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Early View

Task force report

European Respiratory Society Short Guidelines for the use of as-needed ICS/formoterol in mild Asthma

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European Respiratory Society Short Guidelines for the use of as-needed ICS/formoterol in mild Asthma

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Abstract (249 words)

Recent clinical trials of as-needed fixed-dose combination of ICS/formoterol have provided new evidence that may warrant a reconsideration of current practice.

A task force (TF) was set up by the European Respiratory Society to provide evidence-based recommendations on the use of as-needed ICS/formoterol as treatment for mild asthma. The TF defined two questions that were assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach. The TF utilised the outcomes to develop recommendations for a pragmatic guideline for everyday clinical practice.

The TF suggests that adults with mild asthma use as-needed ICS/formoterol instead of regular ICS maintenance treatment plus as-needed short-acting beta-2-antagonists (SABAs), and that adolescents with mild asthma use either as-needed ICS/formoterol or ICS maintenance treatment plus as-needed SABA (Conditional Recommendation; Low Certainty of Evidence). The recommendation for adults places a relatively higher value on the reduction of systemic corticosteroid use and the outcomes related to exacerbations and a relatively lower value on the small differences in asthma control. Either treatment options are suggested for adolescent patients as the balance is very close and data more limited.

The TF recommends that adult and adolescent patients with mild asthma use as-needed ICS/formoterol instead of as-needed SABA (Strong Recommendation; Low Certainty of Evidence). This recommendation is based on the benefit of as-needed ICS/formoterol in mild asthma on several outcomes and the risks related to as-needed SABA in the absence of anti-inflammatory treatment.

The implementation of this recommendation is hampered in countries (including European Union countries) where as-needed ICS/formoterol is not approved for mild asthma.

Introduction

Asthma is primarily an inflammatory disorder of the airways and anti-inflammatory treatment is the cornerstone of asthma management. Until 2018 the Global Initiative for Asthma (GINA) document [1], recommended a pharmacological strategy based on regular scheduled maintenance treatment with an anti-inflammatory controller, with a short-acting β2 agonist (SABA) as rescue intervention. Patients with milder asthma were recommended only as-needed SABA treatment. SABAs effectively induce rapid symptom relief but are ineffective on the underlying inflammatory process.

Despite being labelled as mild asthma, this large group of patients [2, 3] can have active airway inflammation [4] and may experience severe, potentially fatal, asthma attacks (termed asthma exacerbations), [5-7] and the absence of an anti-inflammatory treatment is a potential problem.

Poor adherence to inhaled therapy is a major limitation of maintenance controller treatments,[8] particularly in adolescents. Low rates of adherence are associated with higher risk of severe asthma exacerbations [9]. Indeed, several surveys have highlighted a common pattern in the use of inhaled medication [10]: patients self-manage their condition using the medications when they feel the need and adjust their treatment by increasing the intake of SABA, aiming for immediate relief from symptoms [11]. This may result in SABA overuse which has been associated with an increased risk of severe exacerbations and asthma death in adults [7, 12-14], as well as in children and adolescents [15]. The concomitant use of an inhaled corticosteroid (ICS) in addition to a rapid bronchodilator as reliever medication (i.e. an anti-inflammatory reliever [AIR]) [8] would provide rapid relief while administering anti-inflammatory therapy, titrated according to severity through the vehicle of reliever medication use. This approach was first developed in patients regularly treated with ICS/formoterol where the same combination was used also as reliever therapy, given the rapid onset of action of the Long-Acting β2-agonist (LABA) formoterol. The combination of an ICS and a rapid-acting LABA in one inhaler for both Maintenance And Reliever Therapy (MART) has been tested and found to be effective across the range of asthma severity [16-19].

The same principle was applied in mild asthma in a pilot study showing the equivalence of a rescue ICS/SABA (beclomethasone/salbutamol) combination, in the absence of maintenance treatment, as compared to regular low-dose ICS plus rescue salbutamol, and the superiority compared to as-needed salbutamol alone [20]. The findings of this initial proof-of concept trial have been reinforced by the results of several recent clinical trials of

as-needed fixed-dose combination of ICS/formoterol in mild asthma. Collectively, this evidence supported the current indication of ICS/rapid-acting bronchodilators in the absence of maintenance treatment as first-line therapy for mild asthma in international documents[8] and is recommended in guidelines in multiple countries.
The purpose of the present European Respiratory Society (ERS) Clinical Practice Guideline (CPG) is to provide physicians, healthcare professionals (HCP), patients and other stakeholders with recommendations on the use of rescue ICS/formoterol for the treatment of adult and adolescent patients with mild asthma, based on a systematic review of the literature and application of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [21].

Methods

Rationale for a Short Guideline

This document was developed as a "short ERS Guideline" [22] following the requirements for guidelines of the European Respiratory Society (ERS) [23]. Short guidelines aim to respond quickly to new evidence that could lead to changes in clinical practice. Since the efficacy in mild asthma of as-needed ICS/formoterol combination without its use as maintenance therapy cannot be extrapolated from MART studies, the evidence discussed in this review will focus on the use of as- needed ICS/formoterol in mild asthma in the absence of maintenance treatment. The topic of the document is of primarily clinical importance, with the potential to produce a change in clinical outcomes and impacting also on patients' attitudes/preferences to asthma management.

Methodology (For full details please see the online supplement)

Group composition and management of Conflicts of Interest (COI)

The guideline panel included 3 co-chairs, 12 clinicians with experience in the field of asthma, one ERS early career member representative and a patient representative. The methodological work was overviewed by one of the ERS in-house methodologists. The standard ERS policy for COI management was followed (https://ers.app.box.com/s/cjp3mc9jm7y5nw81ym01en5o3jx6v87x)

Formulation of questions and rating of importance of outcomes

Guideline panel members agreed on the formulation of two PICO (patient, intervention, comparator, outcome) questions [24]. The panel decided that they would review the

evidence separately for adults and adolescents (aged ≥12 to <18 years), when possible. Following GRADE guidance [24], the panel rated the importance of the outcomes for clinical decision making before seeing the evidence (see appendix for the full list of outcomes).

Literature searches and selection of studies

An externally commissioned methodologist designed and conducted the literature searches on Oct 2021 in various databases (see online supplement for full search strategies and databases used).

The identified studies were screened by two authors (FS, IA) based on pre-defined inclusion and exclusion criteria (see online supplement). Disagreements (one single case during full text screening) were resolved by a third author (GB). PRISMA flowcharts for each question are presented in the supplement.

Evidence synthesis

Data extraction, meta-analyses when appropriate, assessment of certainty of the evidence using GRADE [25] and creation of GRADE evidence profiles were performed by the external methodologist and one co-chair (DSF). Thresholds for clinically important changes were agreed upon prior to seeing the evidence (see online supplement, page 3 Evidence synthesis).

The Panel unanimously agreed on thresholds for the clinically important changes.

Formulating and grading recommendations

We used the Evidence to Decision (EtD) framework to structure and document the discussions around the evidence and reach recommendations [26, 27]. Strong or conditional recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (harms) of the intervention, the certainty of evidence, patient values and preferences, feasibility, acceptability, health equity, costs (see online supplement, page 4, Formulating and grading evidence, for detailed grading process). Consensus was reached mainly by discussion. A formal voting also took place for the recommendation statement of each PICO question. A threshold of 70% was considered for voting in favour of a recommendation.

Manuscript preparation

The initial draft of the manuscript and the supplementary material were prepared by AP and edited by DSF. Both the manuscript and the supplementary material were reviewed and approved by all panel members prior to submission.

Results

PICO 1

Is as-needed ICS/formoterol (single inhaler) without maintenance treatment the preferred treatment compared to regular low-dose ICS maintenance treatment plus as-needed SABA in adult/adolescent patients with mild asthma (i.e. GINA [1] treatment steps 1 or 2)?

Summary of the evidence

We identified a total of 547 publications; of which six were finally included [28-33]. All six studies used budesonide as the ICS component of ICS/formoterol combination; terbutaline and salbutamol were the SABAs tested in three [28-30] and one [30] RCTs respectively. The study by Tanaka et al. [33], available only in the form of abstract, does not specify the SABA used. Detailed definitions and data are presented in the supplementary material.

Summary of benefits and harms

The effects in favour of as-needed ICS/formoterol in severe exacerbations prevention (relative risk (RR) 0.82 (95% CI 0.64, 1.04) [28-31], annualised rate of severe exacerbation (rate ratio 0.86 (95% CI 0.71, 1.04)) [28, 29, 31] and ED visits for asthma worsening (RR 0.70 (95%CI 0.44, 1.09))[28, 29] were statistically non-significant. Further, no statistically significant difference was found in hospitalisation for severe asthma exacerbations (RR 0.92 (95%CI 0.52, 1.62)) [28, 29] and number of patients experiencing at least one exacerbation (not limited to severe) (rate ratio 0.88 (95%CI 0.69, 1.13))[18, 28, 31]. There was no clinically important difference in quality of life (QoL) (AQLQ change from baseline, mean difference (MD) −0.10 points (95% CI −0.14, −0.05 points)) [29] and asthma control (ACQ-5 change from baseline, MD 0.13 points (95% CI 0.09, 0.17) [28, 29] and ACQ-5 across all time points, MD 0.09 (95% CI 0.02, 0.17))[30, 31]. Total systemic corticosteroid exposure over 1 year was lower for the as-

needed ICS/formoterol arm (prednisone: MD -7.00 mg (95%CI -13.97, -0.03 mg)[30, 31] and there was a reduction in mean daily ICS dose (budesonide: MD -154 µg (95% CI -206.87, -101.14 µg); mean % reduction 56.5% (95%CI 37.1, 76%)) [28-31]. Change in pre- and post-BD FEV_1 from baseline favoured maintenance ICS (MD -42.50 mL (95%CI -63.68, -21.31 mL) and -23.1 mL (95% CI -41.9, -4.2 mL) respectively[28, 29]). On-treatment FEV_1 across all time points did not differ between treatment strategies (MD 0.01 L (95%CI -0.02, 0.03 L)) [30, 31]. Fractional exhaled nitric oxide (FeNO) values at week 52 were higher with as-needed ICS/formoterol (ratio of geometric means 1.13 (95% CI 1.06, 1.20)) [30, 31]. There was no difference between as-needed ICS/formoterol and maintenance ICS in the number of patients experiencing Adverse Events (AEs) (RR 0.98 [95%CI 0.92, 1.05]) or Serious AEs (SAEs) (RR 1.13 (95%CI 0.83, 1.54)) [28-31]. The data on mortality in the pooled analysis was too limited, leading to very serious imprecision (6 events in total, 2 ICS/formoterol, 4 maintenance ICS) (Peto odds ratio: 0.52 (95%CI 0.10, 2.57)) [28-31].
Detailed data are presented in the online supplementary material.

Benefits and harms – adolescent subgroup

There was no difference between as-needed ICS/formoterol and maintenance ICS plus as-needed SABA on the annualised rate of severe exacerbations (rate ratio 0.97 (95% CI 0.39, 2.40)) or asthma control (ACQ-5, MD 0.06 (95%CI -0.08, 0.21)). There was a reduction in mean ICS dose with as-needed ICS/formoterol at 52 weeks in the SYmbicort Given as needed in Mild *Asthma* (*SYGMA*) 1 study (median (interquartile range) daily ICS dose 35.1 µg (9.3 – 91.6 µg) vs. 292.2 µg (193.6 – 341.9 µg)) and SYGMA 2 trial (42.3 µg (10.4 – 104.7 µg) vs. 198.9 µg (127 – 285.8 µg))[32].

Mean change from baseline in pre-BD FEV_1 was lower with as-needed ICS/formoterol (MD of -2.6% (95% CI -4.95, -0.25)). The proportion of adolescents experiencing an AE (33.9% and 33.2%, no statistical result reported) or a SAE (1.9% and 1.1%, p=0.316) was similar between the two treatment strategies [32].

Recommendations:

- We suggest that <u>adult patients</u> with asthma on GINA [1] treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler without maintenance treatment instead of regular ICS maintenance treatment plus as-needed SABA. (Conditional Recommendation for the intervention; Low Certainty of Evidence).

- We suggest that adolescent patients with asthma on GINA [1] treatment steps 1 or 2 use either as-needed ICS/formoterol in a single inhaler or regular ICS maintenance treatment plus as-needed SABA (Conditional Recommendation; Low Certainty of Evidence).

The panel unanimously approved these recommendations.

Justification of recommendations

- The recommendation for adults places a relatively higher value on the reduction of systemic corticosteroids use and the potential clinical benefit in favour of ICS/formoterol for the outcomes related to severe exacerbations and a relatively lower value on the small and not clinically relevant differences in asthma control and quality of life.
- Due to the low-certainty of evidence we made a conditional recommendation.
- Limited data is available in adolescents compared to adults, therefore the panel suggested either treatment options for adolescent patients as the balance between the two options is very close.

Research needs

Alternative strategies such as the use of ICS as a rescue medication in addition to rapid short-acting bronchodilators in two separate inhalers should be tested further, in those countries where as-needed ICS/formoterol has no regulatory approval for use in mild asthma [34-37], since the current recommendation is off-label in those countries. However, such an approach might be rendered obsolete by the availability of alternative combination ICS/salbutamol inhalers [38] recently approved by the FDA in adults, as a reliever medication across the range of asthma severity [39].

Studies in children are another research priority as this is a population in high need of effective and feasible treatment strategies. Considering the low adherence of adolescents to regular ICS maintenance treatment, studies on adolescents would be of value specially to clarify uncertainty in the effect of as-needed ICS/formoterol on outcomes such as exacerbations and asthma control.

The effects of as-needed budesonide–formoterol on exacerbations are independent of biomarker profile, whereas the benefits of maintenance inhaled budesonide are greater in patients with high blood eosinophil counts than in patients with low counts [40]. Studies undertaken to date found no evidence of an effect modification with severe exacerbation

risk based on a wide range of characteristics such as age, sex, ethnicity, smoking status, exacerbation history, baseline SABA use, level of asthma control, lung function, blood eosinophil level or FeNO [41]. Future studies might further explore additional predictors of responsiveness such as poor perceivers of symptoms.

Values, patients' perspective and preferences

Some clinicians will value differently the importance of the outcomes based on patients' different clinical needs and preferences. The guideline panel is aware that some clinicians and some patients interpret small changes in exacerbations or quality of life as important while others may not regard them as clinically significant.

Patient education is important to help patients understand rationale of treatment recommendations and alleviate any concerns.

As-needed ICS/formoterol combination would be preferable for patients with limited financial resources in healthcare systems where patients pay a prescription charge or co-payment per item prescribed, (e.g. England) [42-44] and where the costs of rescue ICS/formoterol combination is lower than that of regular ICS plus as needed SABA.

Only few cost effectiveness data based on probabilistic models, are available [45-47]. Future cost-effectiveness analyses in different populations would also be of value [43].

PICO 2

Is as-needed ICS/formoterol (single inhaler) without maintenance treatment the preferred treatment compared to as-needed SABA without maintenance treatment in adult/adolescent patients with mild asthma (i.e. GINA [1] treatment steps 1 or 2)?

Summary of the evidence

We identified a total of 547 publications; of which three were finally included [28, 30, 32]. All studies used budesonide as the ICS component of ICS/formoterol combination; terbutaline [28] and salbutamol [30] were used in one study each.

Detailed definitions and data are presented in the online supplementary material.

Benefits and harms

There were statistically significant differences in favour of as-needed ICS/formoterol in the number of patients experiencing at least one severe exacerbation (RR: 0.46 (95%CI 0.36,

0.59)) [28, 30], the annualised severe exacerbation rate (0.36 (95%CI 0.27, 0.48)) [28], the number of patients experiencing at least one ED visit (RR 0.24 (95%CI 0.11, 0.55)) [28] and the annualised exacerbation (not limited to severe) rate ((rate ratio 0.42 (0.35, 0.50)) [28, 30]. The reduction of number of patients requiring hospitalisation in favour of ICS/formoterol (RR 0.40 (95%CI 0.16, 1.03) was non-significant [28].

There was a difference in favour of as-needed ICS/formoterol in asthma control (ACQ-5 change from baseline MD -0.15 (95%CI -0.20, -0.10) [28, 30] and ACQ-5 across all time points MD -0.15 (95%CI -0.24, -0.06)) [30] and in AQLQ score difference after 52 weeks of about 0.10 (reported only in a graph, with apparently overlapping 95% CI) [28].

Total systemic corticosteroid exposure over 1 year was lower for the as-needed ICS/formoterol arm (prednisone: MD - 9.90 mg (95%CI -19.38, -0.42 mg); mean % reduction 56.9% (95%CI 2.4, 111.4%)) [30] as well as rescue medication use (mean change from baseline of daily as-needed inhalations MD -0.16 inhalations/day (95%CI -0.20, -0.12) [28] and mean daily as-needed actuations throughout follow-up, MD 0.48 actuations/day (95% CI -0.7, -0.26)) [30]. Change in pre- BD FEV_1 from baseline favoured as-needed ICS/formoterol (MD 53.80 mL (95%CI 29.07, 78.53 mL)) [28], but on-treatment FEV_1 across all time points was similar between the two treatment groups (MD 0.03 L (95% CI -0.01, 0.07)) [30]. FeNO values at week 52 were lower in as-needed ICS/formoterol (ratio of geometric means 0.83 (95%CI 0.75, 0.92)) [30].

There was no difference between as-needed ICS/formoterol and as-needed SABA in the number of patients experiencing AEs ((RR 0.92 (95%CI 0.85, 1.00)) or SAEs (RR 1.06 (95%CI 0.45, 2.49)) [28, 30]. The data on mortality was too small leading to very serious imprecision (one single event in the ICS/formoterol arm, not asthma or treatment related; Peto OR 7.52 (0.15, 379.21)) [28, 30].

Detailed data are presented in the online supplementary material.

Benefits and harms – adolescent subgroup

There were differences favouring as-needed ICS/formoterol in the annualised rate of severe exacerbations (rate ratio 0.23 (95%CI 0.09, 0.65)), in asthma control (ACQ-5 change from baseline to treatment average MD -0.17 (-0.30, -0.03)) and in the mean daily ICS inhalations (-0.10 inhalations (95%CI -0.22, 0.02)) [32].

There were no differences between treatment arms in the changes in pre-BD FEV_1 from baseline to treatment average (MD 0.9% (95% CI -1.1, 2.8%)) [32].

The proportion of adolescents experiencing an AE (33.9% and 41.9%) or a SAE (1.9% and 4.2%) was lower for as-needed ICS/formoterol than with as-needed SABA respectively (no statistical results reported) [32].

Recommendations

- We recommend that adult and adolescent patients with asthma on GINA [1] treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler instead of as-needed SABA (Strong Recommendation for the intervention; Low Certainty of Evidence). The panel concluded that efficacy and safety of as-needed ICS/formoterol in adolescents is consistent with adult data and that the evidence is sufficient to include adolescents in the overall recommendation.

The panel unanimously approved these recommendations.

Justification of the recommendation

- This strong recommendation places a relatively higher value on the benefit of as-needed ICS/formoterol in mild asthma on several outcomes tested, in particular those related to exacerbations and reduction of systemic corticosteroids use; and a relatively lower value on medication costs. In addition, the panel weighted as important the risks related to as-needed SABA use and overuse in the absence of anti-inflammatory treatment, as consistently reported in population based studies [7, 13, 14, 48-50]. The overall "low" certainty of evidence was imputed to the very serious imprecision in the assessment of mortality. Since the randomised controlled trials assessed are not adequately powered to investigate such a rare event as asthma mortality, the overall balance was considered strongly in favour of as-needed ICS/formoterol vs as-needed SABA. In addition, GRADE has identified a paradigmatic situation in which a strong recommendation may be warranted despite low certainty evidence – when high certainty evidence suggests modest benefit and low certainty evidence suggests possibility of catastrophic harm [51]. Our assessment showed a similar scenario with high or moderate certainty evidence of great benefit with as-needed ICS/formoterol in reducing exacerbation-related outcomes, but with a low

certainty non-significant increased risk of mortality in this treatment arm (due to only one non-asthma or treatment related death).

Research needs

Studies in children are a research priority as this is a population in high need of effective and feasible treatment strategies. Studies on adolescents would be of value especially for the assessment of additional outcomes.

Alternative strategies to use ICS as rescue medication in addition to rapid short-acting bronchodilators such as salbutamol should be tested, to avoid SABA-only use in those countries where as-needed ICS/formoterol has no regulatory approval for use in mild asthma, or where ICS/formoterol is not available.

Only few cost effectiveness data based on probabilistic models, are available [45-47]. Cost effectiveness analyses in different populations are required, and will need to include assessment of the cost of severe exacerbations in terms of both direct medical costs and non-medical costs such as time off work.

Values, patients' perspective and preferences

There is likely to be variability in the interpretation of the clinical importance of the size of the effects. Health professionals should provide information to help patients understand that the combined regime may reduce total oral corticosteroid exposure, as well as explaining differences in side effect profile of ICS and OCS [52, 53].

Since patients consider the speed of onset is important [54], it will be necessary to explain that the speed of onset might not be similar for SABA and ICS/formoterol and that there may be variability between patients [55], with some patients reporting slower onset of efficacy and lower symptom relief from as-needed ICS/formoterol vs as-needed SABA therapy [56, 57].

The cost of ICS/formoterol may be [43] higher than that of SABA and cost can be seen as a disincentive [42, 58-60]. Likely, this is offset by the reduction in exacerbations, ER visits and hospitalizations with better productivity and social integration due to improved outcomes.

General considerations for PICO 1 and PICO 2

Although approved in many countries, (more than 40, including Argentina, Australia, Brazil, Canada, China, Indonesia, Malaysia, New Zealand, Philippines, South Korea, Russia and the United Kingdom) the use of as-needed ICS/formoterol in the absence of

maintenance treatment is off-label in countries (including the countries of the European Union - EU) where the combination has no regulatory approval for use in mild asthma. This is a major barrier to the implementation of these ERS recommendations in EU countries (and in other countries in the same position) where patients have no access to the treatments recommended. Alternative strategies of adding the ICS to the rescue bronchodilator medication such as salbutamol should be considered and further tested [20, 38] (see above).

Discussion

The purpose of this ERS Clinical Practice Guideline (CPG) is to provide recommendations for the use of as-needed ICS/formoterol in the absence of maintenance treatment in mild asthma based on a systematic review of the literature followed by the application of the GRADE approach.

The TF suggests that adult patients with asthma on GINA treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler instead of regular ICS maintenance treatment plus as-needed SABA. (Conditional Recommendation; Low Certainty of Evidence). Due to the more limited evidence available in the adolescent population the TF adopted a more conservative conclusion in this population by suggesting that adolescent patients with asthma on GINA treatment steps 1 or 2 use either as-needed ICS/formoterol in a single inhaler or regular ICS maintenance treatment plus as-needed SABA (Conditional Recommendation; Low Certainty of Evidence). Low adherence is particularly relevant in adolescents and the as-needed ICS/formoterol strategy should be specifically considered for non-adherent patients.

The results of the PICO 1 assessment are in line with recent meta-analyses [16, 61, 62] and the related recommendation is aligned with international and with some asthma management national guidelines [8, 63].

The recommendations recognise the reduction of corticosteroid use and the clinical benefit in favour of ICS/formoterol for the exacerbation outcomes and the minimal differences in asthma control which were substantially below the recognised MCID. Recent data from a post hoc analysis of the Novel-START and Practical studies, confirmed that there were no clinically important differences in the proportions of patients with ‘controlled’ or ‘partly controlled’ asthma symptoms, or proportions who improved or maintained their level of

control, with as-needed budesonide/formoterol versus maintenance budesonide plus as needed SABA [62].

Similar considerations have been taken into account for lung function and only one study provided post-bronchodilator data [29] that were pre-specified for the assessment. Previous studies have shown that i) the differences seen in pre-BD FEV_1 substantially reduce after bronchodilator [20] and that ii) the differences in post-BD FEV_1 occur mainly in the first year of treatment and then they progressively disappear [64]. Notably, the difference between treatments refers to group level assessment, i.e the value will be more or less pronounced in subgroups of patients. Thus in clinical practice, lung function should be monitored over time in patients with mild asthma receiving as-needed ICS/formoterol to detect the fast decliners, as well as in patients who are poorly adherent with maintenance ICS [65]. Also for adolescents with low lung function, and in particular if lung function is worsening [66], regular ICS use treatment should be considered. The reduction in mean daily ICS dose with as-needed ICS/formoterol as compared to maintenance ICS treatment plus as- needed SABA should be considered, in the light of recent evidence of the systemic effect of chronic use of low-dose ICS [67]. The impact of this therapeutic option on structural remodelling should also be further assessed as well as in patients with raised type-2 biomarkers, and those who are poor perceivers of asthma symptoms. Future studies should also further investigate the cost-effectiveness for different healthcare systems.

From the patients' perspective, they value having one inhaler over two separate inhalers with the requirement to use the preventive inhaler on a daily or twice daily basis regardless of symptoms. Indeed, the as-needed budesonide-formoterol regimen was preferred to maintenance ICS treatment in a group of patients with mild asthma enrolled in the Novel START study by semistructured interviews thematically analysed [56]. However, it is important for patients to have a choice and some patients may prefer the regular use of maintenance ICS. In addition, the type of inhaler device may be important for some patient groups: the use of dry powder inhalers is more difficult for patients with impaired inspiratory flow (e.g. older patients and children).

The TF recommend that both adult and adolescent patients with asthma GINA treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler instead of as-needed SABA (Strong Recommendation; Low Certainty of Evidence). Although available data in adolescents is limited with respects to adults, the Panel concluded that efficacy

and safety of as-needed ICS/formoterol in adolescents is consistent with adult data and considered the evidence appropriate to include adolescents in the overall recommendation.

The TF valued the benefit of as-needed ICS/formoterol over as-needed SABA on several outcomes, in particular those related to exacerbations and reduction of systemic corticosteroids use. The Panel considered important the increased risk of severe exacerbations and mortality with SABA overuse in the absence of anti-inflammatory treatment, as consistently reported in population based studies. The evidence for adolescents, though more limited, was considered adequately supportive for a strong recommendation in favour of ICS/formoterol as-needed vs SABA as-needed, with substantial reduction in the risk of severe exacerbations and the need of systemic corticosteroid use.

The results of the assessment are in line with recent meta-analyses [16, 61] and the recommendation is supportive of international and some national guidelines [8, 63, 68]. From the patients' perspective, education is important to help patients understand the rationale of treatment recommendations and alleviate any concerns, such as corticosteroid exposure. Indeed, many patients will have been on SABA-only treatment for many years. It will be important to support them to transition to a new regime, with clear, accessible information, training in inhaler technique [56] and implementation of action plans. Our recommendation cannot be currently implemented in EU, given that as-needed ICS/formoterol has no regulatory approval for mild asthma. This means that patients with mild asthma within the EU might be missing the benefits of this treatment approach.

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Online supplement

European Respiratory Society Short Guidelines for the use of as-needed ICS/formoterol in mild Asthma

Alberto Papi, Diogenes S. Ferreira, Ioana Agache, Eugenio Baraldi, Richard Beasley, Guy Brusselle, Courtney Coleman, Mina Gaga, Carolina Maria Gotera Rivera, Erik Melén, Ian Pavord, Deborah Peñate Gómez, Daniel Schuermans, Antonio Spanevello, Thomy Tonia, Florence Schleich.

Methods

Group composition

This document has been developed following the requirements for guidelines of the European Respiratory Society (ERS) [1, 2]. Two of the guideline panel co-chairs (AP and FS) applied for the TF and the third one (DSF) was recommended by the ERS. They led all aspects of project management and selected the guideline panel, which included 12 clinicians and researchers with experience in the field of asthma, one ERS Early Career Member representative (CMGR) and a patient representative (DPG). The ERS Senior Methodologist (TT) overviewed the methodological work. An external methodologist (AR) was commissioned to undertake various parts of the methodological work. DSF and TT revised the evidence and ensured that all the methodological requirements were met.

Management of Conflicts of Interest (COI)

The standard ERS policy for COI management was followed (for details see https://ers.app.box.com/s/cjp3mc9jm7y5nw81ym01en5o3jx6v87x). In short, upon approval of the project, all panellists completed an online declaration of interest form. A summary of the COI disclosed was submitted to the chairs who were responsible for establishing a management plan. Panellists with major COI(s) were excluded from participating in the TF. Panellists with other COI(s) could participate in the discussions around recommendations but were recused from voting on the recommendations for question(s) linked to their COI. Changes in the COI during the development of the guideline had to be reported to the chairs and the management plan would have to be adopted accordingly.

As a result of this process for each PICO recommendation, 4 members, out of 16 components of the Panel TF, did not vote.

Formulation of questions

Guideline panel members agreed on the formulation of the following two PICO (patient, intervention, comparator, outcome) questions [3].

Question 1. Is as-needed ICS/formoterol (single inhaler) without maintenance treatment the preferred treatment compared to regular low-dose ICS maintenance treatment plus as-needed short-acting β2 agonist (SABA) in adult/adolescent patients with mild asthma (i.e. GINA [4] treatment steps 1 or 2)?

Patient: adult/adolescent patients with mild asthma (i.e. GINA treatment steps 1 or 2); intervention: as-needed ICS/formoterol without maintenance treatment; comparator: regular low-dose ICS maintenance treatment plus as-needed SABA; outcomes: listed below on "Rating the importance of outcomes".

Question 2. Is as-needed ICS/formoterol (single inhaler) without maintenance treatment the preferred treatment compared to as-needed SABA without maintenance treatment in adult/adolescent patients with mild asthma (i.e. GINA [4] treatment steps 1 or 2)?

Patient: adult/adolescent patients with mild asthma (i.e. GINA treatment steps 1 or 2); intervention: as-needed ICS/formoterol without maintenance treatment; comparator: as-needed SABA; outcomes: listed below on "Rating the importance of outcomes".

Rating the importance of outcomes

The guideline panel identified outcomes that they considered important for their questions. Following GRADE guidance [3], each panel member rated the importance of the outcomes for clinical decision making using a scale from 1 to 9 (1–3 not important; 4–6 important; 7–9 critically important). The ratings were discussed within the panel and a final list of outcomes and their importance was agreed for each question, before the literature search. The critical outcomes for PICO 1 question were severe exacerbations (exacerbation risk and annualised rate), exacerbations (annualised rate), hospitalisations (risk), emergency department (ED) visits (risk), health-related quality of life (assessed with the Asthma Quality of Life Questionnaire, AQLQ), asthma control (assessed with the Asthma Control Questionnaire, ACQ), systemic corticosteroid reduction and serious adverse events. Important (but not critical) outcomes were inhaled corticosteroid reduction, lung function (in order of preference post-bronchodilator (BD) forced expiratory volume in 1s (FEV1), pre-BD FEV1), fractional exhaled nitric oxide (FeNO), adverse events and mortality. There were some differences on the outcomes chosen and their importance for PICO 2: critical outcomes were severe exacerbations, exacerbations, hospitalisations, emergency ED visits, health-related quality of life (AQLQ), asthma control (ACQ), serious adverse events and mortality. The important outcomes were systemic corticosteroid reduction, rescue medication use, lung function (in order of preference post-BD FEV1, pre-BD FEV1), FeNO and adverse events.

Adverse events and severe adverse events were included after the literature search was completed and the panel discussed and agreed about their importance for clinical decisions.

Literature searches

A literature search was conducted by the external methodologist (AR) following PRISMA recommendations [5] on Oct 11th, 2021 on MEDLINE, Embase, the US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov), and on the World Health Organization International Clinical Trials Registry Platform (trial search) using pre-defined adapted search strategies (see below). The list of references of the primary studies (clinical trials) and systematic reviews were also checked for additional references. No time or language limits were applied.
The pre-defined inclusion criteria of the studies were the following: clinical trials including patients of any age with mild asthma (defined by GINA treatment step 1 or 2), comparing as-needed ICS formoterol with regular use ICS and/or as-needed SABA and with a minimum duration of 12 weeks. The exclusion criteria were studies in which ICS/formoterol was used as Maintenance and Reliever Therapy (MART) or if participants had severe asthma.

Evidence synthesis

Two authors (FS, IA) selected the studies after review of the full text; disagreements were resolved by a third author (GB). Studies selected for inclusion were approved by the full panel. Data extraction for all outcomes of interest was performed by the external methodologist and checked by DSF. Data was collected in a pre-designed Excel spreadsheet. Study characteristics, types of participants, interventions, outcomes measured and results were extracted from each study. Risk of bias of the included studies was assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [6] by the external methodologist and checked by DSF.
If appropriate, data were pooled and meta-analyses were performed using the software Review Manager (Review Manager (RevMan) [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For dichotomous outcomes, data are presented as pooled risk ratios (RR) or Peto odds ratios (OR) (when events were rare) and 95% CIs. Continuous variables are presented as mean differences with 95% CI, unless otherwise specified. Effect estimates of rate ratios were pooled by the inverse of their variance and are presented as pooled rate ratios with corresponding 95% CIs. All analyses used random-effects meta-analysis, except the calculation of Peto odds ratio which uses a fixed-effect method. The threshold for significance for p values was 0.05.
The external methodologist and DSF assessed the certainty of evidence and created evidence profiles using the GRADE approach [7]. GRADEpro GDT online software (GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from

gradepro.org) was used to develop evidence profiles that summarised the findings for each outcome and the rationale for the certainty of evidence appraisal [8].
Thresholds for clinically important changes (used to judge imprecision) included the following published minimal clinically important differences (MCID): 0.5 change in ACQ-5 [9] and 0.5 change in AQLQ (0.5) [10]. The thresholds for other outcomes were based on the clinical experience of the TF members: 20% change in exacerbations, severe exacerbations, hospitalisations and ED visits; 20% change in the number of treatment courses of systemic corticosteroids; 25% change in the yearly total dose of inhaled corticosteroids; 3 puffs/week change in rescue medication use; 100 mL change in post-BD FEV1 in adults; 5% change in post-BD FEV1 in adolescents; 15% change in adverse events and 10% change in severe adverse events.
We have considered the 95% CI around the absolute effect to judge imprecision, as suggested by GRADE [11], when these absolute effects were estimated with the “absolute effect auto calculation” function in GRADEpro GDT. When only the relative effects were calculated and presented, we used these relative effect estimates with their 95% CI to judge imprecision.
For the analysis of adolescent data in PICO 1 question, we decided to perform a meta-analysis with the results of SYGMA 1 and SYGMA 2 instead of including the pooled results from these two studies as presented by Reddel et al. [12]. We made this decision so we could perform meta-analyses using the same parameters in RevMan software with the adult and adolescent data from the SYGMA studies.

Formulating and grading recommendations

We used the Evidence to Decision (EtD) framework to structure and document the discussions around the evidence and reach recommendations [13, 14]. The EtDs frameworks were drafted by the co-chairmen with the assistance of two co-authors (GB, EM) and the ERS methodologist (TT) and then discussed and completed at an online meeting attended by the majority of the panel members, including a patient representative. Recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (harms) of the intervention, the certainty of evidence, patient values and preferences, feasibility, acceptability, health equity, costs. A strong recommendation was made for an intervention when the panel was certain that the desirable consequences of the intervention outweighed the undesirable consequences, just as a strong recommendation would have been made against an intervention if the panel was certain that the undesirable consequences of the intervention outweighed the desirable consequences. A strong recommendation indicates that most well-informed patients would choose to have or not to have the intervention. A conditional recommendation was made for an intervention when the panel was uncertain that the desirable consequences of the intervention outweighed the undesirable consequences, just as a conditional recommendation would have been made against an intervention if the panel was uncertain that the

undesirable consequences of the intervention outweighed the desirable consequences [15]. Reasons for uncertainty included low or very low certainty of evidence, the desirable and undesirable consequences being finely balanced or the underlying values and preferences or other considered factors playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not to have the intervention. Strong recommendations were formulated with “We recommend” and conditional recommendations with “We suggest” [15]. Consensus was reached mainly by discussion. Formal voting also took place for both PICO questions. Agreement of 100% was reached in favour of the recommendations.

Manuscript preparation

The initial draft of the manuscript and the supplementary material were prepared by AP and edited by DSF. Both the manuscript and the supplementary material were reviewed and approved by all panel members prior to submission.

Extended results

PICO 1

Summary of the evidence

We identified a total of 549 papers; once duplicates were removed, the total was 547 (see PRISMA flowcharts below). Ultimately, six publications reporting on five different studies met all inclusion and no exclusion criteria and were included in the evidence synthesis: five randomised clinical trials (RCTs) (48 to 52 weeks follow-up), of which two were double blind phase 3 industry sponsored studies [16, 17] and two were randomised open label Investigator Initiated Studies supported by pharmaceutical industry [18] and a government health research funding organisation [18, 20]; SYGMA 1 and SYGMA 2 trials reported on a separate publication post-hoc pooled analysis of adolescent patients with mild asthma recruited in these trials [12]; and the fifth trial was an open-label randomised crossover study published as a conference abstract only [19]. The total number of participants in the four trials [16-18, 20] included in the meta-analysis were 9575. There were additionally 28 participants [19] included in the qualitative synthesis only. The number of participants included in the meta-analysis of PICO 1 question, randomised to as-needed ICS/formoterol or maintenance ICS, were 8072.

All studies used budesonide as the inhaled corticosteroid (ICS) component of ICS/formoterol combination; terbutaline and salbutamol were the short-acting beta-agonist (SABA) tested in three [16, 17, 20] and one [18] RCTs respectively. The study by Tanaka et al. [19] did not report on the use of SABA. None of these studies included patients starting their initial treatment while entering the study.

Patients included in the two SYGMA trials [16, 17] were 12 years of age or older and had received a clinical diagnosis of asthma that was confirmed by bronchodilator responsiveness testing. All recruited subjects were eligible to maintenance low-dose inhaled corticosteroids or leukotriene-receptor antagonist plus SABA used as needed (GINA 2014 Step 2) [21].

Novel START [18] recruited subjects 18 to 75 years of age who had received a physician diagnosis of asthma and used SABA as the sole asthma therapy on at least two occasions in the previous 4 weeks, but on an average of two or fewer occasions per day.

There was no such minimum requirement for SABA use for patients who had had a severe exacerbation in the previous 12 months.

Eligible participants to PRACTICAL [20] were subjects aged 18 to 75 with a physician reported diagnosis of asthma who were either taking SABA alone and symptomatic or were partly or well controlled with low to moderate doses of inhaled corticosteroids plus as needed SABA.

Subjects with a smoking history greater than 10 pack-years were excluded from SYGMA studies [15,16], whereas Novel START [18] and PRACTICAL [20] excluded subjects with a smoking history of more than 20 pack-years or ≥ 10 pack-years if the onset of respiratory symptoms had been after the age of 40 years.

Participants in the study by Tanaka et al. [19], were adults 22 to 77 years of age with mild asthma, randomised to daily budesonide or as-needed budesonide/formoterol for 24 weeks. After a four-week washout period, patients were assigned to receive the alternative treatment for additional 24 weeks. This study was published only in short abstract format and did not provide any data for PICO 1 question meta-analysis.

Eight hundred eighty-nine adolescent patients were enrolled in the 2 SYGMA studies (12.5% of the total population of SYGMA 1 [17] and 10% of the total population of SYGMA 2 [16] populations). Overall, 366 adolescent patients were randomised to as-needed budesonide/formoterol and 379 to budesonide maintenance therapy [12].

Pregnancy was an exclusion criterion in 4 studies [16-18, 20]. One study [19] reported no information on the enrolment of pregnant participants.

Benefits and harms

1) Exacerbation end-points

Severe exacerbations were defined in three RCTs [16, 17, 20] as worsening asthma leading to systemic corticosteroid treatment for ≥3 days, hospitalisation, or an emergency department (ED) visit leading to systemic corticosteroid treatment. One RCT [18] defined severe exacerbations slightly different, as worsening asthma leading to the prescription of (but not necessarily use of) systemic corticosteroid for ≥3 days, in addition to hospitalisation or ED visit leading to systemic corticosteroid treatment. But Beasley et al. also presented results of severe exacerbations according to the other RCTs definition.

For the number of patients experiencing at least one severe asthma exacerbation, which was reported with the same definition in four studies [16-18, 20], the effect in favour of as-needed ICS/formoterol was non-significant with relative risk (RR) 0.82 (95% CI 0.64, 1.04).

The annualised severe exacerbation rate was measured in 3 studies [16, 17, 20] with a non-significant rate ratio in favour of as-needed ICS/formoterol of 0.86 (95% CI 0.71, 1.04).

The study by Tanaka et al. [19], reported that one participant discontinued the study because of an asthma exacerbation, but did not provide any further data about exacerbations.

ED visits, asthma hospitalisation

The outcome ED visits for asthma worsening was measured in 2 studies [16, 17]. The difference for the number of patients experiencing at least one ED visit between maintenance ICS plus as needed SABA and as needed ICS/formoterol alone showed an effect in favour of as-needed ICS/formoterol that was non-significant with: RR 0.70 (95%CI 0.44, 1.09).

For the end-point of hospitalisation for severe asthma exacerbations, which was reported in 2 studies [16, 17], no differences were found between groups in the number of patients experiencing at least one severe exacerbation leading to hospitalisation with RR 0.92 (95%CI 0.52, 1.62).

Exacerbations

Asthma exacerbations (not limited to severe) had a slightly different definition in the three RCTs that assessed this outcome [17, 18, 20]. In the Novel START[18] asthma exacerbations were defined as worsening asthma resulting in an urgent medical care consultation or/and a prescription of systemic corticosteroids for any duration or/and an episode of high β2-agonist use (>16 actuations of salbutamol or > than 8 actuations of budesonide–formoterol in 24 hrs).

Moderate and severe exacerbations in the PRACTICAL [20] study were defined as worsening asthma resulting in unplanned medical review (primary care, visit to emergency department, or hospital admission) or worsening asthma resulting in use of systemic corticosteroids for any duration. In SYGMA 1 [17] study moderate-to-severe exacerbation included worsening asthma requiring the addition of inhaled budesonide (200 μg twice daily) or worsening asthma leading to the use of systemic corticosteroids for ≥3 days, inpatient hospitalisation or an ED visit leading to systemic corticosteroids use.

Despite these small differences in definitions, the Task Force members judged they included severe and non-severe exacerbations that could be combined in a single analysis. The meta-analysis found no difference in the annualised rate of exacerbations between the two arms (rate ratio 0.88 (95%CI 0.69, 1.13)).

2) Quality of life

The Asthma Quality of Life Questionnaire (AQLQ) was used in one study [16] and the mean difference (MD) in AQLQ change from baseline to treatment average between the two arms was -0.10 points (95% CI -0.14, -0.05 points). Based on the MCID of 0.50 [9], this finding suggests a very small and clinically irrelevant worsening in quality of life with as-needed ICS/formoterol as compared to regular maintenance ICS.

3) Asthma Control

Asthma Control Questionnaire (ACQ-5) results were presented by four studies [16-18, 20]. The two SYGMA studies [16, 17] reported results of ACQ-5 score mean change from baseline analysed with a mixed-model for repeated measures. The pooled MD was 0.13 (95% CI 0.09, 0.17). Two other studies [18, 20] reported results of ACQ-5 score across all time points, with a combined meta-analysis resulting in MD of 0.09 (95% CI 0.02, 0.17). Based on the MCID of 0.50 [9], these differences do not indicate clinically significant worsening asthma control with as-needed ICS/formoterol. Tanaka et al. [19], reported that mean ACQ-5 scores were not different at 4, 8, 16 and 24 weeks between as-needed ICS/formoterol and maintenance ICS, without providing values for ACQ-5.

4) **Systemic corticosteroid exposure**

The outcome total systemic corticosteroid dose was measured in 2 studies [18, 20] and the mean difference in total dose throughout follow up (expressed as mg of prednisone) was -7.00 mg (95%CI -13.97, -0.03); mean % reduction 31.2% (95%CI 0.13, 62,2%), with a lower exposure for the as-needed ICS/formoterol arm and in line with the observed reduction on exacerbations. There was insufficient data to undertake an analysis of the number of treatment courses of systemic corticosteroids.

5) Inhaled corticosteroid reduction

The meta-analysis of four studies [16-18, 20] showed a MD in mean daily ICS dose throughout 52 weeks of -154 µg (95% CI -206.87, -101.14 µg);); mean % reduction 56.5% (95%CI 37.1, 76%) less with as-needed ICS/formoterol.

6) FEV1

One study [17] reported change in post-BD FEV1 from baseline to treatment period average, the MD favouring maintenance ICS was -23.1 mL (95% CI -41.9, -4.2 mL). This difference is lower than the estimated MCID of 100 mL. Pre-BD FEV1 change from baseline (analysed with a mixed model for repeated measures) has been assessed in 2 studies [16, 17] with the pooled mean difference favouring maintenance ICS (MD -42.50 mL (95%CI -63.68, -21.31 mL)). On-treatment FEV1 across all time points was measured in two studies [16, 18] and did not differ between treatment strategies (MD 0.01 L (95%CI -0.02, 0.03 L). No MCID has been pre-specified in relation to pre-BD FEV1 and on-treatment FEV1.

The study by Tanaka et al. [19], reported no differences in mean change of FEV1 from baseline but did not provide values or specified it as pre- or post-BD.

7) FeNO

FeNO values at week 52, which was reported in 2 studies, [18, 20] were higher with as-needed ICS/formoterol (ratio of geometric mean values 1.13 (95% CI 1.06, 1.20)). The study by Tanaka et al. [19], reported that mean levels of FeNO at weeks 16 and 24 were significantly higher in the ICS/formoterol group, but did not provide numerical results.

8) Serious Adverse Events (SAE), Adverse Events (AE) and Mortality

There was no difference between as-needed ICS/formoterol and maintenance ICS in the number of participants experiencing at least one SAE in the pooled analysis of four studies [16-18, 20] (RR 1.13 (95%CI 0.83, 1.54)). There was no difference either in the relative risk of AEs (patients with at least one AE: RR 0.98 (95%CI 0.92, 1.05)).

The data on mortality was too small in the pooled analysis of 4 studies [16-18, 20] to be informative, leading to very serious imprecision (6 events in total: 2 ICS/formoterol, 4 maintenance ICS) (Peto odds ratio: 0.52 (95%CI 0.10, 2.57)).

Benefits and harms – adolescent subgroup

The systematic review identified data on the subgroup of adolescents for only three of eight critical outcomes. The two SYGMA trials provided results on all the outcomes presented here for this subgroup [12]. The annualised rate of severe exacerbations was not different between maintenance ICS plus as-needed SABA and as-needed ICS/formoterol (rate ratio 0.97 (95% CI 0.39, 2.40)). No differences between groups were detected in ACQ-5 score change from baseline, with a pooled MD of 0.06 (95%CI -0.08, 0.21).

In adolescents there was a reduction in ICS dose with as-needed ICS/formoterol at 52 weeks as reported by SYGMA 1 trial (median (interquartile range) daily ICS dose 35.1 µg (9.3 – 91.6 µg) vs. 292.2 µg (193.6 – 341.9 µg)) and SYGMA 2 trial (42.3 µg (10.4 – 104.7 µg) vs. 198.9 µg (127 – 285.8 µg) [12].

In this subgroup, there was a pooled MD of -2.6% (95% CI -4.95%, -0.25%) in change in pre-BD FEV1 from baseline indicating lower values in the as-needed ICS/formoterol arm.

The proportion of adolescents experiencing a SAE was similar with the two treatment strategies (1.9% and 1.1% respectively, p=0.316). Similarly, the proportion of adolescents experiencing an AE was not different between treatment groups (33.9% and 33.2% respectively); no statistical test result comparing these proportions was reported [12].

Values, patients' perspective and preferences

There is likely to be variability in the interpretation of the clinical relevance of the size of the effects. Some clinicians will value differently the importance of the outcomes based on patients' different clinical needs and preferences. The guideline panel is aware that some clinicians and some patients interpret small changes in exacerbations or quality of life as important while others may not regard them as clinically significant.

Health care professionals should listen to the treatment outcomes and priorities which are important to the individual patient (e.g. reducing total steroid exposure, environmental impact of treatment, simplicity of treatment) in order to support patients to make informed treatment choices. Patient education is important to help patients understand rationale of treatment recommendations and alleviate any concerns.

Patients would value having one inhaler over two separate inhalers with the requirement to use the preventive inhaler on a daily or twice daily basis regardless of symptoms. Indeed, the as-needed budesonide-formoterol regimen was preferred to maintenance ICS treatment in a group of patients with mild asthma enrolled in the Novel START study by semistructured interviews thematically

analysed [22]. However, it is important for patients to have a choice between the intervention and comparison options since they are similar in terms of outcomes and some patients may prefer the regular use of maintenance ICS. In addition, the type of inhaler device (metered-dose inhaler (MDI), dry powder inhaler (DPI)) may be important for some patient groups: dry powder is more difficult for older patients and children to use; when MDI is prescribed, clinicians should ensure a spacer is used. As-needed ICS/formoterol combination would be preferable for patients with limited financial resources in healthcare systems where prescription treatment is paid [23] out of pocket and where the costs of rescue ICS/formoterol combination is lower than that of regular ICS and rescue SABA.

PICO 2

Summary of the evidence

We identified a total of 548 papers; once duplicates were removed, the total was 547 (see PRISMA flowcharts below). Ultimately, three publications reporting on two studies met all inclusion and no exclusion criteria and were included: two 12 months randomised clinical trials, of which one was a double blind phase 3 industry sponsored study (SYGMA 1) [17] and one was a randomised open label Investigator Initiated Study supported by the pharmaceutical industry (Novel START) [18]. The SYGMA 1 trial reported on a separate publication post-hoc analysis of adolescent patients with mild asthma recruited by the study[12].

All studies used budesonide as the ICS component of ICS/formoterol combination, and terbutaline and salbutamol were the SABA used in SYGMA 1 [17] and Novel START [18] respectively. None of the studies included patients starting their initial treatment while entering the study.

The number of participants in the two trials included in the meta-analysis of PICO 2 question, randomised to as-needed ICS/formoterol or as-needed SABA, were 3002. Patients included in the SYGMA 1 trial [17] were 12 years of age or older and had received a clinical diagnosis of asthma that was confirmed by lung function testing of bronchial responsiveness. All recruited subjects were eligible to maintenance low-dose inhaled corticosteroid or leukotriene-receptor antagonist plus SABA used as needed (GINA 2014 Step 2) [21].

Novel START [17] recruited subjects 18 to 75 years of age who had received a physician diagnosis of asthma and used of SABA as the sole asthma therapy on at least two occasions in the previous 4 weeks, but on an average of two or fewer occasions per day.

There was no such minimum requirement for SABA use for patients who had had a severe exacerbation in the previous 12 months.

Subjects with a smoking history greater than 10 pack-years were excluded from SYGMA study [15], while Novel START [18] excluded subjects with a smoking history of more than 20 pack-years or ≥10 pack-years if the onset of respiratory symptoms had been after the age of 40 years.
Eight hundred eighty nine adolescent patients were enrolled in the 2 SYGMA studies (12.5% of the total population of SYGMA 1 [15] and 10% of the total population of SYGMA 2 [16] populations).
The number of adolescent patients included in PICO 2 question meta-analysis were 144 randomised to as-needed terbutaline and 161 randomised to as-needed budesonide/formoterol, all from SYGMA 1 trial [12].
Pregnancy was an exclusion criterion both studies.

Benefits and harms

1) Exacerbation end-points

Severe exacerbations: all studies used the same definition for severe exacerbation (see PICO 1 for details). The meta-analyses showed differences in the efficacy of preventing severe exacerbations between patients receiving as-needed SABA and those receiving as-needed ICS/formoterol and no maintenance treatment.
For the number of patients experiencing at least one severe exacerbation, which was reported in two studies [17, 18], there was a difference in favour of as-needed ICS/formoterol (RR: 0.46 (95%CI 0.36, 0.59)).
The annualised severe exacerbation rate was measured in one study[17] with a difference in favour of as-needed ICS/formoterol and a rate ratio of 0.36 (95%CI 0.27, 0.48).

ED visits, asthma hospitalisation

The outcome ED visits for asthma worsening was measured in one study [17] with a difference in the number of patients experiencing at least one ED visit in favour of as-needed ICS/formoterol with RR 0.24 (95%CI 0.11, 0.55).
For the end-point of hospitalisation for severe exacerbations, which was reported in one study [17], the number of patients experiencing at least one hospitalisation showed a non-significant effect in favour of ICS/formoterol (RR 0.40 (95%CI 0.16, 1.03)).

Exacerbations

Asthma exacerbations (not limited to severe) had a slightly different definition in Novel START trial [17] and SYGMA 1 [17] study (see PICO 1 for details). But the panel considered these two definitions similar enough to be analysed together.
The meta-analysis [17, 18] found a difference in favour of as-needed ICS/formoterol for the annualised exacerbation rate ((rate ratio 0.42 (95% CI 0.35, 0.50)).

2) Quality of life

AQLQ was assessed in one study [17]. However only a graph was presented with the mean change from baseline in AQLQ (95% CI) at different time points and did not provide the exact numerical values. But it is possible to appreciate a difference in favour of as-needed ICS/formoterol over as-needed SABA at 52 weeks of about 0.10 units, with apparently overlapping 95% CI. Based on the MCID of 0.5 [10], this finding suggests a very small and clinically irrelevant improvement in quality of life with as-needed ICS/formoterol.

3) Asthma Control

The Asthma Control Questionnaire (ACQ-5) was used in two studies [17, 18]. The SYGMA 1 study [17] reported ACQ-5 score mean change from baseline (analysed with a mixed-model for repeated measures), with a MD -0.15 (95% CI -0.20, -0.11). The Novel START study [18] reported a MD of -0.15 (95% CI -0.24, -0.06) in ACQ-5 score across all time points. Based on the MCID of 0.50 [9], these findings indicate statistically better asthma control with as-needed ICS/formoterol but probably not clinically important.

4) Systemic corticosteroid exposure

The outcome total systemic corticosteroid dose was measured in one study [18]. Mean difference in total dose throughout 52 weeks (expressed as mg of prednisone was - 9.90 mg (95%CI -19.38, -0.42 mg)); mean % reduction 56.9% (95%CI 2.4, 111.4%) with a lower exposure for the as-needed ICS/formoterol arm and in line with the observed reduction on severe exacerbations. There was insufficient data to undertake an analysis of the number of treatment courses of systemic corticosteroids.

5) Rescue medication use

The outcome mean change from baseline of as-needed inhalations was reported in one study [17] (with a mean difference in favour of as-needed ICS/formoterol of -0.16 inhalation/day (95%CI -0.20, -0.12).

For the endpoint mean daily actuations throughout follow up, which was measured in one study [18], the mean difference between arms was -0.48 actuation/day (95%CI -0.70, -0.26) in favour of as-needed ICS/formoterol. Because of the 1:2 ratio of use of as-needed ICS/formoterol:as-needed SABA per rescue episode, the difference in daily actuations is halved, i.e. in the ICS/formoterol arm there was a reduction in the number of actuations of the rescue medication of one every 4 days, as compared to the as-needed SABA arm.

6) FEV1

Since post-BD FEV1 values were reported in none of the studies, pre-BD FEV1 data have been assessed but no MCID has been pre-specified for this outcome.
The outcome changes in pre-BD FEV1 from baseline was measured in one study [17] and the mean difference between the two arms was in favour of as-needed ICS/formoterol (MD 53.80 mL (95%CI 29.07, 78.53 mL)). On-treatment FEV1 across all time points was similar between the two treatment groups (MD 0.03 L (95% CI -0.01, 0.07)) in another study [18].

7) FeNO

FeNO values at week 52 was reported in 1 study [18] with lower values in the as-needed ICS/formoterol group (ratio of geometric means 0.83 (95%CI 0.75, 0.92)).

8) Serious Adverse Events (SAE), Adverse Events (AE) and Mortality

There were no differences between as-needed ICS/formoterol and as-needed SABA in the number of patients experiencing severe adverse events in the pooled analysis of two studies (RR 1.06 (95%CI 0.45, 2.49)) [17, 18].
There were no differences between as-needed ICS/formoterol and as-needed SABA in the number of patients experiencing AE in two studies (RR 0.92 (95%CI 0.85, 1.00)) [17, 18].
The data on mortality in the pooled analysis of two studies [17, 18] was too small to be informative, leading to a very imprecise estimate (one single event in the ICS/formoterol arm, not asthma or treatment related; Peto OR 7.52 (0.15, 379.21)).

Benefits and harms – adolescent subgroup

SYGMA 1 study provided data about the comparison as-needed ICS/formoterol and as-needed SABA in adolescents [12]. The systematic review identified data on this subgroup for only three of eight critical outcomes.
The annualised severe exacerbation rate ratio was 0.23 (95%CI 0.09, 0.65) in favour of as-needed ICS/formoterol. The mean difference in ACQ-5 change from baseline to treatment average was -0.17 (-0.30, -0.03) in favour of as-needed ICS/formoterol. Rescue medication use, presented as mean daily inhalations during 52 weeks, was -0.10 inhalation/day (95%CI -0.22, 0.02) with as-needed ICS/formoterol.
Changes in pre-BD FEV1 from baseline to treatment average were not different between treatment groups (MD 0.9% (95% CI -1.1%, 2.8%)).
The proportions of adolescents experiencing a SAE and an AE, with as-needed SABA were 4.2% and 41.0% respectively. With as-needed ICS/formoterol these proportions were 1.9% and 33.9% respectively. No statistical test results comparing these proportions were reported [12].

Values, patients' perspective and preferences

There is likely to be variability in the interpretation of the clinical importance of the size of the effects. Some clinicians will value differently the importance of the outcomes based on patients' different clinical needs.

Patient education is important to help patients understand rationale of treatment recommendations and alleviate any concerns, such as steroid exposure. Explaining the differences in side effect profile of ICS and OCS is important.

Many patients will have been on SABA-only treatment for many years. It will be important to support them to transition to a new regime, with clear, accessible information and training in inhaler technique. They will have to mentally adjust from seeing the SABA inhaler as their 'go-to' rescue treatment [22].

Patients consider the speed of onset of efficacy important [24]. It will be necessary to explain that there may be variability in the speed of action of the rescue medication, with some patients reporting slower onset of efficacy and lower symptom relief from combination vs SABA therapy [22].

The cost of ICS/formoterol may be higher than that of SABA and cost can be seen as a disincentive [22, 23]. Likely, this is offset by the reduction in exacerbations, ER visits and hospitalisations with better productivity and social integration due to improved outcomes.

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Literature search strategies

Ovid MEDLINE(R) ALL <1946 to Oct 11th, 2021>

Searches

1 exp Asthma/

2 asthma$.ti,ab.

3 1 or 2

4 Fluticasone/

5 Budesonide/

6 Beclomethasone/

7 exp Triamcinolone/

8 fluticasone.tw.

9 beclomethasone.tw.

10 budesonide.tw.

11 triamcinolone.tw.

12 flunisolide.tw.

13 ciclesonide.tw.

14 (flixotide or flovent).tw.

15 (becotide or beclofort or becodisk or QVAR or vanceril).tw.

16 pulmicort.tw.

17 (kenalog or azmacort or “anti-inflammatory reliever therapy”).tw.

18 bronalide.tw.

19 Alvesco.tw.

20 Mometasone Furoate/

21 mometasone.tw.

22 (inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw.

23 or/4-22

24 exp Adrenergic beta-2 Receptor Agonists/

25 exp Albuterol/

26 Terbutaline/

27 Formoterol Fumarate/

28 Salmeterol Xinafoate/

29 (Salbutamol or albuterol).tw.

30 Terbutaline.tw.

31 Bambuterol.tw.

32 (formoterol or eformoterol).tw.

33 Indacaterol.tw.

34 Olodaterol.tw.

35 salmeterol.tw.

36 or/24-35

37 Fluticasone-Salmeterol Drug Combination/

38 Budesonide, Formoterol Fumarate Drug Combination/

39 Mometasone Furoate, Formoterol Fumarate Drug Combination/

40 Fostair.tw.

41 Symbicort.tw.

42 DuoResp Spiromax.tw.

43 Fobumix.tw.

44 Seretide.tw.

45 Relvar.tw.

46 Ventide.tw.

47 Aerocort.tw.

48 Salbair.tw.

49 or/37-48

50 23 and 36

51 3 and (49 or 50)

52 (controlled clinical trial or randomized controlled trial).pt.

53 (randomized or randomised).ab,ti.

54 placebo.ab,ti.

55 dt.fs.

56 randomly.ab,ti.

57 trial.ab,ti.

58 groups.ab,ti.

59 or/52-58

60 Animals/

61 Humans/

62 60 not (60 and 61)

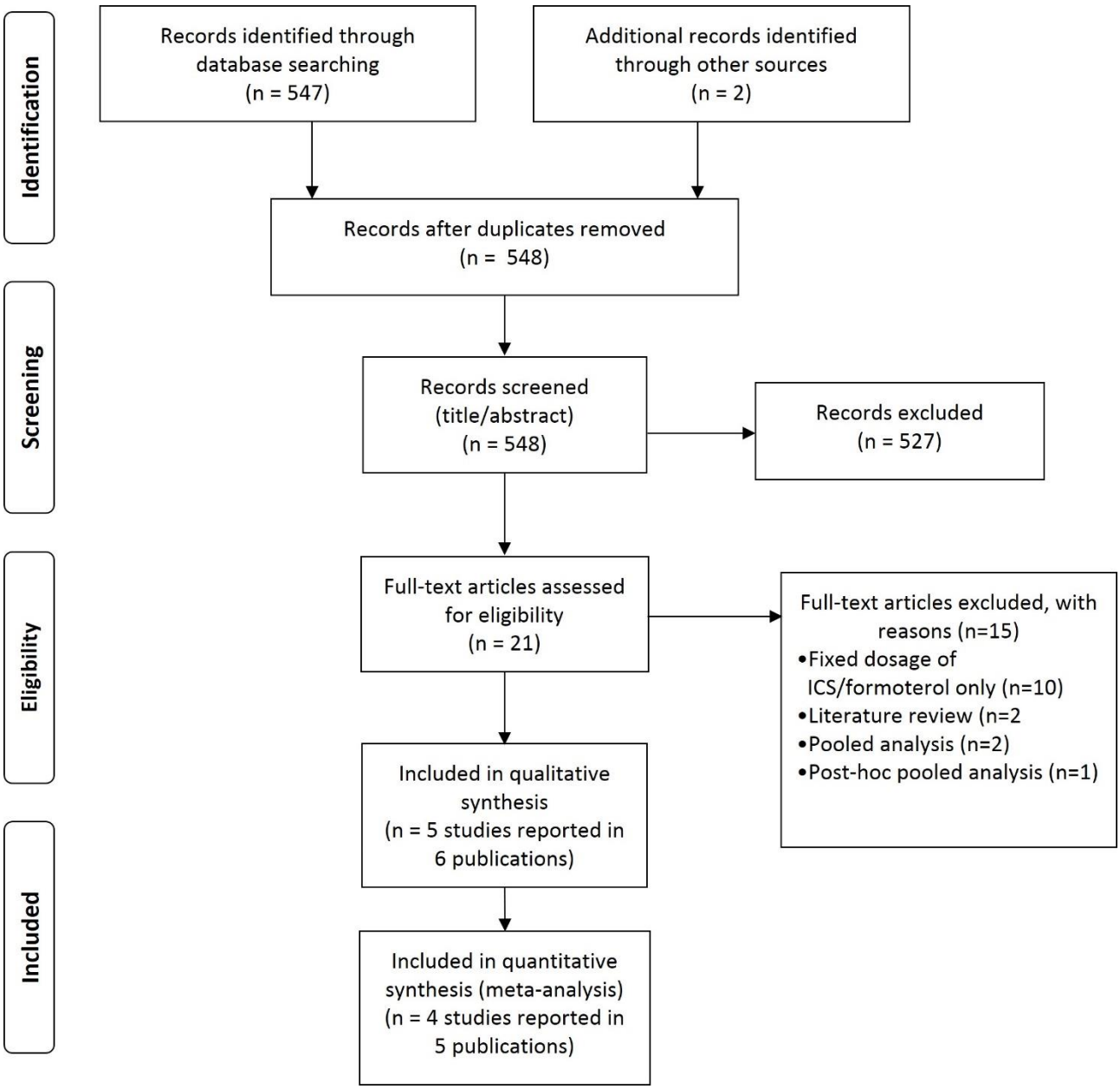
63 59 not 62

64 51 and 63

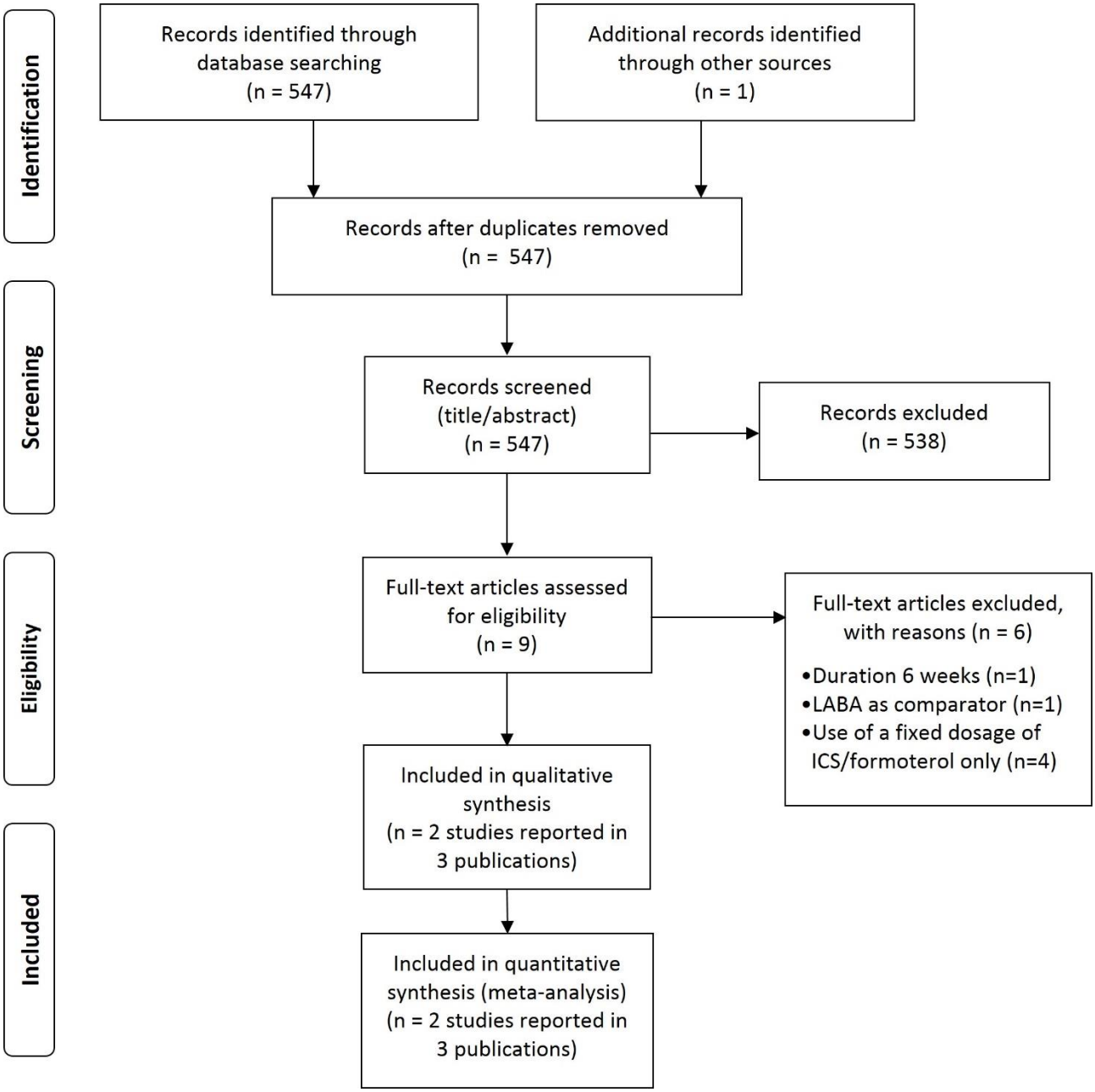
Embase Ovid SP 1974 to to Oct 11th, 2021

(('triamcinolone derivative' OR fluticasone OR beclometasone OR budesonide OR triamcinolone OR flunisolide OR cicloesonide OR flixotide OR flovent OR 'beclomethasone dipropionate' OR 'triamcinolone acetonide' OR (anti AND inflammatory AND reliever AND therapy) OR ciclesonide OR 'mometasone furoate') AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)) AND ((steroid OR corticosteroid OR glucoco) AND exposure AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim))) AND ((('asthma'/exp OR asthma OR asthma:ab,ti) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)) OR (('asthma'/exp OR asthma OR asthma:ab,ti) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)))

PICO 1 PRISMA flowchart



PICO 2 PRISMA flowchart



PICO 1 EVIDENCE PROFILE

Question: As-needed ICS/formoterol compared to low-dose regular ICS maintenance treatment + as-needed SABA for adult/adolescent patients with mild asthma (GINA treatment steps 1 or 2)

Setting: Specialised respiratory clinics and primary care

Bibliography: Bateman 2018, O'Byrne 2018, Beasley 2019, Hardy 2019, Reddel 2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/formoterol on demand	Low-dose regular ICS maintenance treatment + as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
Increase of severe asthma exacerbations (follow-up: 52 weeks; assessed with: Patients with ≥ 1 severe exacerbation; MCID 20% change)												
4 [1,2,3,4]	randomised trials	serious [a]	not serious	not serious	not serious	none	294/4023 (7.3%)	340/4042 (8.4%)	**RR 0.82** (0.64 to 1.04)	**15 fewer per 1,000** (from 30 fewer to 3 more)	⊕⊕⊕◯ Moderate	CRITICAL
Increase of severe asthma exacerbations (follow-up: 52 weeks; assessed with: Annualised severe exacerbation rate; MCID 20% change)												
3 [1,2,4]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3803	3817	**Rate ratio 0.86** (0.71 to 1.04)	**Mean incidence rate (severe exacerbations/patient/year):** Budesonide/formoterol 0.10; Budesonide 0.12	⊕⊕◯◯ Low	CRITICAL
Increase of severe asthma exacerbations (Adolescents) (follow-up: 52 weeks; assessed with: Annualised severe exacerbation rate; MCID 20% change)												
2 [5]	randomised trials	not serious	not serious	not serious	serious [c]	none	366	379	**Rate ratio 0.97** (0.39 to 2.40)	**Mean incidence rate (severe exacerbations/patient/year):** Budesonide/formoterol 0.075; Budesonide 0.075	⊕⊕⊕◯ Moderate	CRITICAL
Increase of exacerbations (any moderate or severe exacerbation) (follow-up: 52 weeks; assessed with: annualised exacerbation rate; MCID 20% change)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/formoterol on demand	Low-dose regular ICS maintenance treatment + as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
3 [2,3,4]	randomised trials	serious [a]	not serious	not serious	serious[b]	none	1939	1950	**Rate ratio 0.88** (0.69 to 1.13)	**Mean incidence rate (exacerbations/patient/year):** Budesonide/formoterol 0.17; Budesonide 0.19	⊕⊕◯◯ Low	CRITICAL
Increase of hospitalisations (follow-up: 52 weeks; assessed with: Patients with ≥ 1 severe asthma exacerbation leading to hospitalisation; MCID 20% change)												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious[d]	none	23/3366 (0.7%)	25/3369 (0.7%)	**RR 0.92** (0.52 to 1.62)	**1 fewer per 1,000** (from 4 fewer to 5 more)	⊕⊕⊕◯ Moderate	CRITICAL
Increase of emergency department visits (follow-up: 52 weeks; assessed with: Patients with > 1 severe asthma exacerbation leading to emergency department visit; MCID 20% change)												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious[e]	none	32/3366 (1.0%)	46/3369 (1.4%)	**RR 0.70** (0.44 to 1.09)	**4 fewer per 1,000** (from 8 fewer to 1 more)	⊕⊕⊕◯ Moderate	CRITICAL
Asthma control (follow-up: 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-5) change from baseline; Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5) [f]												
2 [1,2]	randomised trials	not serious	not serious	not serious	not serious	none	3103	3077	-	MD **0.13 higher** (0.09 higher to 0.17 higher)	⊕⊕⊕⊕ High	CRITICAL
Asthma control (follow-up: 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-5) across all time points; Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
2 [3,4]	randomised trials	serious [a]	not serious	not serious	not serious	none	657	673	-	MD **0.09 higher** (0.02 higher to 0.17 higher)	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/formoterol on demand	Low-dose regular ICS maintenance treatment + as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
Asthma control (Adolescents) (follow-up: 52 weeks; assessed with: ACQ-5 change from baseline to treatment average; Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
2 [5]	randomised trials	not serious	not serious	not serious	not serious	none	356	364	-	MD **0.06 higher** (0.08 lower to 0.21 higher)	⊕⊕⊕⊕ High	CRITICAL
Quality of life (follow-up: 52 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ) change from baseline to treatment average; Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5)												
1 [1]	randomised trial	serious [g]	not serious	not serious	not serious	none	1809	1791	-	MD **0.1 lower** (0.14 lower to 0.05 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Total systemic corticosteroid dose (mg) (follow-up: 52 weeks; assessed with: mean prednisone dose throughout the study; MCID 20% change)												
2 [3,4]	randomised trials	serious [a]	not serious	not serious	serious [h]	none	657	673	-	MD **7 mg lower** (13.97 lower to 0.03 lower)	⊕⊕◯◯ Low	CRITICAL
Inhaled corticosteroid dose (follow-up: 52 weeks; assessed with: Mean daily inhaled corticosteroid dose in micrograms; MCID 25% change)												
4 [1,2,3,4]	randomised trials	serious [a]	serious [i]	not serious	not serious [j]	none	3641	3649	-	MD **154 µg lower** (206.87 lower to 101.14 lower)	⊕⊕◯◯ Low	IMPORTANT
Inhaled corticosteroid dose (Adolescents) (follow-up 52 weeks; assessed with: Median daily inhaled corticosteroid dose in micrograms; MCID 25% change)												
2 [5]	randomised trials	not serious	not serious	not serious	serious [k]	none	Reddel 2021 has reported the median (IQR) daily ICS dose (micrograms) from the SYGMA trials without a statistical test comparing the results: SYGMA 1: as-needed budesonide-formoterol (n=161) 35.1 µg (9.3-91.6). Budesonide (n=173) 292.2 µg (193.6-341.9). SYGMA 2: as-needed budesonide-formoterol (n=205) 42.3 µg (10.4-104.7). Budesonide (n=206) 198.9 µg (127-285.8).				⊕⊕⊕◯ Moderate	IMPORTANT
Lung function (follow-up: 52 weeks; assessed with: Pre-bronchodilator FEV1 (mL), change from baseline; MCID 100 mL) [l]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/formoterol on demand	Low-dose regular ICS maintenance treatment + as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
2 [1,2]	randomised trials	not serious	not serious	not serious	not serious	none	3175	3141	-	MD **42.5 mL lower** (63.68 lower to 21.31 lower)	⊕⊕⊕⊕ High	IMPORTANT
Lung function (follow-up: 52 weeks; assessed with: on-treatment FEV1 (litres) across all time points; MCID 100 mL) [m]												
2 [3,4]	randomised trials	serious [a]	not serious	not serious	not serious	none	657	673	-	MD 0.01 **L higher** (0.02 lower to 0.03 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
Lung function (follow-up: 52 weeks; assessed with: post-bronchodilator FEV1 (mL) change from baseline to treatment average, MCID 100 mL)												
1 [1]	randomised trial	serious [n]	not serious	not serious	not serious	none	1902	1863	-	MD **23.1 mL lower** (41.9 lower to 4.2 lower)	⊕⊕⊕ Moderate	IMPORTANT
Lung function (Adolescents) (follow-up: 52 weeks; assessed with: FEV1 (% predicted), change from baseline to treatment average, MCID 5%) [o]												
2 [5]	randomised trials	not serious	not serious	not serious	not serious	none	359	375	-	MD **2.6% lower** (4.95 lower to 0.25 lower)	⊕⊕⊕⊕ High	IMPORTANT
Exhaled nitric oxide (at week 52) (follow-up: 52 weeks; assessed with: FeNO)												
2 [3,4]	randomised trials	serious [a]	not serious	not serious	not serious	none	595	601	**Ratio of geometric means 1.13** (1.06 to 1.2)	-	⊕⊕⊕◯ Moderate	IMPORTANT
Mortality (follow-up: 52 weeks; assessed with: Number of participants; MCID 1% change)												
4 [1,2,3,4]	randomised trials	not serious [p]	not serious	not serious	very serious [q]	none	2/4025 (0.0%)	4/4044 (0.1%)	**Peto OR 0.52** (0.10 to 2.57)	-	⊕⊕◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/formoterol on demand	Low-dose regular ICS maintenance treatment + as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
Adverse events (follow-up: 52 weeks; assessed with: patients with ≥1 adverse event; MCID 15% change)												
4 [1,2,3,4]	randomised trials	serious [a]	not serious	not serious	not serious	none	1931/4028 (47.9%)	1992/4044 (49.3%)	**RR 0.98** (0.92 to 1.05)	**10 fewer per 1,000** (from 39 fewer to 25 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Adverse events (Adolescents) (follow-up:52 weeks; assessed with: patients with ≥ 1 adverse event; MCID 15% change)												
2 [5]	randomised trials	not serious	not serious	not serious	serious [r]	none	Reddel 2021 reported the proportion of adolescents with ≥ 1 adverse event in the as-needed budesonide-formoterol group (33.9%) and budesonide maintenance group (33.2%), but no statistical test comparing the proportions. [s]				⊕⊕⊕◯ Moderate	IMPORTANT
Serious adverse events (follow-up: 52 weeks; assessed with: patients with ≥ 1 serious adverse event; MCID 10% change)												
4 [1,2,3,4]	randomised trials	serious [a]	not serious	not serious	serious [t]	none	140/4028 (3.5%)	131/4044 (3.2%)	**RR 1.13** (0.83 to 1.54)	**4 more per 1,000** (from 6 fewer to 17 more)	⊕⊕◯◯ Low	CRITICAL
Serious adverse events (Adolescents) (follow-up: 52 weeks; assessed with: patients with ≥ 1 serious adverse event; MCID 10% change)												
2 [5]	randomised trials	not serious	not serious	not serious	serious [u]	none	Reddel 2021 reported the proportion of adolescents with ≥ 1 serious adverse event in the as-needed budesonide-formoterol group (1.9%) and budesonide maintenance group (1.1%), p = 0.316. [s]				⊕⊕⊕◯ Moderate	CRITICAL

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **FeNO**: fractional exhaled nitric oxide; **FEV1:** forced expiratory volume in 1 second; **GINA**: Global Initiative for Asthma; **ICS:** inhaled corticosteroid; **IQR**: interquartile range; **MCID:** minimal clinically important difference; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SABA:** short-acting β2-agonist

Explanatio

a. Two trials were open-label (Beasley 2019 and Hardy 2019).

b. The 95% CI crosses the threshold for appreciable benefit and also includes no benefit.

c. The 95% CI crosses the threshold for appreciable benefit and harm. For this reason, we have rated down one level for imprecision.

d. The 95% CI does not cross the threshold of 20% absolute change in hospitalisations, but the number of events is small. For this reason we have rated down one level for imprecision.

e. The 95% CI does not cross the threshold of 20% absolute change in emergency department visits, but the number of events is small. For this reason we have rated down one level for imprecision.

f. Both trials' duration was 52 weeks (Bateman 2018 and O'Byrne 2018). However the published studies do not clearly specify if these analyses included change in ACQ-5 score from baseline to the final study visit at 52 weeks.

g. High risk of selective under-reporting of data because one study (O'Byrne 2018) presented results in graphical format only, so the data cannot be included in a meta-analysis.

h. The total mean prednisone dose throughout 52 weeks in the budesonide group (mean of two trials) was 22.45 mg, therefore the MCID of 20% corresponds to 2.2 mg. There is imprecision around the effect estimate because the 95% CI includes appreciable benefit and no benefit.

i. There is considerable statistical heterogeneity ($I^2 = 99\%$, $P < 0.00001$). The effect estimate and 95% CI from one study (O'Byrne 2018) do not overlap with the estimates from the other trials. However the direction of effects estimated from each of the trials is the same.

j. The mean daily inhaled corticosteroid dose in the budesonide group (four trials) was 272.5 ug, therefore the MCID of 25% corresponds to 68.1 ug. Hence there is no imprecision around the effect estimate.

k. The results have been presented as median (IQR) and therefore cannot be pooled for meta-analysis. For this reason we have rated down imprecision by one level.

l. Both trials' duration was 52 weeks (Bateman 2018 and O'Byrne 2018). However the published studies do not clearly specify if these analyses included change in pre-BD FEV1 from baseline to the final study visit at 52 weeks.

m. Both studies (Beasley 2019 and Hardy 2019) have described the outcome FEV1 as “on-treatment FEV1” and have not specified it as pre- or post-bronchodilator.

n. There was high risk of bias due to possible selective outcome reporting. The SYGMA 1 trial (O'Byrne 2018) planned the analysis of post-BD FEV1 as stated in the published Supplementary Appendix, but the result of this analysis was not reported.

o. Reddel 2021 has not clearly specified this outcome as pre- or post-bronchodilator.

p. We have considered there is no increased risk of bias for this outcome even though two trials (Beasley 2019 and Hardy 2019) were open-label, because it is unlikely that the knowledge of which intervention was received would affect asthma mortality.

q. The 95% CI crosses the threshold of 1% increase in mortality and it includes both appreciable benefit and harm. In addition, the number of pooled events is very small. For this reason, we have rated down imprecision by two levels.

r. The approximate number of events calculated from the proportion of adolescents with ≥ 1 adverse event and the sample size is only 251 events. Therefore we have rated down one level for imprecision.

s. The Task Force has assumed these are pooled results from SYGMA 1 and 2 trials. The randomised population from SYGMA 1 was n=161 (bud-form) and n=173 (bud) and from SYGMA 2 n=205 (bud-form) and n=206 (bud).

t. The 95% CI does not cross the threshold of 10% absolute change in serious adverse events. However the number of events (patients with ≥ 1 serious adverse event) is small and for this reason we have rated down one level for imprecision.

u. The approximate number of events calculated from the proportion of adolescents with ≥ 1 serious adverse event and the sample size is very small (11 events) and therefore we have rated down one level for imprecision.

References

1. Bateman ED, Reddel HK, O'Byrne PM, et al. As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma. N Engl J Med 2018; 378(20):1877-1887. (SYGMA 2)
2. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med 2018; 378(20):1865-1876. (SYGMA 1)
3. Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. N Engl J Med 2019; 380(21): 2020-2030. (Novel START)
4. Hardy J, Baggott C, Fingleton J, et al. 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. Lancet 2019;394(10202) 919-928.
5. Reddel HK, O'Byrne PM, FitzGerald JM, et al. Efficacy and Safety of As-Needed Budesonide-Formoterol in Adolescents with Mild Asthma. J Allergy Clin Immunol Pract 2021; 9:3069-3077.e6. (SYGMA 1 and 2)

PICO 2 EVIDENCE PROFILE

Question: As-needed ICS/formoterol compared to as-needed SABA for adult/adolescent patients with mild asthma (GINA treatment steps 1 or 2)

Setting: Specialised respiratory clinics and primary care

Bibliography: O'Byrne 2018, Beasley 2019, Reddel 2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	budesonide/formoterol on demand	as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
Increase of severe asthma exacerbations (follow-up: 52 weeks; assessed with: Patients with ≥ 1 severe exacerbation; MCID 20% change)												
2 [1,2]	randomised trials	serious[a]	not serious	not serious	not serious	none	80/1497 (5.3%)	174/1500 (11.6%)	**RR 0.46** (0.36 to 0.59)	**63 fewer per 1,000** (from 74 fewer to 48 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	budesonide/formoterol on demand	as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
Increase of severe asthma exacerbations (follow-up: 52 weeks; assessed with: Annualised severe exacerbation rate; MCID 20% change)												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	1277	1277	**Rate ratio 0.36** (0.27 to 0.48)	**Incidence rate (severe exacerbations/patient/year):** Budesonide/formoterol: 0.07 Terbutaline: 0.20	⊕⊕⊕⊕ High	CRITICAL
Increase of severe asthma exacerbations (Adolescents) (follow-up: 52 weeks; assessed with: Annualised severe exacerbation rate; MCID 20% change)												
1 [3]	randomised trials	not serious	not serious	not serious	serious[b]	none	161	144	**Rate ratio 0.23** (0.09 to 0.65)	**Incidence rate (severe exacerbations/patient/year):** Budesonide/formoterol: 0.04 Terbutaline: 0.17	⊕⊕⊕◯ Moderate	CRITICAL
Increase of exacerbations (any moderate or severe) (follow-up: 52 weeks; assessed with: Annualised exacerbation rate; MCID 20% change)												
2 [1,2]	randomised trials	serious[a]	not serious	not serious	not serious	none	1497	1500	**Rate ratio 0.42** (0.35 to 0.50)	**Mean incidence rate (exacerbations/patient/year):** Budesonide/formoterol: 0.17 Terbutaline (SABA): 0.38	⊕⊕⊕◯ Moderate	CRITICAL
Increase of hospitalisations (follow-up: 52 weeks; assessed with: Patients with ≥ 1 severe asthma exacerbation leading to hospitalisation; MCID 20% change)												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	6/1277 (0.5%)	15/1277 (1.2%)	**RR 0.40** (0.16 to 1.03)	**7 fewer per 1,000** (from 10 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL
Increase of emergency department visits (follow-up: 52 weeks; assessed with: Patients with ≥ 1 severe asthma exacerbation leading to emergency department visit; MCID 20% change)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	budesonide/formoterol on demand	as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	7/1277 (0.5%)	29/1277 (2.3%)	**RR 0.24** (0.11 to 0.55)	**17 fewer per 1,000** (from 20 fewer to 10 fewer)	⊕⊕⊕⊕ High	CRITICAL
Asthma control (follow-up: 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-5) change from baseline; Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5) [c]												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	1241	1225	-	MD **0.15 lower** (0.2 lower to 0.1 lower)	⊕⊕⊕⊕ High	CRITICAL
Asthma control (follow-up: 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-5) across all time points; Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
1 [2]	randomised trials	serious[a]	not serious	not serious	not serious	none	225	223		MD **0.15 lower** (0.24 lower to 0.06 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Asthma control (Adolescents) (follow-up: 52 weeks; assessed with: ACQ-5 change from baseline; Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
1 [3]	randomised trials	not serious	not serious	not serious	serious[b]	none	161	144	-	MD **0.17 lower** (0.3 lower to 0.03 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Quality of life (follow-up: 52 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ) change from baseline; MCID 0.5) [c]												
1 [1]	randomised trials	not serious	not serious	not serious	serious[d]	none	Difference between as-needed ICS/formoterol (n=1079) and as-needed SABA (n=1003) of about 0.10 units with overlapping 95% CIs (both estimated based on a graph).				⊕⊕⊕◯ Moderate	CRITICAL
Total systemic corticosteroid dose (mg) (follow-up: 52 weeks; assessed with: mean prednisone dose throughout the study; MCID 20% change)												
1 [2]	randomised trials	serious[a]	not serious	not serious	serious [e]	none	220	223	-	MD **9.9 lower** (19.38 lower to 0.42 lower)	⊕⊕◯◯ Low	IMPORTANT
Rescue medication use (follow-up: 52 weeks; assessed with: Mean change from baseline in daily as-needed inhalations; MCID 3 inhalations/week)												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	1276	1273	-	MD **0.16 lower** (0.2 lower to 0.12 lower)	⊕⊕⊕⊕ High	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	budesonide/formoterol on demand	as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
Rescue medication use (follow-up: 52 weeks; assessed with: Mean daily actuations; MCID 3 inhalations/week)												
1 [2]	randomised trials	serious[a]	not serious	not serious	serious[f]	none	220	223	-	MD **0.48 lower** (0.7 lower to 0.26 lower)	⨁⨁◯◯ Low	IMPORTANT
Rescue medication use (Adolescents) (follow-up: 52 weeks; assessed with: Mean daily inhalations; MCID 3 inhalations/week)												
1 [3]	randomised trials	not serious	not serious	not serious	serious[b]	none	161	144	-	MD **0.1 lower** (0.22 lower to 0.02 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Lung function (follow-up: 52 weeks; assessed with: Pre-bronchodilator FEV1 (mL), change from baseline; MCID 100 mL) [g]												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	1261	1243	-	MD **53.8 higher** (29.07 higher to 78.53 higher)	⨁⨁⨁⨁ High	IMPORTANT
Lung function (follow-up: 52 weeks; assessed with: On-treatment FEV1 (litres) across all time points; MCID 100 mL) [h]												
1[2]	randomised trials	serious[a]	not serious	not serious	not serious	none	252	223	-	MD **0.3 higher** (0.01 lower to 0.07 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Lung function (Adolescents) (follow-up: 52 weeks; assessed with: FEV1 (% predicted), change from baseline to treatment average; MCID 5%) [i]												
1 [3]	randomised trials	not serious	not serious	not serious	serious [b]	none	161	143	-	MD **0.9 higher** (1.1 lower to 2.8 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Exhaled nitric oxide (follow-up: 52 weeks; assessed with: FeNO at week 52)												
1 [2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	195	196	**Ratio of geometric means 0.83** (0.75 to 0.92)	-	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	budesonide/formoterol on demand	as-needed SABA	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 52 weeks; assessed with: Number of participants; MCID any change)												
2 [1,2]	randomised trials	not serious [j]	not serious	not serious	very serious [k]	none	1/1499 (0.1%)	0/1503 (0.0%)	**Peto OR 7.52** (0.15 to 379.21)	-	⨁⨁◯◯ Low	CRITICAL
Adverse events (follow-up: 52 weeks; assessed with: Patients with ≥1 adverse event; MCID 15% change)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	659/1499 (44.0%)	730/1503 (48.6%)	**RR 0.92** (0.85 to 1.00)	**39 fewer per 1,000** (from 73 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Adverse events (Adolescents) (follow-up: 52 weeks; assessed with: patients with ≥ 1 adverse event; MCID 15% change)												
1 [3]	randomised trials	not serious	not serious	not serious	serious [b]	none	Reddel 2021 reported the proportion of adolescents with ≥ 1 adverse event in the as-needed budesonide-formoterol group (33.9%) and as-needed terbutaline (SABA) group (41%), but no statistical test comparing the proportions. [l]				⨁⨁⨁◯ Moderate	IMPORTANT
Serious adverse events (follow-up: 52 weeks; assessed with: Patients with ≥1 serious adverse event; MCID 10% change)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	49/1499 (3.3%)	56/1503 (3.7%)	**RR 1.06** (0.45 to 2.49)	**2 more per 1,000** (from 20 fewer to 56 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse events (Adolescents) (follow-up: 52 weeks; MCID 10% change)												
1 [3]	randomised trials	not serious	not serious	not serious	serious [b]	none	Reddel 2021 reported the proportion of adolescents with ≥ 1 serious adverse event in the as-needed budesonide-formoterol group (1.9%) and as-needed terbutaline (SABA) (4.2%) but no statistical test comparing the proportions. [l]				⨁⨁⨁◯ Moderate	CRITICAL
Post-BD FEV1 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **FeNO**: fractional exhaled nitric oxide; **FEV1:** forced expiratory volume in 1 second; **GINA**: Global Initiative for Asthma; **ICS:** inhaled corticosteroid; **MCID:** minimal clinically important difference; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SABA:** short-acting bronchodilator

Explanations

a. The Beasley 2019 trial was open-label.

b. The sample size is small and therefore we have rated down imprecision by one level.

c. The O'Byrne (2018) trial duration was 52 weeks. However the published study does not clearly specify if this analysis included change in ACQ-5 or AQLQ score from baseline to the final study visit at 52 weeks.

d. The result has been presented in graphical format only and cannot be analysed statistically. For this reason we have downgraded one level for imprecision.

e. The total mean prednisone dose throughout 52 weeks in the budesonide group was 17.4 mg, therefore the MCID of 20% corresponds to 3.5 mg. There is imprecision around the effect estimate because the 95% CI includes appreciable benefit and no benefit.

f. The 95% CI crosses the threshold (MCID = 3 inhalations per week) for appreciable benefit and no benefit. Therefore we have downgraded imprecision by one level.

g. The O'Byrne 2018 trial duration was 52 weeks. However the published study does not clearly specify if this analyses included change in pre-BD FEV1 from baseline to the final study visit at 52 weeks.

h. The Beasley 2019 trial described the outcome FEV1 as “on-treatment FEV1” and has not specified it as pre- or post-bronchodilator.

i. Reddel 2021 has not clearly specified this outcome as pre- or post-bronchodilator.

j. We have considered there is no increased risk of bias for this outcome even though one trial (Beasley 2019) was open-label, because it is unlikely that the knowledge of which intervention was received would affect asthma mortality.

k. The 95% CI crosses the threshold of any increase in mortality and it includes both appreciable benefit and harm. In addition, the number of pooled events is very small. For these reasons we have rated down imprecision by two levels.

l. The Task Force has assumed the result from the budesonide-formoterol group are pooled data from SYGMA 1 and 2 trials. The randomised adolescent population from SYGMA 1 was n=161 (bud-form) and n=144 (SABA) and from SYGMA 2 n=205 (bud-form).

References

1. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med 2018; 378(20):1865-1876. (SYGMA 1)

2. Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. N Engl J Med 2019; 380(21): 2020-2030. (Novel START)

3. Reddel HK, O’Byrne PM, FitzGerald JM, et al. Efficacy and Safety of As-Needed Budesonide-Formoterol in Adolescents with Mild Asthma. J Allergy Clin Immunol Pract 2021; 9:3069-3077.e6. (SYGMA 1 and 2)

PICO 1 EVIDENCE TO DECISION FRAMEWORK

Is as-needed ICS/formoterol without maintenance treatment the preferred treatment compared to regular low-dose ICS maintenance treatment plus as-needed SABA in adult/adolescent patients with mild asthma (i.e. GINA treatment steps 1 or 2)?	
POPULATION:	Patients with mild asthma (i.e. on GINA treatment steps 1 or 2)
INTERVENTION:	As-needed ICS/formoterol without maintenance treatment
COMPARISON:	Regular low-dose ICS maintenance treatment plus as-needed SABA
MAIN OUTCOMES:	CRITICAL OUTCOMES 1.Severe exacerbations; 2. Exacerbations; 3. Hospitalisations; 4. Emergency department (ED) visits; 5. Health-related quality of life; 6. Asthma control; 7. Systemic corticosteroid reduction; 8.Serious adverse events. IMPORTANT OUTCOMES 9.Inhaled corticosteroid reduction; 10.Lung function; 11.FeNO; 12.Mortality; 13.Adverse events
SETTING:	Specialised respiratory clinics and primary care
PERSPECTIVE:	Individual patient

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes **X Yes** ○ Varies ○ Don't know	Substantial evidence has been generated in recent years in the form of double blind or open label pragmatic trials.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE (adults and adolescents if not otherwise specified)**	**ADDITIONAL CONSIDERATIONS**
○ Trivial X **Small**	**CRITICAL OUTCOMES**	

○ Moderate ○ Large ○ Varies ○ Don't know	Research evidence did not detect relevant differences in critical outcomes in adults. **<u>EXACERBATIONS</u>**: - **Non-significant estimate in favour of as-needed ICS/formoterol on severe exacerbation reduction**: Patients with ≥1 severe exacerbation: RR 0.82 (95% CI 0.64,1.04) [4 studies, moderate certainty evidence]; Annualised severe exacerbation rate; Rate ratio: 0.86 (95% CI 0.71, 1.04) [3 studies, low certainty]. - **No differences between groups in the number of patients with ≥1 asthma hospitalization**; RR of 0.92 (95% CI 0.52, 1.62) [2 studies, moderate certainty] - **Non-significant estimate in favour of as-needed ICS/formoterol for reducing ED visits**: patients with ≥1 ED visit, RR 0.70 (95% CI 0.44, 1.09) [2 studies, moderate certainty] - **No difference between groups for the annualised rate of exacerbations**; Rate ratio: 0.88 (95% CI 0.69, 1.13) [3 studies, low certainty]. **EXACERBATIONS (adolescents)** **- No difference between groups on the annualised rate of severe exacerbations:** rate ratio 0.97 (95% CI 0.39, 2.40) [2 studies, moderate certainty] **<u>ASTHMA CONTROL</u>** -ACQ-5 change from baseline: in favour of maintenance ICS; end of study MD 0.13 (95% CI 0.09, 0.17) [2 studies, high certainty] **-** ACQ-5 across all time points: in favour of maintenance ICS; end of study MD 0.09 (95% CI 0.02, 0.17) [2 studies, moderate certainty] **ASTHMA CONTROL (adolescents)** -ACQ-5 change from baseline: no difference between groups: MD 0.06 (95% CI -0.08, 0.21) [2 studies, high certainty]	Rogliani et al. (2020) network meta-analysis reported that as-needed ICS/formoterol ranked higher/better than low or medium dose ICS plus SABA in severe exacerbation risk. The magnitude of the differences in both asthma control and HRQL scores is minimal: 4-5 times lower than the respective MCID. In addition, this data has been obtained under the optimal condition of a RCT. Monitored adherence to maintenance treatment was of 79% in SYGMA 1, 60% in SYGMA 2 and 56% in Novel Start, i.e. substantially higher than the adherence rates observed in

	HRQL - AQLQ change from baseline: in favour of maintenance ICS; MD at 52 weeks: -0.10 (95% CI -0.14, -0.05) [1 study, moderate certainty] **Reduction of SCS intake** - In favour of as-needed ICS/formoterol MD -7.00 mg (95% CI -13.97, -0.03) [2 studies, low certainty] **IMPORTANT OUTCOMES** **LUNG FUNCTION** -FEV1 pre-BD, change from baseline: favours maintenance ICS: -42.50 mL (95% CI -63.68, -21.31 mL). No MCID has been defined for this measurement [2 studies, high certainty] -FEV1 (on treatment) across all time points: favours maintenance ICS. MD: -0.01 L (95% CI -0.02, 0.03 L) [2 studies, moderate certainty] -FEV1 post-BD, change from baseline to treatment period average: favours maintenance ICS but values lower than the MCID (100 mL): MD -23.1 mL (95% CI -41.9, -4.2 mL) [1 study, moderate certainty] **LUNG FUNCTION (adolescents)** -FEV1 pre-BD, change from baseline to treatment period average: favours maintenance ICS: -2.6% (95% CI -4.95%, -0.25%) [2 studies, high certainty].	real-world studies (Foster JM, et al J Allergy Clin Immunol 2014; Bender BG, et al. J Allergy Clin Immunol 2006) and certainly higher than the rates found in in clinical practice (ranging from 15 to 54%; Engelkes M, et al. Eur Respir J 2015; Demoly et al. 2012). The effectiveness of regular maintenance is amplified in a RCT due to higher rates of adherence. Although lung function shows this significant difference in favour of maintenance ICS, this data refers to group level assessment, i.e the value will be more or less pronounced in a subgroups of patients. Thus in good clinical care, lung function should be monitored over time in patients with mild asthma receiving as-needed ICS/formoterol to detect the fast lung function decliners. In addition, no MCID has been defined for (a) pre-BD FEV1 nor for (b) on-treatment FEV1 ; with the latter difference being on average (see above) minimal. Previous studies have shown that i) the differences seen in pre-BD FEV1 substantially reduce after bronchodilator [Papi et al., 2007] and that ii) the differences in post-BD FEV1 occur mainly in the first year of treatment and then they progressively disappear [Pauwels et al., 2003].

	<u>INHALED CORTICOSTEROID REDUCTION</u> - Mean daily ICS dose: MD -154 µg (95% CI -206.87, -101.17 µg) in favour of as-needed ICS/formoterol [4 studies, low certainty] **INHALED CORTICOSTEROID REDUCTION (adolescents)** - Reduction in ICS dose with as-needed ICS/formoterol as reported by SYGMA 1 trial (median (interquartile range) daily ICS dose 35.1 µg (9.3-91.6 µg) vs. 292.2 µg (193.6-341.9 µg)) and SYGMA 2 trial (42.3 µg (10.4-104.7 µg) vs. 198.9 µg (127-285.8 µg)) [2 studies, moderate certainty]. **<u>FeNO:</u>** Favours maintenance ICS. RR (ratio of geometric mean values at week 52): 1.13 (95% CI 1.06, 1.20); [2 studies, moderate certainty]	Pre-BD FEV1 in adolescents was lower with as-needed ICS/formoterol but below the pre-defined MCID of 5%. The timing of the ICS dose, when titrated through the vehicle of reliever use, is a more important determinant of efficacy than the total daily maintenance dose of ICS. (Beasley et al J Allergy Clin Immunol Pract. 2023 Mar;11(3):762-772.e1; Cardet JC et al Allergy Clin Immunol Pract 2023 Mar;11(3):726-734; Papi A et al Allergy. 2022 Apr;77(4):1325-1327) - Formoterol also contributes to the reduction in risk of severe exacerbations, when compared with SABA reliever (-Rabe KF, et al Lancet 2006;368:744-53. -Tattersfield AE et al Lancet. 2001; 357: 257–61)
Undesirable Effects How substantial are the undesirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE (adults and adolescents if not otherwise specified)	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	**CRITICAL OUTCOMES** -No difference in **severe adverse events (SAE)**, RR 1.13 (95% CI 0.83, 1.54) [4 studies, low certainty] - **Mortality**: very few events and very serious imprecision (6 events in total: 2 ICS/formoterol, 4 maintenance ICS; Peto OR 0.52 (95% CI 0.10, 2.57)) [4 studies, low certainty] **Adolescents** The proportion of adolescents experiencing a **SAE** was similar between as-needed ICS/formoterol and regular ICS maintenance (1.9% and 1.1% respectively, p=0.316, moderate certainty) **IMPORTANT OUTCOMES** No difference in **adverse events (AE)**, RR 0.98 (95% CI 0.92, 1.05) [4 studies, moderate certainty] **Adolescents** The proportion of adolescents experiencing **AE** was similar between as-needed ICS/formoterol and regular ICS maintenance (33.9% and 33.2% respectively, moderate certainty)	As-needed ICS/formoterol treatment is as safe as regular ICS treatment for both adults and adolescents.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low **X Low** ○ Moderate ○ High ○ No included studies	Based on GRADE assessment	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability **X Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	We have not performed a systematic review on this topic.	There is likely to be variability in the interpretation of the size of the effects. Some clinicians will value differently the importance of the outcomes based on patients' different clinical needs The as-needed budesonide-formoterol regimen was preferred to maintenance ICS treatment in a group of patients with mild asthma enrolled in the Novel START study by semistructured interviews thematically analysed [Foster et al., 2022]. In the PRACTICAL study, participants randomised to as-needed budesonide–formoterol reported higher degrees of satisfaction in all three domains investigated (inhaler effectiveness, frequency of use and speed of onset of the reliever inhaler) than those randomised to maintenance budesonide plus as-needed terbutaline. [Baggott ERJ 2020] **Patient perspective** Asthma control and severe exacerbation risk are important outcomes to patients, based on a discrete choice experiment in which no shortness of breath and lowest risk of asthma flare-up were ranked the two highest attributes. [Baggott Thorax 2020]. Patients value having one inhaler over two separate inhalers. Given the intervention and comparison perform similarly, patients should have a choice of inhaler. Regular checks of inhaler technique should be included in periodic asthma reviews, particularly for patients who have switched device (e.g. from metered-dose inhaler (MDI) to dry powder inhaler (DPI)). Inhaler technique required for dry powder formulations may be more difficult in an 'as-needed' situation (i.e. where symptoms such as breathlessness and coughing are high, it may be difficult to get a sufficiently powerful in-breath) Patients prefer inhalers with an in-built dose counter in order to manage their prescription needs. This can be considered especially important for inhalers used 'as-needed' as it is more difficult to keep track of reliever medication use. Some patients weigh-up the environmental impact of their inhalers (e.g. those containing hydrofluorocarbon propellants) and would like 'greener' choices. Patient safety and choice are important.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison **X Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Differences in the comparisons: - Small for Desiderable Effects - Trivial for Undesiderable Effects	The research evidence reveals that there is little difference in outcomes. Based on a) relatively higher value on the reduction of systemic corticosteroids use and the potential clinical benefit in favour of ICS/formoterol for the outcomes related to severe exacerbations and b) a relatively lower value on the small and not clinically relevant differences in asthma control and quality of life, c) taking into account that adherence is a major issue in asthma, and d) patient preferences the Guideline Panel considered that the overall balance probably favours as-needed ICS/formoterol over regular maintenance ICS plus SABA. **Patient perspective** Patients see a practical benefit to only having one inhaler to carry. Patients value the potential of as-needed ICS/formoterol in reducing exacerbations. Having an 'as-needed' inhaler requires patients to develop the habit of carrying their medication at all times and being aware of their exacerbation triggers especially when they might be exposed to them. This can be more difficult in certain situations (e.g. on holidays, during periods of health service closure (weekends, public holidays)).
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **X Varies**	We have not specifically searched for this outcome.	**Patient perspective** In some countries, patients pay a prescription charge or co-payment per item prescribed. Having a single, combined inhaler would therefore reduce health costs for some patients.

○ Don't know		
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Very low ○ Low ○ Moderate ○ High ○ No included studies	We have not specifically searched for this outcome.	The judgement of the task force members was based on clinical experience and patient perspective.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison **X Probably favors the intervention** ○ Favors the intervention ○ Varies ○ No included	We have not specifically searched for this outcome.	At a population level, as-needed budesonide-formoterol resulted in cost-saving compared with low-dose maintenance ICS plus as-needed SABA from the perspective of the public payers (Canada, UK, Colombia) [Sadatsafavi et al., 2021; FitzGerald et al., 2020; Buendía et al., 2021]. **Patient perspective** - In some countries, patients pay a prescription charge or co-payment per item prescribed,. Having a single, combined inhaler would therefore reduce health costs for some patients. - Single/combined treatment would be preferable for patients with limited financial resources and in health systems where prescription treatment is paid for [Cole et al., 2013].

studies		

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced **X Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	We have not specifically searched for this outcome.	**Patient perspective** - Single/combined treatment would be preferable for patients with limited financial resources and in health systems where prescription treatment is paid for. “Cost seen as disincentive to obtaining preventative medicine” [Cole et al., 2013].

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no **X Probably yes** ○ Yes ○ Varies ○ Don't know	We have not specifically searched for this outcome.	The as-needed budesonide-formoterol regimen was preferred to maintenance ICS treatment in a group of patients with mild asthma enrolled in the Novel Start study by semistructured interviews thematically analysed [Foster J et al., 2022]. In the PRACTICAL study, 90% of participants who took budesonide/formoterol during the 12 month study, expressed a preference for this regimen, rather than twice daily preventer and a reliever. [Baggott ERJ 2020] This finding suggests that after an opportunity to try budesonide–formoterol as reliever therapy, most patients will find it an acceptable strategy. Furthermore, participants randomised to as-needed budesonide–formoterol reported higher degrees of satisfaction in all three domains investigated (inhaler effectiveness, frequency of use and speed of onset of the reliever inhaler) than those randomised to maintenance budesonide plus as-needed terbutaline. [Baggott ERJ 2020]

		Patient perspective - Patients value having one inhaler over 2 separate inhalers - Patient education is important to help patients understand rationale of treatment recommendations and alleviate any concerns. Professionals should also listen to the treatment outcomes and priorities which are important to the individual patient (e.g. reducing total steroid exposure, environmental impact of treatment) in order to support patients to make informed treatment choices. - It is important for patients to have a choice between the intervention and comparison options.

Feasibility Is the intervention feasible to implement?			
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**	
○ No ○ Probably no ○ Probably yes ○ Yes **X Varies** ○ Don't know	We have not specifically searched for this outcome.	In some countries, ICS/formoterol combination does not have the approval from regulatory bodies for the as needed use in mild asthma. *An ICS and a SABA can be used on the same occasion on demand from two different devices* [Calhoun et al., 2012; Israel et al., 2022], though adherence to this approach may be difficult in clinical practice. There is no evidence on the use of separate ICS and formoterol inhalers used as needed. **Patient perspective** Patient education and support self-management approaches can help.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	○	●○	X	○

CONCLUSIONS

Recommendation

We suggest that adult patients with asthma on Global Initiative for Asthma (GINA) treatment steps 1 or 2 use as-needed inhaled corticosteroid (ICS)/Formoterol in a single inhaler instead of regular ICS maintenance treatment plus as-needed short-acting β2-agonist(SABA). (Conditional Recommendation; Low Certainty of Evidence).

We suggest that adolescent patients with asthma on GINA treatment steps 1 or 2 use either as-needed) inhaled corticosteroid (ICS)/Formoterol in a single inhaler or regular ICS maintenance treatment plus as-needed short-acting β2-agonist (SABA). (Conditional Recommendation; Low Certainty of Evidence).

Justification

This recommendation places relatively higher value on the consistency of the outcomes related to exacerbations, severe exacerbations and reduction of systemic corticosteroids use, and relatively lower value on the small and not clinically relevant differences in asthma control, quality of life and lung function.

Due to the low certainty of evidence and possible differences in patient preferences we make a conditional recommendation.

Subgroup considerations

Considerations for adolescents
Several studies report a mean adherence rate of 50% or lower in adolescents. Similar data were found for maintenance treatment in SYGMA studies. Non adherence in adolescents is higher compared to children and older patients with asthma. In addition, the transition period from adolescence to adulthood is very challenging for many young patients who often get “lost in translation” with fewer prescriptions and healthcare contacts than recommended [Ödling et al., 2020]. A treatment regimen taken as-needed can have a relevant impact on asthma management in adolescents.

As compared to maintenance low dose ICS, adolescents with mild asthma on as-needed ICS/formoterol had similar incidence rate of severe exacerbations and had no clinically important difference in asthma control. These results were obtained in the ICS/formoterol arm with less than a quarter of the median daily ICS dose compared with ICS maintenance [Reddel et al., 2021]. Changes from baseline in pre-bronchodilator FEV1% was significantly lower with as-needed ICS/formoterol than with ICS maintenance but the difference was not clinically relevant.
Given the above considerations and that limited data is available from adolescents in comparison with adults, the Guideline Panel considered for adolescent patients with asthma on GINA treatment

steps 1 or 2 that either options (as-needed ICS/formoterol or regular ICS maintenance treatment plus as-needed SABA) should be recommended.

In Novel START and PRACTICAL, in pre-specified analyses testing the interaction of randomised treatment with various subgroups, there was no evidence of effect modification with respect to severe exacerbations based on baseline subgroups [Beasley et al., 2019; Hardy et al., 2019;

Based on the clinical experience of the TF members, the Panel concluded that a) patients who are poor symptom perceivers might benefit more from regular low dose maintenance treatment than from as-needed ICS/formoterol b) some patients may have greater trust in the regular use of maintenance ICS, and their preference ought to be sought.

Implementation considerations

Patient education is important to help patients understand rationale of treatment recommendations and alleviate any concerns in order to support patients to make informed treatment choices.

Monitoring and evaluation

Lung function should be monitored and rapid decline (if any) identified, particularly in adolescents.

Need for regular follow-up according to the review, assess and adjust cycle of asthma management (GINA).

Research priorities

Alternative strategies to achieve the international recommendation for the use of ICS as rescue medication in addition to SABAs should be tested, to fill the gap in those countries where as-needed ICS/formoterol has no regulatory approval for use alone in mild asthma.
Studies of longer duration (real-life 3-10 year duration) are required to provide evidence of the long term effects of the ICS/formoterol as needed in the absence of maintenance treatment
Studies in children are also a research priority. Additional studies on adolescents would be of value specially to clarify uncertainty in the effect of as-needed ICS/formoterol on outcomes such as exacerbations and asthma control.

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PICO 2 EVIDENCE TO DECISION FRAMEWORK

Is as-needed ICS/formoterol without maintenance therapy the preferred treatment compared to as-needed SABA in adult/adolescent patients with mild asthma (i.e. GINA treatment steps 1 or 2)?	
POPULATION:	Patients with mild asthma (i.e. on GINA treatment steps 1 or 2)
INTERVENTION:	As-needed ICS/formoterol without maintenance treatment
COMPARISON:	As-needed SABA
MAIN OUTCOMES:	CRITICAL OUTCOMES 1.Severe exacerbations; 2.Exacerbations; 3.Hospitalisations; 4.Emergency department (ED) visits; 5.Health-related quality of life; 6.Asthma control; 7.Mortality; 8.Serious adverse events. IMPORTANT OUTCOMES 9.Systemic corticosteroid reduction; 10.Rescue medication use; 11.Lung function; 12.FeNO; 13.Adverse events.
SETTING:	Specialised respiratory clinics and primary care
PERSPECTIVE:	Individual patient

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes **X Yes** ○ Varies ○ Don't know	More than 100 million people have mild asthma; one third of asthma deaths do occur in patients with so-called mild asthma (GINA 2021).	

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE (adults and adolescents if not otherwise specified)**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate **X Large** ○ Varies ○ Don't know	**CRITICAL OUTCOMES** -The magnitude of the benefit of as-needed ICS/formoterol over as needed SABA is different in relation to the outcomes assessed and it is particularly relevant for severe exacerbations. **EXACERBATIONS** **Severe exacerbations reduction** in favour of as-needed ICS/formoterol: -Patients with ≥1 severe exacerbation: RR 0.46 (95% CI 0.36, 0.59) [2 studies, moderate certainty]; -Annualised severe exacerbation rate; Rate ratio: 0.36 (95% CI 0.27, 0.48), [1 study, high certainty]. **Hospitalisation reduction**: Non-significant estimate in favour of as-needed ICS/formoterol:	Preventing severe exacerbations is an important goal of asthma management. In addition to the acute episode, asthma exacerbations are associated with increased decline in lung function, increased risk of future acute episodes and worse quality of life [Luskin et al., 2014; O'Byrne et al., 2009; Suruki et al., 2017]. In addition the use of OCS courses has significant adverse effects . Price et al. Journal of Asthma and Allergy 2018; Price D, et al. Eur Respir Rev. 2020. Treatment of asthma with SABA alone/overuse of SABA is associated with increased risk of asthma related death and of urgent asthma related health care, even in patients with so-called intermittent asthma. [Janson et al., 2020; Nwaru et al., 2020; Ställberg et al., 2009; Pollack et al., 2022]

	Patients with ≥1 exacerbation leading to hospitalisation, RR 0.40 (95% CI 0.16, 1.03) [1 study, high certainty] **ED visit reduction** in favour of as-needed ICS/formoterol: -Patients with ≥1 ED visit, RR 0.24 (95% CI 0.11, 0.55) [1 study, high certainty] **Exacerbation (any moderate or severe) reduction** in favour of as-needed ICS/formoterol: -Annualised exacerbation rate; Rate ratio: 0.42 (95% CI 0.35, 0.50), [2 studies, moderate certainty]. **Severe Exacerbations reduction (adolescents)** in favour of as-needed ICS/formoterol - Annualised severe exacerbation rate; Rate ratio: 0.23 (95% CI 0.09, 0.65), [1 study, moderate certainty]. - **ASTHMA CONTROL** **-ACQ-5** change from baseline favours as-needed ICS/formoterol MD: - 0.15 (95% CI -0.20, -0.10), [1 study, high certainty] **-ACQ-5** across all time points MD -0.15 (95%CI -0.24, -0.06) [1 study, moderate certainty] **ASTHMA CONTROL (adolescents):** ACQ-5 change from baseline favours as-needed ICS/formoterol: MD: -0.17 (95% CI -0.30, -0.03) [1 study, moderate certainty] **IMPORTANT OUTCOMES** **SCS INTAKE REDUCTION** favours as-needed ICS/formoterol: MD -9.90 mg (95% CI -19.38, -0.42 mg) [1 study, low certainty]	Differences in asthma control are minimal, substantially lower than the MCID.

	<u>LUNG FUNCTION</u> **-FEV1 pre-BD change from baseline**: favours as-needed ICS/formoterol MD: 53.80 mL (95% CI 29.07, 78.53 mL) [1 study, high certainty] **-FEV1 (on treatment) across all time points** : no difference; MD: 0.03 L (95% CI -0.01, 0.07 L) [1 study, low certainty] **LUNG FUNCTION (adolescents)** -FEV1 pre-BD change from baseline to treatment average; No difference: MD: 0.9% (95% CI -1.1%, 2.8%) [1 study, moderate certainty] **<u>RESCUE MEDICATION USE</u>** **Mean change from baseline of as-needed inhalations** favours as-needed ICS/formoterol: MD: -0.16 inhalation/day (95% CI -0.20, -0.12) [1 study, high certainty] **RESCUE MEDICATION USE (adolescents);** mean daily inhalations during the treatment period. MD: -0.10 inhalations (95% CI -0.22, 0.02) [1 study, moderate certainty] **<u>FeNO</u>:** Favours as-needed ICS/formoterol Ratio of geometric mean values at week 52: 0.83 (95% CI 0.75, 0.92) [1 study, low certainty]	The recommended number of actuations was forone 500 terb vs one 6ug B/F in SYGMA

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT ○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	**RESEARCH EVIDENCE(adults and adolescents if not otherwise specified)** **CRITICAL OUTCOMES** **Mortality**: the number of events is too small leading to great imprecision: One single event in the ICS/formoterol arm, not asthma or treatment related; Peto OR 7.52 (95% CI 0.15, 379.21) [2 studies, low certainty] **Severe adverse events (SAE):** No difference between the two arms. Number of patients with at least 1 SAE, RR: 1.06 (95% CI 0.45, 2.49) [2 studies, moderate certainty] **Adolescents** **SAE** The proportion of patients with at least 1 event was higher with SABA (4.2%) than with ICS/formoterol (1.9%) [2 studies, moderate certainty]. **IMPORTANT OUTCOMES** **Adverse events (AE)**, no difference between the two arms. Number of patients with at least 1 event: RR 0.92 (95% CI 0.85, 1.00) [2 studies, moderate certainty] **Adolescents** The proportion of adolescents with at least 1 **AE** was higher with SABA (41%) than with ICS/formoterol (33.9%) primarily due to asthma related events.	**ADDITIONAL CONSIDERATIONS** **Patients' perspective** Some patients experience side effects from SABA (shakiness, heart palpitations) and are therefore reluctant to take it. Use of a spacer may alleviate some of these side effects.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low **X Low** ○ Moderate ○ High ○ No included studies	Based on GRADE assessment.	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X Probably no important uncertainty or variability** ○ No important uncertainty or variability	We have not specifically searched for this outcome.	**Patient perspective** Asthma control and severe exacerbation risk are important outcomes to patients, based on a discrete choice experiment in which no shortness of breath and lowest risk of asthma flare-up were ranked the two highest attributes. [Baggott Thorax 2020]. For patients who have concerns about steroid exposure, the evidence that total systemic corticosteroid exposure is reduced with as-needed ICS/formoterol is important [Foster et al., 2021]. Dry powder formulations of ICS/formoterol may be preferred by some patients, as they do not require a spacer and are therefore potentially easier or more discrete to use in public and for travel [Baggott et al., 2020]. Some patients with as-needed ICS/formoterol report less overall relief action or less speed of action compared with previous SABA inhaler.[Baggott ERJ 2020] This may impact their beliefs about the

		benefits and risks of treatment [Foster et al., 2021].
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention **X Favors the intervention** ○ Varies ○ Don't know	LARGE Desirable TRIVIAL Undesirable	**Patient perspective** Patients agree that this evidence favours the intervention. Concerns that over reliance on SABA can be a risk factor for asthma deaths [National Review of Asthma Deaths, 2014]. Patients prefer inhalers with an in-built dose counter in order to manage their prescription needs. This may be especially important for inhalers used 'as-needed' as it is more difficult to keep track of reliever medication use. Inhaler technique required for dry powder formulations may be more difficult in an 'as-needed' situation (i.e. where symptoms such as breathlessness and coughing are high, it may be difficult to get a sufficiently powerful in-breath). Regular checks of inhaler technique should be included in periodic asthma reviews, particularly for patients who have switched device (e.g. from MDI to DPI). Some patients have used SABA for many years and are very familiar with it, so a switch of inhaler type would require some adjustment [Foster et al., 2021].

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **X Varies** ○ Don't know	We have not specifically searched for this outcome.	The cost of ICS/formoterol may be higher than that of SABA. **Patients' perspective** Patients note that access to combined therapy may be limited in some countries due to licensing restrictions.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low **X Low** ○ Moderate ○ High ○ No included studies	We have not specifically searched for this outcome.	Judgement made based on clinical experience and patient perspective.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the	We have not specifically searched for this outcome.	Though the cost of ICS/formoterol is higher than that of SABA the efficacy is consistently higher and the disease burden and related costs are reduced [Golam SM et al., 2022]. Adolescents: a recent study found that low dose budesonide-

intervention or the comparison **X Probably favors the intervention** ○ Favors the intervention ○ Varies ○ No included studies		formoterol as a reliever is cost effective in adolescents with mild asthma [Buendía et al., 2021].
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased **X Varies** ○ Don't know	We have not specifically searched for this outcome.	**Patients' perspective** Patients note that access to combined therapy may be limited in some countries due to licensing restrictions. Type of inhaler device (MDI, DPI) may be important for some patient groups (dry powder is more difficult for older patients and children to use). When MDI is prescribed, clinicians should ensure a spacer is used. The cost of ICS/formoterol may be higher than that of SABA. Cost can be seen as a disincentive [Cole et al.; 2013].
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no **X Probably yes**	We have not specifically searched for this outcome.	**Patients' perspective** Patient education is important to help patients understand rationale

○ Yes ○ Varies ○ Don't know		of treatment recommendations and alleviate any concerns, such as total steroid exposure. Explaining differences in side effect profile of ICS and OCS. Many patients will have been on SABA-only treatment for many years. It will be important to support them to transition to a new regime, with clear, accessible information and training in inhaler technique. They will have to mentally adjust from seeing SABA as their 'go-to' rescue treatment [Foster et al., 2021]. Patients consider important the speed of onset of efficacy [Baggott et al., 2020]. Some patients with as-needed ICS/formoterol report less overall relief action or less speed of action compared with previous SABA inhaler. [Baggott ERJ 2020] This may impact their beliefs about the benefits and risks of treatment [Foster et al., 2021].
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes **X Varies** ○ Don't know	We have not specifically searched for this outcome.	In some countries, including EU countries, ICS/formoterol does not have the indication for as-needed use in mild asthma. *An ICS and SABA can be used on demand from 2 different devices* [Calhoun et al., 2012; Israel et al., 2022], though adherence to this regimen may be difficult in clinical practice.

		There is no evidence on the use of separate ICS and formoterol inhalers used as-needed. **Patient perspective** Health professionals should be properly trained to support patients with the transition to new treatments.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention	**Probably favors the intervention**	Favors the intervention	Varies	No included studies

	JUDGEMENT						
			or the comparison				
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	X

CONCLUSIONS

Recommendation

We recommend that adult and adolescent patients with asthma on Global Initiative for Asthma (GINA) treatment steps 1 or 2 use as-needed inhaled corticosteroid (ICS)/formoterol in a single inhaler instead of as-needed short-acting β2-agonist (SABA). [Strong Recommendation; Low Certainty of Evidence].

Justification

This recommendation places a relatively higher value on the benefit of as-needed ICS/formoterol in reducing severe asthma exacerbations, any moderate or severe exacerbations and emergency department visits due to asthma and reducing systemic corticosteroids use; and a relatively lower value on medication costs.

The overall certainty of evidence is low because there was very serious imprecision in the assessment of mortality. However, randomised controlled trials are not adequately powered to investigate a rare event such as asthma mortality [O'Byrne et al., 2019] in patients with mild disease, and other studies have shown that overuse of SABA alone is associated with increased risk of severe asthma exacerbations and asthma deaths [Nwaru et al., 2022; National Review of Asthma Deaths, 2014; Ställberg et al., 2009; Pollack et al. 2022]. On the other hand, inhaled corticosteroids reduce asthma mortality [Suissa et al., 2000]. So, even though we are uncertain if as-needed ICS/formoterol reduces asthma mortality in comparison with SABA treatment only, the

panel made a strong recommendation notwithstanding the low overall certainty of evidence related to the imprecision in the assessment of the mortality outcome.

Subgroup considerations

Considerations for Adolescents: There is an overreliance on as-needed SABA alone use in adolescents. Treatment adherence to regular maintenance treatment is a relevant issue in adolescents. As-needed ICS-formoterol does not require adherence to maintenance treatments. Data on as-needed ICS/formoterol in adolescents are limited, but the available evidence support the same conclusion reached by this TF for adults. As-needed ICS/formoterol substantially outperforms as-needed SABA in reducing severe exacerbations in adolescents with mild asthma. Safety of as-needed ICS-formoterol is similar in adolescents and adults.

In Novel START and PRACTICAL, in pre-specified analyses testing the interaction of randomised treatment with various subgroups, there was no evidence of effect modification with respect to severe exacerbations based on baseline subgroups [Beasley et al., 2019; Hardy et al., 2019; Pavord et al., 2020].

Implementation considerations

Availability and affordability of ICS/formoterol as needed for Low and Middle Income Countries (LMIC) is a priority.

Need for regular follow-up according to the review, assess and adjust cycle of asthma management (GINA).

Patient education is important to help patients understand rationale of treatment recommendations.

Monitoring and evaluation

Need for regular follow-up according to the review, assess and adjust cycle of asthma management (GINA).

Patient education is important to help patients understand rationale of treatment recommendations and alleviate any concerns in order to support patients to make informed treatment choices.

Research priorities

Alternative strategies to achieve the international recommendation for the use of ICS as rescue medication in addition to rapid action bronchodilators should be tested, to fill the gap and avoid SABA use only in those countries where as-needed ICS/formoterol has no approval in mild asthma.

Proper cost-effectiveness studies need to be performed, taking into account the specificities of national healthcare systems, local drug costs, and importantly also indirect costs, due to hospital admissions, ED visits, absenteeism from school or work.

Additional studies considering different asthma inflammatory profiles (type 2(T2) or non T2) should be performed.

Studies in children are also a research priority. Additional studied on adolescents could further investigate additional critical outcomes for clinical decision making such as hospitalisations, ED visits and quality of life.

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