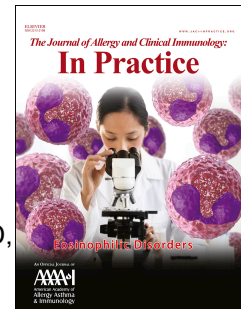


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ARTICLE for JACI: In Practice

A Practical Guide to Implementing SMART in asthma management.

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ABSTRACT (247 words)

The use of a Single inhaler containing the combination of an inhaled corticosteroid (ICS) and formoterol, a specific long-acting bronchodilator (LABA), for both Maintenance And quick Relief Therapy (SMART, or MART) is recommended by both the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee in Steps 3 and 4 of asthma management. This article provides practical advice about implementation of SMART in clinical practice based on evidence and clinical experience.

Fundamental to SMART is that ICS-formoterol provides similarly quick relief of asthma symptoms as short-acting beta2-agonist (SABA) such as albuterol, while reducing the risk of severe asthma exacerbations, at an overall lower ICS exposure. Most SMART clinical trials were in adults and adolescents (≥ 12 years), using budesonide-formoterol 160/4.5 mcg (delivered dose), 1 inhalation once or twice daily (Step 3) and 2 inhalations twice daily (Step 4). For both Step 3 and 4, patients also take additional inhalations of budesonide-formoterol 160/4.5 mcg, 1 inhalation whenever needed for symptom relief, up to a maximum for adults/adolescents of 12 total inhalations in any single day (delivering 54mcg formoterol). The efficacy and safety of SMART with budesonide-formoterol and beclometasone-formoterol have been confirmed, but other ICS-long-acting bronchodilator combinations have not been studied.

The SMART regimen should be introduced with a careful explanation of its role in self-management and preferably with a customized written asthma action plan. The cost to patients and availability of SMART treatment will depend on prescribed dose and national/local payer agreements.

INTRODUCTION

In 2020, the National Asthma Education and Prevention Program published Focused Updates to Asthma Management Guidelines for US clinicians (2020 NAEPP Asthma Update) (1) that preferentially recommended the use of combination inhaled corticosteroid (ICS)-formoterol inhaler for both maintenance and quick symptom relief (Single Maintenance And Reliever Therapy, known as SMART or MART) at Steps 3 and 4, in children ages ≥ 4 years (NAEPP) and in adults. The 2020 NAEPP Asthma Update used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework to evaluate the evidence regarding SMART and to formulate recommendations about its use, and concluded there was high certainty of evidence for benefit of this treatment approach in treatment Steps 3 and 4 compared with same dose ICS-long-acting beta2-agonist (LABA) or higher dose ICS therapy plus as-needed short-acting beta2-agonist (SABA) for individuals with asthma aged ≥ 12 years and moderate certainty evidence for children aged 4 to 11 years. For people with asthma aged ≥ 12 years NAEPP gave a conditional recommendation with high certainty of evidence for SMART compared with higher dose ICS-LABA plus as-needed SABA. For people whose asthma is uncontrolled on daily ICS-LABA treatment plus as-needed SABA, the clinical trial evidence supports switching to SMART at the same or lower maintenance ICS dose before considering a step-up of maintenance treatment (3-5). SMART is also preferentially recommended in Steps 3 and 4 in the Global Initiative for Asthma (GINA) strategy report, the most recent update of which was published in 2021 (2).

The SMART regimen with budesonide-formoterol is approved for adults and adolescents (≥ 12 years) by regulators in more than 120 countries and for children 4–11 years in a small number of countries (Personal communication, AstraZeneca), and budesonide-formoterol is manufactured

by several other companies; SMART with beclometasone-formoterol is approved by regulators in more than 70 countries for adults (≥ 18 years), (Personal communication, Chiesi). For US clinicians, while the combination of budesonide-formoterol is approved for daily use by the Federal Drug Administration (FDA) for individuals 4 years and older (marketed as Symbicort™), SMART regimens are not FDA-approved for any age-group.

For US clinicians, although the change in the 2020 NAEPP Asthma Update is based on moderate (for children aged 4–11 years) or high certainty of evidence (for adults and adolescents aged ≥ 12 years) for Steps 3 and 4, its implementation presents several challenges (6). The global experience using SMART provides a resource that may prove useful for those who are new to the approach. This review addresses these issues and provides practical points for implementing SMART, based on evidence where available, and on clinical experience with this regimen.

This article was prepared by authors who also participated in the development of reports by GINA (HR, EB, JK) and NAEPP (MC, MS, JK), but is not an official joint statement representing the two bodies.

HOW DOES SMART WORK? RATIONALE AND MECHANISM OF ACTION

While maintenance ICS-LABA treatment with as-needed SABA reliever improves asthma control and reduces the background risk of exacerbations compared with ICS plus as-needed SABA, the SMART approach specifically uses ICS-formoterol as both the maintenance inhaler and the reliever inhaler. It titrates additional ICS together with additional formoterol against breakthrough symptoms when symptoms prompt reliever use, and this significantly reduces the risk of severe exacerbations (defined as either an emergency room visit, hospitalization or need for systemic corticosteroids for ≥ 3 days) (7) compared with maintenance ICS or ICS-LABA

regimens with a SABA reliever (2-5). The benefit of SMART in reducing asthma exacerbations is thought to occur partly by providing additional anti-inflammatory treatment during the window period when asthma and airway inflammation are worsening (8,9). Although, in patients taking maintenance ICS or ICS-LABA, as-needed formoterol has been shown to reduce the risk of exacerbations compared with as-needed SABA (10,11,12), the extra doses of both the ICS and formoterol in SMART may contribute to the further reduction in exacerbation risk during this critical window period, which may range from one to several days (8,9,12). Even one day of modestly high SABA use heralds an increased risk of an attack in coming days that is reduced if the reliever is formoterol and reduced further if the reliever is budesonide-formoterol. (8,9)

PRACTICAL POINTS FOR CLINICIANS

Does ICS-formoterol work as quickly as a SABA (e.g., albuterol) for relief of symptoms and bronchoconstriction?

Rapid relief of asthma symptoms is a fundamental need for individuals with asthma. The onset of action of formoterol is similarly rapid as albuterol but has the added advantage of a longer duration of action (13,14). Differences in perceived benefit have been reported by some individuals using a dry powder inhaler as compared with a pMDI device.

What dose of ICS-formoterol should be used for SMART?

Both the 2020 NAEPP Asthma Update and the 2021 GINA report recommend prescribing SMART for adults and adolescents with low-dose maintenance ICS-formoterol in Step 3 and medium-dose maintenance ICS-formoterol in Step 4 (1,2). Formulations of ICS-formoterol and recommended dose ranges of low and medium ICS doses vary between countries.

Internationally, SMART is most commonly prescribed for adults and adolescents with

budesonide-formoterol 160/4.5 mcg delivered dose (mass of drug emitted per actuation that is actually available for inhalation at the mouth; corresponding to a metered dose of 200/6 mcg, the mass of drug that is available within the inhaler per actuation). Examples of suggested doses used internationally in adults and adolescents include 1 inhalation of budesonide-formoterol 160/4.5 mcg once daily or twice daily in Step 3, and 2 inhalations of 160/4.5 mcg twice daily in Step 4, each with 1 inhalation of the same 160/4.5 mcg delivered dose formulation taken whenever needed for symptom relief (Table 1). For children 4–11 years, SMART is usually prescribed in Step 3 as budesonide-formoterol 80/4.5 mcg delivered dose (100/6 metered dose) 1 inhalation once daily with 1 inhalation taken as needed for symptom relief, with the potential to increase the maintenance dose to 1 inhalation twice daily in Step 4. (Table 1)

If ICS-formoterol is administered from a pMDI, should the dose for relief of symptoms be one or two inhalations?

In clinical trials and clinical practice, SMART with budesonide-formoterol has mostly been delivered in a dry powder inhaler which is not available in the US. However, the efficacy and safety of SMART has also been demonstrated with budesonide-formoterol 160/4.5 mcg by pMDI (15), a formulation available in the US, and with beclometasone-formoterol 100/6.5 mcg pMDI (16), both of which are marketed in countries outside the US. In all SMART clinical trials, including the two studies using pMDIs (15,16), the as-needed dose has been 1 inhalation of the ICS-formoterol inhaler, i.e. 4.5 mcg formoterol per occasion of use, and this is also the as-needed dose approved internationally for clinical practice. The rationale for recommending one inhalation per as-needed dose (despite pMDIs in the US being approved only for two inhalations per dose to ensure dosing consistency) is the relief of symptoms and bronchoconstriction

associated with one inhalation, and the potential for too-rapid escalation of the formoterol dose if two puffs were taken on every occasion of as-needed use.

How much ICS-formoterol can be taken with SMART?

The recommendation for as-needed doses of budesonide-formoterol 160/4.5 mcg (200/6 metered dose) is to take 1 inhalation whenever needed for symptom relief. If symptoms persist after a few minutes, another dose can be taken, but no more than 6 doses should be taken on a single occasion (no more than 4 doses for children 4–11 years). The recommended **total maximum** dose that can be taken temporarily on any single day (total of maintenance plus as needed doses) for budesonide-formoterol is 12 inhalations for ages 12 years and older (3,5,17) and eight puffs for ages 4–11 years (18) (Table 1). A maximum of 12 inhalations of budesonide-formoterol 160/4.5 (200/6 metered dose) on a single day corresponds to 54 mcg delivered dose of formoterol (72 mcg metered dose); a maximum of eight inhalations on a single day corresponds to 36 mcg delivered dose of formoterol (48 mcg metered dose). For beclometasone-formoterol 100/6, the recommended maximum dose in any day is 8 inhalations.

However, in clinical trials and in clinical practice, patients typically used far less than this upper limit (which refers to how much could be taken temporarily on any single day). The average frequency of reliever use was not significantly different between conventional and SMART treatment and was approximately one inhalation per day (3,9,15,17), but these trials employed fixed maintenance dosing, with no attempt to optimize treatment by adjusting the maintenance dose. In some trials of SMART, inhaler use for relief was required on fewer than 50% of days

(17) and only 1 or 2 actuations were used on each occasion (9,15,17). Days with excessively high reliever use were less common with SMART than with a conventional SABA reliever (15).

Can SMART be prescribed with other ICS-LABA combinations?

Almost all of the SMART studies have used budesonide-formoterol, with one study using beclometasone-formoterol (16). Caution should be exercised in extrapolating to other ICS-LABA combinations with different pharmacological properties and posology. The LABA must provide rapid-onset bronchodilation and a dose-response relationship that safely permits multiple inhalations if needed, without side-effects. The formulations used for SMART contain a low dose of formoterol (4.5 mcg delivered dose, 6 mcg metered dose). The higher dose budesonide-formoterol formulation (320/9 mcg delivered dose [400/12 mcg metered dose]) available in some countries is not approved or recommended for SMART because the total dose of formoterol with multiple as-needed dosing would increase too rapidly.

There are also insufficient data to assess whether other ICS-formoterol combinations (e.g. mometasone-formoterol pMDI 50/5 or 100/5 mcg, which are available in the US, and fluticasone propionate-formoterol, not available in the US) can be used for SMART. In the U.S., formulary or insurance restrictions may result in mometasone-formoterol being more accessible than budesonide-formoterol for some patients. GINA currently advises against assuming that results obtained with budesonide-formoterol and beclometasone-formoterol combinations will apply to other ICS-formoterol combinations.(2) Data about the harms/benefits of mometasone-formoterol in SMART are needed.

The combination of ICS with salmeterol, which has a slower onset of action and a flat dose-response curve, should not be used for SMART therapy. Similarly, combinations of ICS and

ultra-long-acting beta2-agonists (e.g. indacaterol, vilanterol) should not be used for a SMART regimen due to their efficacy-safety profile and potential accumulation if dosed more frequently.

Can SMART be prescribed with ICS-formoterol as reliever and an alternative ICS-LABA as maintenance therapy?

In patients taking maintenance treatment with ICS-LABA combinations other than ICS-formoterol (e.g., fluticasone propionate-salmeterol), use of ICS-formoterol for quick relief is not recommended by either GINA (2) or the 2020 NAEPP Asthma Update (1), because of the lack of evidence for safety or efficacy with this mixture. In addition, if two different medications are used, patients may be confused about which inhaler to use for relief.

Is SMART with ICS-formoterol safe?

The 2020 NAEPP Asthma Update advises that clinicians should inform their patients that studies involving SMART have found “no difference in documented harms between this type of therapy and daily ICS-LABA” (1). This conclusion is supported by a pooled analysis of six randomized double-blind and seven open-label clinical trials comparing SMART with budesonide-formoterol with alternative treatment options in Steps 3 and 4 (19), and a Cochrane review of 13 trials (4).

Who should be considered for SMART treatment?

Candidates for SMART treatment should require maintenance treatment with ICS-LABA, i.e. 2020 NAEPP Asthma Update or GINA 2021 Steps 3 or 4. There are no recognized patient characteristics that exclude patients from consideration for SMART. As the main advantage of SMART is the reduction of severe exacerbations, with the associated reduction in potential cumulative adverse effects of oral corticosteroids (20), SMART is particularly well suited to

those with a history of asthma exacerbations. SMART has not been tested specifically in individuals who are obese or in pregnant women.

In which patients may it be acceptable or preferable to continue on ICS-LABA plus as-needed SABA treatment?

SMART (compared to ICS-LABA plus as-needed SABA) may offer less added benefit for those whose symptoms are well-controlled, with no exacerbations in the recent past and no risk factors for exacerbations (2). The 2020 NAEPP Asthma Update advises that “The recommended alternate therapy of maintenance ICS-LABA along with SABA as quick-relief therapy does not need to be changed if it is providing adequate control” (1). The GINA 2021 report states that regimens with as-needed SABA are an alternative approach if use of ICS-formoterol reliever (including SMART in Steps 3 and 4) “is not possible or is not preferred by a patient with no exacerbations on their current therapy.” GINA goes on to advise that “Before prescribing a regimen with SABA reliever, consider whether the patient is likely to be adherent with their ICS-containing controller therapy, as otherwise they will be at higher risk of exacerbations” (2).

Is SMART suitable for use in “poor perceivers”.

Perception of changes in airway caliber and other physiological changes in asthma vary widely between individuals with asthma and is influenced by factors such as disease severity, psychological state, age, ethnicity, and sex (21). Although poor perception may result in individuals delaying or underusing their reliever, poor perception is strongly associated with poor adherence with maintenance treatment, and with greater emergency healthcare utilization (22), and risk of near-fatal asthma. There are no studies that have compared treatment modalities (including SMART) in poor perceivers; indeed, because such patients have few symptoms, they

are unlikely to be included in any asthma clinical trials. However, when such patients do perceive the need for symptom relief, receiving an ICS-containing reliever as part of SMART instead of a SABA reliever may be a safer and more effective option, especially if they have been poorly adherent with their maintenance controller (23). In all patients, assessment of asthma control should include evaluation of risk factors for exacerbations, including low lung function and airway inflammation (if able to be assessed), and not just symptom control.

Will patients who use SMART reduce their adherence to maintenance dosing?

In a six-month trial of individuals with asthma and a history of a severe exacerbation in the past year, participants randomized to SMART had fewer days without use of ICS-LABA, or with only one dose of ICS-LABA, based on electronic inhaler monitoring. Thus, symptom-prompted treatment *increased* their overall exposure to an ICS-containing treatment, albeit still lower than prescribed (15). In a randomized open-label study of patients in primary care with documented poor adherence, SMART resulted in higher use of ICS than patients with conventional ICS-LABA plus as-needed SABA (23).

In a patient prescribed SMART, can the maintenance dose be reduced?

Once asthma is well-controlled, the maintenance dose should be adjusted to the lowest dose at which effective control of asthma is maintained. For some adults and adolescents, this can be achieved with reduction of the maintenance dose to once daily. An increase in the need for as-needed doses after a reduction in maintenance dose suggests that the patient should return to their previously prescribed dose. Patients should be reminded to use extra doses of ICS-formoterol when needed for symptom relief. Patients who have lower lung function may benefit

from the higher maintenance dose (2 inhalations twice daily), but the as needed dose remains the same (24) (Table 1).

Is day to day asthma symptom control with SMART inferior to that achieved with regular maintenance ICS-LABA plus SABA?

In studies in which direct comparisons of the two regimens have been made, there is no evidence of significant or clinically important differences in asthma symptom control measured by a variety of methods including Asthma Control Questionnaire (ACQ) (3,5,8). Poor or suboptimal symptom control, which may also be assessed by the need for more frequent use of as-needed ICS-formoterol, should prompt review of maintenance treatment. From clinical experience, individuals with asthma who take an additional as-needed dose of ICS-formoterol almost daily (5 or 6 days a week) on an ongoing basis may agree to a step-up of their maintenance treatment.

Can budesonide-formoterol be used before exercise and replace SABA for this indication?

Pre-exercise formoterol (25,26) or budesonide-formoterol (27) provide greater protection against exercise-induced bronchoconstriction than pre-exercise SABA, but pre-exercise formoterol (alone) is no longer recommended because of concern about the risks of LABA-only treatment. A double blind randomized controlled trial in individuals with mild asthma found that use of low dose ICS-formoterol for symptom relief and before exercise reduced exercise-induced bronchoconstriction at 6 weeks to a similar extent as with regular ICS (27). Based on the data available, it would be reasonable for a patient on SMART who needed exercise prophylaxis to use their as-needed ICS-formoterol before exercise (2,28).

However, if ICS-formoterol is not available, for example in a school setting, it would be acceptable for albuterol to be used for pre-exercise prophylaxis.

What if ICS-formoterol is not available in an emergency?

At present, in the absence of an appropriate combination inhaler, albuterol could be used for rescue therapy in an emergency, for example in a school setting. Concerns about the extra expense of ICS-formoterol for rescue therapy, including in the school setting, could change in time as generic and lower-priced combination inhalers are available.

Is phenotyping based on biomarkers of Type 2 inflammation necessary in selecting patients for SMART?

To date, no study has prospectively selected persons for SMART treatment on the basis of inflammatory biomarker status. Future studies of inflammatory phenotyping for patients requiring Steps 3 or 4 treatment may provide insights in this regard. In a post hoc analysis of one study, beclometasone-formoterol SMART significantly reduced severe exacerbations compared with fixed dose beclometasone-formoterol plus as-needed SABA across the continuum of baseline blood eosinophils, with a trend to greater reduction of severe exacerbations in patients with higher baseline eosinophil counts (29). More studies are needed.

What are the practical barriers to introducing SMART in the US practice setting?

There are specific barriers to using SMART in the US. The first is that budesonide-formoterol is not currently approved by the FDA for use in a SMART regimen, and beclometasone-formoterol is not currently available in the US. The US package insert for budesonide-formoterol recommends against its use for acute asthma and against use of more than 4 puffs per day. However, the clinical trial evidence strongly supports the use of budesonide-formoterol in SMART and the publication of the 2020 NAEPP Asthma Update which strongly recommends

SMART is a first step to seeking approval for use in the US from government-sponsored health care agencies.

A second issue is that many US insurers will only cover the cost of a 30-day supply of maintenance medication at a time. Depending on the number of as needed doses per month, SMART may require more than one inhaler per month. Additionally, this may be problematic for children who need to have inhalers at home and in school and perhaps in other locations (e.g., childcare or after school activities).

These issues need to be addressed. It is hoped that the strong recommendation for SMART with high certainty of evidence in the 2020 NAEPP Asthma Update may stimulate an assessment of this indication by insurers, manufacturers, by the Centers for Medicaid and Medicare, and the FDA. In the meantime, clinicians should continue to engage in shared decision-making with individual patients about potential benefits, risks, costs and feasibility of evidence-based treatment options.

Does as-needed ICS-formoterol involve additional cost?

There is a significant difference in the unit price of albuterol compared to ICS-formoterol formulations that may limit the uptake of SMART in some settings. Optimizing the maintenance dose of ICS-formoterol and ensuring correct inhaler technique can reduce the as needed use to none or a few occasions per week, with increased use only when exacerbations threaten.

However, provision needs to be made for these additional doses when refills are required. The extra cost may be offset by savings resulting from exacerbations prevented by this method, and the long-term effects of repeated courses of systemic corticosteroids cannot be ignored (20).

Longer-term, real-world cost-effectiveness studies of SMART versus alternative controller-

reliever regimens are needed to address this question for each individual country or health system.

HOW DO I INTRODUCE SMART TO MY PATIENTS?

As with all treatments, high patient satisfaction and adherence with treatment are more likely to be achieved through effective communication, education, and shared decision-making (1,2). For patients requiring Step 3 or 4 therapy, SMART provides the option of rapid symptom relief, a single medication, similar daily symptom control, reduced risk of severe exacerbations, and a lower total ICS dose (3,4). Prescription of more than one type of inhaler (as may occur with ICS-LABA plus as-needed SABA) is associated with a lower likelihood of adherence (2) and greater chance of incorrect inhaler technique. In deciding whether to recommend ICS-LABA with as-needed SABA, the patient's willingness and likelihood of adhering to a daily maintenance treatment should be taken into account, because poor adherence could result in their using SABA alone (2).

The provision of a **written action plan** improves outcomes in asthma and is recommended for all patients (2,28). In several countries, a written asthma action plan customized for SMART, originally developed in Australia, has been found to be simple to complete and helpful for introducing SMART to patients. Figure 1 shows an example of such an action plan.

Some key points for communication about SMART are provided in Table 2. The approach to introducing SMART to a patient may differ between those newly diagnosed with asthma and those who currently use SABA as reliever.

CONCLUSIONS

The SMART approach to treatment in patients requiring Steps 3 and 4 therapy is based on strong evidence, is recommended as preferred treatment by both the NAEPP 2020 Focused Update and the GINA 2021 strategy report, and has been widely implemented globally for more than 15 years. Lessons learned in different practice settings provide assurance that the treatment approach can be rapidly and safely introduced to most patients and is easily learned and well accepted by patients and caregivers. SMART is not a substitute for good clinical management but assists by reducing the risk of severe asthma exacerbations without compromising maintenance treatment and may improve long-term asthma control. It also reduces the potential for over-reliance on SABAs. It is best applied with the aid of an individualized written action plan designed for use with SMART, as part of integrated asthma care, addressing symptom control, modifiable risk factors, comorbidities, education and skills training, and with long-term monitoring and review and adjustment of the maintenance dose if needed. Specialists have an important role to play in educating the primary care community about SMART, and in working with pharmacists and insurers to ensure a smooth transition when SMART is prescribed, but additional efforts will be needed to increase reach to primary care audiences and to patients with asthma.

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Table 1. Recommended doses of budesonide-formoterol for SMART based on published studies and international usage

		Step 3		Step 4		Step 3 or 4
	Budesonide-formoterol dose	Maintenance dose	As-needed dose	Maintenance dose	As-needed dose	Maximum total daily inhalations*
Adults and adolescents aged ≥ 12 years	160/4.5 mcg delivered dose (200/6 mcg metered dose)	1 inhalation twice daily or once daily	1 inhalation as needed	2 inhalations twice daily	1 inhalation as needed	12
Children 4–11 years**	80/4.5 mcg delivered dose (100/6 mcg metered dose)	1 inhalation once daily#	1 inhalation as needed	1 inhalation twice daily##	1 inhalation as needed	8

*Total daily inhalations = maintenance doses plus as-needed doses. The maximum number of as-needed doses depends on the number of maintenance doses prescribed and is based on evidence of safety for the total dose of formoterol over a 24-hour period. For example, in an adult who is receiving Step 3 therapy and prescribed a maintenance dose of 1 inhalation twice daily of budesonide-formoterol 160/4.5 delivered dose (i.e., 2 inhalations per day for maintenance), the maximum recommended number of as-needed inhalations of budesonide-formoterol is 10 over a 24-hour period.

**For SMART in children 4 – 11 years, the 2020 NAEPP Focused Update recommends daily low-dose ICS-formoterol at Step 3 and daily medium-dose ICS-formoterol at Step 4 as maintenance treatment 1 once or twice daily.

based on one clinical study (18).

based on expert option.

Note: There are no SMART studies with mometasone-formoterol, but if it was used, the relevant formulations would be mometasone-formoterol 100/5 mcg for adults and 50/5 mcg for children, with the same dosing frequencies as above. The 200/5 mcg formulation of mometasone-formoterol would not be suitable for SMART.

Table 2: Some messaging and practical steps when introducing patients to the SMART approach

Message	Practical steps
What are your goals for your asthma management? What are your concerns?	Tailor the discussion about SMART to the patient's individual goals, preferences and concerns.
Use the new (combination ICS-formoterol) reliever as you used SABA in the past.	Explain that ICS-formoterol replaces SABA completely, and provides similarly rapid relief with less risk of severe exacerbations. As they did with SABA, it should be used without delay when symptoms occur. Formoterol has a longer duration of action; they might find less need for repeated use on a single day.
ICS-formoterol reduces your risk of asthma attacks.	Consider each patient's individual risk profile for severe exacerbations (e.g. one or more in the last 12 months) and address those that are modifiable. Explain the relevance of SMART to their situation (2)
How much ICS-formoterol may you use as reliever in one day?	Advise the patient about the maximum total actuations in any single day (Table 1: for budesonide-formoterol, total 12 actuations for adults, total; 8 actuations for children),

	including both maintenance and as-needed doses. Preferably provide the maintenance dose and reliever instructions in a personalized asthma action plan.
What shall I do if I reach the maximum recommended number of inhalations on any day?	Advise that if they require more than 12 inhalations in total in a single day (8 inhalations for children), or if they worsen rapidly without expected relief from the reliever, they should seek medical assistance urgently (see example in Figure 1). High use (6 or more actuations) on two or more successive days may be reasonably included as a prompt to obtain medical assistance.
Keep your inhaler on hand at all times.	Ensure that the patient carries their ICS-formoterol inhaler with them so that they can use it for symptom relief
Continue your regular maintenance dose of ICS-formoterol. This will be reviewed periodically.	Advise on the number of maintenance doses, once or twice daily and plan for review (Table 1); preferably record the maintenance dose in a customized asthma action plan. Reassure that day-to-day asthma symptom control should be similar with SMART, provided

	they take the prescribed maintenance treatment.
Know your inhaler device.	Instruct and test inhaler technique, demonstrate the dose counter (if available), describe how to recognize when the device is empty, and emphasize storage requirements. Check that they can use it correctly.
SMART treatment is safe. Do you have concerns?	Provide the option of a trial period of ICS-formoterol as reliever with SABA as back-up. If necessary, review safety data. Address concerns about switching from their trusted SABA reliever. Various approaches may be used. Indicate clearly that the intention is that no further SABAs will be prescribed or issued once they have made the transition. This is important as continued access to a SABA inhaler may result in a return to its preferential use, over-reliance on SABA alone, and possibly poor adherence with maintenance treatment. If faced with reluctance, the following approach may be helpful: <i>“For the next while, carry both the</i>

	<i>old and new reliever with you. When you feel the need for your reliever, first try the new (combination) reliever. If it does not provide the expected effect within minutes, you have the option to resort to the SABA.”</i> This simple advice usually addresses their initial concern and permits them to explore and experience relief from the new treatment, and the SABA prescriptions may be stopped at the next visit.
Mouth rinsing is not necessary after reliever use.	Mouth rinsing is reserved for after maintenance dosing but is not necessary after as-needed doses. This instruction has been provided in studies of over 30,000 patients with SMART and as-needed-only treatment with budesonide-formoterol, with no increased risk of oral candidiasis compared with using SABA as the reliever (19).
Issues relating to obtaining your medication.	Patients may require an initial supply of two inhalers for use in different locations. This may reduce the chance of them running out as the second inhaler can serve as a back-up while the other is replaced. How clinicians

	write out the prescription may assist the process of obtaining more than one inhaler. For example: <i>“ICS-formoterol x actuations in the morning and xx inhalations in the evening every day, and ICS-formoterol x ... actuations as needed for asthma symptoms. Dispense 2”</i>. Clearly stating on the prescription, <i>“one for home and one for school”</i> may also be helpful.
Do you require information for other care givers/teachers/ school nurse concerning the new treatment?	Parents, other care givers, and teachers may need to be educated on the new treatment that has replaced the more familiar SABA reliever, including inhaler technique training, and advice about dosage.
Understand your instructions and action plan	As a final step, check that the information offered to patients and care givers has been understood. As adherence is closely related to perception of need for a medication and concerns about safety and/or cost (30), these aspects must be discussed at the first and preferably also at subsequent visits. As with all asthma management, limited duration of

	appointment times may reduce the feasibility of providing comprehensive education during routine clinic visits. Involvement of nurses, asthma educators and trained lay educators may be helpful. An asthma action plan may be used to facilitate and reinforce understanding.
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My Asthma Action Plan

For Single Inhaler Maintenance
and Reliever Therapy (SMART)
with budesonide/formoterol

Name: _____ Action plan provided by: _____

Date: _____ Doctor: _____

Usual best PEF: _____ L/min Doctor's phone: _____

(If used)

Normal mode

■ My SMART Asthma Treatment is:

☐ budesonide/formoterol 160/4.5 (≥ 12 years)

☐ budesonide/formoterol 80/4.5 (4-11 years)

■ My Regular Treatment Every Day:

(Write in or circle the number of doses prescribed for this patient)

Take [1, 2] inhalation(s) in the morning

and [0, 1, 2] inhalation(s) in the evening, every day

■ Reliever

Use 1 inhalation of budesonide/formoterol
whenever needed for relief of my asthma symptoms

I should always carry my budesonide/formoterol inhaler

■ My asthma is stable if:

• I can take part in normal physical activity without
asthma symptoms

AND

• I do not wake up at night or in the morning
because of asthma

Other Instructions

Asthma Flare-up

■ If over a Period of 2-3 Days:

- My asthma symptoms are getting worse **OR NOT**
improving **OR**
- I am using more than 6 budesonide/formoterol reliever
inhalations a day for those 12 years or older,
or more than 4 inhalations a day for those 4-11 years

I should:

- ☒ Continue to use my regular everyday treatment
PLUS 1 inhalation budesonide/formoterol whenever
needed to relieve symptoms
- ☐ Start a course of prednisolone
- ☐ Contact my doctor

Course of Prednisolone Tablets:

Take _____ mg prednisolone tablets
per day for _____ days **OR**

■ If I need more than **12 budesonide/formoterol**
inhalations (Total) in any day, (or more than
8 inhalations for children 4-11 years)

I **MUST** see my doctor or go to the hospital
the same day

Asthma Emergency

■ Signs of an Asthma Emergency:

- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from my
budesonide/formoterol reliever inhalations.

If I have any of the above danger signs,
I should dial _____ for an ambulance and
say I am having a severe asthma attack.

■ While I am waiting for the ambulance start my asthma first aid plan:

- Sit upright and stay calm
- Take 1 inhalation of budesonide/formoterol.
Wait 1-3 minutes. If there is no improvement take
another inhalation of budesonide/formoterol
(up to a maximum of 6 inhalations on a single occasion)
- If only albuterol is available, take 4 puffs
as often as needed until help arrives
- Start a course of prednisolone tablets (as directed)
while waiting for the ambulance
- Even if my symptoms appear to settle quickly,
I should see my doctor immediately after
a serious attack