ORIGINAL RESEARCH ARTICLE

Pharmacoeconomics 2006; 24 (7): 695-708
1170-7690/06/0007-0695/$39.95/0

Cost Effectiveness of Budesonide/Formoterol for Maintenance and Reliever Therapy versus Salmeterol/Fluticasone plus Salbutamol in the Treatment of Asthma

Gunnar Johansson,[1] *Emma B. Andreasson*,[2] *Per E. Larsson*[3] and *Claus F. Vogelmeier*[4]

1 Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
2 Nycomed, Roskilde, Denmark
3 AstraZeneca R&D, Lund, Sweden
4 Marburg University, Marburg, Germany

Abstract

Introduction: Budesonide/formoterol (Symbicort®) Maintenance And Reliever Therapy (SMART) is an effective and well tolerated treatment option for patients with asthma. We compared the cost effectiveness from a societal perspective of this one-inhaler regimen with that of maintenance salmeterol/fluticasone propionate (Seretide®) plus salbutamol (albuterol) as needed (Seretide® Fixed Combination [SFC]).

Study design: A cost-effectiveness analysis was performed based on effectiveness and resource-utilisation data collected prospectively in a randomised, 12-month study performed in 2143 patients in 16 countries. Resource utilisation data were pooled and unit costs (€, year 2003 values) from Italy, France, the UK and Germany were used to generate estimates of direct and total costs per patient per year and cost per severe exacerbation avoided.

Methods: Adolescents and adults with asthma (n = 2143; mean forced expiratory volume in 1 second [FEV_1] 73% predicted; mean inhaled corticosteroid [ICS] dose 884 μg/day) were randomised to SMART or SFC. The effectiveness measure used was the number of severe exacerbations per patient per year. Direct costs included medication use (budesonide/formoterol 160μg/4.5μg or salmeterol/fluticasone 50μg/100μg, 50μg/250μg or 50μg/500μg plus salbutamol) and nonmedication-related resource use, including days in hospital, emergency room visits, specialist or primary care physician visits and other healthcare provider contacts. Indirect costs, including the number of days when the patient or their carer was unable to attend to their normal daily activities, were also assessed. The study assumed a European societal perspective (i.e. including direct and indirect costs).

Results: Treatment with SMART resulted in significantly fewer severe exacerbations per patient per year compared with SFC (0.24 vs 0.31 events per patient per year; p = 0.0025). Resource use was low in both groups. Medication costs accounted for the majority of the total costs. The increased effectiveness of SMART was achieved at a reduced or similar cost compared with SFC. SMART dominated when German unit costs were applied (i.e. there was a statistically

significant reduction in both costs and number of exacerbations). In all other countries, the incremental cost-effectiveness ratios showed that there was a reduction in mean total cost per exacerbation avoided; however, this difference was not statistically significant.

Conclusion: This analysis demonstrates that, compared with SFC, SMART may be cost effective from a societal perspective for the treatment of patients with asthma in Italy, Germany, France and the UK. SMART provided a reduction in the number of severe exacerbations per patient per year, at no statistically significant increase in cost – or even at a lower cost – compared with SFC plus as-needed reliever salbutamol.

Asthma is a variable disease, characterised by periodic worsening of symptoms and lung function, as well as periods of reduced symptoms. Treatment guidelines currently recommend a fixed daily dose of appropriate maintenance medication (such as an inhaled corticosteroid [ICS]) with additional inhalations of a rapid-onset bronchodilator for symptom relief.[1] For patients whose asthma is not well controlled by an ICS alone, treatment with an ICS plus a long-acting β_2-adrenoceptor agonist (LABA) is the gold standard maintenance therapy. The combination of both agents in one inhaler represented a significant advance in asthma therapy, greatly simplifying treatment and potentially improving adherence to maintenance medication.[2] Addition of a regular fixed dose of a LABA to regular ICS therapy has been shown to provide better asthma control at a lower overall corticosteroid dose than ICS alone.[3-5] Two combination ICS/LABA inhalers are currently available worldwide: budesonide/formoterol (Symbicort®)[1] and salmeterol/fluticasone propionate (Seretide®), both of which are effective and well tolerated in patients with asthma.[6-14]

The current treatment algorithm of prescribing a regular fixed dose of maintenance medication with a short-acting β_2-agonist (SABA), such as salbutamol (albuterol) or terbutaline, for as-needed symptom relief is being challenged following the recent publication of results from a large clinical trial programme.[15,16] Three large studies showed that budesonide/formoterol for both maintenance and reliever therapy (abbreviated to SMART [Symbicort® Maintenance And Reliever Therapy][17]) to be more effective than fixed dosing with budesonide alone in reducing the rate of severe exacerbations and improving lung function and asthma symptoms.[17-19] In addition, SMART was more effective in reducing the risk of exacerbations than fixed-dose budesonide/formoterol plus terbutaline as needed for symptom relief.[17]

In the current economic climate, where healthcare providers are under increasing pressure to deliver improved patient outcomes at a reduced cost, it is important to demonstrate more than improved efficacy when evaluating a new treatment option. Previous economic analyses have shown that combining budesonide and formoterol in one inhaler may be cost effective compared with administration of the monocomponents in separate inhalers[20] and that the addition of formoterol to budesonide provides improved effectiveness at a modest additional cost compared with budesonide alone.[21] In addition, the use of formoterol as needed for symptom relief may provide significant improvements in effectiveness measures with no (or limited) increase in healthcare costs compared with salbutamol.[22] The cost effectiveness of SMART is of particular interest, as it is possible that the replacement of a relatively inexpensive SABA, such as salbutamol, with the more costly budesonide/formoterol has the potential to considerably affect healthcare budgets. An economic evaluation of this novel regimen has yet to be performed.

The current analysis was undertaken to determine the relative cost effectiveness of SMART versus salmeterol/fluticasone (Seretide® Fixed Combination [SFC]) plus as-needed reliever salbutamol from a societal perspective. This analysis is based on data

1 The use of trade names is for product identification purposes only and does not imply endorsement.

from a randomised, open-label study by Vogelmeier et al.,[23] in which patients received either SMART or SFC in a 12-month effectiveness study.

Methods

Clinical Trial

Design

This economic analysis was based on a 12-month multinational, randomised study conducted in 246 centres in 16 countries (study SD-039-0691).[23] A study design was chosen that would reflect normal clinical practice more closely than can be achieved with a standard controlled, double-blind clinical trial design. Therefore, the study was open-label in design and sales packs were used so that any features that differentiate the products – which might affect patient behaviour – were captured. Moreover, physicians decided whether or not maintenance medication should be titrated up or down over the study period, in line with usual clinical practice. Patients were also allowed to use other asthma controller medications (e.g. other ICS, intravenous or oral corticosteroids, leukotriene receptor antagonists or nedocromil), if considered necessary by the physician. Patients did not keep daily diaries, as this might have served as a reminder that they were taking part in a clinical study and hence have influenced their behaviour. However, patients were asked to record in a notebook details regarding their resource use when an asthma-related event occurred. Scheduled clinic visits were kept to a minimum so as not to influence patients' behaviour and their physician-contact patterns.

Patients with asthma were enrolled if they were aged ≥12 years and had been using ≥500 μg/day of budesonide or fluticasone (or ≥1000 μg/day of another ICS) for at least 1 month before study entry. Patients' pre-terbutaline forced expiratory volume in 1 second (FEV_1) had to be 40–90% of predicted normal and they must have experienced one or more severe exacerbations (defined in the following Cost-Effectiveness Analysis – Clinical Effectiveness section) in the year before study entry; patients who had experienced a severe exacerbation in the 2 weeks before study entry were not enrolled. Furthermore, patients had to have used at least one inhalation of as-needed medication on at least 4 of the last 7 days of run-in prior to randomisation. Patients were randomised in chronological order at each centre according to a computer-generated code, and treatment was communicated via an Interactive Voice Response System.

The study design is shown in figure 1. After a 2-week run-in period, during which patients continued to use their existing ICS (and LABA if used prior to study entry) plus as-needed medication, patients were randomised to treatment with either two inhalations twice daily of SMART (budesonide/formoterol 160μg/4.5μg) plus additional inhalations for reliever therapy or one inhalation twice daily of

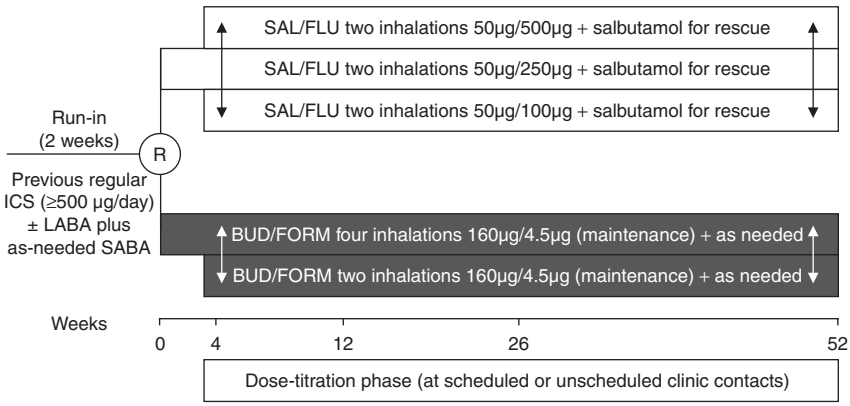

Fig. 1. Study design (reproduced from Vogelmeier et al.,[23] with permission). **BUD/FORM** = budesonide/formoterol; **ICS** = inhaled corticosteroid; **LABA** = long-acting β_2-adrenoceptor agonist; **R** = randomisation; **SABA** = short-acting β_2-adrenoceptor agonist; **SAL/FLU** = salmeterol/fluticasone.

SFC (salmeterol/fluticasone 50μg/250μg) plus salbutamol as needed (via dry-powder inhaler or pressurised metered-dose inhaler [pMDI]). Patients attended clinic visits at the beginning and end of run-in, and after 1, 3, 6 and 12 months of treatment (visits 1–6). Additional patient-initiated contacts (telephone contacts or unscheduled visits) were permitted at any time during the study.

From week 4 onwards, treatment for both groups of patients was assessed by physicians, either at regular scheduled visits or at patient-initiated contacts. The maintenance dose of budesonide/formoterol could be down-titrated from 160μg/4.5μg two inhalations twice daily to a low daily maintenance dose of two inhalations per day. The SFC dose could be down-titrated to a low daily maintenance dose of 50μg/100μg one inhalation twice daily or increased to a high maintenance dose of 50μg/500μg one inhalation twice daily (figure 1). These are the maintenance dose ranges recommended in the product labels for budesonide/formoterol[24] and salmeterol/fluticasone.[25]

All efficacy analyses were performed using intent-to-treat analysis on the full analysis set. The number of severe exacerbations was compared between groups using a Poisson regression model with treatment and country as factors and time in the study as an offset variable. No other adjustment was made for any other potential confounders.

Baseline Demographics

A total of 2143 patients were randomised to treatment: 1067 to SMART and 1076 to SFC. Patients were included from Belgium (132), Canada (147), China (132), Denmark (228), France (283), Germany (149), Hong Kong (8), Iceland (25), Italy (199), Korea (80), Norway (104), Spain (215), Sweden (98), Taiwan (100), Thailand (95) and the UK (148). Eight patients had no data and were excluded from the analysis; the remaining 2135 patients with data were included in the efficacy analysis. Of these, 2123 patients had healthcare resource use data. Baseline demographics were comparable in both groups (table I). Of the 298 patients who discontinued treatment prematurely, 34 agreed to take part in a follow-up of resource use for the remainder of the study period. These data were included in the analysis of treatment costs.

Cost-Effectiveness Analysis

The cost-effectiveness analysis was performed from a societal perspective, taking into account direct and indirect costs, including time taken off work by patients and their carers.

Clinical Effectiveness

The effectiveness variable used in the cost-effectiveness analysis was the number of severe exacerbations per patient per year. The primary endpoint in the clinical study was time to first severe exacerba-

Table I. Baseline demographics of all patients included in the clinical trial[a]

Characteristic	SFC (n = 1076)	SMART (n = 1067)
Male/female (n)	429/647	451/616
Age [y (range)]	45.1 (12–84)	45.3 (12–80)
FEV_1 pre-bronchodilator (% predicted)	73	73
ICS dose at entry (μg/day)	881	888
Inhaled LABA use at study entry [n (% of patients)]	409 (38)	402 (38)
Reliever use [no. of inhalations/24h (range)]	2.7 (0.3[b]–33.7)	2.6 (0.2[b]–10.7)
Employment [n (%)]		
full-time employed	530 (49)	501 (47)
part-time employed	87 (8)	84 (8)
not in the workforce[c]	459 (43)	482 (45)

a All values presented as means unless otherwise indicated.

b Deviation from inclusion criteria (included in the intention-to-treat population).

c House-person, student, retired or unemployed.

FEV_1 = forced expiratory volume in 1 second; **ICS** = inhaled corticosteroid; **LABA** = long-acting β_2-adrenoceptor agonist; **SFC** = Seretide® (salmeterol/fluticasone) Fixed Combination; **SMART** = Symbicort® (budesonide/formoterol) Maintenance And Reliever Therapy.

Table II. Unit costs (€, year 2003 values)

Variable	Unit	Costs			
		Italy	France	UK[a]	Germany
Hospitalisation					
intensive care	Day	929.6[32]	1109.0[33]	568.1[34]b	870.6[35]
general care	Day	1 day = 270.6 >1 day = 3000[36]c	365.0[33]	240.0[37]d	240.1[35]
Emergency room	Visit	20.7[32]	71.0[38]e	120.4[39]	25.0[40]f
Professional visit					
specialist (pulmonologist)	Visit	20.7[32]	23.0[41]	158.1[39]	10.7[42]
general care physician	Visit	11.8[43]	20.0[41]	26.1[39]	14.8[42]
other healthcare professional	Visit	4.8[43]	14.3[41]	19.6[39]	14.8[42]
Home visit					
physician	Visit	23.7[43]	30.0[41]	81.2[39]	14.8[42]
other healthcare professional	Visit	4.8[44]	14.4[45]	46.4[39]	14.8[42]
National average wage rate	Day	140.0[43]	134.0[46]g	137.5[47]	158.3[48]
Medication costs	Inhalation				
budesonide/formoterol 160μg/4.5μg		0.58[26]	0.48[27]	0.46[28]	0.57[29]
salmeterol/fluticasone 50μg/100μg		0.77[26]	0.71[27]	0.81[28]	0.81[29]
salmeterol/fluticasone 50μg/250μg		1.08[26]	0.86[27]	0.96[28]	1.14[29]
salmeterol/fluticasone 50μg/500μg		1.45[26]	1.17[27]	1.06[28]	1.72[29]
salbutamol (albuterol)[h]		0.02[26]	0.03[27]	0.04[28]	0.07[29]
prednisolone	Day	0.62[26]	0.76[27]	0.15[28]	0.22[29]

a £1 = €1.45 (3 Dec 2004).

b Assumes an average stay of 3.4 days.

c For total stay.

d Assumes an average stay of 4.5 days.

e The total cost of all emergency room visits was divided by the number of visits per year.

f No national figure available; negotiated with each regional association of Statutory Health Insurance-accredited physicians.

g Yearly gross wage for full-time employed: €28 529 divided by an average of 1600 hours' work per year (assuming a 7.5-hour working day).

h As-needed medication cost calculations in the salmeterol/fluticasone group were based on the following estimates of salbutamol inhaler use, i.e. pMDI or Diskus® inhalers: France 100% CFC-free pMDI; Italy 100% CFC-free pMDI; UK: 78% CFC-free pMDI and 22% unit-dose powder inhaler; in Germany, only generic salbutamol was available.

CFC = chlorofluorocarbon; **pMDI** = pressurised metered-dose inhaler.

tion. However, this endpoint was not considered suitable for the cost-effectiveness analysis; therefore the number of severe exacerbations was chosen *a priori* as the primary effectiveness measure for this analysis. A severe exacerbation was defined as deterioration in asthma requiring any one of the following: hospitalisation or emergency room (ER) treatment; oral corticosteroid treatment for at least 3 days; or an unscheduled visit (i.e. one that was initiated by the patient) leading to a change in asthma treatment.

Resource Utilisation

Direct and indirect resource use was assessed during the study using patient notebooks, and medication use was recorded at the scheduled study visits. Direct resource use consisted of medication use (study drug and other asthma medication use) and nonmedication-related resource use, which included the number of days in hospital, the number of ER visits, specialist or primary care physician visits and the number of other healthcare provider contacts. Maintenance medication therapy was based on the prescribed dose while as-needed use and other asthma medication use was based on patient recall of the 2-week period prior to each clinic visit. This was

then extrapolated to the entire treatment period. Oral corticosteroid use was costed based on the average daily dose of the most commonly used oral corticosteroid in each country.

Indirect resource use consisted of sick leave as well as the number of days when another person, e.g. parent/carer, was unable to perform his or her usual daily activities as a result of having to assist the patient. Sick leave was recorded in patient notebooks based on the number of days patients were unable to perform their usual daily activities (specifically school work, employment or housework) during the last 7 days, where ≤4 hours was classified as half a day and >4 hours as 1 day.

Scheduled study visits were omitted from the resource use analysis, as these were likely to have been protocol-driven and thus not representative of normal clinical practice, and also because these costs were expected to be comparable in both treatment groups. While omitting these costs may lead to an underestimation of total costs, this was considered preferable to overestimation.

Unit Costs

Unit costs from four European countries were applied to the pooled resource utilisation data collected in the Vogelmeier study.[23] Study medication costs (table II) were taken from official price lists[26-29] (for 2003 where possible; where 2003 prices were not available, prices were adjusted using the consumer price index) in the four major European countries (defined *a priori*) used in the analysis – Italy, France, the UK and Germany. As salbutamol Diskus® and salbutamol pMDI were used in the study (both of which were assumed to be equivalent[30]), market-specific data[31] were used to estimate the relative proportions of Diskus® and pMDI used in each of the countries included in the analysis. One exception was Germany, where only generic salbutamol was available.

The unit costs for nonmedication-related resource use are displayed in table II.[32-48] Specifically, the cost of healthcare visits was based on data from national registries and literature estimates. Where possible, asthma-specific estimates were used to determine the cost of intensive care-related and general care hospitalisations; where this was not possible, generic average costs were used. In countries where only the costs for diagnosis-related groups (DRGs) [i.e. a cost covering a hospital stay] were available, the unit cost was divided by the average number of treatment days to estimate a daily cost. A specialist visit was defined as the cost of a visit to a pulmonologist. The generic cost of a visit to a GP was used. The cost of other healthcare contacts was also included, defined as a visit to a nurse, physiotherapist, occupational therapist or similar professional; these costs were estimated based on the mean cost of a nurse and a physiotherapist visit, where available. In Germany, where these costs were not available, the cost for a visit to and a home visit from a primary care physician were used instead.

Indirect costs were calculated. Only employed patients' indirect resource use was costed based on the national average daily wage, including social benefits.

Economic Analysis

For the purposes of this analysis, healthcare utilisation data were pooled from all countries participating in the study. Unit costs for Germany, France, Italy and the UK were applied to these data.

The economic analysis was performed using a group mean approach, with means that were calculated as in equation 1.

$$\frac{\text{Sum of all resource use (and corresponding costs) in the group}}{\text{Total number of observation days in the group}} \times 365.25 \quad \text{(Eq. 1)}$$

Incremental cost-effectiveness ratios (ICERs), which relate the difference in cost between two treatments with the difference in effectiveness (i.e. the number of severe exacerbations per patient per year), were calculated as in equation 2.

$$\text{ICER} = \frac{\text{Direct cost of SMART} - \text{Direct cost of SFC}}{\text{Effectiveness of SMART} - \text{Effectiveness of SFC}} \quad \text{(Eq. 2)}$$

ICERs were calculated in a similar manner for total cost (direct plus indirect cost) per exacerbation

avoided. As the study did not assess outcomes or costs after 12 months, discounting was not applied.

Statistical Analysis

All patients with efficacy data in the clinical trial were included in the health economic evaluation. For each variable, all patients with data for that variable were included; when a variable consisted of the sum of two or more variables (e.g. direct resource use, which consists of several components), only patients with data for both variables were included.

Confidence intervals were calculated using a nonparametric bootstrap method. Bootstraps were drawn with replacement from individual data consisting of observation time, resource use or cost and effectiveness measures where appropriate. Each sample used observation time, resource use or cost and effectiveness measure from the same patients. Confidence intervals were calculated from the percentiles. For differences in resource use, cost and cost-effectiveness comparisons, 10 000 bootstrap samples were used. The clinical study was not powered to detect differences in resource utilisation.

Results

Clinical Effectiveness

Both treatments provided improvements in lung function and asthma symptoms. The number of severe exacerbations (total number of events and mean number of events per patient per year) in each treatment group is shown in table III. The overall exacerbation burden was statistically significantly reduced in patients treated with SMART compared with SFC ($p = 0.0025$). The mean number of events per year was reduced from 0.31 with SFC to 0.24 with SMART, i.e. the relative exacerbation rate for SMART versus SFC was 0.78. In absolute numbers, the SMART regimen was associated with 0.07 fewer severe exacerbations per patient per year, and this difference in effectiveness was the input for ICER calculations in the Cost-Effectiveness Analysis section. In addition, SMART recipients had reduced as-needed medication use compared with those in the SFC group.[23]

Table III. Severe exacerbations in the intent-to-treat study population

Exacerbations	SFC	SMART	SMART vs SFC[a]	
			95% CI	p-value
Total no. of events	329	255		
Events/patient/year	0.31	0.24	0.78 (0.66, 0.91)	0.0025

a The total number of severe asthma exacerbations was compared between the treatments using a Poisson regression model. The difference between treatments is shown as a ratio.

SFC = Seretide® (salmeterol/fluticasone) Fixed Combination; **SMART** = Symbicort® (budesonide/formoterol) Maintenance And Reliever Therapy.

Healthcare Resource Utilisation and Cost Analysis

Most resource use (summarised in table IV) was comparable in both treatment groups. Specialists' visits and other healthcare contacts or home visits were statistically significantly lower in patients treated with SMART.

Analysis of study medication use revealed that the most commonly used SFC dosage was 50μg/250μg twice daily (used on 63% of days). The 50μg/100μg twice daily and 50μg/500μg twice daily dosages were used on 12% and 25% of days, respectively. Overall, 55% of SFC patients switched inhaler at least once during the study period. The average use of salbutamol was 0.93 inhalations per patient per day in the SFC group. SMART patients had just one 160μg/4.5μg inhaler and the average use was 3.94 inhalations per day (maintenance and as-needed medication use combined). Overall, 12.7 inhalers per patient were administered in the SMART group and 11.6 salmeterol/fluticasone inhalers per patient were administered in the SFC group, in addition to 5.0 SABA inhalers per patient. Oral corticosteroid use was statistically significantly higher with SFC patients than with SMART patients (mean 3 vs 2 days with oral steroids per patient per year; $p = 0.024$). The use of other medication was low (≤1% per anatomical therapeutic chemical [ATC]-coded medication group) and similar in both treatment groups. This would have had little effect on the cost estimation and was therefore not included in the analysis.

Table V summarises treatment costs per patient per year when country-specific costs were applied to the resource utilisation data generated in the study

Table IV. Resource use per patient per year by treatment group (intent-to-treat population)

Resource	SFC	SMART	SMART vs SFC		
	(n = 1076)	(n = 1067)	mean difference	95% CI	p-value[a]
Hospitalisation					
intensive care	0.005	0.009	0.004	−0.015, 0.027	0.66
general care	0.09	0.05	−0.042	−0.122, 0.025	0.24
Emergency room visit	0.06	0.04	−0.018	−0.050, 0.014	0.28
Professional visit					
specialist	0.24	0.17	−0.069	−0.128, 0.010	0.021
primary healthcare physician	0.37	0.32	−0.047	−0.140, 0.046	0.31
Other healthcare contacts	0.10	0.05	−0.051	−0.091, 0.014	0.0042
Home visit					
physician	0.04	0.03	−0.005	−0.031, 0.019	0.68
other healthcare professional	0.01	0.00	−0.014	−0.041, 0.000	<0.0001
Sick leave, total days	2.1	1.5	−0.597	−1.838, 0.354	0.27
Days with oral corticosteroid treatment	3	2	−1.039	−2.031, 0.124	0.024

a No adjustment was made for multiple testing.

SFC = Seretide® (salmeterol/fluticasone) Fixed Combination; **SMART** = Symbicort® (budesonide/formoterol) Maintenance And Reliever Therapy.

by Vogelmeier et al.[23] Study medication costs accounted for the majority (78–86%) of total costs in both treatment groups. Despite the fact that patients in the SMART group used additional inhalations of their ICS/LABA combination for symptom relief rather than a SABA, direct costs (i.e. resource use, study medication and oral steroid costs) were statistically significantly lower for SMART than for SFC when UK and German unit costs were used ($p = 0.002$ and $p < 0.0001$, respectively). Direct costs were comparable in both treatment groups when Italian and French unit costs were applied; however, medication costs were marginally higher in SMART patients. In terms of total costs, SMART was a statistically significantly less costly treatment option than SFC when German unit costs were applied (total cost per patient per year of €959 vs €1077; $p = 0.024$); total costs were similar in Italy, France and the UK.

Cost-Effectiveness Analysis

Results of the cost-effectiveness analysis are presented in table VI. The negative ICERs obtained using UK and German unit costs indicate that SMART is a dominant treatment alternative in the direct cost comparison, as a reduction in the number of severe exacerbations is achieved at a lower direct cost. This was also the case for the total cost comparison when German unit costs were used. When Italian and French costs were applied, direct costs were numerically higher for SMART; however, none of these differences were statistically significant. Total costs per exacerbation avoided were numerically lower for SMART when Italian, French and UK costs were applied; once again, these differences were not statistically significant.

Cost-effectiveness ratios were estimated with confidence intervals of the point estimates (estimated with bootstrap technique). The distributions of cost and effect pairs are plotted in cost-effectiveness planes (figure 2). Examination of the cost-effectiveness planes for direct costs shows that the majority of cost-effect pairs lay on the right-hand side of the y-axis when unit costs from all four countries were applied, indicating that SMART was more effective than SFC. Figure 2c and 2d show that SMART was dominant when German and UK unit costs were used. As shown in figure 2a and 2b, there was no statistically significant difference in costs when French and Italian unit costs were used; therefore, since SMART is more effective, it may be considered a cost-effective treatment.

Discussion

SMART is a novel, effective and well tolerated treatment option that is in line with the intentions of asthma treatment guidelines,[1] providing excellent

Table V. Costs (€, year 2003 values) per patient per year using Italian, French, UK and German unit costs applied to resource-use data from all 16 countries included in the resource-utilisation analyses

Cost	No. of patients		Costs									
			Italy			France			UK[a]			Germany		
	SFC	SMART	SFC	SMART	p-value	SFC	SMART	p-value	SFC	SMART	p-value	SFC	SMART	p-value
Resource use[b]	1065	1058	66	48	0.39	59	43	0.37	85	60	0.07	39	29	0.44
Study medication	1051	1050	815	835	0.04	665	691	0.002	701	668	<0.001	910	821	<0.0001
Oral corticosteroids	1071	1064	1.9	1.2	0.02	2.3	1.5	0.022	0.4	0.3	0.024	0.7	0.4	0.024
Direct cost[c,d]	1051	1050	876	884	0.74	715	736	0.27	779	729	0.002	942	850	<0.0001
Indirect cost[d,e]	1071	1064	126	98	0.57	120	94	0.60	123	96	0.596	142	111	0.56
Total cost[d]	1051	1050	996	981	0.82	830	828	0.99	896	824	0.13	1077	959	0.024

a £1 = €1.45 (3 Dec 2004).

b Excluding medication.

c Direct costs include all costs related to the healthcare sector, i.e. medication use, inpatient, outpatient and home visits.

d Since the numbers of patients with data available differed slightly between the various measures (resource use, study medication, sick leave) the total cost is not exactly equal to the sum of direct and indirect costs.

e Indirect costs are those related to sick leave.

SFC = Seretide® (salmeterol/fluticasone) Fixed Combination; **SMART** = Symbicort® (budesonide/formoterol) Maintenance And Reliever Therapy.

asthma control at a low corticosteroid dose.[17-19] The study by Vogelmeier et al.[23] compared this simplified maintenance and reliever regimen with SFC plus reliever salbutamol in a multinational, randomised, open-label study in which resource utilisation data were collected. In this study, both treatment regimens improved all outcome measures from baseline and were well tolerated. In addition, SMART was statistically significantly more effective in reducing the rate of severe exacerbations than SFC. Results from our economic analysis have shown that the improved asthma control associated with SMART was achieved at a cost that was lower than or similar to that of SFC. Therefore, compared with SFC, SMART may be considered a cost-effective treatment from a societal perspective in Italy, France, Germany and the UK. In addition, since Vogelmeier et al.[23] also demonstrated that SMART was more effective than SFC in reducing exacerbations when unscheduled visits were excluded from the definition of a severe exacerbation, we can conclude that SMART may also be cost effective when this more rigorous definition of a severe exacerbation is applied.

The greater efficacy of SMART in reducing the incidence of exacerbations compared with traditional fixed dosing regimens plus SABA as needed[17-19,23] is likely to be a result of small, timely increases in use of both the anti-inflammatory and bronchodilatory medications. Evidence suggests that exacerbations are preceded by a period of increasing symptoms lasting between 3 and 5 days,[49] during which increases in ICS can decrease inflammation and potentially prevent the worsening symptoms from developing into an exacerbation, while the LABA component provides effective symptom relief and protection from challenge by bronchoconstrictor stimuli.

Medication costs constituted the majority of the direct and total costs for both treatment regimens in the present study; use of other resources was low. As patients in the SMART group used additional budesonide/formoterol inhalations for symptom relief (cost per inhalation €0.46–0.58) – in contrast to the relatively inexpensive salbutamol (cost per inhalation €0.02–0.07) – there is potential for the use of SMART to have a considerable budgetary impact. Despite this cost difference, SMART did not

Table VI. Estimated incremental cost-effectiveness ratios (ICERs) for Symbicort® (budesonide/formoterol) Maintenance And Reliever Therapy (SMART) vs Seretide® (salmeterol/fluticasone) Fixed Combination (SFC)

Country	Cost-effectiveness ratio[a] (95% CI)	
	mean direct cost per severe exacerbation avoided (€)[b]	mean total cost per severe exacerbation avoided (€)[b]
Italy	100 (−485, 6 494)	Dominant (−2 276, 4 384)
France	267 (−164, 6 501)	Dominant (−1 584, 5 351)
UK[c]	Dominant (−12 183, −293)	Dominant (−9 582, 412)
Germany	Dominant (−14 220, −601)	Dominant (−15 713, −262)

a In this analysis, negative ICERs indicate that SMART is more effective than SFC and at a lower cost. SMART is considered to be dominant where it provides a reduction in both costs and number of exacerbations; if both confidence intervals are negative, this can be considered to be a statistically significant result. Positive ICERs indicate that SMART provides greater efficacy, but at a greater cost.

b 2003 values.

c £1 = €1.45 (3 Dec 2004).

significantly increase treatment costs, as it provided increased effectiveness and allowed for less maintenance therapy, i.e. four inhalations per day on average for both maintenance and as-needed reliever in the present study. This compares favourably with the standard dose used in previous fixed maintenance dose studies (budesonide/formoterol 160μg/4.5μg two inhalations twice daily).[6,14] Study medication costs were lower for the SMART group in the UK and France and higher in Italy and Germany. This variation is a result of differences in drug acquisition costs between countries. In addition, SMART patients had statistically significantly fewer specialist visits and a trend towards fewer visits to primary healthcare physicians compared with those in the SFC group. This could be due in part to the fact that when SFC is used as prescribed, patients need to visit their doctor to obtain a prescription for a higher strength inhaler. With the SMART concept, patients can increase their use of as-needed medication during times of worsening symptoms without having to consult a doctor, which can allow even earlier intervention to further reduce the rate of severe exacerbations.

A comprehensive economic evaluation of a new treatment regimen does not just look at medication costs, but should also include an evaluation of healthcare resource use, indirect costs, such as time lost from work, and less tangible aspects such as quality of life.[50,51] When applying this broader perspective, we have shown that the improved effectiveness of SMART comes at a significantly lower cost than SFC in Germany, and with no statistically significant difference in costs in Italy, France or the UK.

While there are many advantages to collecting resource utilisation data from randomised, double-blind clinical studies, these evaluations are often criticised for lack of external validity. On the other hand, conducting cost-effectiveness analyses on data from open-label studies may be more relevant, as patients in open-label studies behave more as they would under normal conditions and not as they do under the carefully controlled conditions of a randomised, double-blind clinical study.

Specific measures were taken in the present study to mimic conditions that are encountered in everyday clinical practice. To achieve this, the study was open-label in design, clinic visits were kept to a minimum, there were few inclusion and exclusion criteria so as to ensure recruitment of patients with a range of asthma severities and daily diary cards were not completed. However, such a study design has potential limitations that need to be considered when interpreting the results. Patients estimated their as-needed medication use during the 2 weeks prior to each clinic visit (as diary cards were not used) and these estimates were then extrapolated to the entire study period. Although patient recall may be less reliable than the use of diary cards,[52] both methods tend to provide slight overestimations of medication use.[53] This overestimation was equally possible in either group and is therefore unlikely to have resulted in a bias towards either group. In addition, self-reported medication use at clinic visits was 95% of that expected from dispensing data. Since unused medication remaining in inhalers may

account for the extra 5%, patient recall appears to have been reliable in this study.

Patients in the SMART group used one inhaler for maintenance and reliever therapy throughout the study, whereas SFC patients could have had up to three maintenance inhalers, plus their salbutamol inhaler for symptom relief. Therefore, a further limitation of our study was that we did not directly assess the costs associated with switches between one inhaler and another in the SFC group or the impact of this practice, which could have incurred extra costs as a result of medication being left unused in the inhaler. However, the cost of switching inhalers was at least partly captured because some exacerbations that occurred in the SFC group incurred additional visits to the physician or another healthcare professional that required only a prescription for a higher strength inhaler or an additional inhaled medication. As 55% of patients in the SFC group changed their inhaler at least once, the vast majority of changes occurred at scheduled visits and were not costed.

Another limitation of the study may be the pooling of cost and resource utilisation data across disparate countries. Since this study was not powered to produce statistically significant differences in costs at a country level, we chose to pool data from all countries involved in the study and apply costs from four major markets (the choice of which was made *a priori*) for which costs were readily available. While the costs determined in our study will not apply to every country from which patients were recruited, total costs were consistent across the four sample countries chosen. Although there is no clear consen-

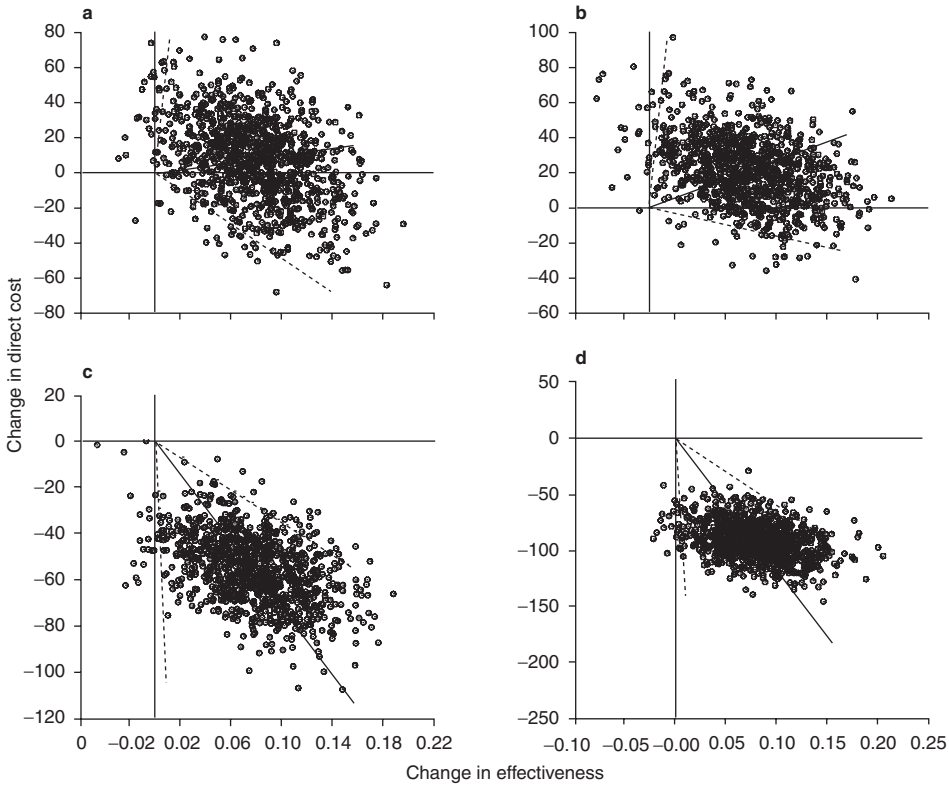

Fig. 2. Cost-effectiveness planes: bootstrap results for direct costs (€; 2003 values) per severe exacerbation avoided using (**a**) Italian unit costs, (**b**) French unit costs, (**c**) UK unit costs and (**d**) German unit costs. The mean cost-effectiveness ratio is represented by the solid line and the 95% confidence intervals for the ratio are represented by dashed lines. Where the 95% confidence intervals lie in the bottom right quadrant [(**c**) and (**d**)], this indicates increased effectiveness of Symbicort® (budesonide/formoterol) Maintenance And Reliever Therapy at a significantly lower cost than with Seretide® (salmeterol/fluticasone) Fixed Combination.

sus on how best to represent the results of cost-effectiveness evaluations conducted alongside multinational clinical trials,[54-56] the methodology chosen for this study is widely used.[55,57] However, a shortcoming of this method is that practice patterns, costs and cultural differences may shape the resource use differently across countries. Since drug acquisition costs accounted for the largest proportion of the total costs, the results of this cost-effectiveness analysis are more likely to be valid in countries where similar unit costs and medication use apply. Economic guidelines state that uncertainty arising from fixed parameters, such as unit costs and discount rates, should be assessed by use of sensitivity analysis.[58] No direct sensitivity analysis was carried out to explain the uncertainty around the cost estimates and assumptions in this analysis. Since resource use was low and similar between treatment groups, it was not considered feasible to carry out sensitivity analyses for each item for all four countries.

Conclusion

The results of this study demonstrate that, for patients with asthma, SMART may be a cost-effective treatment option from a societal cost perspective, compared with SFC, in Italy, Germany, France and the UK. SMART provides a reduction in severe exacerbations at no statistically significant difference in cost – or even at a lower cost – compared with SFC plus salbutamol for symptom relief, based on the assumptions made in this study. These findings highlight the effectiveness of the SMART treatment approach and demonstrate the ease with which it can be incorporated into normal clinical practice.

Acknowledgements

Gunnar Johansson and Claus Vogelmeier were involved in the clinical study and in the interpretation of the data and the writing of the manuscript. Emma Andreasson was involved in the design and implementation of the study, interpretation of data and development of the manuscript. Per Larsson contributed to the study design, statistical analysis and interpretation of results. All authors had free and unlimited access to the clinical study report and statistical reports. All authors were involved in the decision to submit the manuscript. All authors made final decisions on all aspects of the manuscript and hence are in agreement with, and approve, the final version of the submitted manuscript.

AstraZeneca provided financial support for this study as recommended by national guidelines and approved by local ethics committees. AstraZeneca provided study medication, clinical trial materials and study monitors, and paid other study-related costs.

Emma Andreasson was employed by AstraZeneca, Lund, Sweden, at the time this article was written.

Gunnar Johansson does not hold any stocks or shares in any organisation that could gain or lose financially from the results of this study. He has conducted clinical trials for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline and Merck, Sharpe & Dohme and has also been an invited speaker for these companies during the last 5 years. Emma Andreasson was an AstraZeneca employee at the time of the study. Per Larsson is an AstraZeneca employee. During the last 5 years, Claus Vogelmeier has presented at symposia sponsored by Altana, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, GlaxoSmithKline and Merck Darmstadt. He has also been a paid consultant for Altana, AstraZeneca, Bayer, Boehringer Ingelheim and GlaxoSmithKline.

We acknowledge the contribution of Deirdre Carman from Adelphi Communications, who provided medical writing services on behalf of AstraZeneca.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. National Institutes of Health publication No. 02-3659 (updated 2004). Bethesda (MD): National Institutes of Health, 2004 [online]. Available from URL: http://www.ginasthma.org [Accessed 2005 Jul 6]
2. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, et al. Adherence to asthma controller medication regimens. Respir Med 2005 Oct; 99 (10): 1263-7
3. Greening AP, Ind PW, Northfield M, et al. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994 Jul; 344 (8917): 219-24
4. Pauwels RA, Lofdahl C-G, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997 Nov; 337 (2): 1405-11
5. Woolcock A, Lundback B, Ringdal N, et al. Comparison of addition of salmeterol to inhaled steroids with doubling the dose of inhaled steroids. Am J Respir Crit Care Med 1996 May; 153 (5): 1481-8
6. Aalbers R, Backer V, Kava TT, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin 2004 Feb; 20 (2): 225-40
7. Bateman ED, Bantje TA, Joao Gomes M, 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 (3): 275-81
8. Buhl R, Creemers JPHM, Vondra V, et al. Once-daily budesonide/formoterol in a single inhaler in moderate persistent asthma. Respir Med 2003 Apr; 97 (4): 323-30
9. FitzGerald JM, Sears MR, Boulet L-P, et al. Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbations compared with traditional fixed dosing: a five-month multicentre Canadian study. Can Respir J 2003 Nov-Dec; 10 (8): 427-34
10. Kavuru M, Melamed J, Gross G, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation de-

vice for the treatment of asthma: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 2000 Jun; 105 (6 Pt 1): 1108-16
11. Lalloo UJ, Malolepszy J, Kozma D, 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 May; 123 (5): 1480-7
12. Shapiro G, Lumry W, Wolfe J, 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 Feb; 161 (2 Pt 1): 527-34
13. Stallberg B, Olsson P, Jorgensen LA, et al. Budesonide/formoterol adjustable maintenance dosing reduces asthma exacerbations versus fixed dosing. Int J Clin Pract 2003 Oct; 57 (8): 656-61
14. Zetterström O, Buhl R, Mellem H, et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. Eur Respir J 2001 Aug; 18 (2): 262-8
15. Gibson PG. Teaching old drugs new tricks: asthma therapy adjusted by patient perception or noninvasive markers. Eur Respir J 2005 Mar; 25 (3): 397-9
16. Barnes PJ. A single inhaler for asthma? Am J Respir Crit Care Med 2005 Jan 15; 171 (2): 95-6
17. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005 Jan; 171 (2): 129-36
18. Rabe KF, Pizzichini E, Ställberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild to moderate asthma: a randomized, double-blind trial. Chest 2006 Feb; 129 (2): 246-56
19. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 2004 Sep; 20 (9): 1403-18
20. Rosenhall L, Borg S, Andersson F, et al. Budesonide/formoterol in a single inhaler (Symbicort®) reduces healthcare costs compared with separate inhalers in the treatment of asthma over 12 months. Int J Clin Pract 2003 Oct; 57 (8): 662-8
21. Jonsson B, Berggren F, Svensson K, et al. An economic evaluation of combination treatment with budesonide and formoterol in patients with mild-to-moderate persistent asthma. Respir Med 2004 Nov; 98 (11): 1146-54
22. Lindgren B, Sears MR, Campbell M, et al. Cost-effectiveness of formoterol and salbutamol as asthma reliever medication in Sweden and Spain. Int J Clin Pract 2005 Jan; 59 (1): 62-8
23. Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J 2005 Nov; 26 (5): 819-28
24. Medical Products Agency, Uppsala, Sweden. Seretide Diskus mite, Seretide Diskus, Seretide Diskus forte (salmeterol/fluticason) [online]. Available from URL: http://www.lakemedelsverket.se/Tpl/MonographyPage____597.aspx [Accessed 2006 May 25]
25. Medical Products Agency, Uppsala, Sweden. Symbicort Turbuhaler/Symbicort mite Turbuhaler [online]. Available from URL: http://www.lakemedelsverket.se/Tpl/MonographyPage____604.aspx [Accessed 2006 May 25]
26. National formulary 2004, Official Gazette No. 4, 2003 Jan 7th ed. Rome: Italian Ministry of Health, 2004
27. Groupement pour l'Elaboration et la Réalisation de Statistiques. Paris: 2004 [online]. Available from URL: http://www.giegers.fr/ [Accessed 2005 Mar]
28. Monthly Index of Medical Specialties (MIMS) 2004 Jun ed. London: Haymarket Publications, 2004
29. Lauer-Taxe: WINAPO® Lauer-Taxe, Lauer-Fischer, Germany [online]. Available from URL: http://www.arz.de/LAUER-FISCHER/default.htm [Accessed 2004 Jul]
30. Arvidsson P, Mellen A, Palmqvist M, et al. Equivalent therapeutic ratio of salbutamol given by Turbuhaler and Diskus. Respir Med 2000 Jun; 94 (6): 574-7
31. IMS Health, IMS MIDAS Quantum MAT/Q2/04 [database]. London: IMS Health, 2005
32. Italian Ministry of Health. Official gazette No. 209, 1997 Sept 8. Ordinary Supplement, 1997 March 12
33. MEDTAP. Database of international unit costs for economic evaluations in health care. London: MEDTAP International Inc, 2002 Dec 18 [online]. Available from URL: http://www.medtap.com/products/unitcost.cfm [Accessed 2006 May 30]
34. NHS reference costs 2003 and national tariff 2004, Appendix 4. National schedule of reference costs: NHS Trusts and Primary Care Trusts combined; TCCS, Service Code CC1 [online]. Available from URL: http://www.dh.gov.uk/assetRoot/04/07/01/16/04070116.xls [Accessed 2005 Jul 6]
35. PKV, Zahlenbericht 2002/2003, PKV Verband der privaten Krankenversicherung e.V., Köln, Germany [online]. http://www.pkv.de/downloads/Zb031.pdf [Accessed 2006 May 24]
36. Potena A, Ballerin L, Putinati S, et al. The intensive respiratory care units in Italy: analysis of clinical activity and coding system. Rev Pathol Respir System 2002; 17: 96-105
37. NHS reference costs 2003, HRG code D22 [online]. Available from URL: http://www.nhselect.org.uk/downloads/nhselect_price_list_2005-06a.htm [Accessed 2005 Jul 6]
38. Arrêté du 2 Août 2004 fixant les tarifs de référence nationaux par activité. Annexe 1 titre II et III. Journal Officiel de la République Française (JORF) du 22 août 2004 [online]. Available from URL: http://www.legifrance.gouv.fr/ [Accessed 2006 May 25]
39. Curtis L, Netten A. Unit costs of health and social care 2004. Canterbury (UK): PSSRU, University of Kent at Canterbury, 2004
40. Deutsche Krankenhausgesellschaft, DKG-NT/BG Tariff, 2002/2003. Germany: Kohlhammer Verlag, 2003
41. Nomenclature Générale des Actes Professionnels, Union des Caisses Nationales de Sécurité Sociale (UCANSS), 2004 [online]. Available from URL: http://www.ucanss.fr/ucanss.nsf/ [Accessed 2005 Jul 6]
42. Kölner Kommentar zum EBM. Kommentierung zum einheitlichen Bewertungsmaβstab Manfred Moewes, Erhard Effer, Rainer Hess. Köln: Deutscher Ärzteverlag, 1994 (updated October 2002)
43. Lucioni C, Mangrella M, Mazzi S, et al. Treatment of patients with asthma with a fixed combination of budesonide and formoterol: a pharmacoeconomic evaluation vs some therapeutic alternatives. Pharmacoeconomics Italian Res Articles 2002; 4 (1): 15-23
44. Bondonio P, Eandi M. The times and costs of work associated to the pharmacological treatment: analysis of some cost-saving opportunities. Farmeconomia 1995; 2: 36-45
45. Démarches des soins infirmiers. Paris: CNAMTS (Caisse nationale d'Assurance Maladie des Travailleurs Salariés), 2002 [online]. Available from URL: http://www.ameli.fr/ [Accessed 2006 May 30]
46. INSEE Première No 1007. France: INSEE (National Institute for Statistics and Economic Studies), 2005 Mar [online]. Available from URL: http://www.insee.fr/ [Accessed 2006 May 30]
47. United Kingdom National Statistics. New earning survey 2003 [online]. Available from URL: http://www.statistics.gov.uk/pdfdir/nes1003.pdf [Accessed 2005 Jul 6]

48. Statistisches Jahrbuch für die Bundesrepublik Deutschland 2003. Wiesbaden: Statistisches Bundessamt (Federal Statistics Office), 2003
49. Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. Am J Respir Crit Care Med 1999 Aug; 160 (2): 594-9
50. Mellis CM, Peat JK, Woolcock AJ. The cost of asthma: can it be reduced? Pharmacoeconomics 1993 Mar; 3 (3): 205-19
51. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis: I. Assessing the economic impact. J Allergy Clin Immunol 2001 Jan; 107 (1): 3-8
52. Hufford MR, Shiffman S. Assessment methods for patient-reported outcomes. Dis Manage Health Outcomes 2003; 11 (2): 77-86
53. Butz AM, Donithan M, Bollinger ME, et al. Monitoring nebulizer use in children: comparison of electronic and asthma diary data. Ann Allergy Asthma Immunol 2005 Mar; 94 (3): 360-5
54. Sullivan SD, Liljas B, Buxton M, et al. Design and analytic considerations in determining the cost-effectiveness of early intervention in asthma from a multinational clinical trial. Control Clin Trials 2001 Aug; 22 (4): 420-37
55. Jönsson B, Weinstein MC. Economic evaluation alongside multinational clinical trials: study considerations for GUSTO IIb. Int J Technol Assess Health Care 1997; 13: 49-58
56. Reed SD, Anstrom KJ, Bakhai A, et al. Conducting economic evaluations alongside multinational clinical trials: towards a research consensus. Am Heart J 2005; 149: 434-43
57. Buxton MJ, Sullivan SD, Andersson LF, et al. Country-specific cost-effectiveness of early intervention with budesonide in mild asthma. Eur Respir J 2004; 24: 568-74
58. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health 2005 Sep-Oct; 8 (5): 521-33

Correspondence and offprints: Dr *Gunnar Johansson*, Vårdcentralen Nyby, Heidenstamsgatan 69, 754 27 Uppsala, Sweden.
E-mail: gunnar.johansson@pubcare.uu.se