

**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).

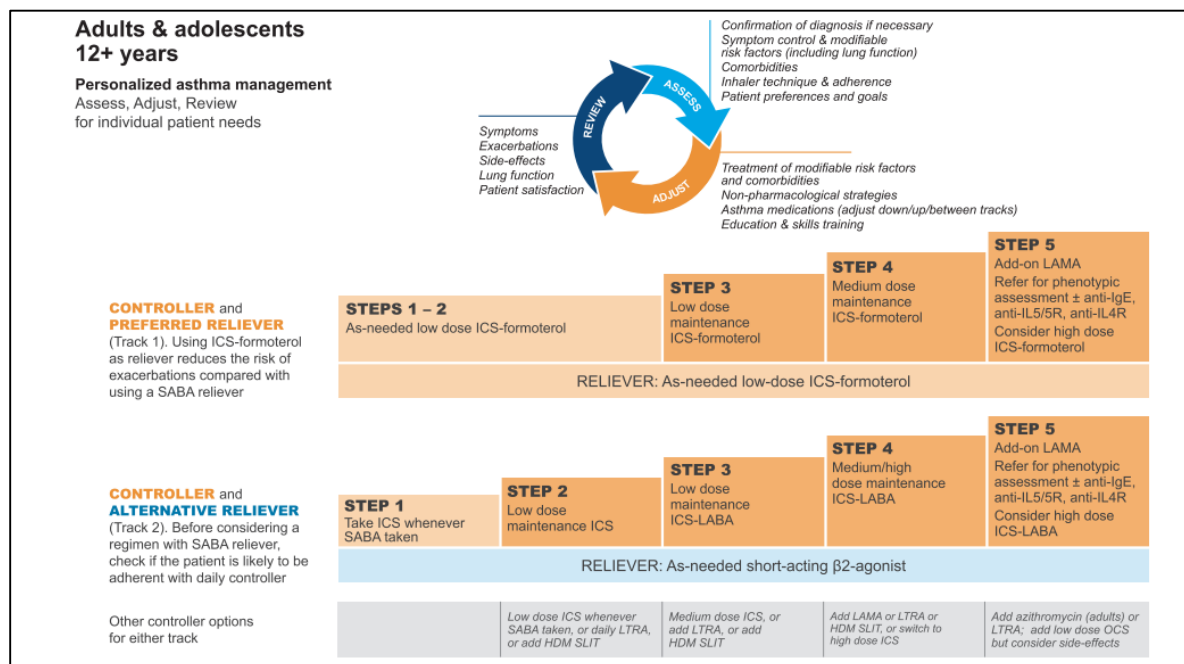


Figure 1: Personalized management for adults and adolescents to control symptoms and minimise risk

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.

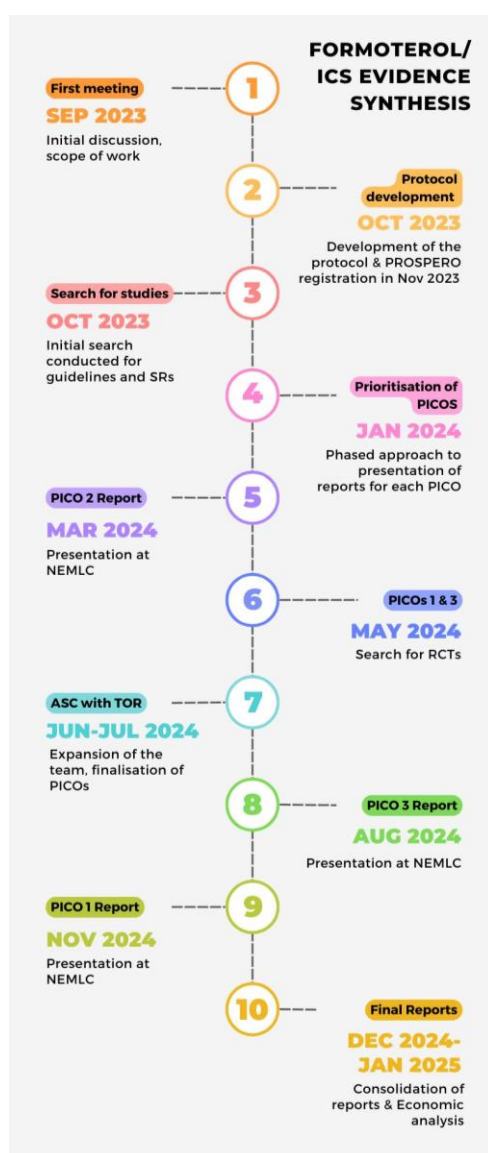


Figure 2: Overview of study phases

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.

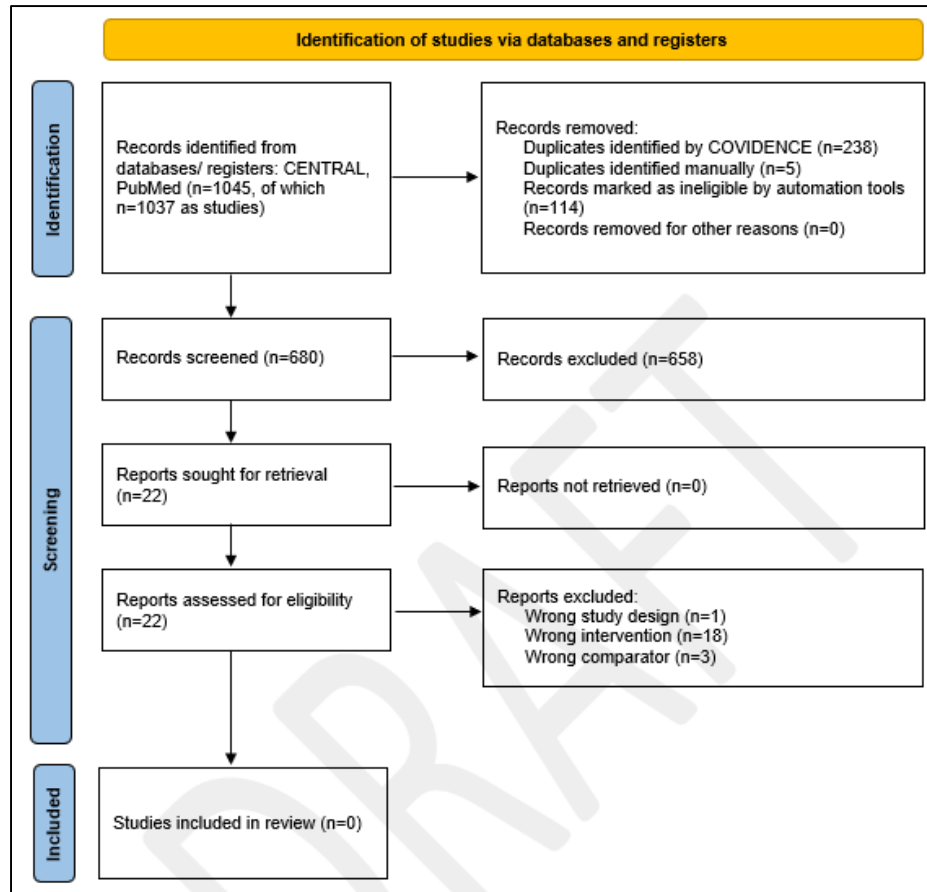


Figure 3: PRISMA flow diagram for review, PICO 1

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).

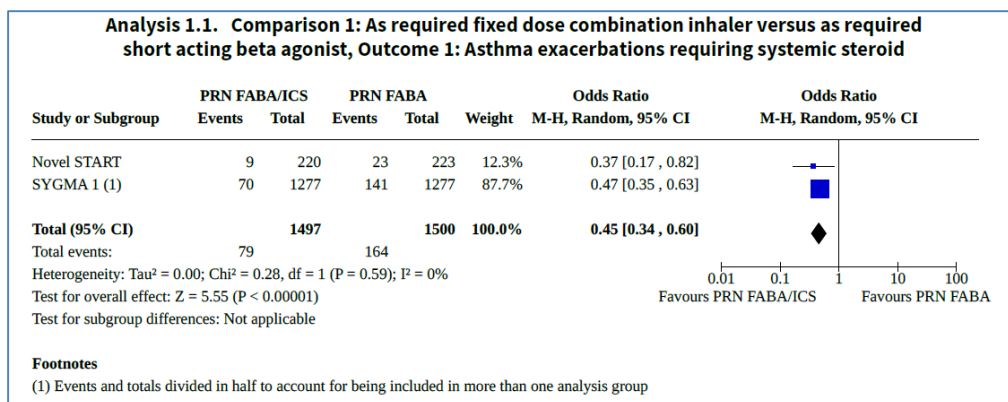


Figure 4: Forest plot of ICS/Formoterol reliever vs SABA reliever: Exacerbations requiring systemic corticosteroids

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.

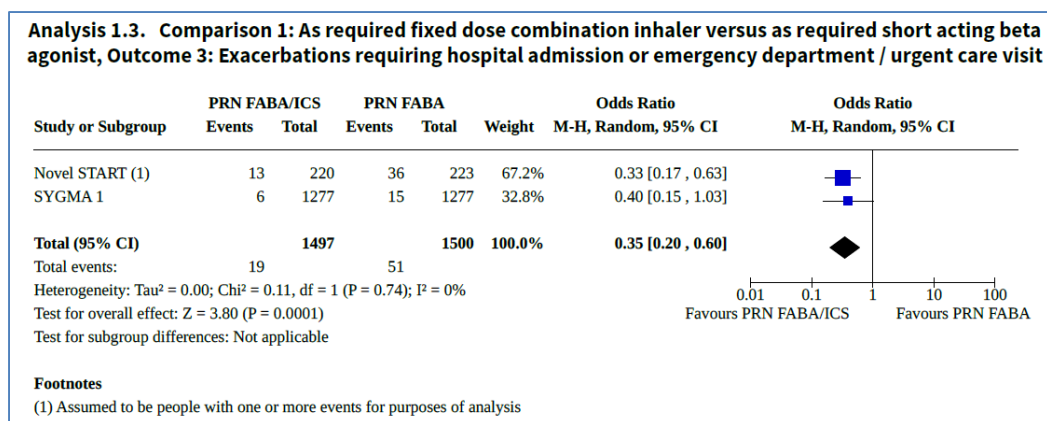


Figure 5: Forest plot of ICS/Formoterol reliever vs SABA reliever: Exacerbations requiring hospital admission or emergency department/urgent care visit

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
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		<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
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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).

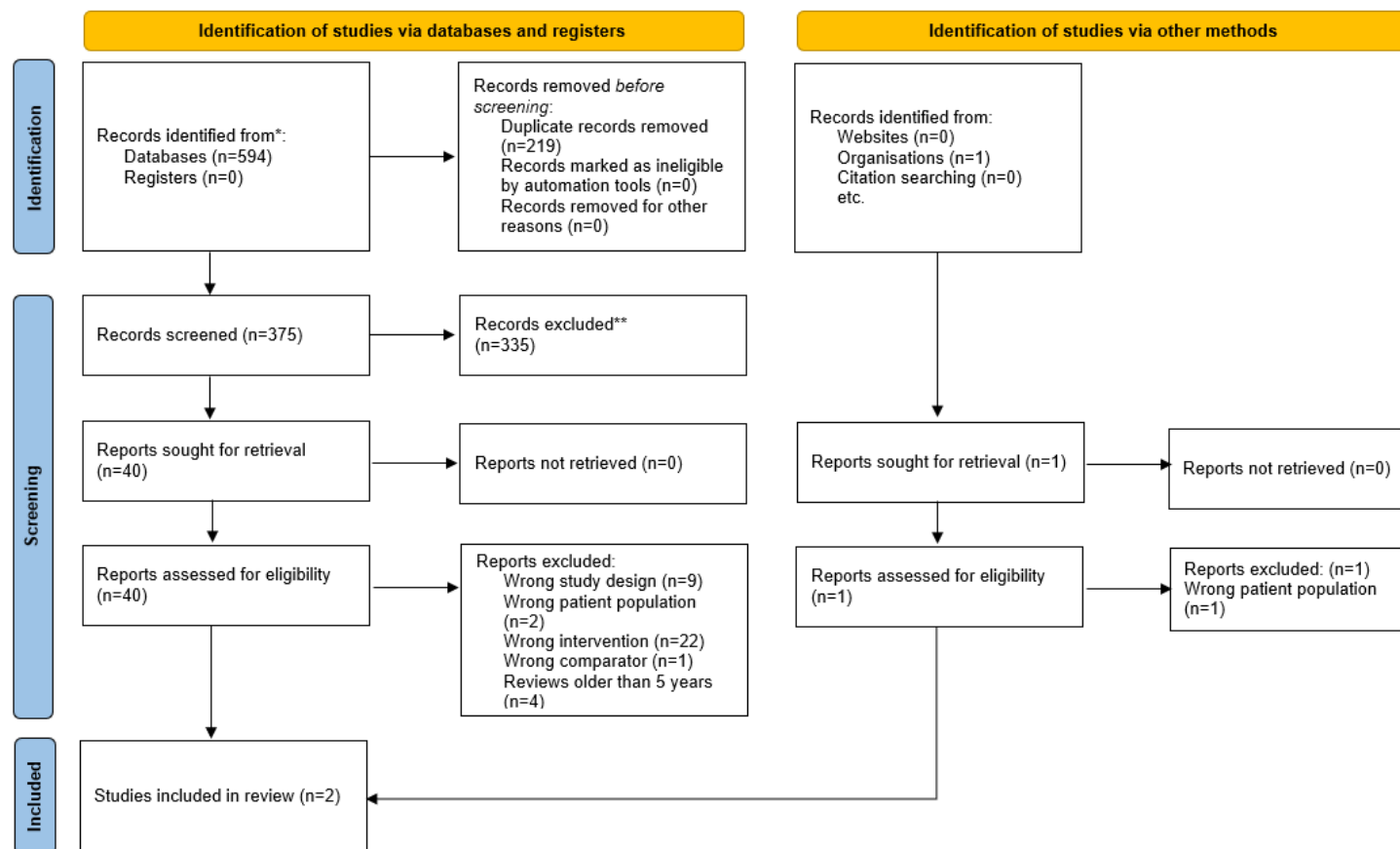


Figure 6: PRISMA flow diagram for review, PICO 2

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.

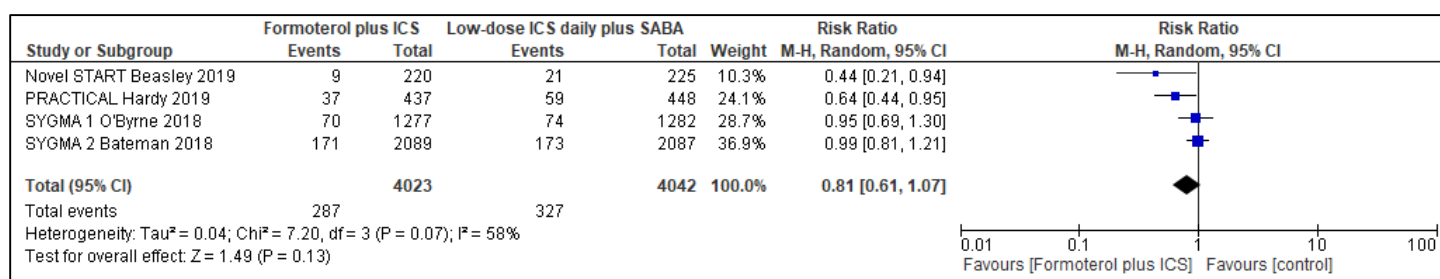


Figure 8: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: acute severe exacerbations requiring systemic steroid

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.

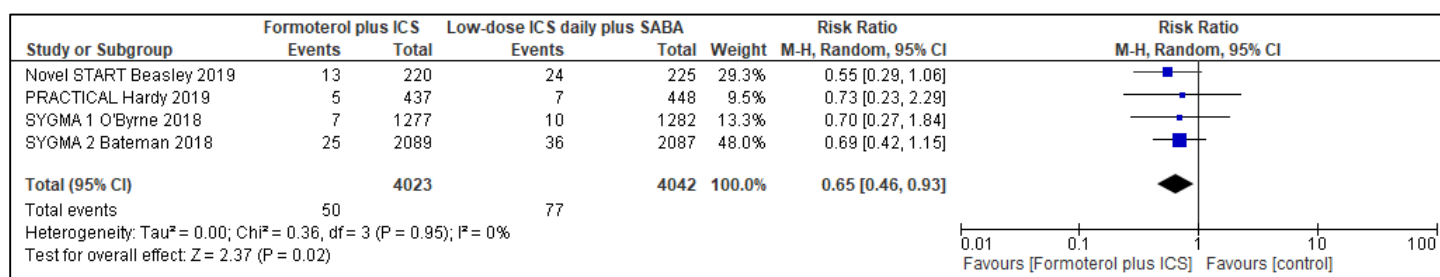


Figure 9: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: asthma-related visits to the emergency room

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.

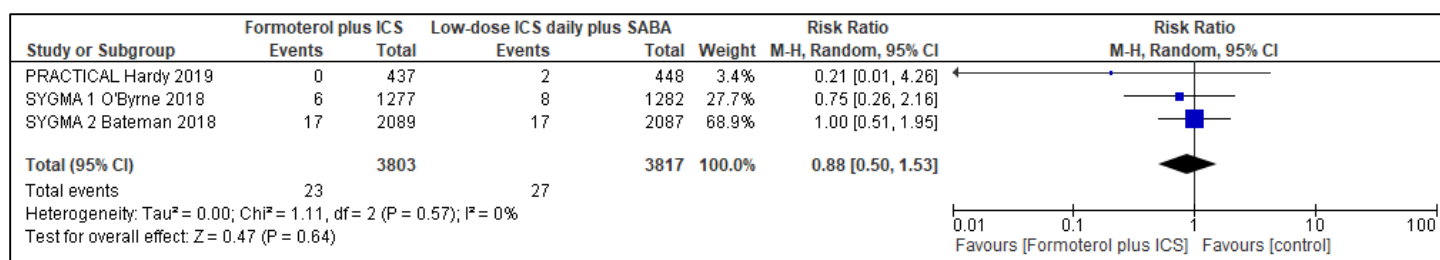


Figure 10: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: asthma-related hospital admissions

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.

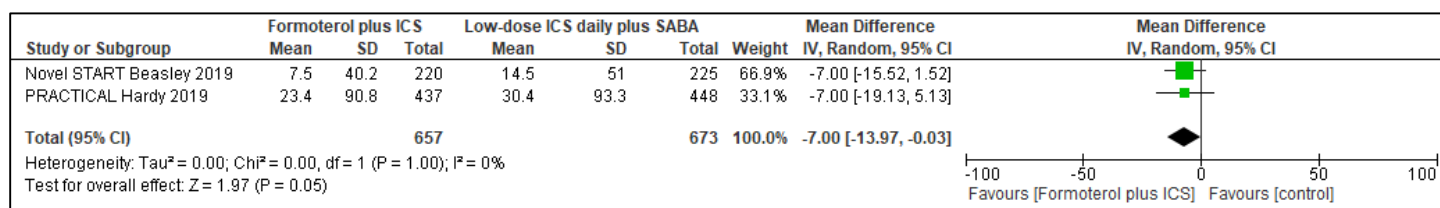


Figure 11: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: total systemic corticosteroid dose

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.

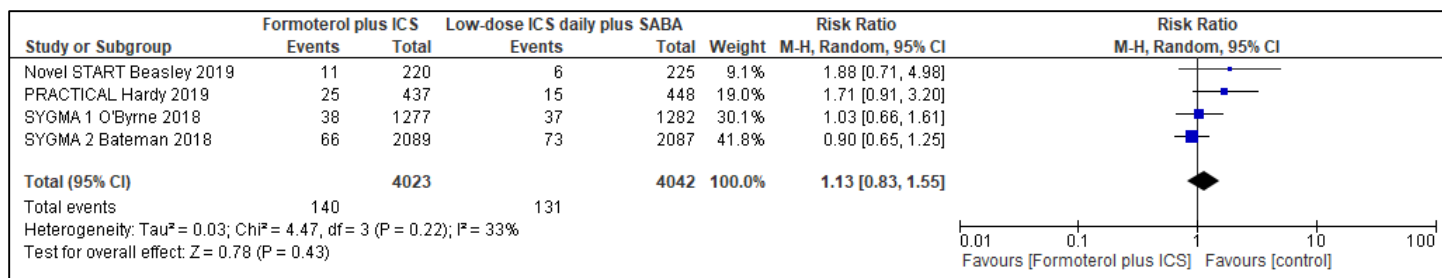


Figure 12: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: serious adverse events

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.

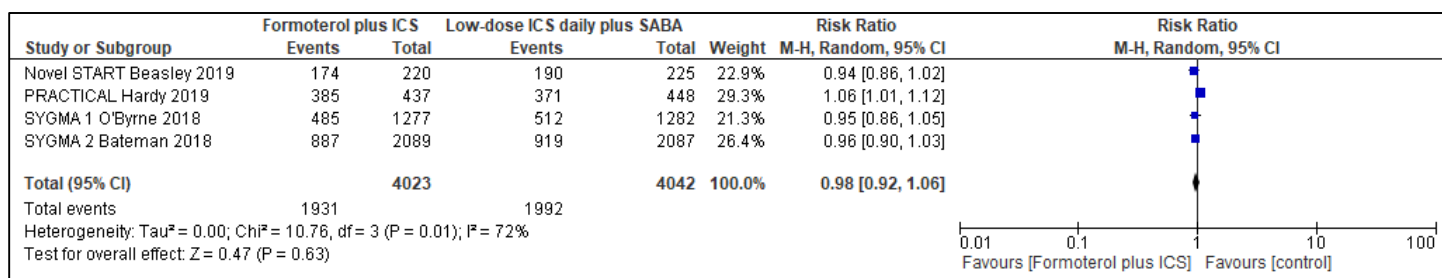


Figure 13: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: all adverse events

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.

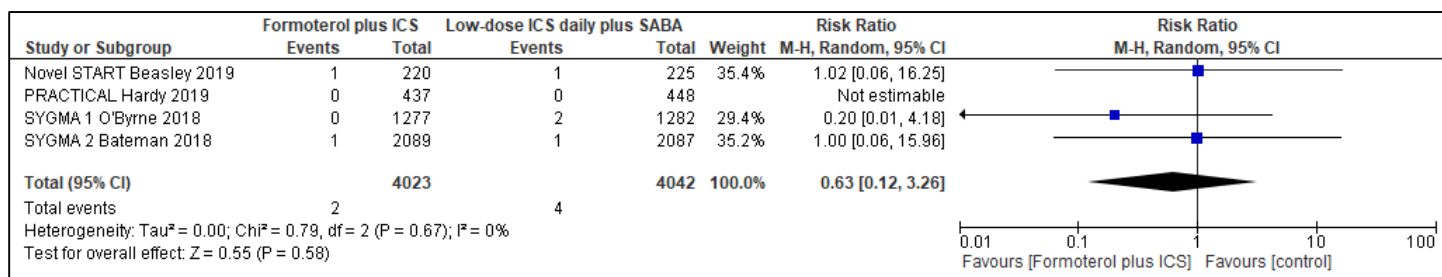


Figure 14: Forest plot of Formoterol plus ICS as needed vs Low-dose ICS daily plus SABA reliever: mortality

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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FEASIBILITY	Is the implementation of this recommendation feasible? Yes No Uncertain ☒ ☐ ☐		- 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.																																	

		- 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; Ställberg, 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.

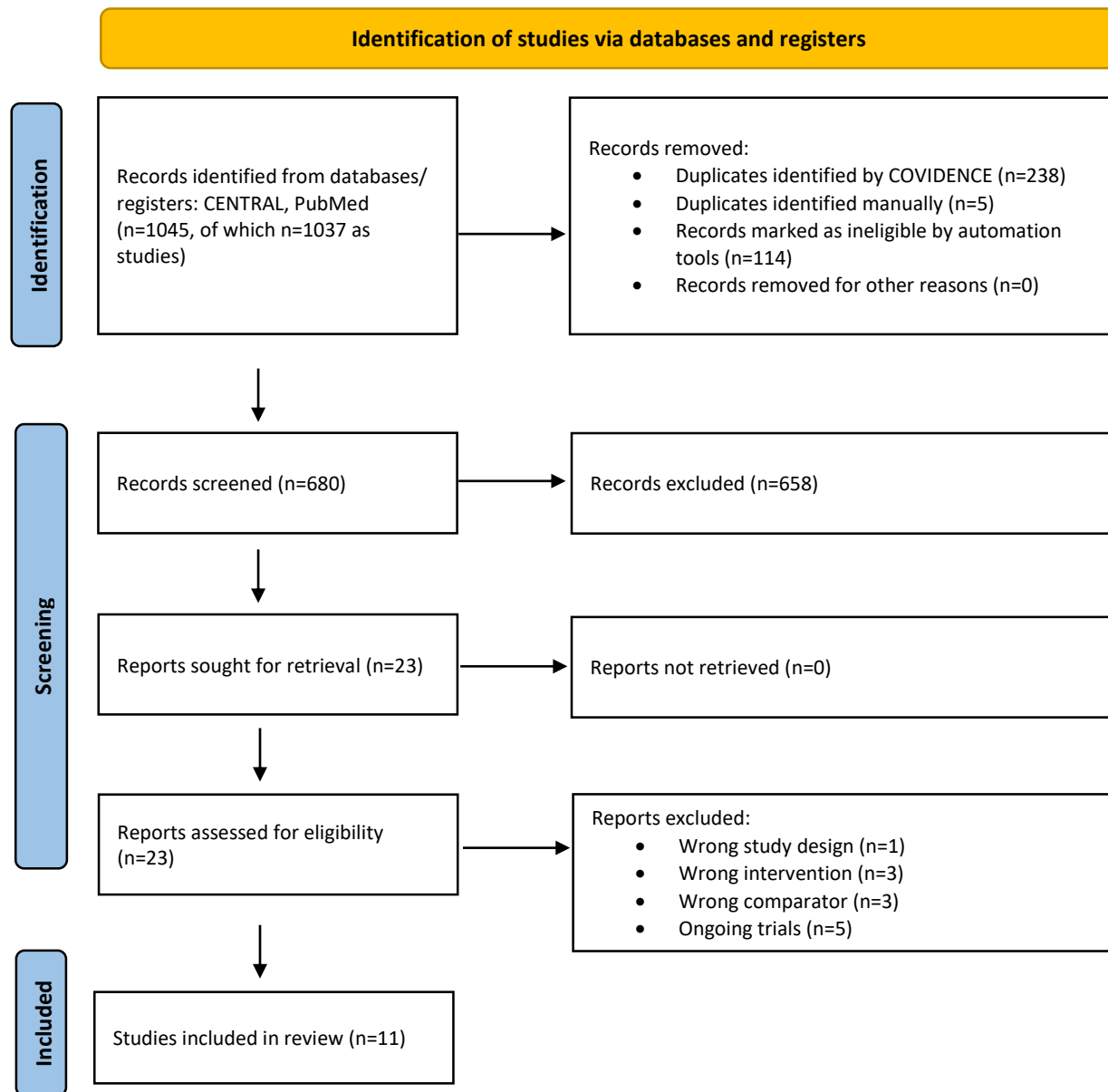


Figure 15: PRISMA flow diagram for review, PICO 3

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.

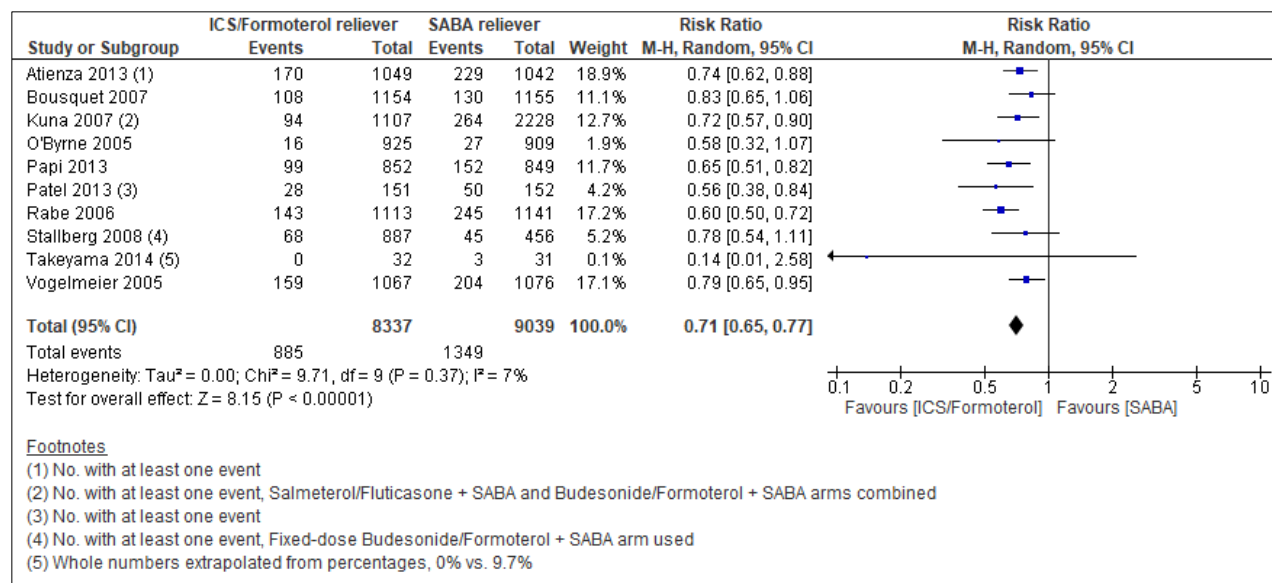


Figure 16: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Severe asthma exacerbation

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).

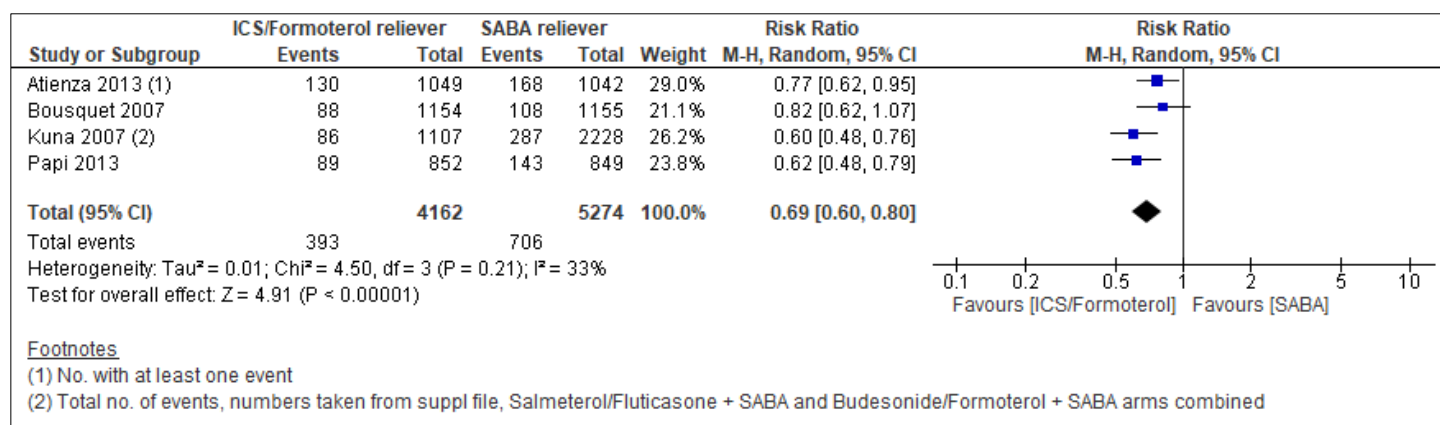


Figure 17: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Systemic corticosteroid use

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.

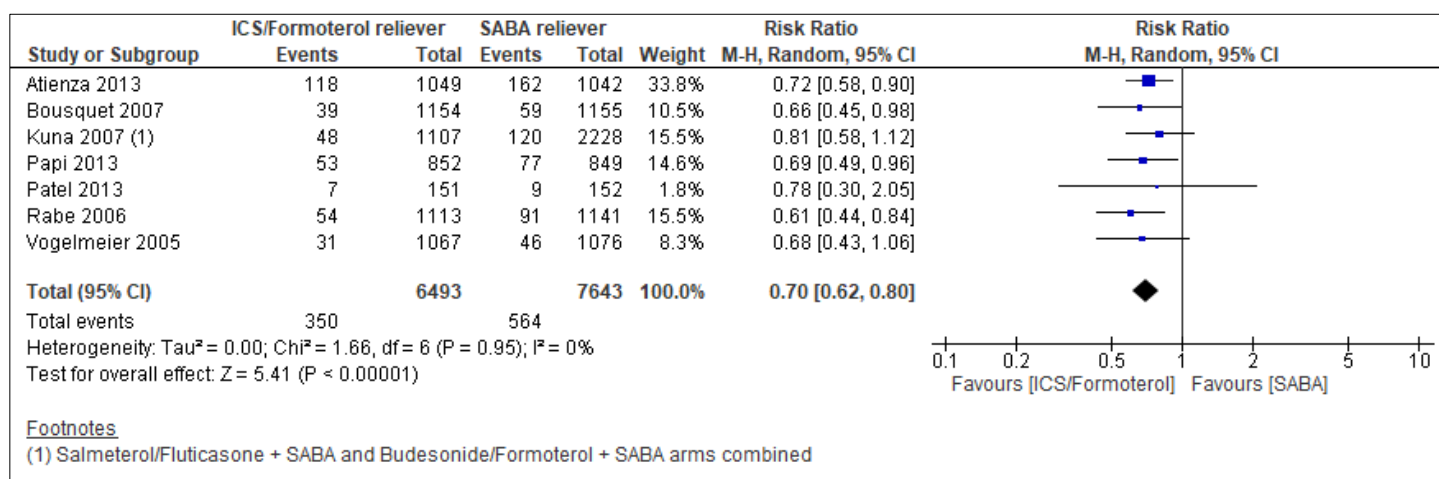


Figure 18: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related visits to the emergency room (ER) and/or hospital admissions

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.

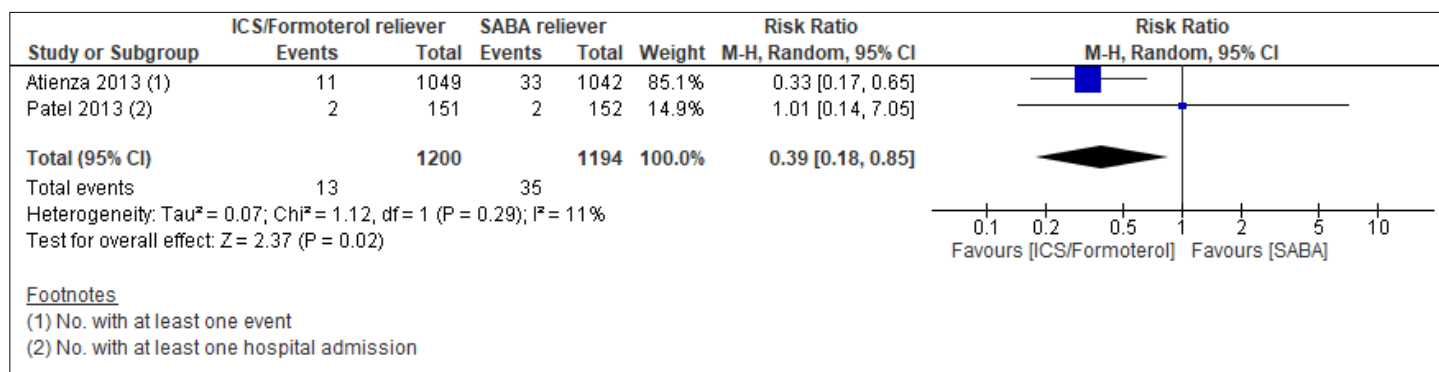


Figure 19: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related hospital admissions

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.

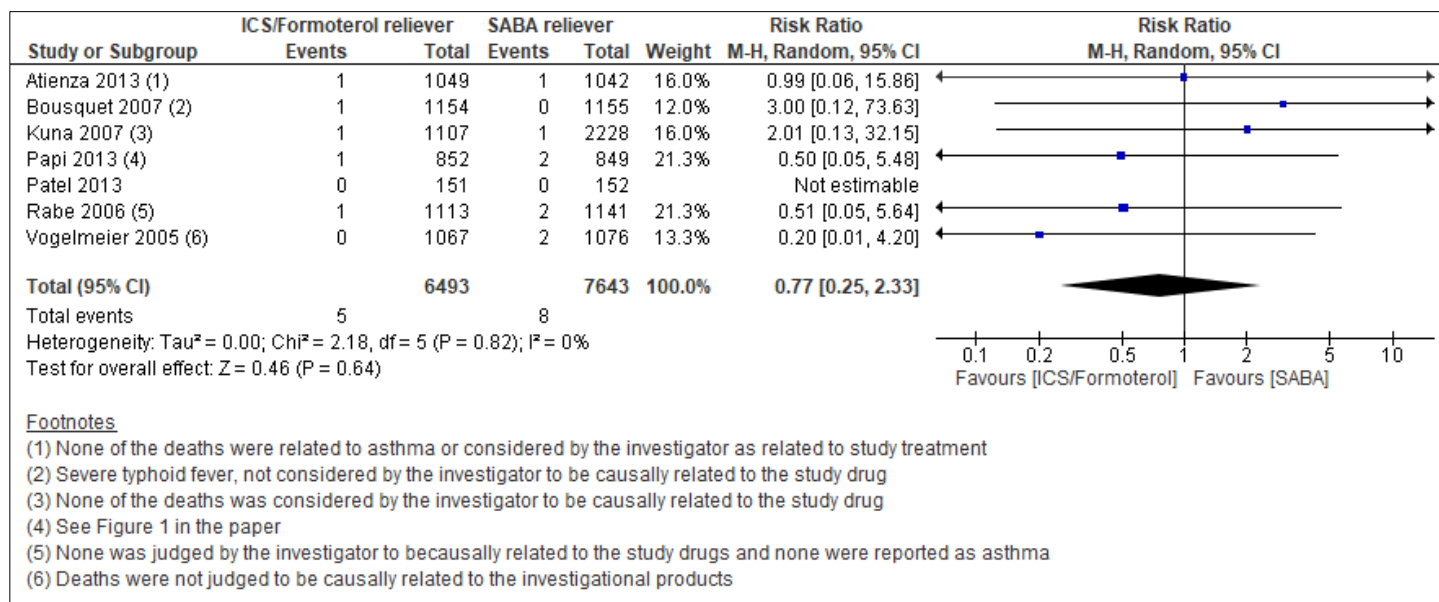


Figure 20: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Mortality

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.

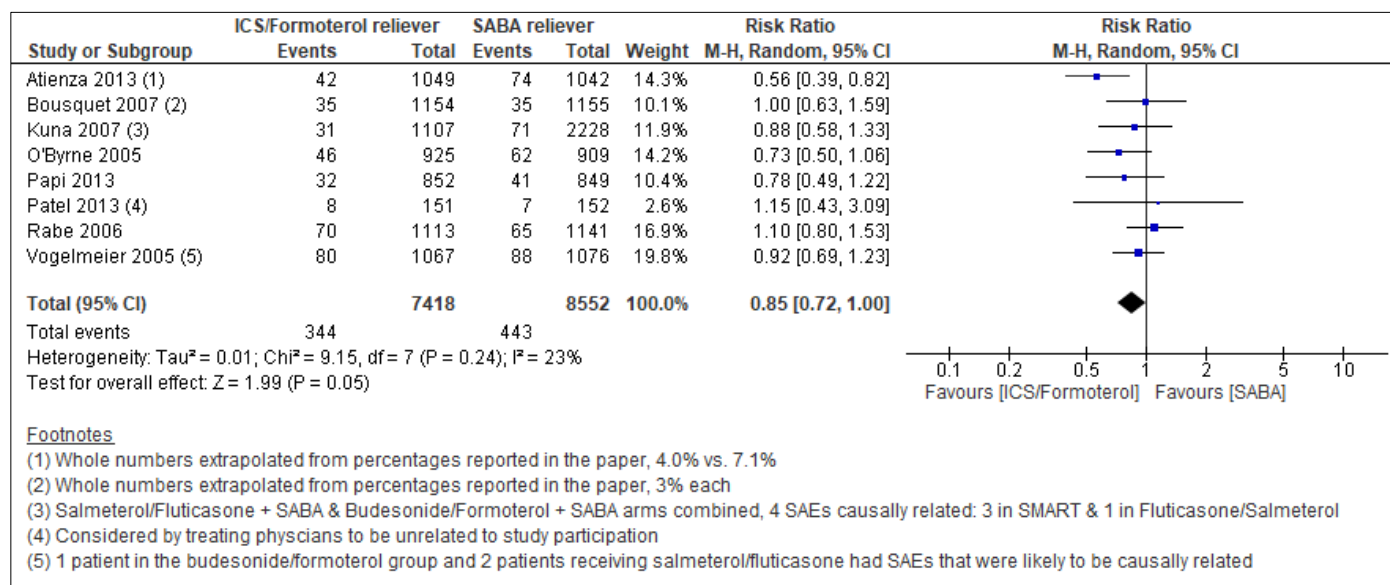


Figure 21: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Serious adverse events

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).

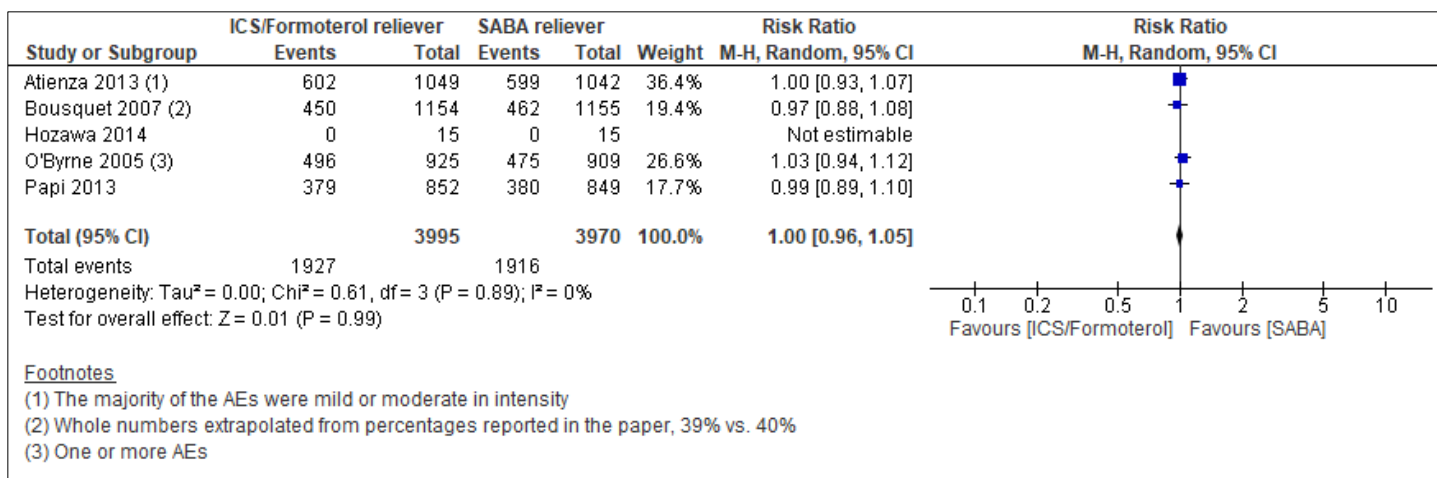


Figure 22: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Adverse events

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.

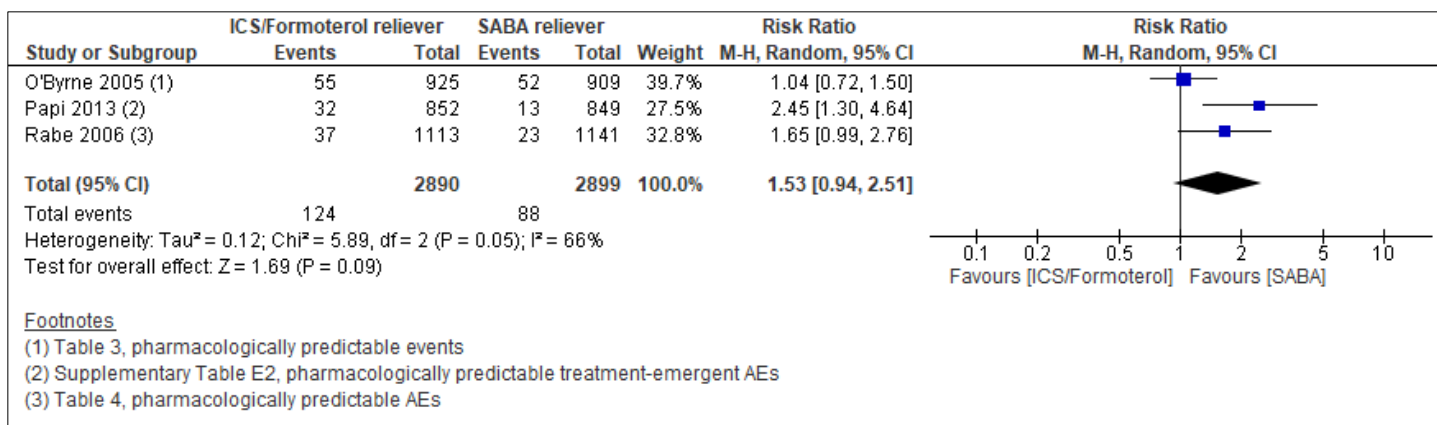


Figure 23: Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Pharmacologically predictable AEs

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**

Created with the AGREE II Online Guideline Appraisal Tool.

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Co-ordinator:

Date: 18 January 2024

Email: sumayyah.ebrahim@mrc.ac.za

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

Created online at www.agreetrust.org 18 January 2024

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

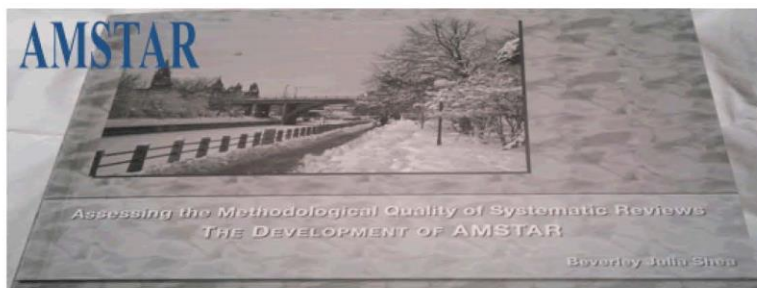
I. Crossingham 2021 (Reviewer 1: SE)

11/23/23, 11:33 AM

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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
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

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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

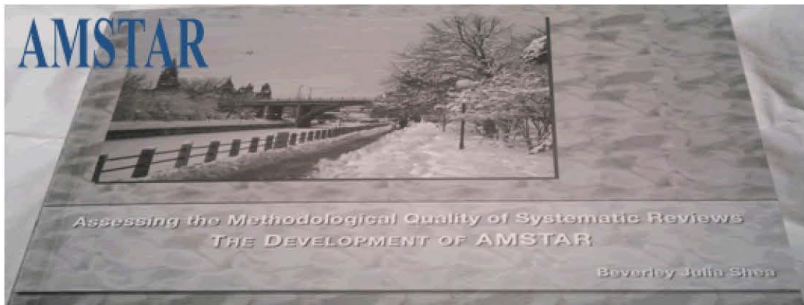
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
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16. Did the review authors report any potential 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:
Combination fixed-dose beta agonist and steroid inhaler as required for adu

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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 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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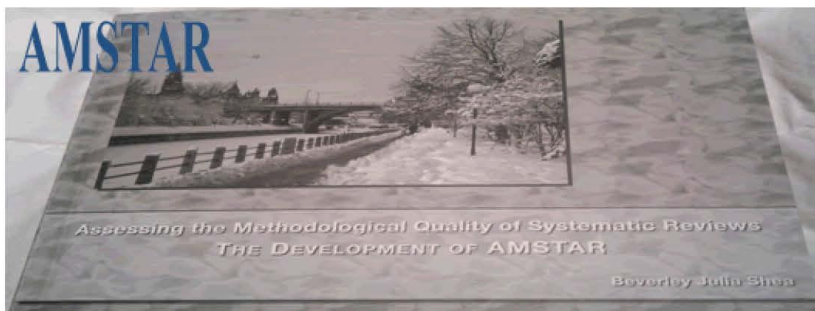
III. Hatter 2021 (Reviewer 1: SE)

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

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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

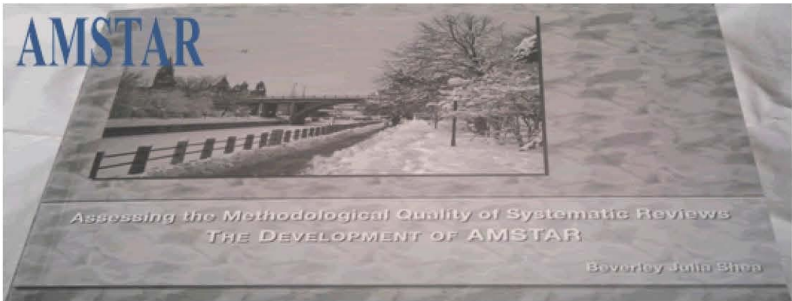
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Yes

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
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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
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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/ajrccm-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* *See definitions in paper, pages 34-35 <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. <i>Pulm Pharmacol Ther.</i> 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.

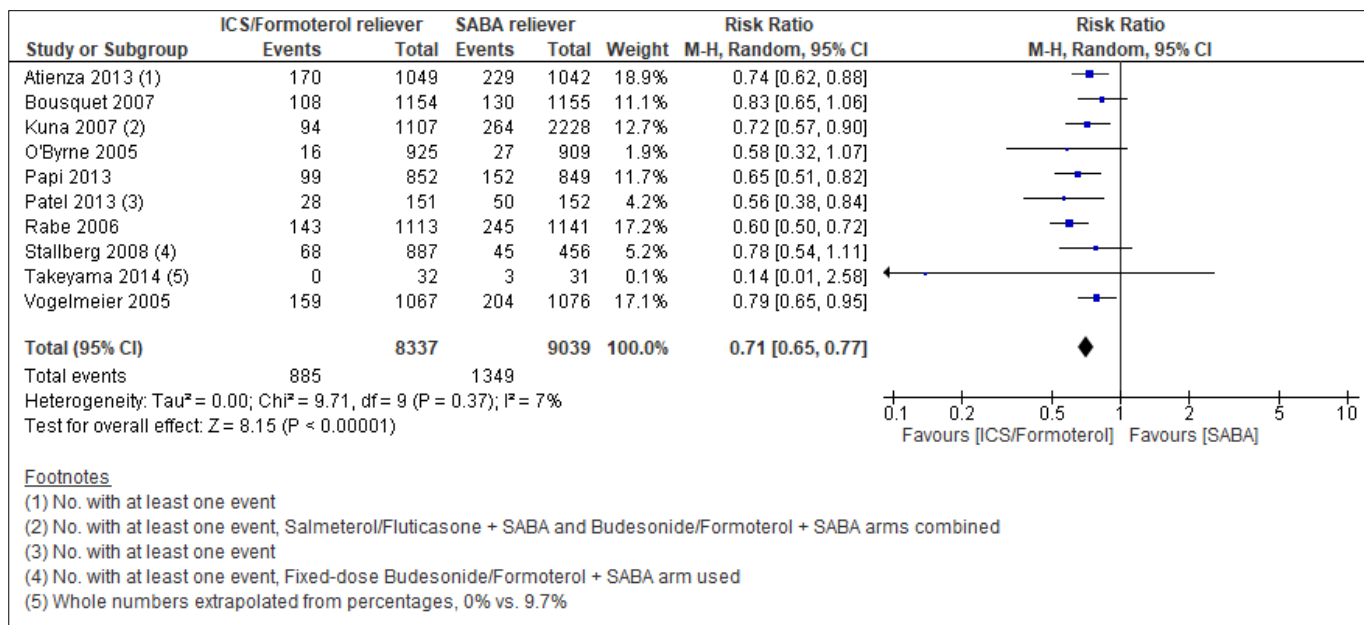


PICO 3_Doses
across studies_v3.xls

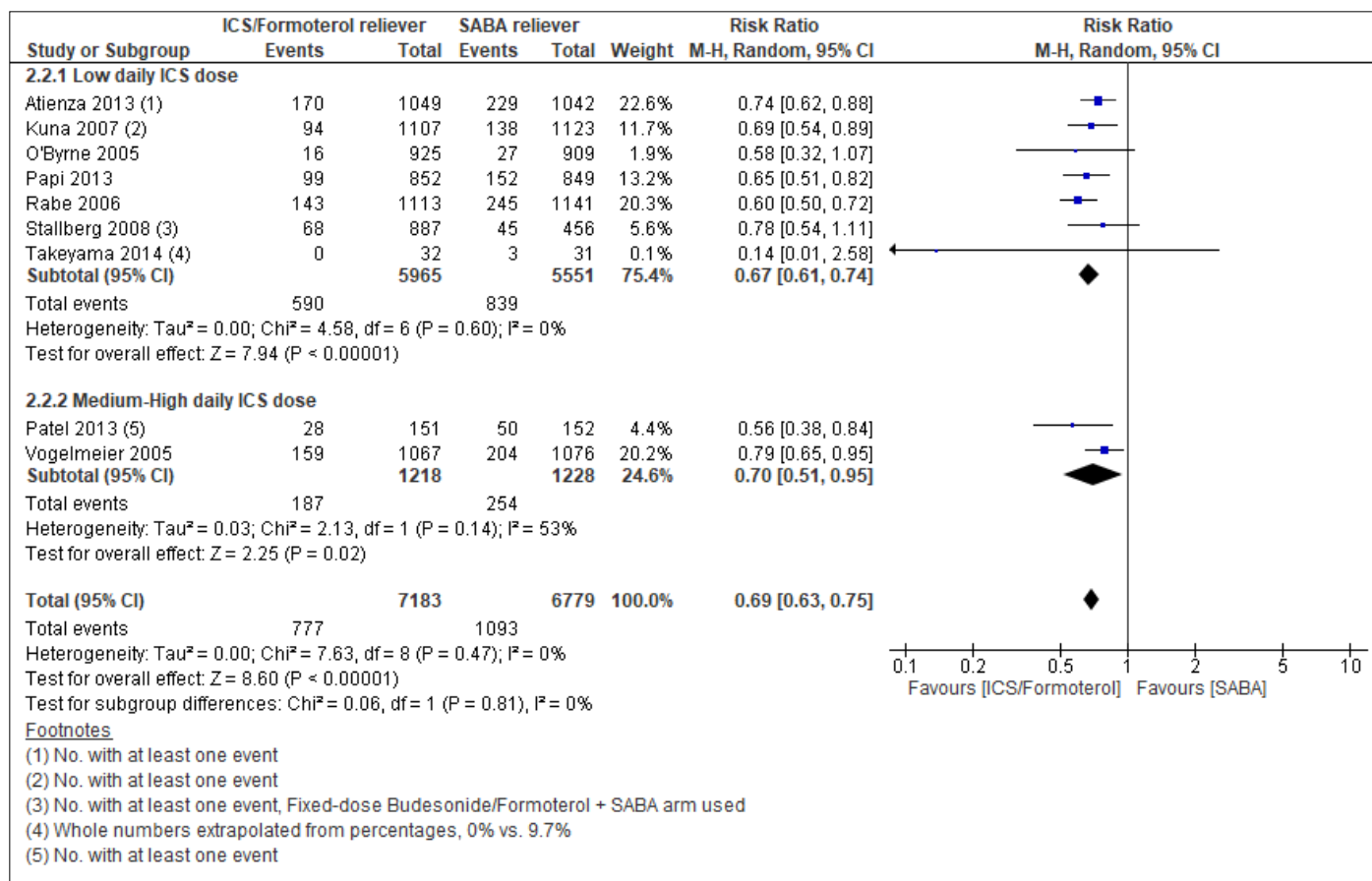
Effects of the intervention

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

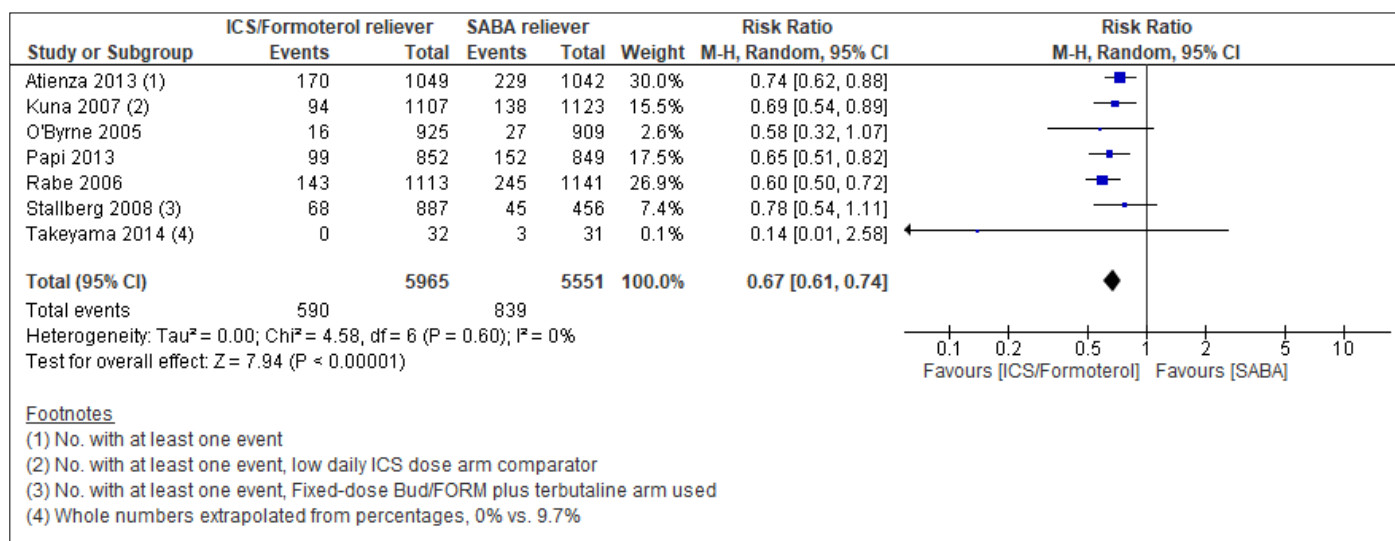
1. Severe asthma exacerbations



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

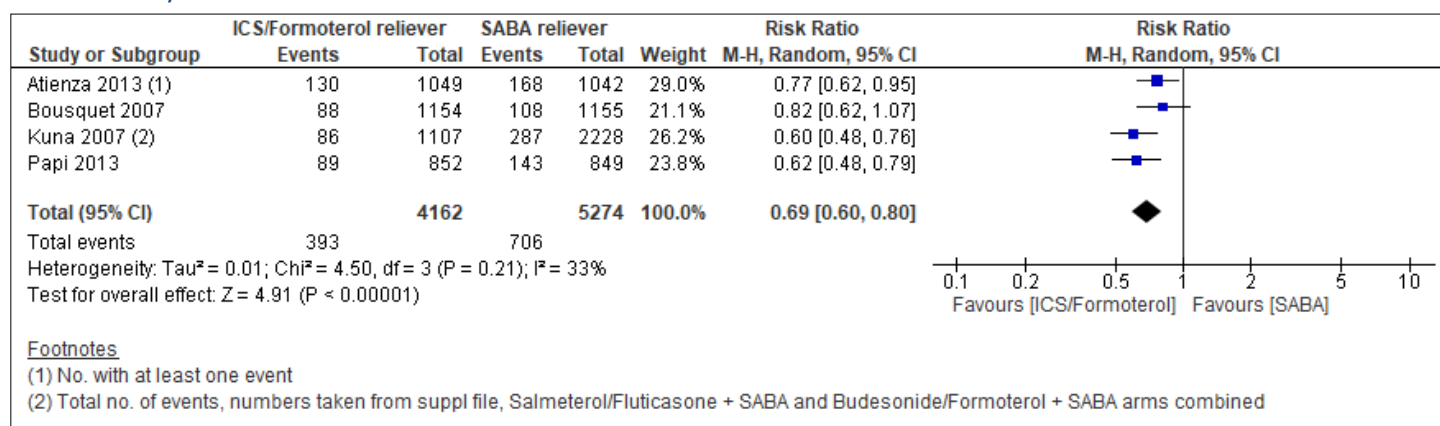


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Severe asthma exacerbation (Subgroup analyses)

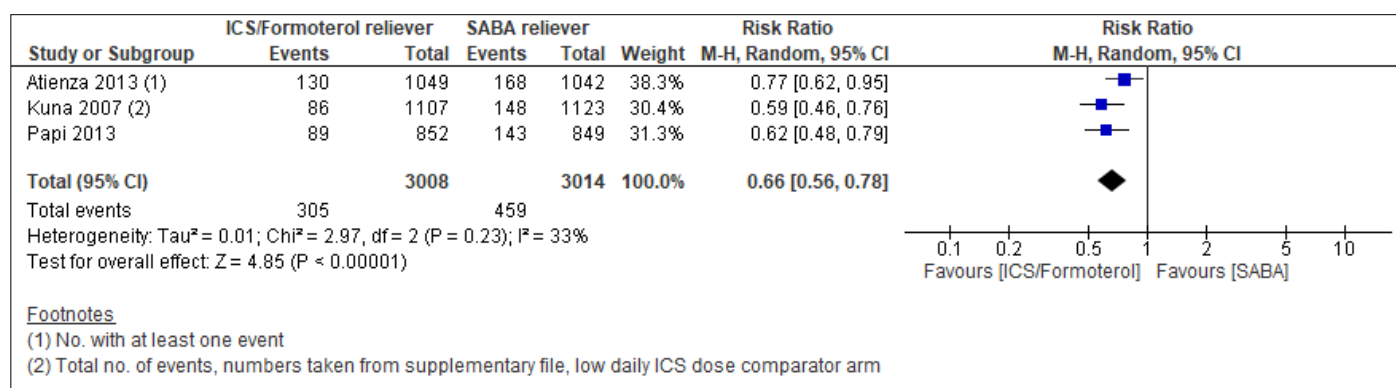


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Severe asthma exacerbation (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

2. Systemic corticosteroid use*



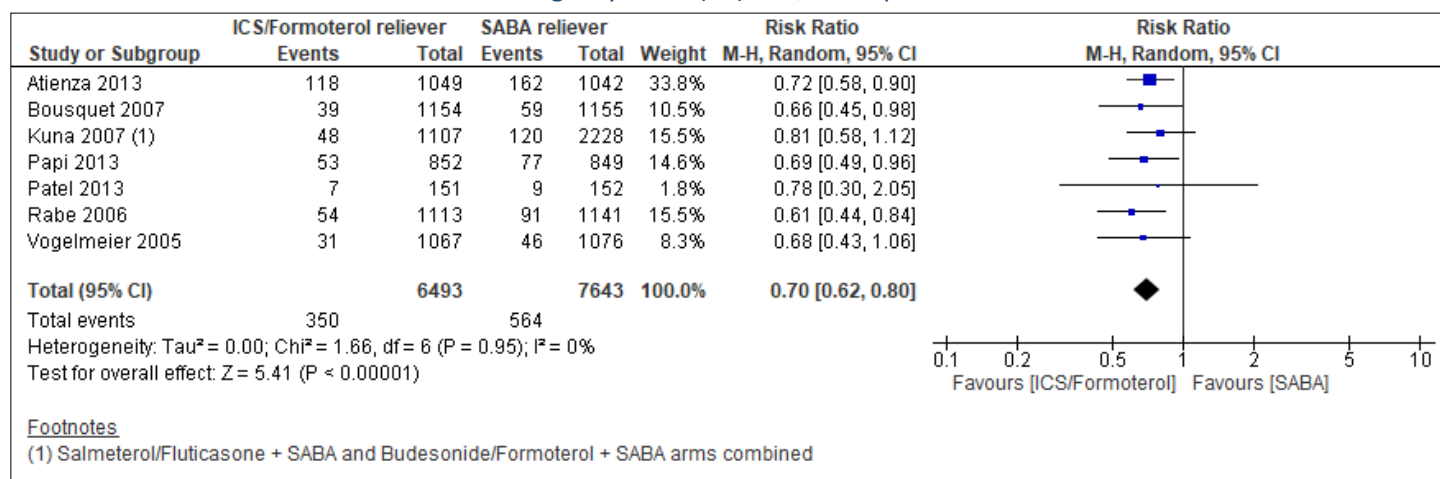
Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Systemic corticosteroid use (Original)



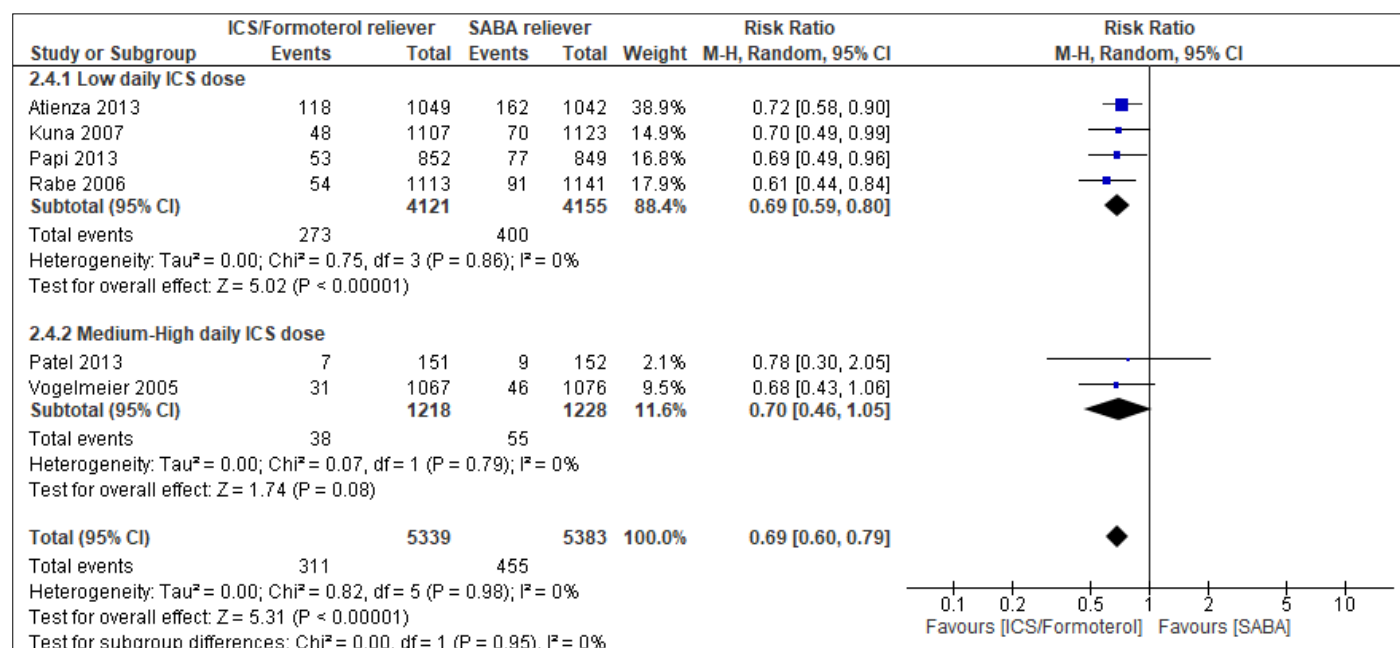
Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Systemic corticosteroid use (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

*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.

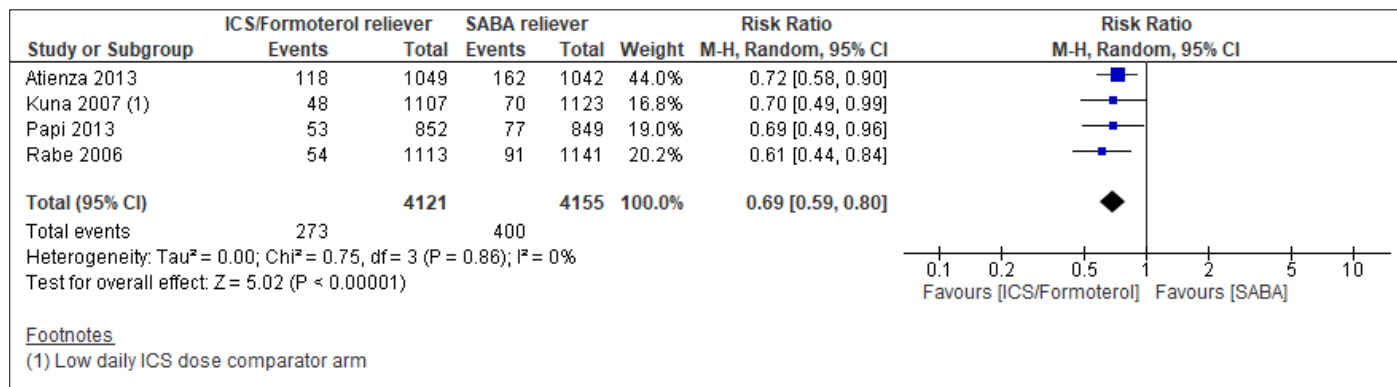
3. Asthma-related visits to the emergency room (ER) and/or hospital admissions



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)

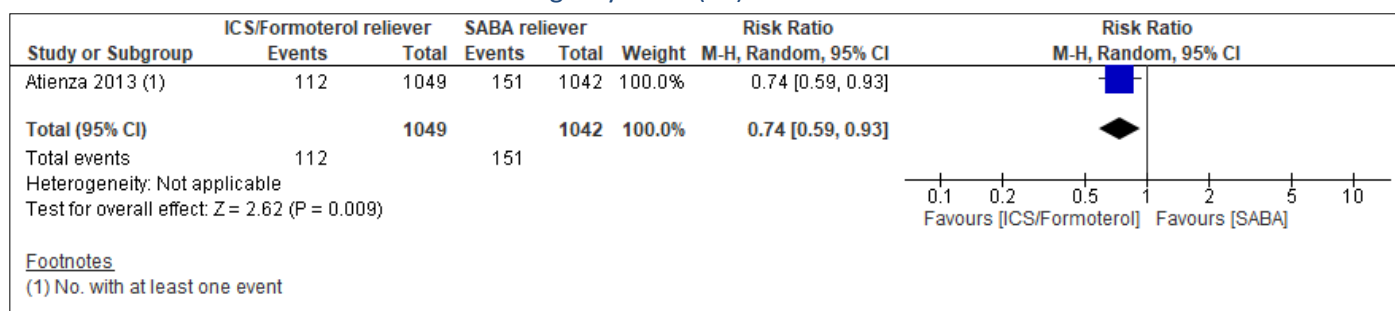


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related visits to the emergency room (ER) and/or hospital admissions (Subgroup analyses)



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)

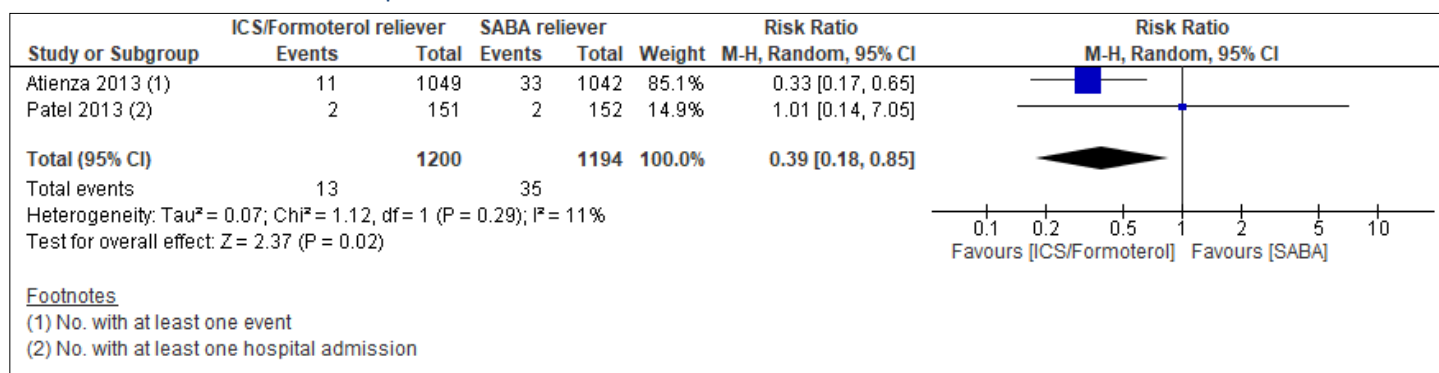
4. Asthma-related visits to the emergency room (ER)**



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

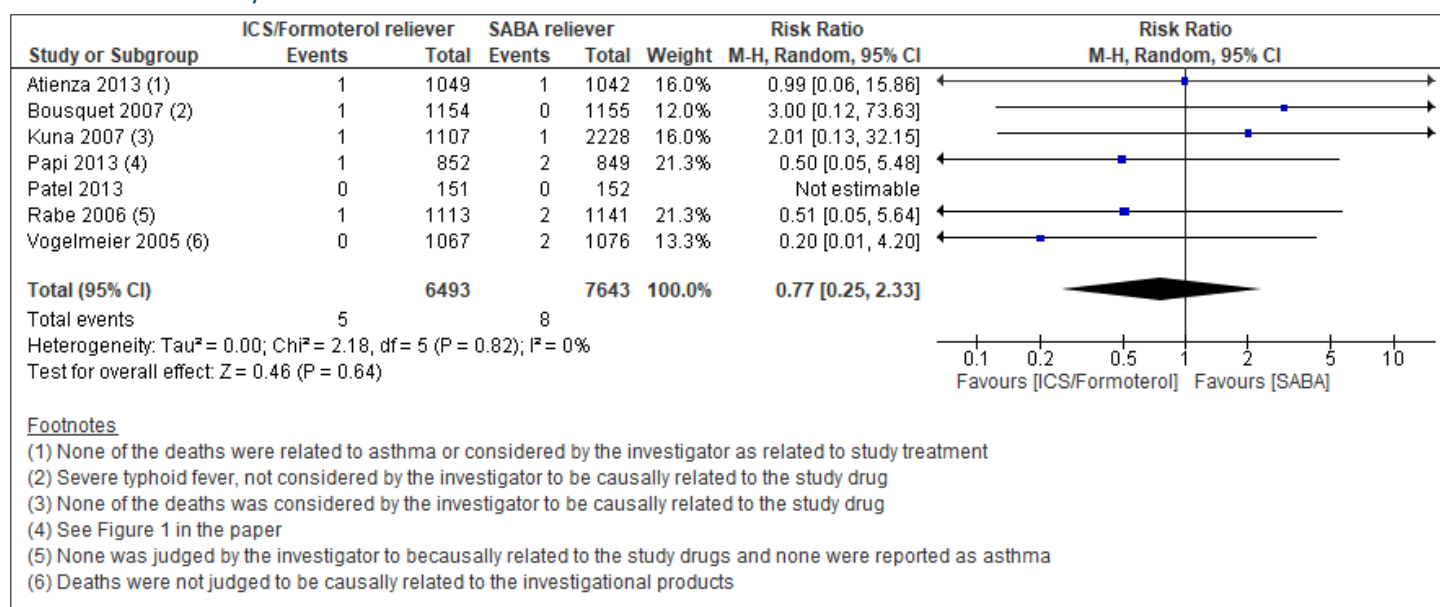
5. Asthma-related hospital admissions***



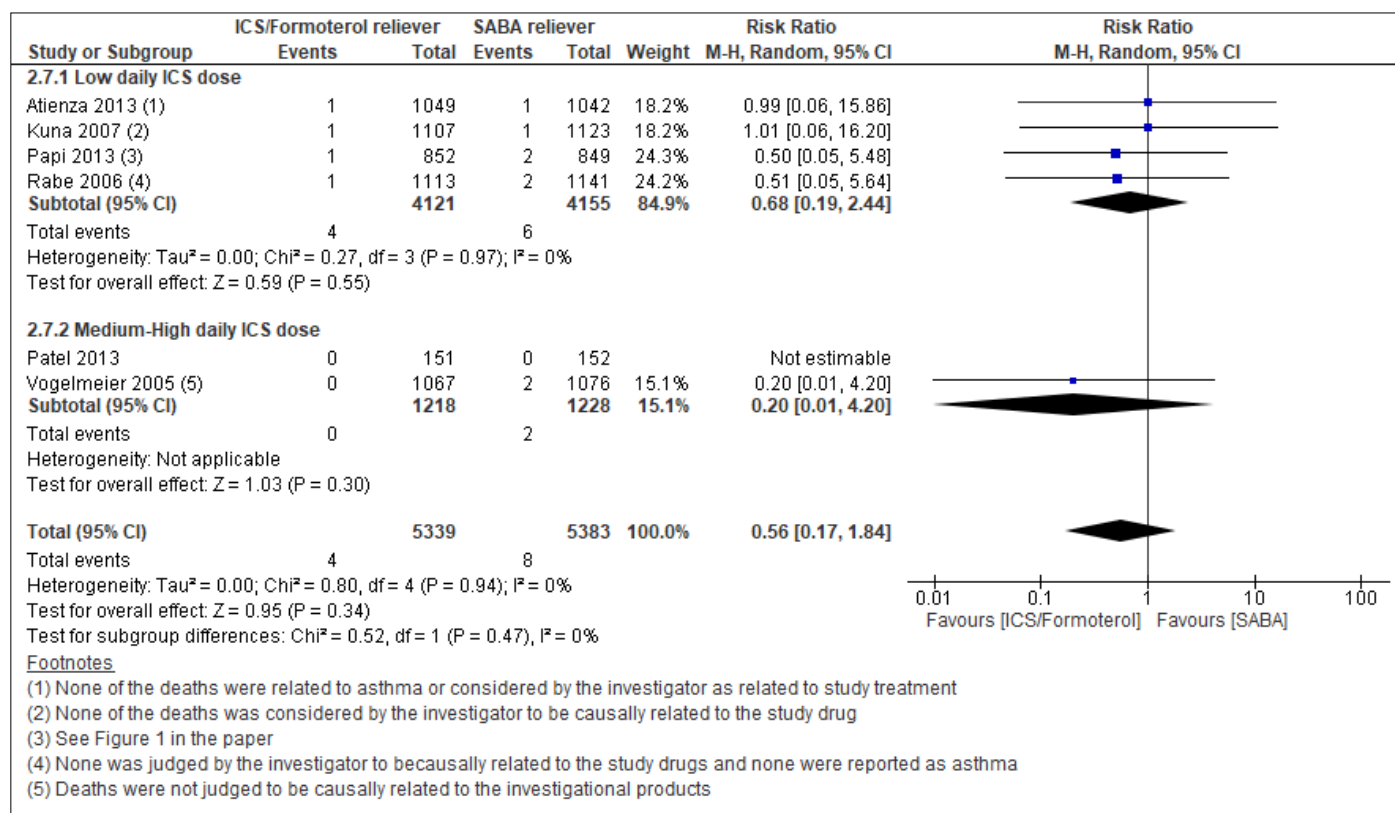
Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Asthma-related hospital admissions (Original)

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

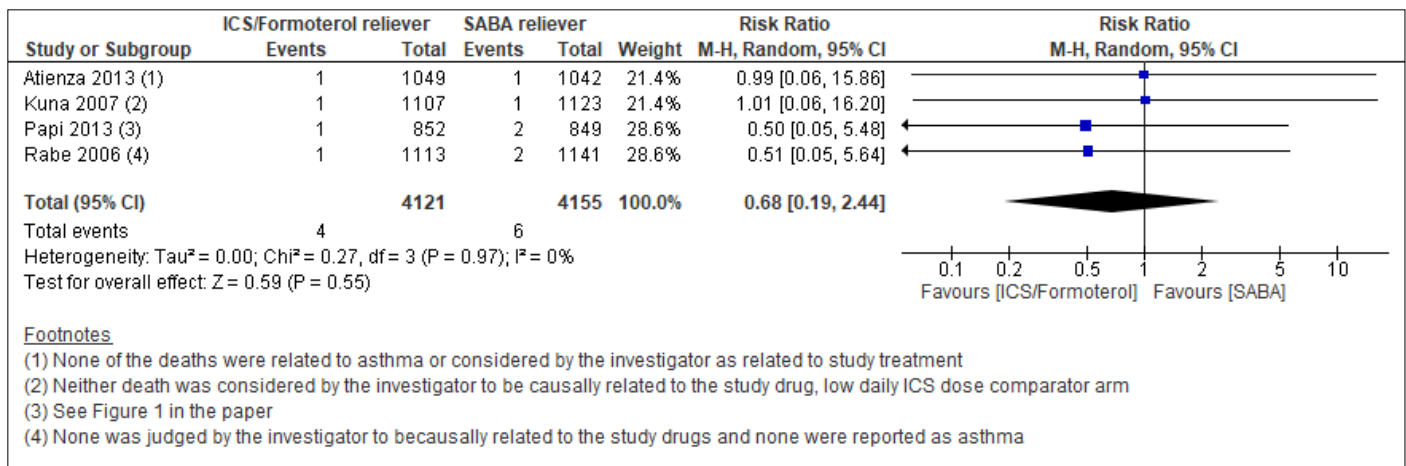
6. Mortality



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

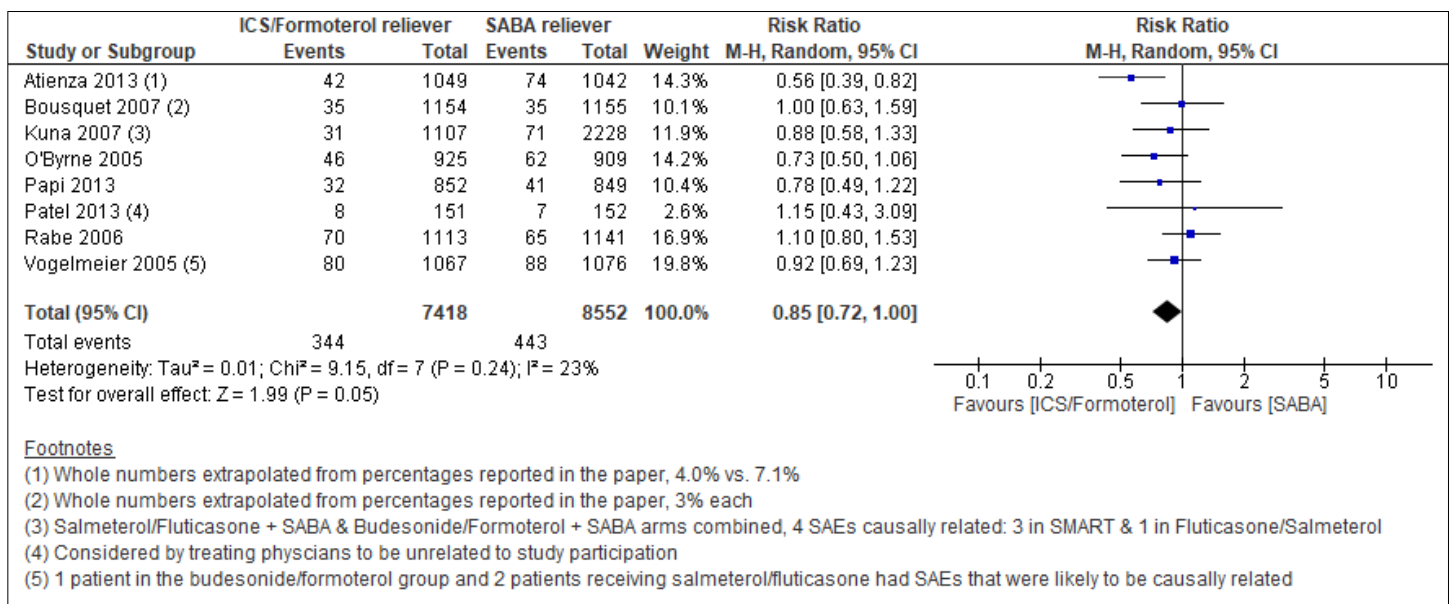


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Mortality (Subgroup analyses)

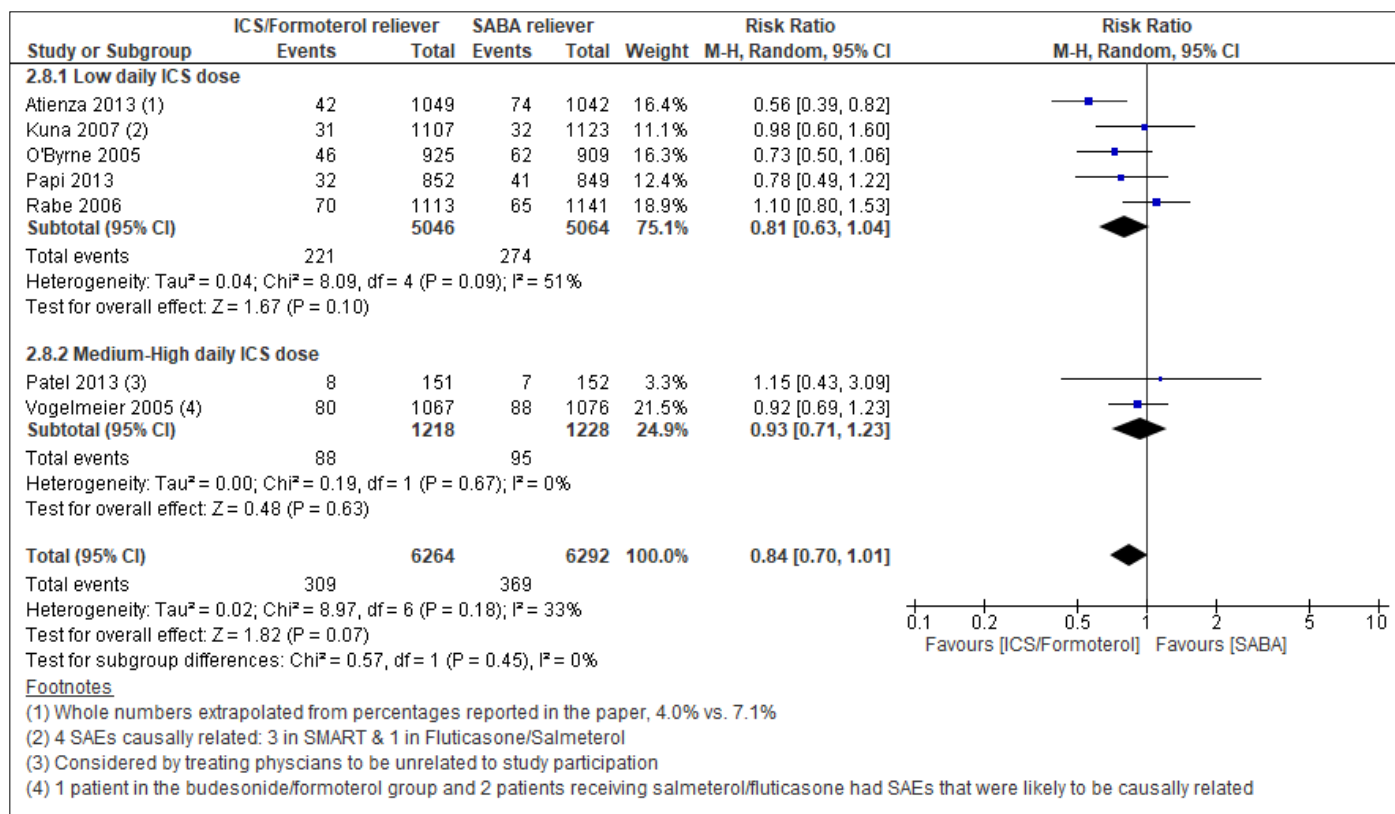


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Mortality
(Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

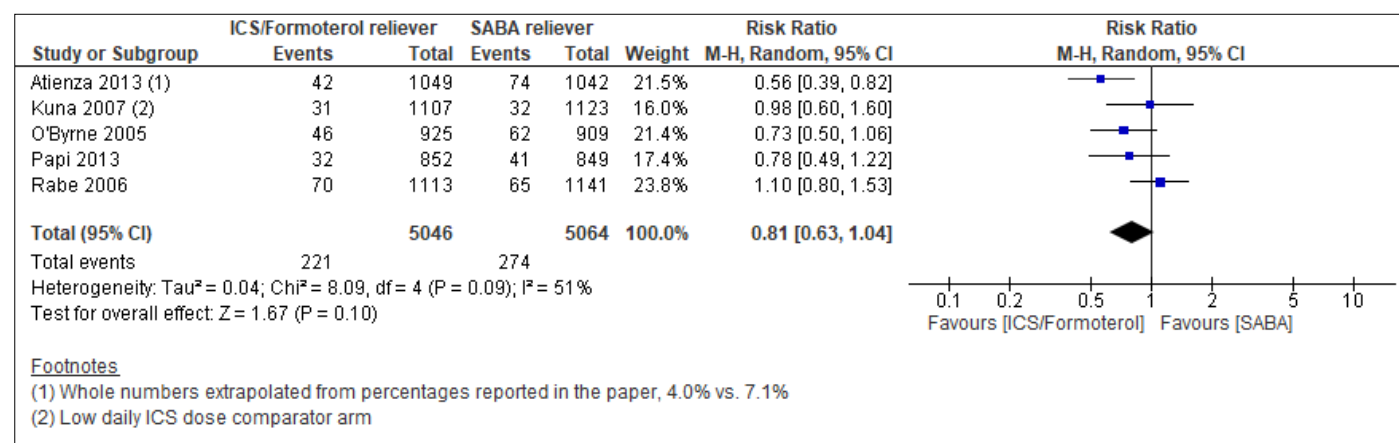
7. Serious adverse events (SAEs)



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

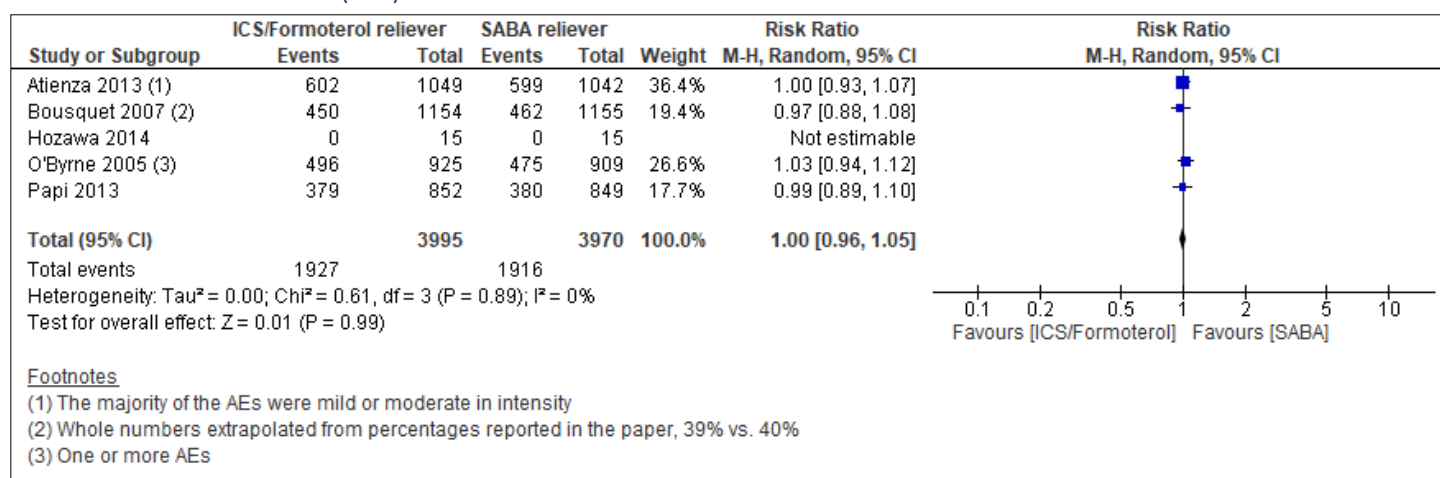


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Serious adverse events (Subgroup analyses)

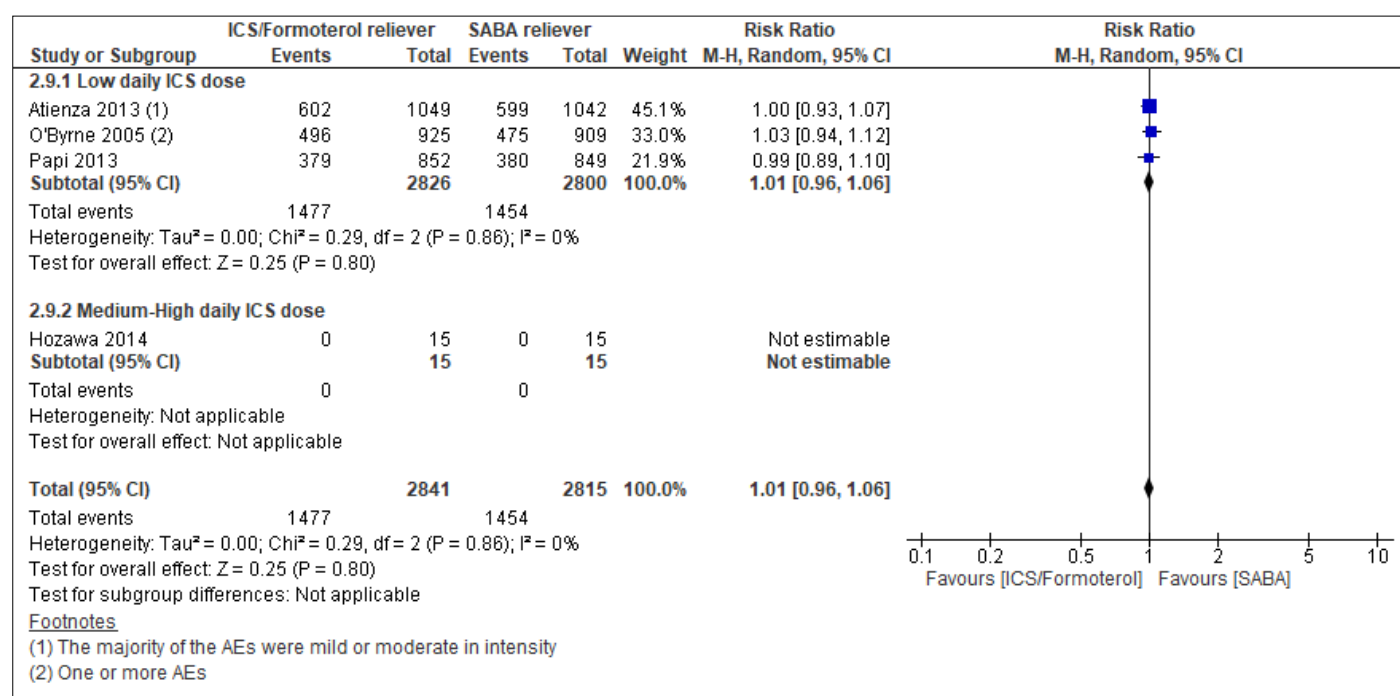


Forest plot of ICS/Formoterol maintenance and reliever vs. ICS/Formoterol maintenance and SABA reliever: Serious adverse events (Sensitivity analyses i.e. without medium-high daily ICS dose comparator arms/studies)

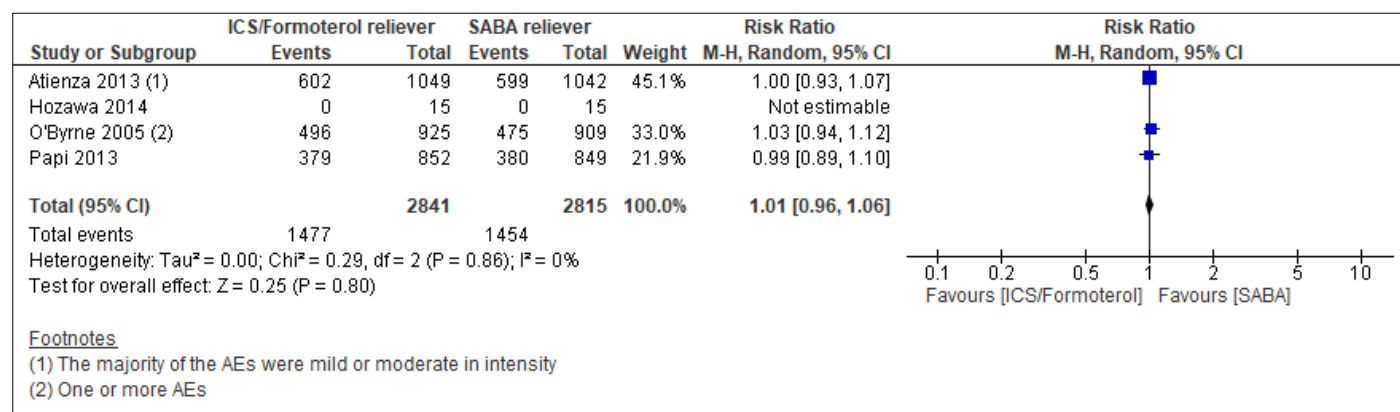
8. Adverse events (AEs)



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)