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Budesonide + formoterol delivered via Spiromax® for the management of asthma and COPD: The potential impact on unscheduled healthcare costs of improving inhalation technique compared with Turbuhaler®

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ABSTRACT

Background: Fixed-dose combinations of inhaled corticosteroids and long-acting β_2 agonists are commonly used for the treatment of asthma and COPD. However, the most frequently prescribed dry powder inhaler delivering this medicine – Symbicort® (budesonide and formoterol, BF) Turbuhaler® – is associated with poor inhalation technique, which can lead to poor disease control and high disease management costs. A recent study showed that patients make fewer inhaler errors when using the novel DuoResp® (BF) Spiromax® inhaler, compared with BF Turbuhaler®. Therefore switching patients from BF Turbuhaler® to BF Spiromax® could improve inhalation technique, and potentially lead to better disease control and healthcare cost savings.

Methods: A model was developed to estimate the budget impact of reducing poor inhalation technique by switching asthma and COPD patients from BF Turbuhaler® to BF Spiromax® over three years in Germany, Italy, Sweden and the UK. The model estimated changes to the number, and associated cost, of unscheduled healthcare events. The model considered two scenarios: in Scenario 1, all patients were immediately switched from BF Turbuhaler® to BF Spiromax®; in Scenario 2, 4%, 8% and 12% of patients were switched in years 1, 2 and 3 of the model, respectively.

Results: In Scenario 1, per patient cost savings amounted to €60.10, €49.67, €94.14 and €38.20 in Germany, Italy, Sweden and the UK, respectively. Total cost savings in each country were €100.86 million, €19.42 million, €36.65 million and €15.44 million over three years, respectively, with an estimated 597,754, 151,480, 228,986 and 122,368 healthcare events avoided. In Scenario 2, cost savings totalled €8.07 million, €1.55 million, €2.93 million and €1.23 million over three years, respectively, with 47,850, 12,118, 18,319, and 9789 healthcare events avoided. Savings per patient were €4.81, €3.97, €7.53 and €3.06.

Conclusions: We demonstrated that reductions in poor inhalation technique by switching patients from BF Turbuhaler® to BF Spiromax® are likely to improve patients' disease control and generate considerable cost savings through healthcare events avoided.

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1. Background

1.1. Asthma and chronic obstructive pulmonary disease (COPD) in Europe

Asthma and COPD are common chronic inflammatory respiratory diseases affecting approximately 16 and 23 million adults across Europe, respectively [1]. Despite available treatment options, both diseases can have a considerable negative impact on patients' physical and psychological wellbeing [2–4], and impose a substantial burden on healthcare providers and society as a whole.

Guidelines from international regulatory bodies recommend that patients with asthma and COPD are treated in an escalating series of steps, with different combinations of medicines administered at each step, until disease control is achieved [5,6]. The guidelines recommend that patients with persistent asthma and COPD – defined as requiring third-step treatment or higher – should be given a fixed-dose combination (FDC) treatment of inhaled corticosteroid (ICS) plus long-acting β_2 agonist (LABA) [5,6], such as budesonide + formoterol [7,8]. Budesonide + formoterol (BF) is most frequently administered using Symbicort® Turbuhaler® (BF Turbuhaler®) [9], which is the most commonly prescribed dry powder inhaler (DPI) in Europe [10].

1.2. The burden of poor inhalation technique

Multiple studies have shown that BF Turbuhaler® can be difficult to use, with both patients and prescribers often demonstrating poor inhalation technique [11–19]. For example, a cross-sectional study of 1664 Italian asthma and COPD patients found that 44% of patients prescribed BF Turbuhaler® made at least one critical error when using their inhaler, such as failure to keep the device upright or not inhaling forcefully [12]. These findings are supported by data from a real-life, observational study of 3811 asthma and COPD patients in France, where 54% of patients could not use BF Turbuhaler® correctly [13]. Furthermore, healthcare professionals (HCPs) – who are charged with training patients to use their inhalers correctly – also make errors when using BF Turbuhaler®, with as many as 100% of HCPs demonstrating poor inhalation technique [14–16].

Poor inhalation technique has been associated with an increased risk of disease exacerbations, which can necessitate unscheduled healthcare resources being required, such as hospitalisation, emergency department (ED) visits and additional courses of antimicrobials or oral corticosteroids (OCS) [12]. These additional events contribute substantially to the direct cost burden of asthma and COPD to healthcare providers. We recently estimated the annual cost of poor inhalation technique with DPIs in Spain, Sweden and the United Kingdom (UK) to be €62 million, €26 million and €17 million, respectively, equating to 15.6%, 17.0% and 16.3% of the direct costs of unscheduled healthcare events due to asthma and COPD in these countries, respectively [20].

1.3. BF Spiromax® and the benefit of an intuitive, easy-to-use inhaler

BF Spiromax® (DuoResp® Spiromax®) is a DPI dispensing budesonide + formoterol, indicated for use in the same adult asthma and COPD populations as the equivalent delivered dose strengths of BF Turbuhaler®. Recently published data from the ELIOT trial – a twelve-week, parallel-group, open-label study investigating the ability of 151 naïve asthma patients to master BF Turbuhaler® and BF Spiromax® – found that significantly fewer patients made inhaler errors using BF Spiromax® compared with BF Turbuhaler® ($p < 0.001$) [21]. These data are supported by a study carried out in Finland, where 7% of healthy volunteers made errors with BF Spiromax®, compared with 23% making errors with BF Turbuhaler® ($p < 0.001$) [22]. Additionally, significantly more patients maintained perfect inhalation technique with BF Spiromax® than with BF Turbuhaler® after twelve weeks, as assessed by video review of the ELIOT study ($p < 0.001$) [21]. Given that poor inhalation technique is associated with an increased risk of incurring costly unscheduled healthcare events, these data suggest that switching patients from BF Turbuhaler® to BF Spiromax® could result both in patients experiencing fewer unscheduled healthcare events and cost savings for healthcare providers. Using a modelling approach, we estimated the cost savings associated with the improvement in inhalation technique, and reduction in healthcare resource use, of switching patients from BF Turbuhaler® to BF Spiromax® in four European countries.

2. Methods

2.1. Model design

A budget impact model with a three-year time horizon was developed from the perspective of healthcare payers in four European countries: Germany, Italy, Sweden and the UK. These countries were chosen to provide a diversity of population size, geographical location and healthcare systems. The model used a decision-tree based approach to assimilate population, incidence and cost data to estimate the overall cost of unscheduled healthcare events (hospitalisations, ED visits and additional courses of antimicrobials or OCS) and the contribution of poor inhalation technique to these costs. The model then estimated the effect of switching patients from BF Turbuhaler® to BF Spiromax® – assuming improvements in inhalation technique based on the available clinical data described earlier – on the incidence and resulting cost of unscheduled healthcare events.

2.2. Parameters

2.2.1. Population

The number of patients using BF Turbuhaler® eligible to switch to BF Spiromax® in each country was estimated based on the total number of adults (≥18 years), the prevalence of asthma and COPD, the percentage of patients with asthma and COPD receiving ICS + LABA FDC therapy, and the proportion of those patients using BF Turbuhaler® (Table 1). Patients receiving the lowest dose of BF Turbuhaler® were not considered eligible to switch – as BF Spiromax® is not currently available at this dose strength – and were therefore excluded from the model.

Several assumptions were made about the patient population. Changes in prevalence or diagnosis of asthma and COPD, or mortality, were not considered and the population in each country was assumed to be constant over the three-year time horizon of the model. Individual patients were not followed over the course of the model, and the cost of switching patients from BF Turbuhaler® to BF Spiromax® was assumed to be absorbed by differences in acquisition costs.

2.2.2. Unscheduled healthcare events

The number, type, and cost of unscheduled healthcare events used in the model are shown in Table 2. Input data sources were country-specific where available; otherwise, the most appropriate alternative sources were used (i.e. data from populations that were considered to be representative of the country in question). Such alternative sources have been clearly marked in Table 2. For each event, per patient costs were estimated by multiplying the number of events per patient per year by the cost per event (Table 2). Where

Table 1
Epidemiological/management pattern-specific parameters.

Country	Size of adult population	Prevalence of disease		Patients receiving ICS and LABA		Proportion of patients using BF Turbuhaler®	Proportion of patients eligible for BF Spiromax®
		Asthma	COPD	Asthma	COPD		
Germany	60,939,939 [37]	9.9% [38]	10.0% [39]	52.7% [40]	21.4% [40]	39.4% [40]	95.0% [41]
Italy	50,631,962 [42]	4.3% [43]	3.8% [43]	35.4% [44]	32.5% [44]	28.0% [41]	100% [41]
Sweden	7,772,932 [45]	8.0% [46]	7.0% [47]	50.0% [46]	39.7% [47]	74.7% [48]	98.9% [41]
UK	50,909,098 [49]	6.1% [50]	1.8% [50]	35.5% [51]	35.5%[a]	31.1% [41]	91.4% [41]

[a] Assumed to be the same as for asthma.

Table 2
Unscheduled healthcare event parameters.

Country	Asthma		COPD	
	Number per patient per year (n)	Cost per event (€)	Number per patient per year (n)	Cost per event (€)
Hospitalisation				
Germany	0.08 [52]	1508.97 [53,54]	0.18 [55]	2368.47 [53,54]
Italy[a]	0.02 [56,57]	1832.00 [58]	0.12 [56,57]	3063.00 [58]
Sweden	0.12 [57,59],[b]	748.15 [57,60],[b,d]	0.38 [57,61],[b]	1915.26 [57,60],[b,d]
UK	0.02 [56,57]	1753.68 [62]	0.12 [56,57]	3554.73 [62]
ED visits				
Germany	0.15 [63]	79.91 [64]	0.03 [55]	79.91 [64]
Italy[a]	0.02 [56,57]	54.12 [58]	0.12 [56,57]	54.12 [58]
Sweden	0.20 [65]	177.67 [60],[d]	0.31 [47]	177.67 [60],[d]
UK	0.02 [56,57]	182.12 [62]	0.12 [56,57]	182.12 [62]
Additional courses of antimicrobials				
Germany	0.70 [66],[c]	36.77 [67]	1.51 [68]	7.89 [67]
Italy[a]	0.70 [66],[c]	18.56 [58,69,70]	1.51 [68]	2.13 [71,72]
Sweden	0.50[e]	1.07 [73]	2.00[e]	1.07 [73]
UK	0.70 [66],[c]	25.65 [69,70]	1.51 [68]	2.94 [71,72]
Additional courses of OCS				
Germany	0.13 [74]	53.02 [75]	0.66 [76]	53.02 [75]
Italy[a]	0.14 [77]	40.00 [78]	0.68 [68]	40.00 [78]
Sweden	0.20[e]	2.34 [73]	1.60[e]	2.34 [73]
UK	0.14 [77]	55.28 [78]	0.68 [68]	55.28 [78]

[a] Data from the Lombardy region were assumed to be representative of the whole of Italy.
[b] Calculated using average length of stay data from UK hospitals [70].
[c] Data reported by a study of Irish GP practices [66] – assumed to be representative of Germany, Italy and the UK.
[d] Data from the Skåne region were assumed to be representative of the whole of Sweden.
[e] Values based on the opinion of a clinical expert.

necessary, costs were inflated to 2015 values based on healthcare-specific consumer price indices (CPIs) [23–26]. It was assumed that costs were fixed across the three years of the model, i.e. no inflation or discounting was applied.

2.2.3. Poor inhalation technique

The proportion of patients demonstrating poor inhalation technique with BF Turbuhaler® (43.5%; i.e. patients that make at least one critical inhaler error) was based on a cross-sectional, observational study carried out in Italy in 2008 by Melani and colleagues [12]. The results of this study were assumed to be representative of all countries included in the model. The proportion of patients demonstrating poor inhalation technique with BF Spiromax® (21.8%) was estimated based on the findings of the ELIOT study, where twelve weeks after training the proportion of patients making inhaler errors with BF Spiromax® was half that of patients using BF Turbuhaler® [21]. This relative reduction was applied to the proportion of patients demonstrating poor inhalation technique with BF Turbuhaler® to give the estimated value for BF Spiromax® [12]. Patients with poor inhalation technique were at increased risk of incurring unscheduled healthcare use, compared with patients with good inhalation technique, as reported in the study by Melani and colleagues [12]. The increased risks are shown in Table 3, and were assumed to be the same across all countries and devices in this analysis.

2.3. Scenario and sensitivity analysis

Two scenarios were modelled as follows: in Scenario 1 all patients were immediately switched from BF Turbuhaler® to BF Spiromax®, and the cost of unscheduled healthcare events measured over three years; in Scenario 2 a total of 4%, 8% and 12% of patients were switched from BF Turbuhaler® to BF Spiromax® in year one, two and three of the model, respectively.

One-way, deterministic sensitivity analyses were performed by varying the following parameters:

- Proportion of patients using ICS + LABA FDCs (±10%) – variation accounts for changes in prescription habits

Table 3
Increased risk of incurring unscheduled healthcare events for patients demonstrating poor inhalation technique.

Unscheduled healthcare event	Increased risk[a]
Hospitalisation	47%
ED visit	62%
Course of antimicrobials	50%
Course of OCS	54%

[a] Based on the increased risk over patients with correct inhaler technique (odds ratio) of at least one critical inhaler error and self-reported utilisation of healthcare resources used in the year since the critical inhaler error [12].

- Cost of hospitalisation (±20%)
- Cost of ED visits (±20%)
- Cost of additional courses of antimicrobials (±20%)
- Cost of additional courses of OCS (±20%)
- Proportion of patients with poor inhalation technique (±20%)

3. Results

3.1. Scenario 1

The annual number of patients using BF Turbuhaler® or BF Spiromax® with poor inhalation technique is shown in Table 4. The model estimated the annual number and cost of unscheduled healthcare events incurred by patients using BF Turbuhaler® or BF Spiromax® (Table 5). With both BF Turbuhaler® and BF Spiromax®, the highest annual number of unscheduled healthcare events occurred in Germany, and was more than double the annual number of events of the next highest country (Sweden), while the lowest annual number of unscheduled healthcare events occurred in Italy. The highest annual cost of unscheduled healthcare events occurred in Germany (Table 5), followed by Sweden, Italy and the UK, respectively.

Per patient costs were almost two-fold higher in Sweden than the other three countries with both BF Turbuhaler® and BF Spiromax® (Table 5). These findings are in line with our previously published observations [20]. The per patient cost of unscheduled healthcare events in Germany were similar to those in Italy, indicating that the high overall costs in Germany are mostly due to the large population size.

In Scenario 1, all patients using BF Turbuhaler® were immediately switched to BF Spiromax®. The per patient reduction in the number and cost of unscheduled healthcare events after three years are shown in Fig. 1 (For a breakdown of the costs, see Supplementary Table 1). Reducing poor inhalation technique in switching all patients from BF Turbuhaler® to BF Spiromax® was predicted to result in cost savings for all countries modelled.

In Sweden, 0.59 unscheduled healthcare events were avoided per patient, resulting in savings of €94.14 per patient over three years (Fig. 1). For all countries, hospitalisation was the largest contributor to the cost burden of unscheduled healthcare events – despite accounting for only 7% of the reduction in the number of unscheduled healthcare events. In Germany, hospitalisations were responsible for 81% of the estimated cost savings. The cost offsets of switching patients from BF Turbuhaler® to BF Spiromax® were also substantial in the other countries modelled, with savings per patient of €38.20–€60.10, accounting for 8% of the current cost of unscheduled healthcare events.

3.2. Scenario 2

In the more conservative Scenario 2, 4%, 8% and 12% of patients were switched from BF Turbuhaler® to BF Spiromax® in year 1, 2 and 3 of the model, respectively. The number of patients with poor inhalation technique is shown in Table 6.

As with Scenario 1, the greatest reduction in total number and cost of unscheduled healthcare events occurred in Germany (Table 7). The model estimated that switching patients from BF Turbuhaler® to BF Spiromax® would result in cost savings over three years of €8.07 million, €1.55 million, €2.93 million and €1.23 million in Germany, Italy, Sweden and the UK, respectively.

Switching patients from BF Turbuhaler® to BF Spiromax® gradually over three years resulted in an estimated 0.05 fewer unscheduled healthcare events per patient in Sweden (Fig. 2A), resulting in cost savings of €7.53 (Fig. 2B). Substantial cost savings were also predicted for all of the other countries studied, with a per patient cost saving over three years of €4.81, €3.97 and €3.06 in Germany, Italy and the UK, respectively.

3.3. Sensitivity analyses

The results of the one-way, deterministic sensitivity analyses are shown in Fig. 3. The model was moderately sensitive (defined as changes to the budget impact of <±25%) to the proportion of patients using ICS + LABA FDCs, the proportion of patients with poor inhalation technique (both BF Turbuhaler® and BF Spiromax®), the increased risk of unscheduled healthcare events due to poor inhalation technique, and the cost of hospitalisation across all four countries. The ranking of these five parameters was identical across the countries investigated, except for Germany where variations in the increased risk of unscheduled healthcare events had a greater effect on the model outputs than changes in the cost of hospitalisation. The model was not sensitive to the cost of ED visits, additional courses of antimicrobials or additional courses of OCS for any of the countries investigated.

4. Discussion

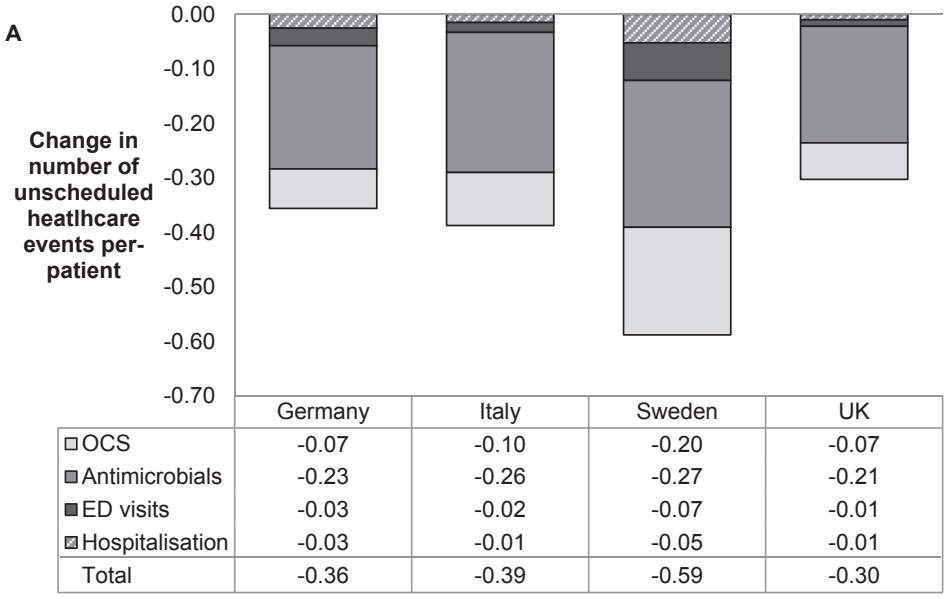
In the current study, we modelled the impact on unscheduled healthcare costs of reducing poor inhalation technique by switching patients with asthma and COPD from BF Turbuhaler® to BF Spiromax®. As poor inhalation technique is associated with increased risk of unscheduled healthcare events [12], we hypothesised that improving inhalation technique could reduce healthcare resource use requirements and therefore generate cost savings. Data from the ELIOT trial showed that patients using BF Spiromax® made fewer inhaler errors than patients using BF Turbuhaler® (19% vs 40%, respectively, $p < 0.001$) [21], indicating that switching

Table 4
Number of patients with poor inhalation technique in Scenario 1.

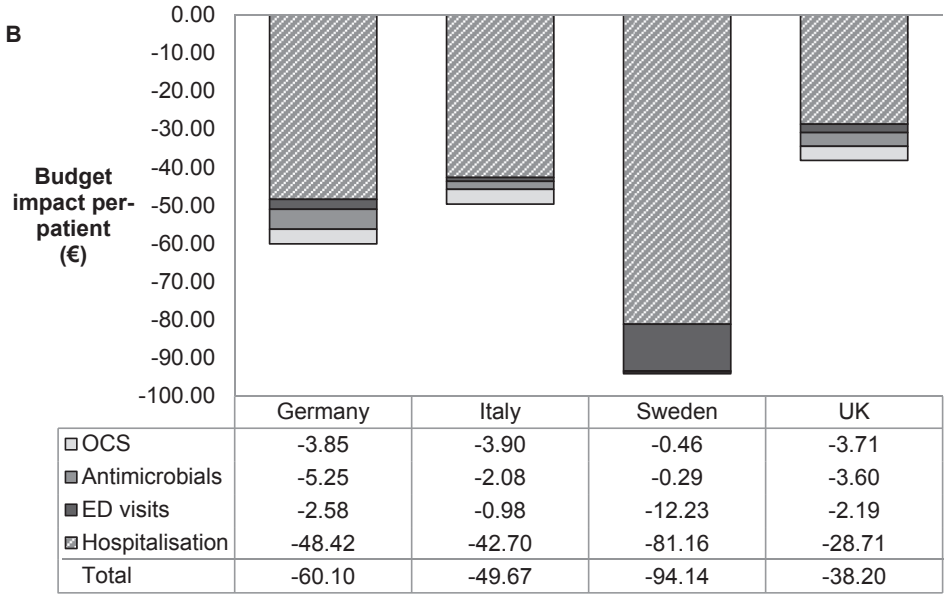
Country	Eligible patients	Patients demonstrating poor inhalation technique	
		Current (all patients using BF Turbuhaler®)	Revised (all patients using BF Spiromax®)
Germany	1,678,187	730,011	365,845
Italy	390,887	170,036	85,213
Sweden	389,285	169,339	84,864
UK	404,066	175,769	88,086

Table 5
Annual number, cost and per patient cost of unscheduled healthcare events.

Country	Number (n)		Total cost (€)		Per-patient cost (€)	
	BF Turbuhaler®	BF Spiromax®	BF Turbuhaler®	BF Spiromax®	BF Turbuhaler®	BF Spiromax®
Germany	2,423,210	2,223,958	428,927,702	395,308,895	256	236
Italy	615,363	564,869	82,969,617	76,497,700	212	196
Sweden	918,911	842,582	154,888,440	142,673,316	398	367
UK	498,280	457,490	65,249,826	60,104,232	161	149



	Germany	Italy	Sweden	UK
OCS	-0.07	-0.10	-0.20	-0.07
Antimicrobials	-0.23	-0.26	-0.27	-0.21
ED visits	-0.03	-0.02	-0.07	-0.01
Hospitalisation	-0.03	-0.01	-0.05	-0.01
Total	-0.36	-0.39	-0.59	-0.30



	Germany	Italy	Sweden	UK
OCS	-3.85	-3.90	-0.46	-3.71
Antimicrobials	-5.25	-2.08	-0.29	-3.60
ED visits	-2.58	-0.98	-12.23	-2.19
Hospitalisation	-48.42	-42.70	-81.16	-28.71
Total	-60.10	-49.67	-94.14	-38.20

Fig. 1. Change in per-patient number and cost of unscheduled healthcare events over three years when switching all patients from BF Turbuhaler® to BF Spiromax®. A: Estimated reduction in the number of unscheduled healthcare events per-patient over three years when switching all patients from BF Turbuhaler® to BF Spiromax®. B: Estimated per-patient reduction in cost when switching all patients from BF Turbuhaler® to BF Spiromax® over three years.

Table 6
Number of patients with poor inhalation technique over three years.

Country	Current		Revised					
			Year 1		Year 2		Year 3	
	Symbicort® Turbuhaler®	DuoResp® Spiromax®	Symbicort® Turbuhaler®	DuoResp® Spiromax®	Symbicort® Turbuhaler®	DuoResp® Spiromax®	Symbicort® Turbuhaler®	DuoResp® Spiromax®
Germany	730,011	0	700,811	14,634	671,610	29,268	642,410	43,901
Italy	170,036	0	163,234	3409	156,433	6817	149,631	10,226
Sweden	169,339	0	162,565	3395	155,792	6789	149,018	10,184
UK	175,769	0	168,738	3523	161,707	7047	154,677	10,570

patients to BF Spiromax® could reduce the number of unscheduled healthcare events that patients experience.

By switching all eligible patients from BF Turbuhaler® to BF Spiromax®, we found that per patient cost savings ranged from

Table 7
Total number of events and total cost of gradually switching patients to BF Spiromax® over three years (Scenario 2).

Country	Current		Revised						Difference	
			Year 1		Year 2		Year 3			
	Number (n)	Cost (€)	Number (n)	Cost (€)	Number (n)	Cost (€)	Number (n)	Cost (€)	Number (n)	Cost (€)
Hospitalisation										
Germany	183,068	351,762,671	182,504	350,679,223	181,940	349,595,776	181,376	348,512,328	3383	6,500,684
Italy	25,326	72,261,330	25,248	72,038,761	25,170	71,816,192	25,092	71,593,624	468	1,335,412
Sweden	88,206	136,767,344	87,934	136,346,093	87,663	135,924,842	87,391	135,503,592	1630	2,527,503
UK	17,288	50,215,244	17,235	50,060,578	17,181	49,905,913	17,128	49,751,247	319	927,993
ED visits										
Germany	193,152	15,434,809	192,429	15,377,030	191,706	15,319,250	190,983	15,261,471	4338	346,676
Italy	25,326	1,370,658	25,231	1,365,527	25,137	1,360,396	25,042	1,355,265	569	30,786
Sweden	95,411	16,951,713	95,054	16,888,255	94,697	16,824,798	94,340	16,761,340	2143	380,747
UK	17,288	3,148,472	17,223	3,136,686	17,158	3,124,900	17,094	3,113,114	388	70,717
Additional courses of antimicrobials										
Germany	1,570,116	36,446,403	1,565,057	36,328,956	1,559,997	36,211,509	1,554,937	36,094,062	30,358	704,681
Italy	415,440	3,366,820	414,101	3,355,971	412,762	3,345,121	411,424	3,334,272	8032	65,097
Sweden	434,019	464,400	432,620	462,904	431,222	461,407	429,823	459,911	8392	8979
UK	357,420	6,010,687	356,268	5,991,318	355,116	5,971,948	353,964	5,952,579	6911	116,215
Additional courses of OCS										
Germany	476,873	25,283,820	475,250	25,197,741	473,626	25,111,663	472,003	25,025,584	9741	516,472
Italy	149,270	5,970,809	148,762	5,950,482	148,254	5,930,154	147,746	5,909,827	3049	121,966
Sweden	301,275	704,984	300,249	702,583	299,224	700,183	298,198	697,783	6154	14,401
UK	106,285	5,875,423	105,923	5,855,420	105,561	5,835,417	105,199	5,815,414	2171	120,017
Total										
Germany	2,423,210	428,927,702	2,415,240	427,582,950	2,407,270	426,238,198	2,399,300	424,893,446	47,820	8,068,514
Italy	615,363	82,969,617	613,343	82,710,740	611,323	82,451,864	609,303	82,192,987	12,118	1,553,260
Sweden	918,911	154,888,441	915,858	154,399,836	912,805	153,911,231	909,752	153,422,626	18,319	2,931,630
UK	498,280	65,249,826	496,649	65,044,002	495,017	64,838,178	493,386	64,632,354	9789	1,234,942

€94.14 in Sweden to €38.20 in the UK over three years. In a more conservative scenario, where patients were switched gradually from BF Turbuhaler® to BF Spiromax® over three years (4% in year 1, 8% in year 2 and 12% in year 3), the model estimated per patient cost savings of €3.06–€7.53 in the countries considered (Fig. 2), totalling €13.79 million potential savings across the four countries. Differences in per patient costs between the countries studied are most likely due to differences in the cost of hospitalisation, as this was the largest contributor to the cost of poor inhalation technique.

We previously estimated that 16.4% and 15.7% of the unscheduled healthcare costs were due to poor inhalation technique in Sweden and the UK, respectively [20]. In the current study, costs due to poor inhalation technique were estimated to account for 17% of the total cost of unscheduled healthcare events in year three of the conservative scenario across all countries, which is in agreement with our previous findings. Data from the current study are therefore in agreement with our previously published results.

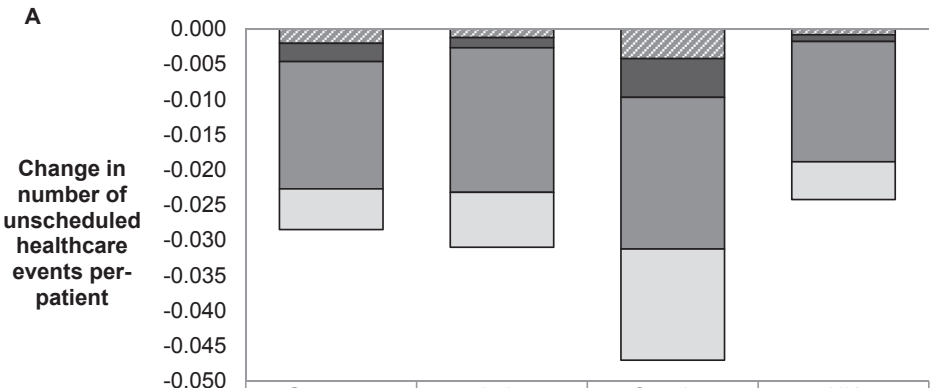
In addition to potentially improving inhalation technique, there may be other benefits to switching patients from BF Turbuhaler® to BF Spiromax®. International regulatory bodies and HCPs recognise that choice of inhaler is a critical decision in the management of asthma and COPD [27–29]. Patient satisfaction with their inhaler and adherence to treatment are associated with improved disease control [30], and it has been suggested that incorrect choice of inhaler device for patients with COPD may lead to suboptimal adherence to treatment [31]. As such, the use of innovative inhalers that are intuitive to use and address patient needs could improve patient satisfaction and adherence to therapy [32]. Several small-scale trials have shown that people prefer BF Spiromax® to BF Turbuhaler® [33–35], suggesting that switching patients to BF Spiromax® may improve adherence to medication, and therefore disease control. However, there are at present no studies that have measured adherence to medication among patients using BF Spiromax®.

The model was moderately sensitive to five of the inputs tested (Fig. 3). The model was most sensitive to the proportion of patients using BF Spiromax® with poor inhalation technique. This is likely because the model is only assessing changes in unscheduled healthcare costs.

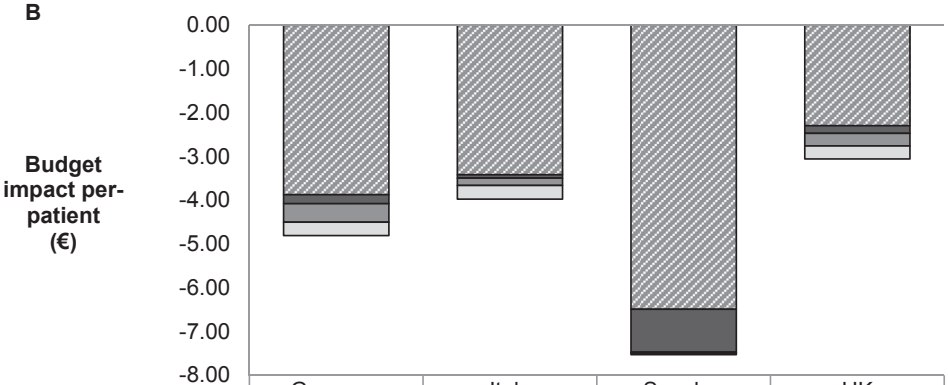
The model has several limitations which should be acknowledged. Firstly, there is no straightforward relationship between healthcare consumption and inhaler errors as adherence to medication is an important factor in the control of respiratory diseases [1]. However, a recent study has shown that patients making any one of 13 different inhaler errors with BF Turbuhaler® are significantly more likely to have poorly or uncontrolled asthma [36]; supporting the premise that improvements in inhalation technique will lead to reductions in unscheduled healthcare resource use.

Secondly, only direct unscheduled healthcare costs were considered. In some countries, the acquisition costs of BF Spiromax® may be lower than for BF Turbuhaler®. Therefore, in those countries, switching patients to BF Spiromax® may generate drug acquisition cost savings in addition to those predicted here by improving poor inhalation technique. While the model does not take into account the cost of switching patients from BF Turbuhaler® to BF Spiromax®, we expect that this cost will be absorbed by the savings of using an inhaler with a lower acquisition cost. We previously showed that indirect costs, such as the cost of lost productivity, far outweigh the direct costs discussed here [20]. Therefore we expect the impact of reducing poor inhalation technique on indirect costs to be considerable.

Thirdly, the proportion of patients using BF Spiromax® with poor inhalation technique was assumed to be half of that reported for patients using BF Turbuhaler®. This relative reduction was based on observations from the ELIOT study, where video assessment of inhalation technique twelve weeks after training found that 19% of patients made inhaler errors with BF Spiromax® compared with 40% of patients using BF Turbuhaler® [21]. However, the ELIOT study did not differentiate between inhaler errors and critical inhaler errors, i.e. those errors reported by Melani and colleagues



	Germany	Italy	Sweden	UK
OCS	-0.006	-0.008	-0.016	-0.005
Antimicrobials	-0.018	-0.021	-0.022	-0.017
ED visits	-0.003	-0.001	-0.006	-0.001
Hospitalisation	-0.002	-0.001	-0.004	-0.001
Total	-0.03	-0.03	-0.05	-0.02



	Germany	Italy	Sweden	UK
OCS	-0.31	-0.31	-0.04	-0.30
Antimicrobials	-0.42	-0.17	-0.02	-0.29
ED visits	-0.21	-0.08	-0.98	-0.18
Hospitalisation	-3.87	-3.42	-6.49	-2.30
Total	-4.81	-3.97	-7.53	-3.06

Fig. 2. Change in per-patient number and cost of unscheduled healthcare events over three years by progressive uptake of BF Spiromax®. A: Estimated reduction in the number of unscheduled healthcare events per patient over three years when patients were gradually switched from BF Turbuhaler® to BF Spiromax®. B: Estimated per-patient cost reductions of switching patients gradually from BF Turbuhaler® to BF Spiromax® over three years.

which impact the risk of unscheduled healthcare events [12]. Since the relative difference in the occurrence of inhaler errors and critical inhaler errors between BF Turbuhaler® and BF Spiromax® is likely to be similar, we assumed that the 50% reduction in inhaler errors with BF Spiromax® observed in the ELIOT trial would be applicable to the results of Melani and colleagues with BF Turbuhaler®, and would therefore be a more representative estimate of the proportion of patients using BF Spiromax® with poor inhalation technique.

The model also assumed that the increased risk of incurring unscheduled healthcare events due to poor inhalation technique was the same across all four countries investigated [12]. Furthermore, the uptake of BF Spiromax® in Scenario 2 was assumed to be the same across all countries studied. This is a simplification, as the uptake of BF Spiromax® will be influenced by local markets and healthcare provider policies, and is likely to be different in each of the countries investigated. Finally the model did not account for patient adherence to medication, and thus the associated economic impact, nor did it consider non-economic measures such as patient health-related quality of life.

5. Conclusion

Our model suggests that switching patients from BF Turbuhaler® to BF Spiromax® could lead to improved inhalation technique, thereby reducing the frequency of unscheduled healthcare events. Our analysis reveals that reducing poor inhalation technique in this way gradually over three years could result in

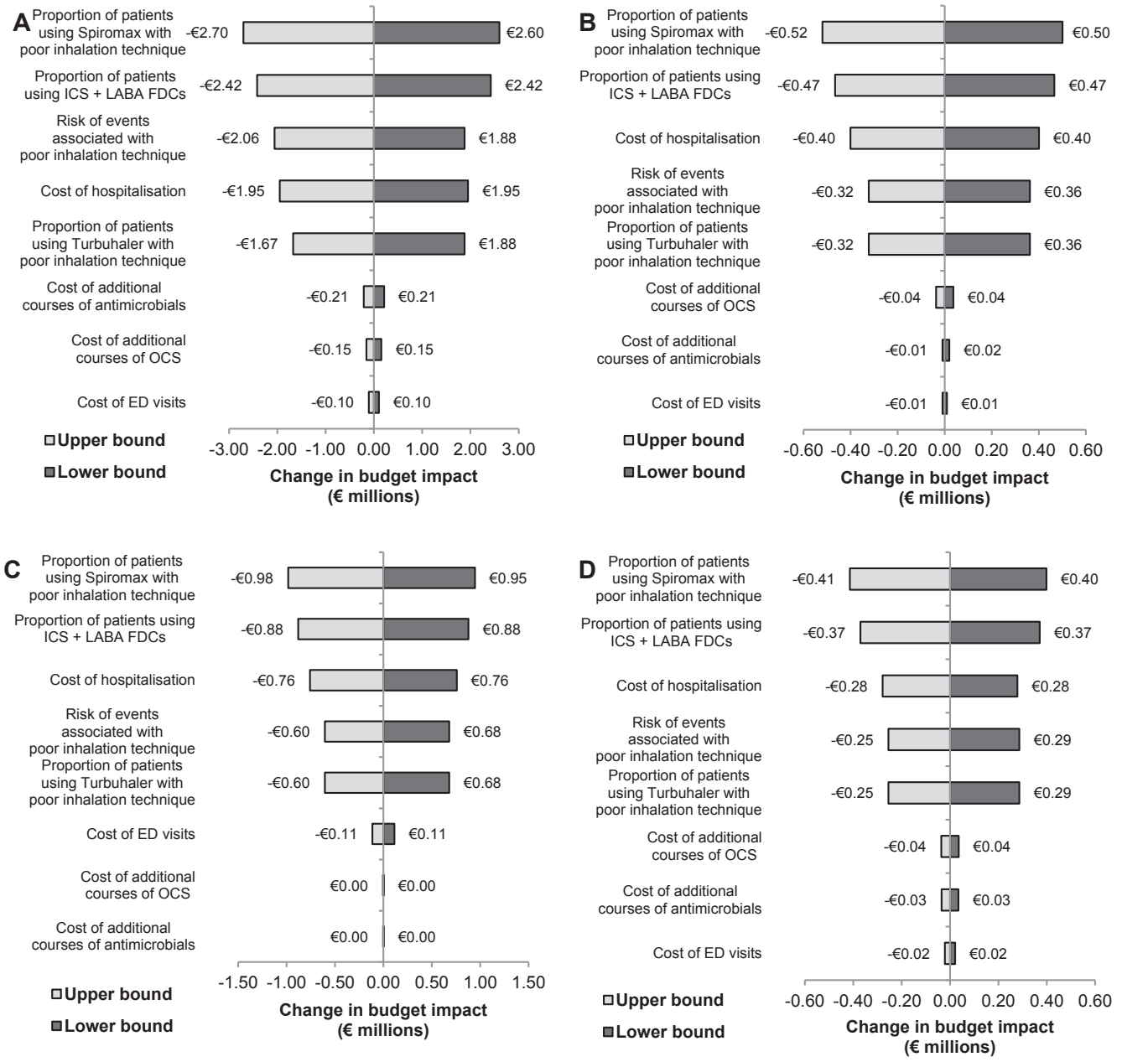


Fig. 3. One-way sensitivity analyses. One-way sensitivity analyses for Germany (A), Italy (B), Sweden (C) and the UK (D). The change in budget impact was recorded following variation of one of the parameters. All parameters were varied ±20%, with the exception of the proportion of patients using ICS + LABA, which was varied by ±10%.

cost savings of €8.07 million, €1.55 million, €2.93 million and €1.23 million in Germany, Italy, Sweden and the UK, respectively.

Competing interests

Alexandra Lewis, Alex Watson and Michael Blackney are employees of Covance Market Access, London. Covance Market Access, London received funding from Teva Pharmaceuticals Europe B.V. to conduct this study and develop the manuscript.

Katharina Kolbe and York Zollner of Econ-Epi, Wentorf/Hamburg received funding from Teva GmbH to deliver German data and validate the model for Germany.

Saku Torvinen and Adam Plich are employees of Teva Pharmaceuticals Europe B.V.

In the last three years, Richard Dekhuijzen and/or his department have received research grants, unrestricted educational grants, and/or fees for lectures and advisory board meetings from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MundiPharma, Novartis, Takeda and Teva Pharmaceuticals Europe B.V.

In the last three years, Andera S Melani has received fees for lectures and advisory board meetings from Almirall, Artsana, AstraZeneca, Chiesi, GlaxoSmithKline, Guidotti/Malesci, MundiPharma, Novartis, and Teva Pharmaceuticals Europe B.V.

Henry Chrystyn has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with some consultant agreements and honoraria for presentations from several pharmaceutical companies that market inhaled products (Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda, MundiPharma, Napp

Pharmaceuticals, NorPharma, Orion, Sanofi, Teva Pharmaceuticals, Truddell Medical International, UCB, Zentiva). He has also received research sponsorship from grant-awarding bodies (EPSRC and MRC).

Authors' contributions

Alexandra Lewis, Michael Blackney, Saku Torvinen and Adam Plich contributed to the development of the model, data collection and validation. Alex Watson performed the country-wise data analysis, and along with Alexandra Lewis and Michael Blackney drafted the manuscript. Richard Dekhuijzen, Henry Chrystyn, Andrea Melani, York Zöllner, Katharina Kolbe, Saku Torvinen and Adam Plich provided critical review of the manuscript and guidance. All authors contributed to the writing of the final manuscript, and have approved it for publication.

Conflict of interest statement

The study was conducted and written by employees of Covance Market Access, London and Teva Pharmaceuticals Europe B.V., in collaboration with Prof P.N.R. Dekhuijzen of Radboud University, Prof H. Chrystyn of the University of Plymouth, Prof A.S. Melani of the Azienda Ospedaliera Universitaria Senese, Dr K. Kolbe of Econ-Epi and Prof Y. Zöllner of the Hamburg University of Applied Sciences. The study was funded by Teva Pharmaceuticals Europe B.V. The model used for this analysis is proprietary, and owned by Teva Pharmaceuticals Europe B.V.

In the last three years, Richard Dekhuijzen and/or his department have received research grants, unrestricted educational grants, and/or fees for lectures and advisory board meetings from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MundiPharma, Novartis, Takeda and Teva Pharmaceuticals Europe B.V.

In the last three years, Andrea Melani has received fees for lectures and advisory board meetings from Almirall, Artsana, AstraZeneca, Chiesi, GlaxoSmithKline, Guidotti/Malesci, MundiPharma, Novartis, and Teva Pharmaceuticals Europe B.V.

Henry Chrystyn has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with some consultant agreements and honoraria for presentations from several pharmaceutical companies that market inhaled products (Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda, MundiPharma, Napp Pharmaceuticals, NorPharma, Orion, Sanofi, Teva Pharmaceuticals, Truddell Medical International, UCB, Zentiva). He has also received research sponsorship from grant-awarding bodies (EPSRC and MRC).

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List of abbreviations

BF	Budesonide + formoterol
COPD	Chronic obstructive pulmonary disease
CPI	Consumer price index
DPI	Dry powder inhaler
ED	Emergency department
ELIOT	Easy low instruction of time
FDC	Fixed dose combination
HCP	Healthcare professional
ICS	Inhaled corticosteroid
LABA	Long-acting β2 agonist
OCS	Oral corticosteroids
UK	United Kingdom

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2017.06.018.

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