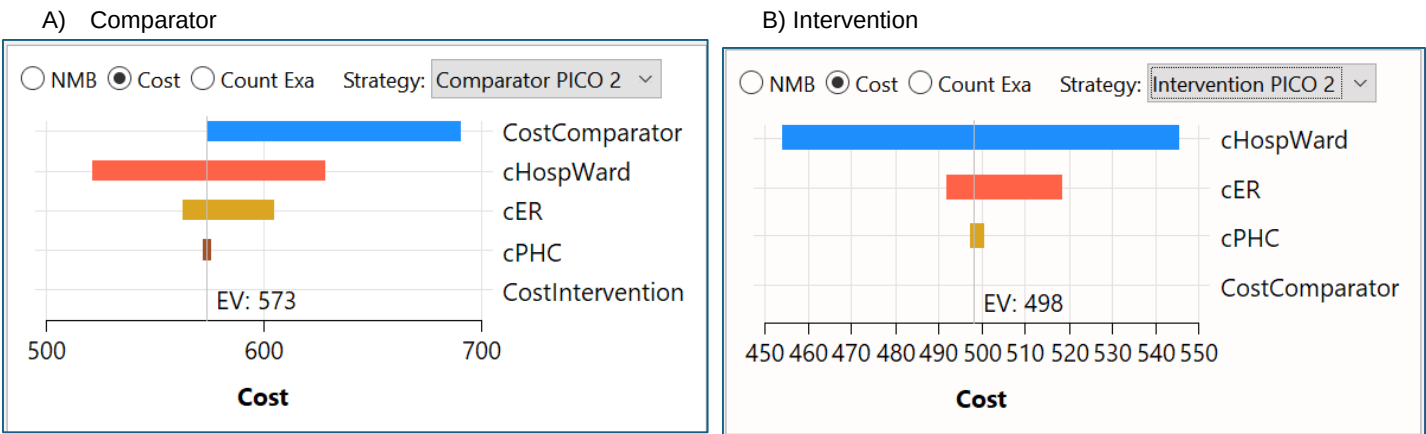


Figure 6: Tornado diagrams for comparator and intervention for mild persistent asthma (PICO 2)

Abbreviations: CostComparator =Annual per patient cost of standard of care; CostIntervention=Annual per patient cost of new intervention; cER=Cost of emergency room visit; CHospWard=Cost of stay in a general ward; cPHC=Cost of PHC care; EV=expected value

PICO 3

For moderate asthma, the sensitivity analysis highlighted that variation in general ward admission costs was a major driver of the budget impact, followed by variation in ICU and ER costs—although the impact of ICU costs was less pronounced due to the low proportion of patients requiring ICU admission. The cost of the standard of care may also be higher due to increased dispensing of SABA inhalers.

ICS/formoterol was cheaper than standard of care due to substantial reductions in exacerbations and hospitalisation despite higher treatment costs. (Refer to the tornado diagram in Figure 7).

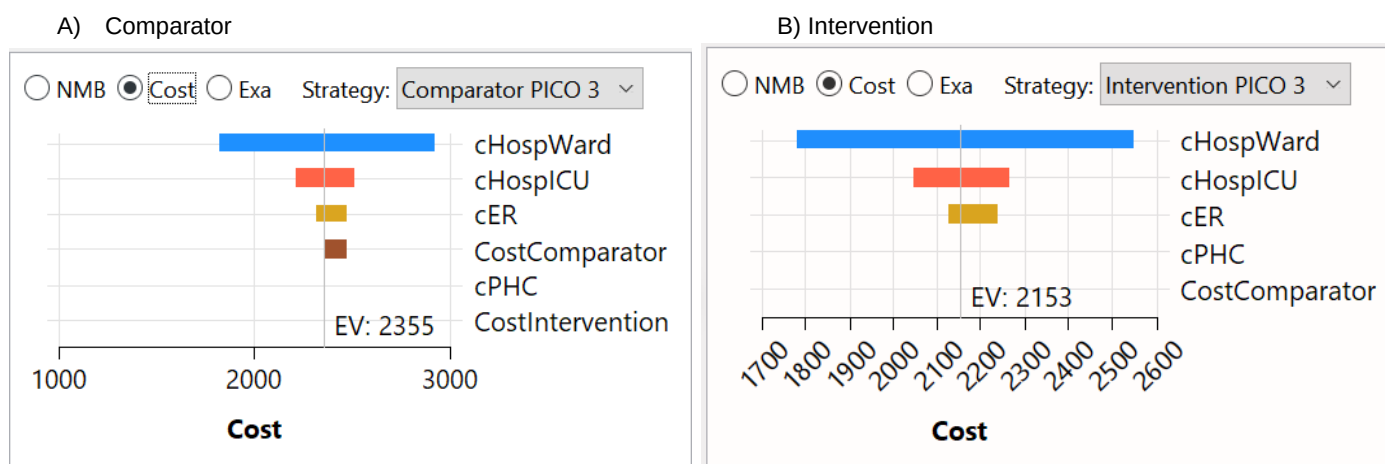


Figure 7: Tornado diagrams for comparator and intervention for moderate asthma (PICO 3)

Abbreviations: CostComparator =Annual per patient cost of standard of care; CostIntervention=Annual per patient cost of new intervention; CER=Cost of emergency room visit; CHospWard=Cost of stay in a general ward; cHospICU=Cost of intensive care unit stay; cPHC=Cost of PHC care; EV=expected value

PICO 3: Severe asthma prevalence

For the BIA model, the prevalence of severe asthma amongst adults in South Africa was informed by expert opinion. Thus, a sensitivity analysis was undertaken, varying the rate from 1% to 7%.

The base model demonstrated that pharmaceutical costs were higher in the ICS/formoterol group compared to standard of care, but this was offset by lower non-pharmaceutical costs (mostly hospitalisation).

The sensitivity analysis (Table 15) showed that uncertainty around the proportion of patients with severe asthma has a considerable impact on the total budget impact of managing asthma.

Table 15: Sensitivity analysis adjusting for prevalence of severe asthma among adults

Comparator vs Intervention:	Model	Full eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	1,806,000(629,000-2,983,000)	47,000(40,000-109,000)					
A: RAPID ADOPTION (20% per annum)								
Status quo implementation scenario (rapid)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	870,000	1,571,220,000 (547,230,000-2,595,210,000)	40,894,033 (34,800,000-94,830,000)	32,715,226 (27,840,000-75,864,000)	24,862,754 (21,157,704-57,654,743)	16,795,619 (14,292,734-38,947,701)	8,509,500 (7,241,414-19,732,853)	0(0, 0)
Healthcare resource use costs	1,485,000	2,681,910,000 (934,065,000-4,429,755,000)	69,795,000 (59,400,000-161,865,000)	55,836,000 (47,520,000-129,492,000)	42,433,964 (36,114,012-98,410,683)	28,665,557 (24,396,219-66,479,697)	14,523,405 (12,360,344-33,681,938)	0(0, 0)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,284,955 (1,481,295,000-7,024,965,000)	110,689,033 (94,200,000-256,695,000)	88,551,226 (75,360,000-205,356,000)	67,296,718 (57,271,716-156,065,426)	45,461,176 (38,688,953-105,427,398)	23,032,905 (19,601,758-53,414,791)	0(0, 0)
Rapid adoption of new technology	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	1,109,000	2,003,189,555 (697,561,000-3,308,147,000)	52,131,733 (44,360,000-120,881,000)	10,426,347 (8,872,000-24,176,200)	21,130,034 (17,979,995-48,995,487)	32,116,595 (27,328,694-74,470,690)	43,391,661 (36,922,887-100,614,867)	54,960,962 (46,767,452-127,441,306)
Healthcare resource use costs	1,044,000	1,885,464,000 (656,676,000-3,114,252,000)	49,068,000 (41,760,000-113,796,000)	9,813,600 (8,352,000-22,759,200)	19,888,242 (16,926,163-46,123,795)	30,229,133 (25,726,922-70,105,862)	40,841,574 (34,758,786-94,717,693)	51,730,959 (44,026,348-119,971,798)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,153,000	3,888,653,555 (1,354,237,000-6,422,399,000)	101,199,733 (86,120,000-234,677,000)	20,239,947 (17,224,000-46,935,400)	41,018,276 (34,906,158-95,119,282)	62,345,728 (53,055,615-144,576,552)	84,233,235 (71,681,674-195,332,560)	106,691,921 (90,793,800-247,413,104)
NET BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400 (-127,058,000-602,566,000)]	[-9,489,300 (-8,080,000; -22,018,000)]	108,791,173 (92,584,000-252,291,400)	108,314,994 (92,177,874-251,184,708)	107,806,904 (91,744,569-250,003,950)	107,266,140 (91,283,432-248,747,351)	106,691,921 (90,793,800-247,413,104)
B: SLOW ADOPTION (10% per annum)								
Status quo implementation scenario (slow)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	870,000	1,571,374,955 (547,230,000-2,595,210,000)	40,894,033 (34,800,000-94,830,000)	36,804,629 (31,320,000-85,347,000)	33,150,339 (28,210,272-76,872,991)	29,392,333 (25,012,285-68,158,477)	25,528,501 (21,724,242-59,198,558)	21,556,692 (18,344,312-49,988,249)
Healthcare resource use costs	1,485,000	2,681,910,000 (934,065,000-4,429,755,000)	69,795,000 (59,400,000-161,865,000)	62,815,500 (53,460,000-145,678,500)	56,578,619 (48,152,016-131,214,244)	50,164,725 (42,693,383-116,339,469)	43,570,214 (37,081,033-101,045,815)	36,791,415 (31,311,842-85,324,770)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,130,000 (1,481,295,000-7,024,965,000)	110,689,033 (94,200,000-256,695,000)	99,620,129 (84,780,000-231,025,500)	89,728,957 (76,362,288-208,087,235)	79,557,058 (67,705,668-184,497,946)	69,098,715 (58,805,274-160,244,373)	58,348,106 (49,656,154-135,313,019)
Slow adoption of new technology	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	1,109,000	2,003,189,555 (697,561,000-3,308,147,000)	52,131,733 (44,360,000-120,881,000)	5,213,173 (4,436,000-12,088,100)	10,565,017 (8,989,998-24,497,743)	16,058,297 (13,664,347-37,235,345)	21,695,830 (18,461,444-50,307,434)	27,480,481 (23,383,726-63,720,653)
Healthcare resource use costs	1,044,000	1,885,464,000 (656,676,000-3,114,252,000)	49,068,000 (41,760,000-113,796,000)	4,906,800 (4,176,000-11,379,600)	9,944,121 (8,463,082-23,061,897)	15,114,567 (12,863,461-35,052,931)	20,420,787 (17,379,393-47,358,846)	25,865,479 (22,013,174-59,985,899)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,153,000	3,888,653,555 (1,354,337,000-6,422,399,000)	101,199,733 (86,120,000-234,677,000)	10,119,973 (8,612,000-23,467,700)	20,509,138 (17,453,079-47,559,641)	31,172,864 (26,527,808-72,288,276)	42,116,617 (35,840,837-97,666,280)	53,345,961 (45,396,900-123,706,552)
NET BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400 (-127,058,000 - 602,566,000)]	-9,489,300 (-8,080,000, -22,018,000)	109,740,103 (93,392,000-254,493,200)	110,238,095 (93,815,367-255,646,876)	110,729,922 (94,233,476-256,786,222)	111,215,332 (94,646,111-257,910,653)	111,694,067 (95,053,054-259,019,571)

Threshold price

A threshold price analysis was conducted to determine the maximum price at which budesonide/formoterol 160/4.5 mcg (60 doses) would be cost-neutral relative to current standard care, from a public payer perspective. The aim was to support government tender negotiations by identifying break-even prices that would result in no net increase in total treatment costs, after accounting for both medication and healthcare use.

Methodological approach

1. Total per-patient treatment costs were estimated for both ICS/formoterol and standard of care regimens. This included medication prices and healthcare resource use (e.g., outpatient visits, emergency care, hospitalisations), which were adjusted based on expected reductions from improved asthma control under ICS/formoterol.
2. For PICO 3, a weighted average cost of the ICS/formoterol was calculated to reflect the mixed use of both budesonide/formoterol 160/4.5 mcg and 320/9 mcg formulations, based on the assumption that 39.5% of patients would require the higher-dose strategy. The percentage of 39.5% was derived from National Surveillance data used in the status quo and BIA models.
3. The price of each ICS/formoterol inhaler was then iteratively adjusted until the total average cost per patient matched that of the current standard of care, identifying the threshold (break-even) price at which the new regimen would be cost-neutral.

Findings

- Across all three scenarios, the threshold (cost-neutral) price for budesonide/formoterol 160/4.5 mcg (60 doses) was estimated at R50.54.
- In PICO 3, the price threshold for budesonide/formoterol 320/9 mcg (60 doses) was estimated at R109.25.

By explicitly incorporating realistic patient proportions and dosing strategies across the three scenarios, this analysis supports transparent and evidence-based procurement decisions aligned with national health priorities.

Discussion

For PICO 1 and 2, medicine costs are lower for ICS/formoterol than standard of care, whilst healthcare resource costs lower for PICO 2 and 3. For PICO 2, both medicine and health care utilisation costs are lower for ICS/formoterol, resulting in overall savings to the public health sector. For PICO 3, the higher medicine costs are offset by lower healthcare utilisation costs, resulting in an overall lower cost of treatment. Implementing new asthma management guidelines at scale does however require investments in procurement, health provider training, and patient education to ensure adherence.

Sensitivity analyses indicate uncertainty surrounding the costs of emergency room visits, hospitalisations and ICU admissions, as well as the proportion of people referred from PHC for hospitalisation. There is further uncertainty around the utilisation patterns of medicines for the standard of care, which may result in higher treatment costs. Furthermore, there is high uncertainty around the prevalence of adults with severe asthma, which could significantly impact the total budget impact for managing asthma. Overall, local epidemiological data for asthma are very limited. Engaging in price monitoring or negotiations could maintain or lower the price of budesonide/formoterol inhalers, respectively. Comprehensive diagnostic work-up of asthma, rational prescribing and use of asthma medications and patient adherence may improve the t access to budesonide/formoterol inhalers and ultimately result in improved patient outcomes.

A budget impact analysis conducted in Egypt over 3 years showed that as-needed budesonide/formoterol amongst mild persistent asthma was a budget-saving option compared to low-dose ICS controller therapy with as-needed SABA, from the economic perspective of the payer (Health Insurance Organization) and patient (Elsisi, 2019). Conversely, two economic analyses conducted in Southeast Asia (Aggarwal, 2022; Bunupuradah 2021) comparing total direct treatment costs of standard of care (fluticasone/salmeterol controller therapy with as-needed SABA) to budesonide/formoterol MART amongst those with moderate asthma, from a health payer's perspective, estimated that standard of care cost was lower than MART primarily due to lower medication costs. These analyses provide a platform for funders to negotiate lower prices with pharmaceutical suppliers for ICS/formoterol.

Strengths

This budget impact analysis offers a robust and comprehensive evaluation of the economic implications of implementing ICS/formoterol for the treatment of asthma. Several methodological strengths ensure the reliability and relevance of the findings for local healthcare decision-making.

Rigorous triangulation of prevalence estimates was undertaken. The analysis estimated prevalence from a diverse range of sources, including published studies, local utilisation patterns, and asthma inhaler dispensing data. Furthermore, expert opinion was systematically integrated to refine these estimates, ensuring that the estimates reflect the best possible local prevalence of asthma disaggregated by severity. This approach accounts for the variations in asthma severity distribution and provides a nuanced understanding of the target population.

Both pharmaceutical and non-pharmaceutical health resource costs were included in the BIA models. We accounted for direct pharmaceutical costs and estimated health resource utilisation costs, such as emergency visits and hospitalisations. Health resource costs were derived using Markov modelling, which employed inputs from a meta-analysis of data from the PICO 1, 2 and 3 systematic reviews of available clinical trials. This ensures that the cost estimates are based on high-quality, evidence-based data.

Local contextualisation was considered ensuring that the analysis aligns global evidence with local data, ensuring its relevance for decision-makers. Adjustments for local pricing, healthcare resource availability, and patient demographics enhance its applicability to the South African public healthcare setting.

Economic evidence to support evidence-based policy decisions was provided, and the comprehensive approach provides policymakers with actionable insights to evaluate the economic feasibility of implementing new treatment regimens. It balances cost considerations with potential health system savings and patient outcomes. However, to account for uncertainty in the input parameters, the BIA model incorporated both univariate and multivariate sensitivity analyses. By varying key cost drivers individually and in combination, the analysis provided a robust understanding of how parameter uncertainty may influence outcomes. This approach ensures that decision-makers are equipped with insights into the range of possible budgetary impacts under different scenarios, enhancing confidence in the results.

Lastly, a threshold price was estimated to identify the price point at which the cost of the new treatment regimen would result in net zero budget impact compared to the current standard of care.

Limitations

Several limitations should be noted when interpreting the findings of the BIA research, primarily due to the poor quality or lack of local epidemiological data regarding South African adolescent and adults with asthma and COPD populations.

This includes limited data on the prevalence of intermittent, mild to moderate, and severe asthma, ICU and hospital admission rates for severe asthma, emergency room treatments, and the current use of relievers in those with intermittent, moderate, and severe asthma within this demographic. The available published data on asthma prevalence are inconsistent, using varying definitions and study methodologies, highlighting the need for global standardised definitions, methodologies and denominators.

For COPD, the GOLD guidelines were used to indirectly estimate utilisation rates of ICS/LABA used by COPD patients.

Proxies were calculated using national surveillance data to proportion coverage of inhalers to the different sub-populations.

National procurement surveillance data suggest that SABA inhalers may be used irrationally in practice, a factor that has not been included in the BIA model. Furthermore, published literature documents the underdiagnosis of asthma, particularly among adolescents with severe asthma.

For practical purposes, a linear model was used for the BIA, rather than a Markov model, considering the "step-up" and "step-down" probabilities over adolescent/adults' lifetimes. To estimate coverage over five years, only annual population growth was considered, without considering any potential increase in eligible population coverage through programmatic improvements.

To address uncertainties, sensitivity analyses were performed where applicable; however, these were not conducted on efficacy estimates related to treatment. Additionally, there is a paucity of data directly comparing the efficacy and safety of ICS/SABA to ICS/formoterol for mild intermittent asthma, and although expert opinion suggests that these agents are comparable in this clinical setting, further research is required to determine the effects.

Most of the ICS/formoterol studies were based on dry powder inhalations (DPI) rather than aerosol-metered dose devices (MDI). Pragmatic considerations for the DPI include ease of patient use and possibly reduced environmental impact compared to the MDI (Refer to the rapid evidence review for PICO 1).

Conclusion

The budget impact analysis demonstrates that adopting ICS/formoterol treatment strategies for asthma, has the potential to yield cost savings for the South African public health sector. Across the different PICO scenarios, the reduction in healthcare utilisation costs (primarily from fewer hospitalisations, emergency visits, and ICU admissions) and the lower medicine costs for PICOs 1 and 2 lead to net savings. The higher medicine costs for the intervention group in PICO 3 are also offset by the lower healthcare utilisation costs, due to improved patient outcomes.

Key factors influencing the budget impact include the price of budesonide/formoterol inhalers, the prevalence of asthma, the relative population cohorts based on disease severity, and uncertainties surrounding healthcare utilisation patterns. While the analysis highlights potential economic benefits, successful implementation of revised asthma guidelines requires additional investments in procurement, health provider training, and patient education to ensure adherence and optimal treatment outcomes. Given the limited availability of local epidemiological data, further research is needed to refine cost estimates and validate assumptions. Policymakers may also consider engaging in price monitoring and negotiations for budesonide/formoterol inhalers to enhance affordability and sustainability. By aligning treatment strategies with cost-effective interventions, the health system can improve asthma management, while optimising resource allocation.

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Appendices

Appendix A: Prevalence studies

Supplementary Table 1: Summary of prevalence studies

S African prevalence rates	Children				Adolescents				Adults			
	Age (yrs)	P	Definition	Refs	Age (yrs)	P	Definition	Refs	Age (yrs)	P	Definition	Refs
Overall asthma	6-7	11.2%	Questionnaire Parent/guardian surveyed: Has your child had wheezing or whistling in the chest in past 12 months.	Polokwane, ISAAC 3 (2007) [1]	13-14	16.0%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Cape Town, ISAAC 1 (1995)[2]	18-45	14.4%	Wheezing symptoms: During the last 12 months have you experienced attacks of wheezing or whistling breath?"	South Africa, WHS (2003) [5]
					13-14	20.3%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Cape Town, ISAAC 3 (2002)[2]	18-45	6.09%	Clinical asthma: doctor-diagnosed asthma and/or a positive response in either of 2 questions "Have you ever been treated for asthma" or "Have you been taking any medications or treatment for asthma during the last 2 weeks?"	South Africa, WHS (2003) [5]
					13-14	18.0%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Polokwane, ISAAC 3 (2007) [1]	18-45	5.92%	Doctor diagnosed asthma	South Africa, WHS (2003) [5]
					13-14	21.3%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Cape Town, GAN Phase 1 (2017) [3]	Adults	6-10%	Data on adults in SA are less reliable but the estimated prevalence of asthma 6-10% and rising	South Africa, Zar (2013) [6]
					13-14	13.1%	Diagnosis of asthma ever	Cape Town, ISAAC 1 (1995) [2]	5-69	13.2% (10.5-16.5)	Self-reported current wheezing	African region, SR (2022) [7]
					13-14	14.4%	Diagnosis of asthma ever	Cape Town, ISAAC 3 (2002) [2]	5-69	11.3% (9.0-14.1)	Diagnosis of asthma ever (by a physician)	African region, SR (2022) [7]
					13-14	16.6%	Diagnosis of asthma ever	Cape Town, GAN Phase 1 (2017) [3]	≥15	3.5% (3.1-4.0)	DHS 2016 + self-reported past diagnosis by healthcare worker	South Africa, modelled-based study (2024) [8]
					13-14	13.7%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling	Durban/Richards Bay (2021) [4]				

Severe asthma							in the chest in the past 12 months.					
					13-14	12.9 %	Diagnosis of asthma ever	Durban/Richards Bay (2021) [4]				
	6-7	5.7 %	Questionnaire Parent/guardian surveyed: severe wheeze if ≥ 2 of ffg: (1) ≥ 4 attacks in the last 12 months; (2) speech disturbance in the last 12 months; (3) > 1 night of sleep disturbance in the last 12 months; (4) wheezing with exercise in the last 12 months	Polokwane, ISAAC 3 (2007) [1]	13-14	7.3 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Cape Town, ISAAC 1 (1995) [2] [9]	Adults	3.6 % (3-4.1)	Questionnaire: participants identified from pharmacy databases & surveyed Definition of severe asthma	Netherlands, questionnaire of diagnosed asthmatics (2011) [10]
					13-14	9.5 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Cape Town, ISAAC 3 (2002) [2] [9]	Adults	8.1 %	Utilisation data: Nationwide prescription database	Denmark, prescription database (2010) [11]
					13-14	11.8 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Cape Town, GAN Phase 1 (2017) [3] [9]	Children & adults	5-10%	"Little is understood regarding the prevalence of severe asthma in adults or children, especially when using rigorous definitions as outlined here. However, figures of 5-10% of the total asthma population are often estimated".	Global (2014) [12]
					13-14	9.1 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Durban/Richards Bay (2021) [4]	13-36	25.60%	Severe asthma was defined by pulmonologist(s) as asthma that required treatment with guideline-suggested medications for GINA step 4-5 asthma (high-dose ICS and long-acting β -agonist or leukotriene modifier/theophylline) for the previous year or systemic corticosteroid therapy for $\geq 50\%$ of the previous year to prevent it from becoming uncontrolled, or disease that remained uncontrolled despite this therapy. Uncontrolled asthma was defined as consistently having an ACQ score of ≥ 1.5	East Africa (Uganda, Kenya, Ethiopia), prospective cohort study (2023) [18]
					13-15	3.7 %	Diagnosis of severe asthma with reported severe asthma symptoms	Durban/Richards Bay (2021) [4]	≥ 17	7.80 %	Patients with severe asthma were defined as patients prescribed 1600 mg per day	Japan, health insurance

								budesonide equivalent dosage or a greater ICS dosage plus at least one controller (LABA, leukotriene receptor antagonist (LTRA), or theophylline) during 12 months before the index date. The budesonide equivalent dosage of ICS was calculated based on the prescriptions before the index date. Patients with 183 or more prescription days for systemic corticosteroids within 12 months before the index date were also defined as patients with severe asthma.	claims database (2017) [19]
		Children & adults	5-10 %	"Little is understood regarding the prevalence of severe asthma in adults or children, especially when using rigorous definitions as outlined here. However, figures of 5–10% of the total asthma population are often estimated"	Global (2014) [12]	≥18	21.70%	Difficult-to-treat or severe asthma was defined by poor symptom control, exacerbations and/or oral corticosteroid/biologic use despite medium/high-dose inhaled therapy.	Australia, cross-sectional survey (2021) [20]
COPD	n/a			n/a		Adults	8.0 % (6.2 - 10.2)	Population-based studies & modelling systematic review using the GOLD & LLN definitions of COPD	South Africa, SR & modelling based on BOLD study (2019) [13] [17]
						Adults	8% (6-11)	Systematic review of published literature, conference proceedings.	SSA, SR & MA (2020) [14]
						Adults	22%	Nkhoma 2023: In Africa, COPD has a prevalence rate of around 20% in South Africa, cited the BOLD study; Buist 2007 (BOLD study): Cape Town site COPD prevalence of 22% using patient questionnaires.	Cape Town, prevalence survey (BOLD study) cited (2007) [16][17]
						≥15	1.8 % (1.5 - 2.2)	DHS 2016 + self-reported symptoms suggestive of the condition Note: Association between asthma and COPD: OR 14.6 (10.3-19.9)	South Africa, modelled-based study (2024) [8]
						COPD Group E	26.7 %	The GOLD ABCD classification was changed to ABE in 2023 such that Groups C and D are now grouped together and termed Group E. In the COPD Gene cohort, GpA=37.0%; GpB=26.7%; GpC=22.3%; GpD=22.3% (i.e. GpE= GpC+GpD=26.7%) [22]; COPD Gold GpE are COPD patients with acute eosinophilic exacerbation with blood eosinophils ≥300/μL [21] [22] Studies suggest that the age-onset of COPD is ≥40 years [17][24]	USA, cross-sectional & longitudinal data from the Genetic Epidemiology of COPD Study (2010); associations of GOLD 2011 vs 2017 classifications [23]

Abbreviations: COPD=chronic obstructive pulmonary disease; P=prevalence, SR=systematic review

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Appendix B: Dispensing data (Western Cape)

Supplementary Table 2: Western Cape dispensing data of inhaled corticosteroid inhalers from 1 July 2023 to 30 June 2024

Age group	Datasource	Drugname	Formulation	Strength (mcg)	Doses per inhaler	Number of dispensings	Number of distinct patients issued to	Pack Size	Packs Issued
>40 yr	CDU	budesonide	Inhaler	200	300	11208	11191	1	12899
	JAC	beclometasone	Inhaler	200	200	31984	30406	1	72136
	JAC	budesonide	Inhaler	200	300	15369	15204	1	21857
>15 yr	CDU	budesonide	Inhaler	200	300	12503	12484	1	14328
	JAC	beclometasone	Inhaler	200	200	39631	37670	1	87885
	JAC	budesonide	Inhaler	200	300	18658	18458	1	26440
12-14yr	CDU	budesonide	Inhaler	200	300	143	143	1	144
	JAC	beclometasone	Inhaler	200	200	675	630	1	1250
	JAC	budesonide	Inhaler	200	300	269	268	1	365
Average packs per annum				Number of distinct patients issued to		Packs Issued	Average packs issues/patient/ annum	Rounded up	
Beclomethasone 200mcg inhaler, 200 doses				68706		161271	2.35	3	
Budesonide 200mcg inhaler, 300 doses				57748		76033	1.32	2	

Note: A CDU patient may receive at least one dispensing from the facility when the repeat prescription is issued.

Thus, assumed that 4 x beclomethasone inhalers (200 dose) and 3 x budesonide inhalers (300 dose) dispensed per patient per annum.

Abbreviations: CDU=Chronic Dispensing Unit; JAC=Pharmacy management system; mcg=microgram

Supplementary Table 3: Estimated number of inhalers per annum for PICO 1 (mild intermittent asthma)

	Medicine (Inhaler)	Doses/ inhalations	Dosing	Modelled Inhalers	Annual doses	Wastage accounted
Comparator	Beclometasone; 200mcg; Inhaler	200	1 inhalation as required	2	180	Unknown
	Budesonide; 200mcg; Inhaler	300	1 inhalation as required	2	180	Unknown
	Salbutamol; 100mcg; Inhaler	200	2 inhalations as required	2	360	Unknown
Intervention	Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	1 inhalation as required	3	180	Unknown

*Wastage cannot be accurately estimated as treatment is used intermittently as needed. Furthermore, SABA/ICS is not available as a fixed-dose combination formulation and thus one ICS and one SABA are assumed to be dispensed per prescription. The number of modelled inhalers was guided by expert opinion.

Supplementary Table 4: Estimated number of inhalers per annum for PICO 2 ("mild" persistent asthma)

	Medicine (Inhaler)	Doses/ inhalations	Daily mcg dosing*	Annual doses/ inhalations	Annual Inhalers	Modelled Inhalers	Wastage
Comparator	Beclometasone; 200mcg; Inhaler	200	275	495	2.48	4	38%
	Budesonide; 200mcg; Inhaler	300	275	495	1.65	3	45%
	Salbutamol; 100mcg; Inhaler	200	0.48	720	3.60	6	40%
Intervention	Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	108	243	4.06	6	32%

*From Hatter et al, assuming beclometasone is equivalent to budesonide and verified by Western Cape Central Dispensing Unit utilisation data of ICS over 12 months – see Table 6, below.

Supplementary Table 5: Estimated number of inhalers per annum for PICO 3 moderate asthma)

	Medicine (Inhaler)	Doses	Daily mcg dosing	Annual doses/ inhalations	Annual Inhalers	Modelled Inhalers	Wastage
Comparator	Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	720	12	12	0%
	Budesonide, Formoterol; 320mcg, 9mcg; Inhaler	60	640/18 mcg	720	12	12	0%
	Salbutamol; 100mcg; Inhaler	200	200 mcg	720	3.6	6	40%
Intervention*	A: Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	720	12	12	0%
	A: Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	360	6	6	0%
	B: Budesonide, Formoterol; 320mcg, 9mcg; Inhaler	60	640/18 mcg	720	12	12	0%
	B: Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	360	6	6	0%

*The intervention may be either:

A) Budesonide/ formoterol 160/4.5mcg 12 hourly as controller therapy with 160/4.5 mcg as needed for symptomatic relief: or

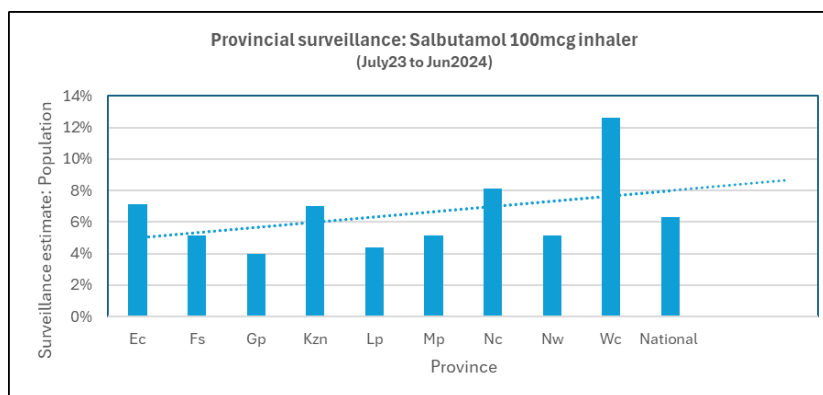
B) Budesonide/formoterol 320/9 mcg 12 hourly as controller therapy with 160/4.5 mcg as needed for symptomatic relief.

Appendix C: Comparative analysis of the different utilisation data sets

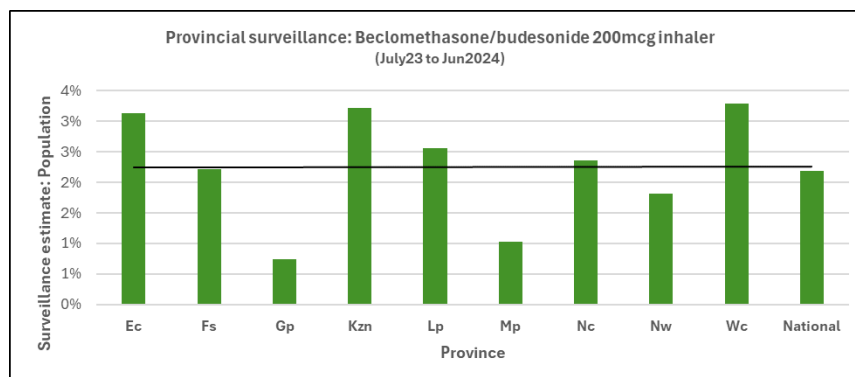
Supplementary Table 6: Uptake rates for the status quo scenario, comparing treatment access to asthma prevalence rates

	PICO 3 (adolescents)			PICO 3 (adults)		
	Uptake rate for status quo					
Prevalence estimate	8%	10%	6%	4%	5%	3%
Tender estimate	39.13%	31.30%	52.17%	14.30%	11.41%	19.09%
National surveillance data	99.68%	79.74%	132.90%	26.92%	21.51%	35.93%
WC Province surveillance data	2.01%	1.64%	2.61%	13.08%	10.42%	17.48%
WC Dispensing (CDU & Pharmacy)	0.64%	0.51%	0.85%	17.83%	14.19%	23.85%
	PICO 2 (adolescents)			PICO 2 (adults)		
	Uptake rate for status quo					
Prevalence estimate	22%	27%	17%	10%	14%	6%
Tender estimate	44.48%	36.24%	57.56%	44.48%	31.77%	74.13%
National surveillance data	38.85%	31.66%	50.28%	38.85%	27.75%	64.76%
WC Province surveillance data	6.50%	5.30%	8.41%	6.50%	4.64%	10.83%
WC Dispensing (CDU & Pharmacy)	0.83%	0.67%	1.07%	5.62%	4.01%	9.37%
	PICO 1 (adolescents)			PICO 1 (adults)		
	Uptake rate for status quo					
Prevalence estimate	22%	27%	17%	10%	14%	6%
Tender estimate	20.96%	17.08%	27.13%	62.26%	44.29%	104.05%
National surveillance data	1.91%	1.56%	2.48%	45.21%	32.16%	75.55%
WC Province surveillance data	4.48%	3.65%	5.80%	7.25%	5.16%	12.11%
WC Dispensing (CDU & Pharmacy)	0.95%	0.78%	1.23%	11.45%	8.15%	19.14%

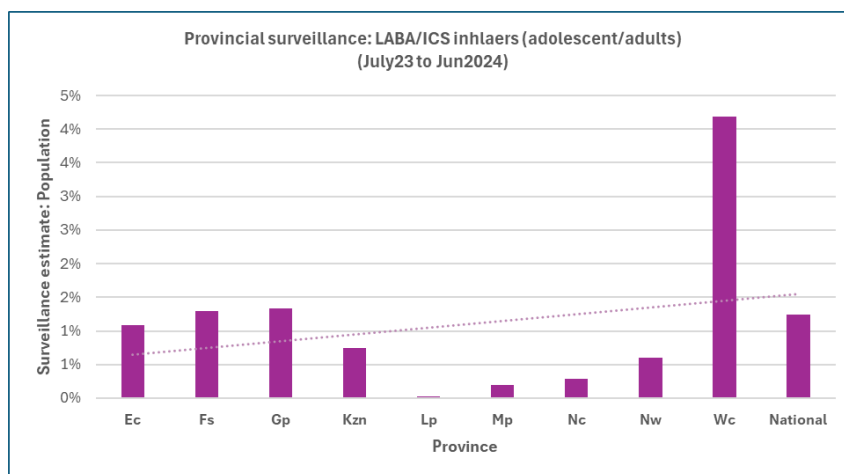
To better understand the variable data, a comprehensive analysis of the provincial surveillance data relative to the provincial population was conducted.



Supplementary Figure 1: Salbutamol 100mcg inhaler - Surveillance data: Population estimate

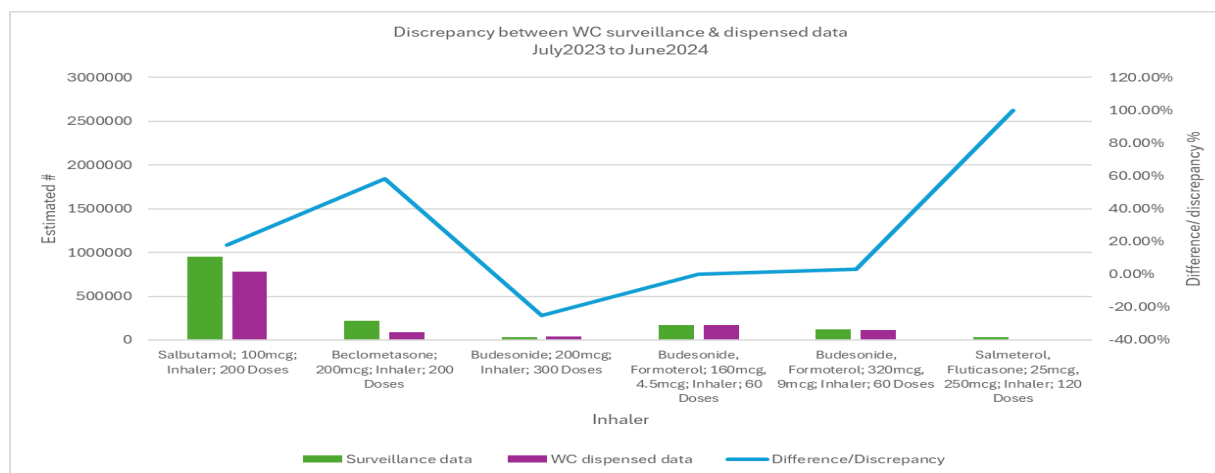


Supplementary Figure 2: Inhaled corticosteroid - Surveillance data: Population estimate



Supplementary Figure 3: ICS/LABA - Surveillance data: Population estimate

Supplementary Figures 2 to 4 show that Western Cape is an outlier, except for provincial surveillance data on budesonide/ beclomethasone 200mcg inhalers. This may suggest a higher prevalence of asthma or better clinical management of adolescent/ adult asthmatics. A comparison of procurement data with actual dispensed data revealed discrepancies regarding inhaled corticosteroids (budesonide and beclomethasone 200mcg inhalers). Notably, the 2020 edition of the PHC STGs and EML recommends ICS/LABA inhalers as doctor-initiated, with continued prescribing by nurse practitioners. Furthermore, Supplementary Figure 1 does not differentiate between acute, in-patient, outpatient, and chronic use of salbutamol inhalers due to limited data.



Supplementary Figure 4: Discrepancy between WC surveillance and dispensed data

It seems reasonable to base the status quo uptake rates on national surveillance data while applying sensitivity analyses to address any uncertainties.

The limitations of the model used to determine the status quo uptake rates include:

- A linear static model was used, which did not consider the "step-up" and "step-down" probabilities over the lifetime of adolescent/adult asthmatics.
- Asthma prevalence rates in South Africa are limited, including for different asthma "severities" and age groups.
- Frequent reports of underdiagnosis, particularly among adolescents with severe asthma, which may inflate ICS inhaler uptake rates beyond modelled expectations, and ICS/LABA inhaler uptake rates may fall below modelled expectations.
- Implementation of guideline changes typically takes 2-3 years, a factor to consider in forecasting.
- The model does not reflect inhaler use for acute exacerbations in healthcare facilities, or potential wastage.

Appendix D: Estimated doses/ inhalations for as-needed β 2-agonist reliever therapy

Supplementary table 7: Difference in number of as-needed β 2-agonist reliever inhalations used per day between ICS/FABA compared to standard of care.

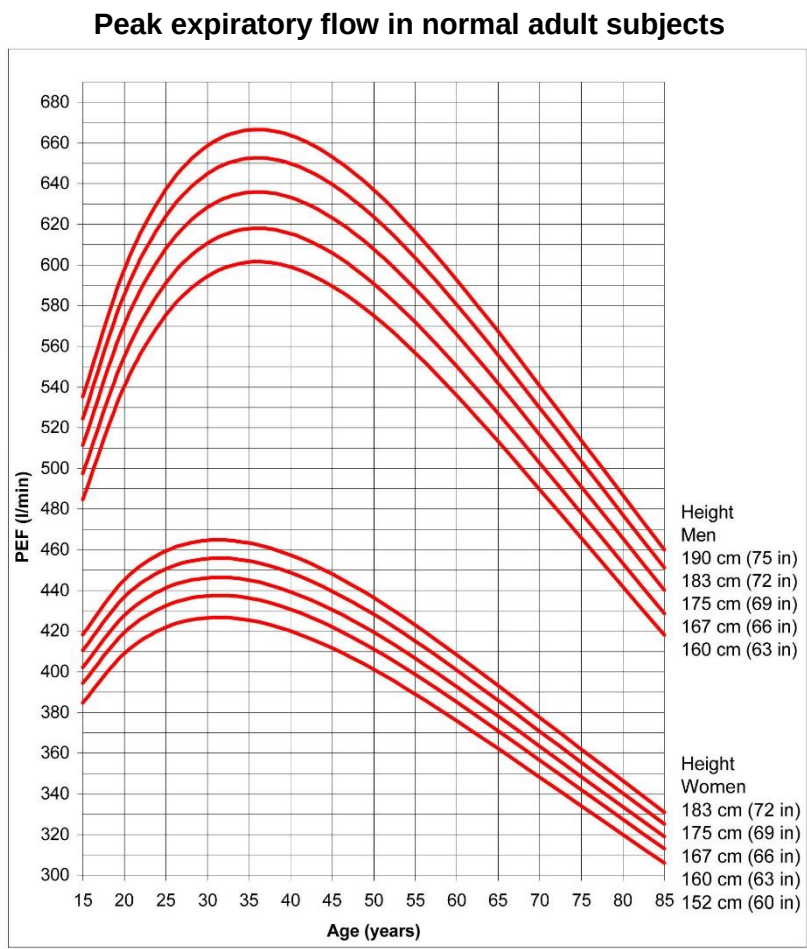
Research question	RCTs (n)	Estimate for intervention versus control
PICO 1	N/A	Assumed that there is no difference based on expert opinion*
PICO 2	4 (7290)	Mean difference: 0.08, 95% CI 0.05 to 0.10), I^2 94.2
PICO 3	7 (15175)	Mean $\pm$ SD: 0.90 $\pm$ 0.26 vs 0.99 $\pm$ 0.24

*There are no available RCTs comparing ICS/SABA to ICS/FABA for mild intermittent adolescent/adult asthmatics

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- ii. SYGMA 1: O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK. Inhaled combined budesonide–formoterol as needed in mild asthma. *New England Journal of Medicine*. 2018;378 (20): 1865-76. Available from: <https://doi.org/10.1056/NEJMoa1715274>
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- v. PRACTICAL: Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, Corin A, Sparks J, Hall D, Sabbagh D, Mane S. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *The Lancet*. 2019;394(10202):919-28. Available from: [https://doi.org/10.1016/S0140-6736\(19\)31948-8](https://doi.org/10.1016/S0140-6736(19)31948-8)
- vi. Hatter L, Bruce P, Braithwaite I, Holliday M, Fingleton J, Weatherall M, Beasley R. ICS-formoterol reliever versus ICS and short-acting β 2-agonist reliever in asthma: a systematic review and meta-analysis. *ERJ Open Research*. 2021;7(1). Available from: <https://doi.org/10.1183/23120541.00701-2020>.

PEAK EXPIRATORY FLOW RATES



Adapted with permission from Nunn AJ Gregg I, Br Med J 1989;298;1068-70 and Clement Clarke International.

CALCULATING % PREDICTED PEAK FLOW RATE

- Take the best of 3 of the patient's observed peak flow rates (l/min):
e.g. 200, 180, 190 performed – so take 200.
- Find the patient's sex, age and height predicted value from the nomogram.
e.g. 440 l/min for a woman of age 25 years and height 167 cm
- Divide patient's observed peak flow rate over their predicted peak flow rate: e.g. $200/440 = 0.45$
- Multiply by 100: e.g. $0.45 \times 100 = 45\%$

So, in this example, the patient's observed peak flow rate is 45% of their predicted.

CALCULATING BRONCHODILATOR RESPONSIVENESS USING PEAK FLOW IN ADULTS

Perform peak flow testing and select the best of the 3 values to use as the pre-bronchodilator peak flow.

- Administer salbutamol 400 µg using a metered dose inhaler and spacer without a mask.
- Wait 15 minutes before repeating peak flow
- Repeat peak flow testing to obtain a post-bronchodilator peak flow.
- Subtract the pre-bronchodilator reading from the post-bronchodilator reading.
- Divide the difference by the pre-bronchodilator reading.
- Multiply by 100.

For example, a patient with readings that improve from 300 to 400, has reversibility of 33%. Measurements that improve by >20% strongly suggest a diagnosis of asthma. (See Sections 16.1: Asthma, acute and 16.2: Asthma, chronic persistent).

CALCULATING PEAK FLOW VARIABILITY IN CHILDREN AND ADULTS

- Perform peak flow measurements 4 times per day spread over the course of the day.
- Subtract the lowest reading of each day from the highest reading.
- Calculate the mean/average reading by adding all 4 readings from that day and dividing total by 4.
- Calculate PEF variability:

$$\text{PEF variability} = \frac{(\text{Highest PEF} - \text{Lowest PEF})}{\text{Mean PEF}} \times 100.$$

Determine this value on each day over two weeks, and average the results. Excessive diurnal PEF variability defined as >10% in adults and >12% in children strongly supports a diagnosis of asthma.

ASTHMA CONTROL TEST™

This is a validated measure of clinical asthma control that can be completed by the patient (after initial instruction) at each visit to the clinic prior to consultation. A value of ≥ 19 suggests adequate asthma control.

Online version of the test is accessible at: <https://www.asthmacontroltest.com/>

Reference: Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004 Jan;113(1):59-65. <http://www.ncbi.nlm.nih.gov/pubmed/14713908>

INHALER DEVICES

SPACER DEVICES

- » Spacers are vital for an adequate therapeutic effect of inhaled therapy.
- » Spacer devices should be used for all inhaled medications in all age groups to improve efficacy of medicine delivery and limit adverse effects.
- » Use a spacer that is appropriate for the patient's age.

	Spacer volume	Valve	Delivery	Technique
Infants <3 years	150–250 mL	Required	Face mask	Deep tidal breathing
Children 3 to 6 years	500 mL	Required	Mouthpiece	Deep tidal breathing
Children >7 and adults	500 mL	Optional	Mouthpiece	Single inhalation and breath-hold

- » Inhalation spacer devices enable optimal aerosol delivery.
- » Children < 3 years of age should have a spacer with a face mask, while older children and adults should use the spacer with a mouth piece directly.
- » Demonstrate the relevant inhaler technique more than once to ensure the correct procedure (see below).

LoE: IVb¹

Patient and caregiver education on inhaler and spacer techniques:

- » If patients are switched between different types of devices (e.g. from MDI to DPI), patients need to be re-educated on inhaler technique.
- » If changing from a DPI to MDI, consider if a spacer is required, and the optimal technique for inhalation.
- » Doses may not be equivalent between different inhaler devices – ensure that patients are prescribed the correct dose when switching between devices.

METERED DOSE INHALERS (MDIs)

- » A mask attachment must be used with the spacer for children < 3 years of age and be removed as soon as the child is able to use the mouthpiece.

A. Inhalation therapy without a spacer in adults: Single breath inhalation technique

1. Remove the cap from the mouthpiece.
2. Shake the inhaler well.
3. While standing or sitting upright, breathe out as much air as possible.
4. Immediately place the mouth piece of the inhaler between the lips and gently close the lips around it.
5. Start breathing in slowly.

6. Immediately press down the canister of the metered dose inhaler once to release one puff while simultaneously breathing in as deeply as possible.
7. Hold breath for 5 to 10 seconds, if possible.
8. Breathe out slowly through the nose and rest for a few breaths (30–60 seconds).
9. Repeat steps 2–8 for each puff prescribed.
10. Rinse mouth after inhalation of corticosteroids.

LoE:IVb²

B. Inhalation therapy with a spacer in adults and older children: Single breath inhalation technique

1. Remove the caps from the inhaler and the spacer.
2. Shake the inhaler well.
3. Insert the mouthpiece of the metered dose inhaler into the back of the spacer.
4. Insert the mouthpiece of the spacer into the mouth and close the lips around the mouthpiece.
5. Exhale fully into the spacer.
6. Start inhalation and immediately press down the canister of the metered dose inhaler once to release one puff into the spacer.
7. Breathe in slowly to full inhalation and hold the breath for 5 to 10 seconds.
8. Breathe out through the nose.
9. Repeat steps 2–8 for each puff prescribed, waiting at least 30 seconds between puffs.
10. Rinse mouth after inhalation of corticosteroids.

C. Inhalation therapy with the spacer alone in younger children or in adolescent and adults unable to do single inhalation: Deep tidal breathing technique

1. Remove the caps from the inhaler and the spacer.
2. Shake the inhaler well.
3. Insert the mouthpiece of the spacer into the mouth and close the lips around the mouthpiece.
4. Press down the canister of the metered dose inhaler once to release one puff into the spacer.
5. Breathe slowly and deeply in and out of the spacer continuously for at least 6 breaths
6. If breathing through the nose as well as the mouth, pinch the nose gently while breathing from the spacer.

D. Inhalation therapy with a spacer and mask for infants and children < 3 years:

1. Remove the caps from the inhaler and the spacer.
2. Infants may be preferably placed on the caregiver's lap or alternatively laid on a bed while administering the medication.
3. Shake the inhaler well.
4. Apply the mask to the face, ensuring that the mouth and nose are well covered.

5. With the mask held firmly onto the face, press down the canister of the metered dose inhaler once to release one puff into the spacer.
6. Keep the mask in place for at least six breaths, then remove.
7. Repeat steps 3–6 for each puff prescribed, waiting at least 30 seconds between puffs.

DRY POWDER INHALERS (DPIs)

E. Inhalation therapy with a dry powder inhaler (DPI) for adults and children over 6 years of age:

1. There is no need to shake a DPI.
2. Open, twist or click the device to load the medication dose.
3. Stand or sit up straight and breathe out completely (away from the device, not into the mouthpiece).
4. Immediately place the mouthpiece into the mouth, close lips tightly around it and breathe in quickly and forcefully to full inhalation.
5. Remove the DPI from the mouth, hold breath for 5-10 seconds, then exhale slowly.
6. Optimise positioning and repeat steps 2–5 for each puff prescribed, waiting at least 30 seconds between puffs.
7. Rinse mouth with water after inhalation of corticosteroids.

NEBULISERS

The guidance below is tailored to the use of jet nebulisers which are primarily used in the public sector.

1. Ensure the nebuliser cup is filled sufficiently to allow effective nebulisation (approx. 4 mL minimum volume). Volume must be more than the equipment dead space to be sufficient. The dead space in a nebuliser refers to the volume of the nebulizer chamber and tubing that remains filled with medication after treatment. This volume is not delivered to the patient and can vary depending on the nebulizer design. Typical dead space volumes in jet nebulizers is 2-3 mL.
2. Hold the nebuliser upright.
3. Select a flow rate of oxygen of 6 to 8 L/min for jet nebulisers.
4. Use a mouthpiece rather than a facemask in adults and in any child able to hold a mouthpiece between their lips and breathe via their mouths.
Better medication delivery: The T-piece allows for more direct delivery of medication to the lungs, reduced medication loss, improved patient comfort, enhanced cooperation, reduced risk of skin irritation and easier observation of the patient's mouth and nose.

5. Place the mouthpiece in the patient's mouth. Advise the patient to keep their lips firmly around the mouthpiece. If using a facemask, place it over the mouth and nose.
6. Ensure patient is calm and relaxed.
7. Advise patient to breathe slowly and deeply through the mouth as far in and as far out as possible until all the medication is used.

The following should be avoided when using nebulisers:

- » Rapid or forceful inhalation (including crying)
- » Nebulising whilst sleeping
- » Using a facemask when a mouthpiece is possible
- » A loose-fitting facemask or placing the nebuliser near a child's nose and mouth rather than securing a facemask

LoE:IVb³

¹ Spacers: Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res. 2018 Jun 18;4(2):00065-2018. doi: 10.1183/23120541.00065-2018. PMID: 29928649; PMCID: PMC6004521.

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² Optimal aerosol delivery: Levin ME. Optimal aerosol delivery. Current Allergy & Clinical Immunology. 2011; 24(1):27-30

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³ Optimal aerosol delivery: Levin ME. Optimal aerosol delivery. Current Allergy & Clinical Immunology. 2011; 24(1):27-30

COMPARATIVE DOSE TABLES

The tables below are NEMLC approved recommendations for comparative dosing across therapeutic classes. The recommended doses do not necessarily imply dose equivalence or equipotency (i.e. switching patients from low dose of one medicine to low dose of another medicine may represent an increase or decrease in potency). These tables are intended to serve as a pragmatic guide of comparative doses for different medicine classes, and are informed by best available evidence and local product availability. The aim of this guidance is to support procurement decisions and the switching of patient treatment across various therapeutic alternatives.

HMG-CoA REDUCTASE INHIBITORS (STATINS)

NEMLC approval for STG indications as follows:

- Low intensity statins approved for primary prevention.
- Moderate intensity statins approved for secondary prevention.
- High intensity statin approved for familial hypercholesterolemia.

Comparative Doses for STG Indications				Drug-drug Interactions
Statin Intensity	LOW	MODERATE	HIGH	<i>Co-administration with protease inhibitor (PI) ARVs or Amlodipine</i> LoE:IVb¹
STG Indication	PRIMARY PREVENTION	*SECONDARY PREVENTION	FAMILIAL HYPERCHOLESTERAEMIA	
Statin	Recommended dose			
Atorvastatin		20mg	80mg	PI: Max dose 10mg/day**
Pravastatin	20mg	80mg		PI: Avoid Potential interaction with LPV/r – no data available for recommended dosing.
Simvastatin	10mg	40mg		PI: Contraindicated Amlodipine: Use max 10-20 mg.
Rosuvastatin		10mg	40mg	PI: Max dose 10mg/day**
Notes: *Reduce dose if myalgia suspected. **Recommended maximum doses may vary for different protease inhibitors (PIs). NEMLC recommends the lowest recommended statin dose for ease of implementation.				

INHALED CORTICOSTEROIDS (ICS)

Adults and adolescents ≥ 12 years

LoE:IVb²

Adults and adolescents ≥12 years			
Drug	Daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate CFC MDI	200–500	>500–1 000	>1 000
Beclometasone dipropionate HFA MDI	100–200	>200–400	>400
Budesonide DPI or HFA	200–400	>400–800	>800
Ciclesonide HFA	80–160	>160–320	>320
Fluticasone furoate DPI	100	n/a	200
Fluticasone propionate DPI	100–250	>250–500	>500
Fluticasone propionate HFA	100–250	>250–500	>500
Mometasone furoate	110–220	220–440	>440
CFC: chlorofluorocarbon propellant HFA: hydrofluoroalkane propellant MDI: metered dose inhaler DPI: dry powder inhaler			

¹ Interaction with Pls: Ansari R, Khalili H, Mohammadi K. Optimizing statin therapy in HIV-infected patients: a review of pharmacotherapy considerations. BMC Cardiovasc Disord. 2025 May 31;25(1):421. doi: 10.1186/s12872-025-04887-2. PMID: 40450213; PMCID: PMC12125728.
² Global Initiative for Asthma (GINA). (2024). Global Strategy for Asthma Management and Prevention, 2024. <https://ginasthma.org/2024-report/>