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Original article

Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy

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Background: Budesonide/formoterol (Symbicort®) Maintenance and Reliever Therapy (SMART) is an effective asthma-management approach that treats symptoms with rapid increases in budesonide/formoterol. The cost-effectiveness of SMART *vs* higher fixed-dose budesonide/formoterol or salmeterol/fluticasone is unknown.

Methods: This 6-month, double-blind study randomized patients with asthma uncontrolled by inhaled corticosteroids alone ($n = 3335$; age ≥12 years) to budesonide/formoterol 160/4.5 μg b.i.d. plus additional doses as needed (SMART), budesonide/formoterol 320/9 μg b.i.d. plus as-needed terbutaline, or salmeterol/fluticasone 50/250 μg b.i.d. plus as-needed terbutaline. Economic analysis, assuming health care and societal perspectives, applied 2004 UK and Australian unit costs to pooled resource-use data. The effectiveness variable was the rate of severe exacerbations/patient/6 months.

Results: Patients treated using the SMART approach experienced fewer severe exacerbations than fixed-dose budesonide/formoterol and salmeterol/fluticasone patients (0.12 *vs* 0.16 and 0.19 events/patient/6 months, respectively; $P \leq 0.0048$). Budesonide/formoterol (Symbicort®) Maintenance and Reliever Therapy provided similar improvements in other markers of asthma control at a lower overall daily inhaled corticosteroid dose compared with fixed-dose treatment. Study drug costs accounted for a majority of both direct costs (DC; 78–87%) and total costs (TC; 50–63%) for all treatments, and were significantly lower in the SMART group compared with the fixed-dose groups ($P \leq 0.0014$). Direct and TC per patient/6 months were lower for SMART *vs* salmeterol/fluticasone (DC:–AUS$154, $P < 0.0001$; TC:–AUS$163, $P = 0.0036$;–£87, $P = 0.0026$) and *vs* budesonide/formoterol using UK costs (DC:–£73, $P < 0.0001$; TC:–£91, $P = 0.0014$). Costs tended to be lower for SMART *vs* budesonide/formoterol using Australian costs (DC:–AUS$35, $P = 0.16$; TC:–AUS$70, $P = 0.20$). Results were stable under sensitivity testing. Indirect resource use and cost were not significantly different between groups.

Conclusion: Compared with higher fixed-dose budesonide/formoterol and salmeterol/fluticasone, SMART reduces the incidence of severe exacerbations at a lower or similar overall cost and can be considered a cost-effective treatment regimen.

Key words: asthma; budesonide/formoterol; cost effectiveness; salmeterol/fluticasone; budesonide/formoterol (Symbicort®) Maintenance and Reliever Therapy.

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Clinical guidelines suggest that an appropriate treatment paradigm for persistent asthma uncontrolled by inhaled corticosteroids (ICS) alone, is maintenance therapy with an ICS/long-acting β_2-agonist (LABA) combination administered twice daily, plus a short-acting β_2-agonist (SABA) as needed for symptom relief (1, 2). The two ICS/LABA combination inhalers currently available – budesonide/formoterol (Symbicort®; AstraZeneca, Lund, Sweden) and salmeterol/fluticasone (Seretide™; GlaxoSmithKline, Brentford, UK) – are effective in patients with persistent asthma that is uncontrolled by ICS alone (3–7).

Despite the availability of effective therapies, asthma control in clinical practice remains suboptimal (8, 9). Asthma exacerbations are found to have a major impact on patients' daily lives and are a major cause of the morbidity and mortality associated with the disease (10). Prevention of severe exacerbations is a key goal of successful asthma management (1). Indeed, the latest Global Initiative for Asthma (GINA) guidelines indicate that for a patient to be considered as controlled, they must be free of asthma exacerbations for a year, and minor daily symptoms can occur up to twice per week (1).

However, an international survey of almost 11 000 patients with asthma (9) revealed that up to 23% of participants in the USA and western Europe reported hospital emergency room (ER) visits in the previous 12 months, while up to 29% reported unscheduled visits to other healthcare providers; 7–9% of patients reported at least one hospital admission, a factor associated with increased risk of fatal asthma (11). Asthma also continues to restrict normal physical activity in many patients (9).

Symbicort Maintenance and Reliever Therapy (Symbicort SMART®; AstraZeneca) (12, 13) is a new therapeutic approach to asthma which employs budesonide/formoterol for maintenance therapy plus additional inhalations for symptom relief as needed, without a separate SABA reliever medication. This treatment option has been recommended in the latest GINA guidelines for the prevention of exacerbations and improvement in asthma control (1). This treatment option is approved in the European Union for the treatment of asthma, where the use of an ICS/LABA combination is appropriate. Symbicort Maintenance and Reliever Therapy is a simplified regimen, which allows patients to adjust their anti-inflammatory and reliever medication at the first sign of breakthrough symptoms using only one inhaler, and to default to a regular maintenance dose of budesonide/formoterol when symptom-free. Symbicort Maintenance and Reliever Therapy improves asthma control compared with a fixed-dose combination of budesonide/formoterol plus SABA (14). Moreover, in a recent large-scale, 1-year, dose-titration study, SMART reduced the risk of severe asthma exacerbations compared with traditional treatment with titrated maintenance doses of salmeterol/fluticasone, adjusted in line with clinician judgement (15).

A recent systematic literature review confirmed the efficacy of ICS/LABA combination therapy from a clinical and cost perspective, compared with ICS alone, higher dose ICS or alternative ICS combinations (16). Previously, the SMART regimen was reported to achieve daily control at least as good as that obtained with traditional fixed-dose ICS/LABA therapy, but achieved with a lower maintenance dose. However, as budesonide/formoterol costs more per inhalation than standard reliever medication, this potentially adds to the cost of the SMART approach, and, while the efficacy of SMART has been clearly demonstrated (14, 15, 17, 18), the cost implications of this approach have been investigated in only one previous study. This previous clinical trial reported that, compared with titration of salmeterol/fluticasone plus salbutamol as needed, SMART may be a cost-effective treatment option from a societal cost perspective (19). However, the majority of patients using the SMART regimen in this study remained on two inhalations twice daily for maintenance therapy throughout the 12-month period. In our study, a cost-effectiveness evaluation was conducted from a healthcare provider and societal perspective to compare the treatment costs of SMART at a lower maintenance dose (one inhalation twice daily) against those of two higher fixed-dose ICS/LABA regimens supplemented by SABA reliever therapy: salmeterol/fluticasone plus terbutaline as needed, at its most frequently prescribed dose, and a comparable fixed maintenance dose of budesonide/formoterol plus terbutaline as needed.

Methods

Patients and clinical study design

The clinical study (study code SD-039-0735) methodology by Kuna et al. (20) has been described elsewhere and full details can be found therein. Cost-effectiveness data were collected during a 6-month, double-blind, randomized, multi-centre, parallel-group study performed in 16 countries according to the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients aged ≥12 years with asthma (21) for ≥6 months who had been using ICS for at least 3 months and at a constant dose (≥500 μg/day) for ≥1 month were recruited. Following a 2-week run-in period, during which patients continued with their existing ICS medication but discontinued any LABA treatment they had been taking, patients were randomized to double-blind treatment with: budesonide/formoterol 160/4.5 μg (Symbicort®; AstraZeneca), one inhalation twice daily plus additional inhalations, as needed (Symbicort SMART®); budesonide/formoterol 320/9 μg, one inhalation twice daily (640/18 μg/day) plus terbutaline (Bricanyl® Turbuhaler®; AstraZeneca) as needed; or salmeterol/fluticasone 25/125 μg (Seretide™/Advair™ Evohaler™; GlaxoSmithKline), two inhalations twice daily (100/500 μg/day) plus terbutaline as needed.

Effectiveness variables and analysis

The primary endpoint in the clinical study was time to first severe exacerbation of asthma; however, neither this, nor symptom-free days, were considered suitable endpoints for a cost-effectiveness analysis. In order to relate average incremental cost to average incremental effect per patient per 6 months, the efficacy endpoint prospectively defined for this analysis was the rate of severe asthma exacerbations (number of events/patient/6 months in each treatment group). Current guidelines also recommend that therapy be directed towards preventing the occurrence of exacerbations (1). A severe exacerbation was defined as deterioration in asthma requiring hospitalization/ER treatment or use of oral steroids for ≥3 days. Other effectiveness variables, including morning and evening peak expiratory flow (PEF) and asthma symptoms, were recorded in patient diaries, and the following were measured at clinical visits: forced expiratory volume in 1 second (FEV_1); asthma control, measured using the five-item Asthma Control Questionnaire (ACQ-5) (22, 23); and quality of life, assessed using the Standardized Asthma Quality of Life Questionnaire [AQLQ(S)] (24). Overall ICS drug load was calculated by converting ICS doses to beclomethasone dipropionate (BDP)-equivalent doses based on GINA estimates of equipotence of ICS in metered doses (1).

The rate of severe asthma exacerbations was compared among treatment groups using a Poisson regression model with treatment and country as factors and time spent in the study as an offset variable. Rate ratios (RR) and 95% confidence intervals (CI) were calculated. statistical methods used to analyse other variables have been described elsewhere (20).

Economic variables

The cost-effectiveness analysis was conducted from both healthcare provider and societal (assessing healthcare plus sick-leave costs) perspectives. Asthma-related healthcare resource use and asthma-related sick-leave data were collected prospectively during the period between treatment randomization and the final clinic visit. Patients were provided with a notebook to record any asthma-related healthcare events. Patients who discontinued treatment prematurely owing to asthma-related causes were contacted by the investigator 12–16 days after their final visit and asked about asthma-related healthcare resource use when discontinuation.

Direct (medication and non-medication) and indirect resource-use data were pooled across participating countries. Medication costs included study drug and oral steroid use. Nonmedication resources comprised ambulance transport, days in hospital (general or intensive care), visits to healthcare providers (ER, specialist, primary care physician or other healthcare professionals, e.g. nurse, physiotherapist) and home visits (by physicians and other healthcare professionals). Costs associated with scheduled study visits and associated tests and interventions were excluded. Indirect resource use was based on the number of days on which patients were unable to perform their usual daily activities (defined as school work, employment work or household work), plus the number of days when a person assisting the patient was unable to perform their usual daily activities as a result of the patient's asthma. Indirect costs were only calculated for employed patients and carers.

Healthcare costs were defined from a healthcare system perspective, regardless of payer. Unit costs from Australia and the UK (Table 1) were used in the analyses of cost and cost-effectiveness. These countries were chosen because both have regulatory authorities that request health economic data for new drugs, and because both were represented in the study. Unit costs were collected using national registers and surveys representing 2004 prices. As the study did not assess outcomes or costs after 6 months, discounting was not applied. The national average wage rate, including social benefits, was used for costing work days lost. Part-time employed days were costed at half the cost of the full-time employed rate.

The full study population was used in the health economic analyses. For each variable, all patients with data for that variable (and for all components within a compound variable) were included.

The basis for the cost-effectiveness evaluation was that, if one treatment was found to be more effective but more costly, costs were related incrementally to the primary effectiveness variable by deriving an incremental cost-effectiveness ratio (ICER). A more effective treatment is said to be dominant if its cost was lower than that of the comparator and weakly dominant if similar in cost. Missing data for patients who prematurely withdrew from the study were handled, using the group mean approach, whereby all patients were weighted proportionally according to their exposure time within the study. For each sample, group mean differences were estimated.

Confidence intervals and *P*-values for differences in costs were calculated using a bootstrap method. Bootstrap samples (n = 10 000) were drawn with replacement from individual data consisting of observation time and cost from the same patients.

Sensitivity analyses

Two sensitivity analyses were undertaken in this study. The first examined the robustness of the pooled data, because this data set included resource use in patients from a variety of countries, many of which have different healthcare systems. Therefore, a subgroup analysis was performed to investigate whether the results from the pooled data set were comparable to those from patients in South Africa, Australia and those European countries with similar healthcare systems. Medication costs and direct, indirect and total costs (TC) were calculated as described above. Comparisons between the pooled data set and the subgroup were descriptive and no statistical comparisons were made.

Because asthma medication is a major component in the cost of asthma treatment, it is important to see how changes in drug costs, because of consumption or price, impact on the cost-effectiveness of treatment regimens. An analysis was undertaken to examine how increases in the cost of budesonide/formoterol 160/4.5 μg would affect the results of the comparison SMART *vs* salmeterol/fluticasone. The cost of budesonide/formoterol 160/4.5 μg was increased by 5%, 10%, 15%, 20% and 25% for the purpose of this analysis. Confidence intervals were derived using the same method as for the primary cost analysis.

Results

Patients

A total of 4399 patients were enrolled at 235 centres in 16 countries, of whom 3335 (76%) satisfied the study entry criteria and were randomized to treatment (patients: Argentina 329; Australia 121; Bulgaria 191; Czech Republic 134; Hungary 381; India 76; Malaysia 59; Mexico 437; the Netherlands 125; the Philippines 176; Poland 514; South Korea 86; South Africa 483; Thailand 54; the UK 120 and Vietnam 49). Patients received treatment with SMART (n = 1107), fixed-dose budesonide/formoterol with terbutaline as needed (n = 1105) or salmeterol/fluticasone with terbutaline as needed (n = 1123).

The demographic and baseline clinical characteristics of the three treatment groups are shown in Table 2. There were no significant differences between treatment groups with regard to patients' demographics, clinical characteristics or employment status. Adherence to medication, as reported by patients, was high: according to the diary cards, virtually all (99%) patients in the different treatment groups took >80% of their total daily maintenance dose.

Efficacy

The time to first severe asthma exacerbation was significantly longer for patients in the SMART group than for those in the higher fixed-dose budesonide/formoterol group (P = 0.023) and the fixed-dose salmeterol/fluticasone group (P = 0.0034) (20). The mean rate of severe exacerbations was 0.12 events/patient/6 months in the SMART group, 0.16 events/patient/6 months in the fixed-dose budesonide/formoterol group and 0.19 in the fixed-dose salmeterol/fluticasone group. Thus, SMART reduced the rate of severe asthma exacerbations by 28% compared with fixed-dose budesonide/formoterol (RR 0.72; 95% CI 0.57–0.90; P = 0.0048) and by 39% compared with fixed-dose salmeterol/fluticasone (RR 0.61; 95% CI 0.49–0.76; P < 0.001).

Table 1. The UK and Australian unit costs collected using national registers and surveys (2004 prices)

Medical resource use	Unit	Cost (AUS$)*	Cost (£)*
Ambulance transport	Emergency transport	262[a]	211[b]
Hospitalization			
Intensive care unit	Bed day	472[c]	295[d]
General care unit	Bed day	472[c]	166[e]
Healthcare visits			
Emergency room (general)	Visit	67[f]	105.59[g]
Medical consultant/specialist (pulmonologist)	Visit	72.60[h]	38[i]
Primary care physician	Visit	30.85[h]	19[j]
Other healthcare contact	Visit	45.35[k]	13.5[l]
Home visit – physician	Visit	51[m]	59[n]
Home visit – other	Visit	23.33[m]	32[o]
Oral steroid:			
Deltacortil 5 mg (UK)	Per 8 tablets (daily dose; UK)	0.33[p]	0.1[q]
Prednisolone 25 mg (Australia)	Per tablet (Australia)		
Study medication			
Budesonide/formoterol 200/6 μg dose[r]	Per inhalation	0.49[p]	0.32[q]
Budesonide/formoterol 400/12 μg dose[s]	Per inhalation	0.73[p]	0.63[q]
Salmeterol/fluticasone 25/125 μg dose	Per inhalation	0.49[p]	0.31[q]
Bricanyl Turbohaler 0.4 mg dose	Per inhalation	0.08[p]	0.07[q]
Indirect costs (sick leave)	Per day	195[t]	101[u]

*AUS$1.00 = €0.62; £1.00 = €1.46 (11 January 2006).
[a] Reference (25).
[b] Reference (26).
[c] Cost divided by the average number of days in hospital (3.7 days) (27).
[d] NHS Reference Costs 2004. Based on TCCS HRG CC1 (intensive therapy unit/intensive care unit) cost of £1327.80 and the assumption that an average stay lasted 4.5 days (28).
[e] Weighted average of TNELIP HRGs D21 (asthma with complications) and D22 (asthma without complications), giving a cost of £746.42 per stay (an average stay lasted 4.5 days) (28).
[f] Reference (29).
[g] Reference (28).
[h] Reference (30).
[i] Assumes a 20-min visit at a cost of £114/h (26).
[j] Assumes a 9.36-min visit (26).
[k] Based on the average cost of a physiotherapist (AUS$41.35/h), occupational therapist (AUS$63.85/h) (Commonwealth Department of Health and Aging 2002) and physician visit (AUS$30.85 per visit); nurse visit not applicable in Australia (29).
[l] Average of the cost of a nurse visit (£9 per practice nurse consultation) and community physiotherapist visit (£18 per 30-min consultation) (26).
[m] Assumes a 25-min consultation (30).
[n] Assumes a 13.2-min visit plus 12 min' travel time (26).
[o] Average of the cost of a nurse visit (£16 per 27-min practice nurse consultation) and community physiotherapist visit (£18 per 60-min consultation) (26).
[p] Reference (31).
[q] Reference (32).
[r] Metered dose; corresponds to a delivered dose of 160/4.5 μg.
[s] Metered dose; corresponds to a delivered dose of 320/9 μg.
[t] Based on a weekly salary of AUS$973.20 (private and public sectors), assuming a 5-day working week (33).
[u] Based on full-time employees: weekly gross pay £505 assuming a 5-day working week (34).

All three treatments produced similar improvements from baseline in other asthma control measures (symptom-free days, symptom scores, nocturnal awakenings and asthma-related quality of life). Lung function variables (FEV_1 and morning and evening PEF rates) were also similar between the treatment groups. As needed medication use decreased to a similar extent in all three treatment groups (20).

While individual mean doses varied in SMART-treated patients as a consequence of the treatment concept, patients in the SMART group had an overall reduction in average daily ICS dose compared with both higher fixed-dose groups [mean daily dose 483 μg (755 μg BDP equivalent), 640 μg (1000 μg BDP equivalent) and 500 μg (1000 μg BDP equivalent); calculations based on GINA estimates of equipotence of ICS in metered doses: fluticasone 500 μg = budesonide 800 μg = BDP 1000 μg (1) for the SMART, higher fixed-dose budesonide/formoterol and salmeterol/fluticasone groups, respectively]. The rate of exacerbations requiring hospitalization or ER treatment was significantly reduced in the SMART group compared with the salmeterol/fluticasone group (39% reduction; $P = 0.0015$); there was no significant difference between the two budesonide/formoterol groups in this

Table 2. Baseline demographics and clinical characteristics

Characteristic	Fixed-dose SAL/FLU (n = 1123)	Fixed-dose BUD/FORM (n = 1105)	SMART (n = 1107)
Male, n (%)	484 (43)	448 (41)	479 (43)
Mean age, years (range)	38 (12–83)	38 (12–83)	38 (11–79)
Median time as diagnosis, years (range)	10 (0–66)	10 (1–69)	9 (0–70)
Mean FEV_1 (% predicted)	73	73	72
Mean FEV_1 reversibility (%)	23	25	24
Mean ICS at study entry (μg/day)	744	750	740
Mean SABA use during run-in (inhalations/day)	2.3	2.3	2.3
Full-time employed, n (%)	512 (46)	496 (45)	508 (46)
Part-time employed, n (%)	120 (11)	112 (10)	98 (9)
Not in the workforce, n (%)	491 (44)	497 (45)	501 (45)

BUD/FORM, budesonide/formoterol (320/9 μg twice daily), plus terbutaline, as needed; SABA, short-acting β_2-agonist; SAL/FLU, salmeterol/fluticasone (50/250 μg twice daily), plus terbutaline, as needed; SMART, Symbicort® for Maintenance and Reliever Therapy (budesonide/formoterol 160/4.5 μg twice daily, with additional doses, as needed); FEV_1, forced expiratory volume in first second; ICS, inhaled corticosteroids.

outcome. In addition, the number of days with oral steroids in the SMART group was reduced by 41% and 45%, respectively, compared with the fixed-dose budesonide/formoterol and salmeterol/fluticasone groups (619, 1044 and 1132 days, respectively).

Economic analysis

A summary of healthcare resource use and sick leave is presented in Table 3. Most events were similar between the treatment groups. When UK and Australian unit costs for healthcare resources were applied to medical resource use, study drug costs accounted for the majority of both the direct (78–87%) and total (50–63%) costs for all treatments (Table 4). Despite the fact that SMART patients used additional inhalations of budesonide/formoterol as needed rather than the less expensive terbutaline, study drug costs were significantly lower in the SMART group than in the fixed-dose groups where a higher maintenance dose was used (all $P \leq 0.0014$; Table 5). Direct costs (DC) were significantly lower in the SMART group than in the salmeterol/fluticasone group using either Australian or UK costs (both $P < 0.001$; Table 6). Direct costs were significantly lower in the SMART group than in the higher fixed-dose budesonide/formoterol group when UK costs were used ($P < 0.001$), although the difference between the two budesonide/formoterol groups was not statistically significant when Australian costs were used ($P = 0.16$).

Table 3. Healthcare resource use

	Mean/patient/6 months		
	Fixed-dose SAL/FLU (n = 1103)	Fixed-dose BUD/FORM (n = 1099)	SMART (n = 1119)
Ambulance transport (times)	0.011	0.007	0.003
Hospitalization (intensive and general care) (days)	0.154	0.101	0.061
Emergency room visits (times)	0.089	0.061	0.067
Visits to primary healthcare physician (times)	0.135	0.178	0.141
Visits to specialist (times)	0.204	0.195	0.157
Other healthcare visits (times)	0.048	0.037	0.037
Home visits, physician (times)	0.008	0.013	0.003
Home visits, other health care (times)	0.022	0.003	0.003
Oral steroids (days)	1.12	1.06	0.63
Sick-leave[a]	1.11	1.16	0.93

BUD/FORM, budesonide/formoterol (320/9 μg twice daily), plus terbutaline, as needed; SABA, short-acting β_2-agonist; SAL/FLU, salmeterol/fluticasone (50/250 μg twice daily), plus terbutaline, as needed; SMART, Symbicort® Maintenance and Reliever Therapy (budesonide/formoterol 160/4.5 μg twice daily, with additional doses, as needed).

[a] Sick leave for employed patients and caregivers.

There was no statistically significant difference between the three treatment groups in indirect resource use and cost. The mean number of sick-leave days per patient over 6 months was 2.48, 3.11 and 2.36 in patients treated with SMART, fixed-dose budesonide/formoterol and salmeterol/fluticasone, respectively. The resulting indirect costs comprised 27–37% of the TC when Australian costs were used, and 24–30% of the TC with UK costs.

Combining indirect and DCs resulted in significantly lower TCs for SMART *vs* salmeterol/fluticasone when Australian and UK costs were used ($P = 0.0036$ and $P = 0.0026$, respectively) and *vs* higher fixed-dose budesonide/formoterol when UK costs were used ($P = 0.0014$). Total costs were lower in the SMART group compared with the fixed-dose budesonide/formoterol group when Australian costs were used, but the difference was not statistically significant ($P = 0.20$).

Evaluation of cost-effectiveness

As SMART was more effective in reducing the incidence of severe asthma exacerbations, achieved similar day-to-

Table 4. Direct and indirect costs (mean cost/patient/6 months) during treatment with SMART, fixed-dose SAL/FLU or fixed-dose BUD/FORM

	Mean cost per patient per 6 months[a]					
	Australia (AUS$)			UK (£)		
Variable	Fixed-dose SAL/FLU	Fixed-dose BUD/FORM	SMART	Fixed-dose SAL/FLU	Fixed-dose BUD/FORM	SMART
Medical resource costs, excluding study drug						
Ambulance transport	2.86	1.86	0.79	2.30	1.50	0.64
Hospitalizations[b]	72.81	47.87	29.45	26.76	17.80	13.16
Visit						
Emergency room	5.98	4.08	4.47	9.42	6.43	7.04
Specialist	14.83	14.14	11.38	7.76	7.40	5.95
Primary health physician	4.16	5.48	4.33	2.56	3.37	2.67
Other healthcare contacts	2.16	1.66	1.70	0.64	0.49	0.50
Home visit – physician	0.40	0.67	0.15	0.47	0.78	0.18
Home visit – other	0.51	0.07	0.07	0.70	0.10	0.10
Oral steroids	0.37	0.35	0.21	0.11	0.11	0.06
Total medical cost	104	76	52	50	38	31
Study drug costs						
Combination therapy	354	263	268	224	227	175
Terbutaline 0.4 mg	14	15	0	12	13	0
Total study drug cost	368	279	268	236	241	175
Total direct cost	472	353	318	287	278	205
Indirect cost (sick leave)	177	204	170	92	105	88
Total costs	649	556	486	378	383	292

BUD/FORM, budesonide/formoterol (320/9 μg twice daily), plus terbutaline as needed; SAL/FLU, salmeterol/fluticasone (50/250 μg twice daily), plus terbutaline as needed; SMART, Symbicort® for Maintenance and Reliever Therapy (budesonide/formoterol 160/4.5 μg twice daily, with additional doses, as needed).
[a] AUS$1.00 = €0.62; £1.00 = €1.46 (11 January 2006).
[b] Includes all types of asthma-related hospitalizations.

Table 5. Statistical comparisons of mean costs/patient/6 months during treatment with SMART, fixed-dose SAL/FLU or fixed-dose BUD/FORM

		Australian unit costs (AUS$)			UK unit costs (£)		
Variable	Comparison	Mean difference	95% CI	*P*-value	Mean difference	95% CI	*P*-value
Medical resource cost	SMART *vs* fixed-dose SAL/FLU	−52	−107 to 4	0.0740	−20	−44 to 6	0.1326
	SMART *vs* fixed-dose BUD/FORM	−24	−74 to 26	0.3318	−7	−29 to 17	0.5196
Study drug cost	SMART *vs* fixed-dose SAL/FLU	−101	−107 to −94	<0.0001	−62	−66 to −57	<0.0001
	SMART *vs* fixed-dose BUD/FORM	−11	−17 to −4	0.0014	−66	−70 to −61	<0.0001
Total direct costs	SMART *vs* fixed-dose SAL/FLU	−154	−211 to −97	<0.0001	−82	−107 to −55	<0.0001
	SMART *vs* fixed-dose BUD/FORM	−35	−84 to 15	0.1614	−73	−95 to −48	<0.0001
Indirect costs	SMART *vs* fixed-dose SAL/FLU	−7	−92 to 80	0.8486	−4	−48 to 41	0.8534
	SMART *vs* fixed-dose BUD/FORM	−33	−120 to 57	0.4520	−17	−63 to 29	0.4502
Total costs	SMART *vs* fixed-dose SAL/FLU	−163	−272 to −52	0.0036	−87	−141 to −31	0.0026
	SMART *vs* fixed-dose BUD/FORM	−70	−176 to 39	0.2030	−91	−145 to −36	0.0014

BUD/FORM, budesonide/formoterol (320/9 μg twice daily), plus terbutaline as needed; CI, confidence interval; SAL/FLU, salmeterol/fluticasone (50/250 μg twice daily), plus terbutaline as needed; SMART, Symbicort® for Maintenance and Reliever Therapy (budesonide/formoterol 160/4.5 μg twice daily, with additional doses as needed).

day control of asthma and was less costly than salmeterol/fluticasone when Australian and UK costs were used, SMART can be considered the dominant treatment regimen, both from a healthcare provider and societal perspective, under these conditions. Compared with higher fixed-dose budesonide/formoterol, SMART was the dominant treatment from both perspectives when UK costs were used. Differences in DC and TCs were not statistically significant using Australian unit costs. Hence, for this comparison SMART can be considered a weakly dominant and cost-effective treatment regimen. As the greater efficacy of SMART was achieved at a lower or similar cost, calculation of ICERs was not relevant.

Sensitivity analysis

Resource use in the subgroup of patients from developed countries ($n = 2064$) was slightly different to resource use

Table 6. Comparison of direct and total costs generated using resource use data from patients in European countries, Australia and South Africa

Comparison	Australian unit costs, AUS$ (95% CI)		UK unit costs, £ (95% CI)	
	Pooled data set (n = 3321)	Subgroup (n = 2064)	Pooled data set (n = 3321)	Subgroup (n = 2064)
SMART *vs* SAL/FLU				
Direct costs	−154 (−211 to −97)	−166 (−242 to −96)	−87 (−119 to −59)	−82 (−107 to −55)
Total costs	−163 (−272 to −52)	−212 (−364 to −61)	−111 (−185 to −37)	−87 (−141 to −31)
SMART *vs* BUD/FORM				
Direct costs	−35 (−84 to 15)	−22 (−74 to 27)	−67 (−91 to −47)	−73 (−95 to −48)
Total costs	−70 (−176 to 39)	−64 (−195 to 71)	−89 (−156 to −19)	−91 (−145 to −36)

BUD/FORM, budesonide/formoterol (320/9 μg twice daily), plus terbutaline as needed; CI, confidence interval; SAL/FLU, salmeterol/fluticasone (50/250 μg twice daily), plus terbutaline as needed; SMART, Symbicort® for Maintenance and Reliever Therapy (budesonide/formoterol 160/4.5 μg twice daily, with additional doses, as needed).

in the pooled data set. However, the differences in DC and TCs between the SMART and fixed-dose budesonide/formoterol and salmeterol/fluticasone groups were comparable to those of the pooled data set when Australian and UK unit costs were applied, and the significance of the differences remained (Table 6). Results of the cost analysis are shown in Fig. 1. Direct costs were significantly lower in the SMART group compared with the salmeterol/fluticasone group, up to the highest simulated cost increase for budesonide/formoterol (25%). Total costs remained significantly lower for SMART up to a 15% increase in the cost of budesonide/formoterol, but the difference was not significant when the cost of budesonide/formoterol was increased by 20%.

Discussion

The recently updated GINA guidelines recommended SMART as an effective option for the prevention of exacerbations and improvement of control in asthma patients (1), highlighting the suitability of SMART for use in clinical practice. To date, several clinical studies demonstrated that while fixed dosing with ICS/LABA combination regimens can provide well-controlled asthma for many patients, even greater benefits could be achieved using the SMART approach (14, 15, 17, 18, 20). Using resource-use data from the study by Kuna et al. (20), conducted on patients with moderate to severe persistent asthma, and applying Australian and UK unit costs, we showed that the increased efficacy of SMART is achieved at a lower DC and TC compared with traditional fixed dosing regimens when UK costs are used, and at a similar or lower DC and TC when Australian costs are used. Therefore, SMART can be considered a dominant cost-effective treatment option from both a societal and healthcare provider perspective.

Previous studies have demonstrated that the SMART approach is feasible and well tolerated by asthma patients (15, 20). Kuna et al. (20) demonstrated that SMART, at a recommended starting dose in adults (aged ≥18 years) within the European Union (budesonide/formoterol 160/4.5 μg twice daily plus as needed), compared with a twofold higher fixed maintenance dose of budesonide/formoterol or a corresponding dose of salmeterol/fluticasone plus SABA, reduces severe exacerbations, while maintaining similar daily asthma control at a lower overall drug load in patients with moderate to severe persistent asthma (20). A 12-month study by Vogelmeier et al. (15) compared SMART with a titrated (low–high) maintenance dose of salmeterol/fluticasone (plus salbutamol, as needed) using a design that closely mirrored clinical practice. In this setting, SMART, at a higher daily dose, prolonged the time to first severe exacerbation, reduced the number of severe exacerbations, reduced as-needed medication use and provided similar sustained improvements in other asthma control measures compared with salmeterol/fluticasone. In the related health economic evaluation, Johansson et al. (19) found SMART to be a cost-effective treatment option. However, the impact of the cost-effectiveness of SMART when patients are confined to the lower recommended starting dose, as in the study by Kuna et al. (20), needed to be explored further.

The cost-effectiveness analysis of the present study demonstrated that SMART could be considered a dominant cost-effective treatment option from both a healthcare provider and a societal perspective. The as needed component of the SMART regimen was more expensive per inhalation than the terbutaline used in the alternative ICS/LABA regimens. However, patients treated with the SMART approach used a lower maintenance dose, and did not require increased use of reliever; consequently, overall asthma medication costs were significantly lower with the SMART regimen than with both fixed-dose regimens ($P \leq 0.0014$). The lower maintenance dose used with SMART largely contributed to the lower cost observed, although cost for other medical resource use and indirect costs were also slightly lower but did not reach statistical significance. Symbicort Maintenance and Reliever Therapy was a dominant treatment option over salmeterol/fluticasone (i.e., more effective at a lower cost) in terms of the number of asthma exacerbations prevented, using either the UK or Australian unit costs. Symbicort Maintenance and Reliever Therapy was also

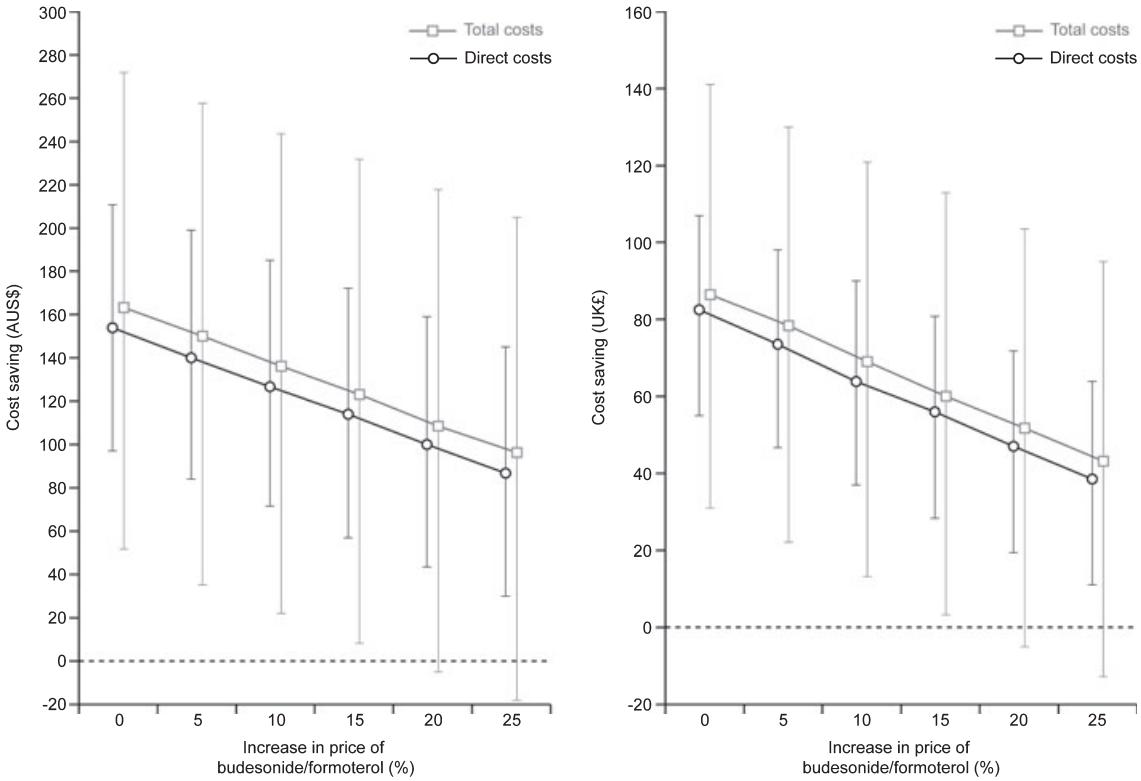

Figure 1. Effect of projecting hypothetical increases in the cost of budesonide/formoterol on the direct and total cost of treatment with SMART (160/4.5 μg twice daily plus as needed) compared with salmeterol/fluticasone (50/250 μg twice daily plus terbutaline, as needed). Differences are shown as potential cost savings per patient per 6 months in AUS$ and UK£. Zero on the *y*-axis represents equal costs. The vertical lines represent 95% CIs to demonstrate the certainty of the cost savings.

dominant over higher fixed-dose budesonide/formoterol in preventing severe exacerbations when the UK costs were used and weakly dominant, i.e. more effective at a similar cost, using the Australian costs.

Certain limitations of this analysis' external validity should be acknowledged. The diary may have increased patients' treatment compliance, and some medical consultations may have been replaced by planned study visits. The present 6-month study was limited by the time span of data collection; however, the results in terms of relative resource use and efficacy are in agreement with recent findings from the 12-month cost-effectiveness analysis by Johansson et al. (19). The present study, although the largest double-blind study ever performed with multiple ICS/LABA therapies in asthma, is limited by the population size required to investigate medical resource use, which is unequally distributed among patients. A very large population sample would be needed to show statistically significant differences for this cost category. However, the study was neither designed nor powered for this purpose, and, in some cases, results for individual cost components were inconclusive. A shortcoming of pooling resource use and applying country-specific costs is that practice patterns, costs and cultural factors shape resource use differently between countries. However, an analysis of resource-use data from a subgroup of the present study population, comprising the European countries, Australia and South Africa, yielded results that were consistent with the results from the entire population. A further sensitivity analysis, performed to examine the effects of drug cost, demonstrated that the results of the primary analysis were stable under the conditions of increasing budesonide/formoterol cost, up to a limit of 25% for DCs and 15% for TCs. This suggests that even if a considerable increase in the main cost driver occurs, or if the cost differential between the drugs changes, SMART is still a cost-saving treatment approach compared with salmeterol/fluticasone. The sensitivity analysis also indicates that the overall results are not very dependent on minor differences in the relative drug prices or drug consumption, thus increasing the transferability of the cost-effectiveness results to other countries. However, it should be acknowledged that a country's specific unit costs and drug prices need to be comparable to the ones applied in this analysis before transferring the results.

In conclusion, the results of the present study demonstrate that, compared with a moderate fixed dose of salmeterol/fluticasone, SMART is a cost-effective treatment option for patients with moderate or severe persistent asthma. Symbicort Maintenance and Reliever Therapy also reduces the incidence of severe asthma

exacerbations at a similar or lower overall cost compared with a higher fixed dose of budesonide/formoterol. The combination of improved efficacy, greater simplicity and cost-effectiveness means that SMART represents an attractive treatment option for patients and healthcare providers alike, compared with conventional fixed-dose ICS/LABA regimens, which have until now been considered the most effective way to manage patients with moderate or severe persistent asthma.

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References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2006. http://www.ginasthma.com; accessed April 2007.
2. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma, a national clinical guideline, 2005. http://www.brit-thoracic.org.uk/; accessed July 2006.
3. Shapiro G, Lumry W, Wolfe J, Given J, White MV, Woodring A et al. Combined salmeterol 50 μg and fluticasone propionate 250 μg in the diskus device for the treatment of asthma. Am J Respir Crit Care Med 2000;**161**: 527–534.
4. Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. Eur Resp J 2001;**18**:262–268.
5. Bateman ED, Bantje TA, Joao GM, Toumbis MG, Huber RM, Naya I et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. Am J Respir Med 2003;**2**:275–281.
6. Lalloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest 2003;**123**:1480–1487.
7. Aalbers R, Backer V, Kava TT, Omenaas ER, Sandstrom T, Jorup C et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin 2004;**20**:225–240.
8. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J 2000;**16**:802–807.
9. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol 2004;**114**: 40–47.
10. Andersson F, Borg S, Stahl E. The impact of exacerbations on the asthmatic patient's preference scores. J Asthma 2003;**40**:615–623.
11. Alvarez GG, Schulzer M, Jung D, FitzGerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. Can Respir J 2005;**12**:265–270.
12. Barnes PJ. A single inhaler for asthma? Am J Respir Crit Care Med 2005;**171**:95–96.
13. Gibson PG. Teaching old drugs new tricks: asthma therapy adjusted by patient perception or noninvasive markers. Eur Respir J 2005;**25**:397–399.
14. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;**171**:129–136.
15. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J 2005;**26**:819–828.
16. Akazawa M, Stempel DA. Single-inhaler combination therapy for asthma: a review of cost effectiveness. Pharmacoeconomics 2006;**24**:971–988.
17. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S et al. Efficacy and safety of budesonide/formoterol single inhaler therapy *vs* a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 2004;**20**:1403–1418.
18. Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest 2006;**129**:246–256.
19. Johansson G, Andreasson EB, Larsson PE, Vogelmeier CF. Cost effectiveness of budesonide/formoterol for maintenance and reliever therapy *vs* salmeterol/fluticasone plus salbutamol in the treatment of asthma. Pharmacoeconomics 2006;**24**:695–708.
20. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007;**61**:725–736.
21. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;**136**:225–244.
22. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999a;**14**:902–907.
23. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005;**99**:553–558.
24. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest 1999b;**115**:1265–1270.
25. Private Health Insurance Administration Council (PHIAC) A Report. Part 6. Canberra, Australia: Australian Government PHIAC, 2004.
26. Curtis L, Netten A. Unit Costs of Health & Social Care, 2004. Canterbury, England: Personal Social Services Research Unit (University of Kent), 2004.

27. National Hospital Cost Data Collection Round 6: Australian Refined Diagnosis Related Groups (AR-DRG). version 4.2 2001–2002. Public sector.
28. NHS Reference Costs 2004. National Health Service Trusts & Primary Care Trusts Combined. London: UK Department of Health, 2004.
29. Commonwealth Department of Health and Ageing. Manual for resource items and their associated costs for use in major submissions to the pharmaceutical benefits advisory committee involving economic analyses. Canberra, Australia: Australian Government of Health and Ageing, 2002.
30. Medicare benefits schedule. Canberra: Australian Government Department of Health and Ageing, 2004a.
31. Schedule of pharmaceutical benefits. Canberra, Australia: Australian Government Department of Health and Ageing, 2004b.
32. Monthly Index of Medical Specialities (MIMS). February 2005 edition. London: Haymarket Medical Limited L2, 2005.
33. Australian Bureau of Statistics. Popular statistics: 6302.0 average weekly earnings. Canberra, Australia: Australian Bureau of Statistics, 2004.
34. Annual Survey of Hours & Earnings (ASHE). London: UK Office for National Statistics, 2004.