

Cost-effectiveness of early intervention with once-daily budesonide in children with mild persistent asthma: results from the START study

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The inhaled Steroid Treatment As Regular Therapy in early asthma (START) study has shown that early intervention with inhaled budesonide in mild persistent asthma improves clinical outcomes in both adults and children. The aim of this study was to estimate the incremental cost-effectiveness of early treatment with budesonide Turbuhaler in children aged 5–10 yr who participated in START. Direct and indirect costs associated with asthma were determined for 1974 children participating in the double-blind, 3-year part of the study. Randomization was to placebo or to budesonide 200 µg once daily in each case in addition to usual asthma care. Cost-effectiveness ratios were calculated from the healthcare payer's and societal perspectives (using US prices). The addition of once-daily budesonide therapy to usual asthma care was associated with 16 additional symptom-free days (SFDs) per child over the 3-yr period ($p < 0.001$), with a substantial reduction (50%) in the mean number of days spent in hospital, and with reduced frequency of emergency room visits and missed school and caregiver work days. From the healthcare payer's perspective (direct costs), the increase in mean direct cost over 3 yr with budesonide was \$169, which translated into an incremental cost of early intervention with budesonide in children of \$10.50 (95% CI \$1.20–33.30) per SFD gained. From the societal perspective, there was a cost reduction over 3 yr of \$192 with budesonide relative to placebo. From a societal perspective, budesonide was therefore dominant. In conclusion, early intervention with once-daily budesonide added to usual asthma care in children with mild persistent asthma is cost-saving from a societal perspective and is acceptably cost-effective when viewed from a healthcare payer perspective.

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It is difficult to overstate the burden imposed by asthma on modern society. Around 150 million people worldwide were estimated to have the disease in the mid-1990s (1) and, in contrast to other conditions, prevalence is increasing as living standards improve (2). Data obtained from US population and healthcare survey data from the National Center for Health Statistics showed that the total cost of asthma for the year 1994

was \$10.7 billion (3). Furthermore, adjustment of costs for the year 1985–94 dollar values suggested that the total cost of asthma had increased by 54.1%, with a 20.4% increase in direct medical expenditures, over the 10-yr period covered (3).

Although these estimates refer to the global asthmatic population, the cost of the disease to health care providers and the community varies

widely across differing severities. It is logical to assume that the greatest proportion of resources is consumed by persons with moderate-to-severe asthma, and this is indeed borne out by research. Canadian data from the early 1990s suggested that the 70% of patients with the mildest asthma accounted for only 13% of the total cost of the disease, while the 10% most severely affected accounted for 54% of the resources consumed (4).

The overall picture, however, may not be as straightforward as these findings indicate. Patients with mild disease form the largest subpopulation of persons with asthma, and are frequently undertreated, particularly in the primary care environment (5, 6). Inappropriate use of asthma medication (specifically overuse of inhaled short-acting β_2 -agonists with underuse of inhaled corticosteroids) is associated with increased levels of symptomatic disease and increased healthcare resource consumption (7), and benefits in terms of both cost and asthma control have been shown in patients with mild asthma treated with a regular inhaled corticosteroid (5).

These observations have particular relevance to the management of children with asthma, as this condition is the most common chronic disease and the most frequent cause of hospitalization in the young (6). Despite the expert recommendation that infants and children with mild persistent asthma be treated with daily anti-inflammatory medication (8, 9), data collected from over 13,000 children aged from 3 to 15 yr have shown the use of such treatment in fewer than 40% of cases overall (6). The implications of these findings are underlined by the specific effects of asthma on children and on those caring for and supervising them. School attendance can be disrupted by the disease, with the number of schooldays lost per year estimated at 10 million in 1997 by one US survey (10). This in turn is likely to interfere with a child's educational achievement and future career prospects, and poses considerable problems for parents and caregivers who have to take time off work unexpectedly to care for a child with asthma. The loss in productivity attributable to this time away from work has been estimated at around \$1 billion each year (10).

Evidence indicates that early use of inhaled corticosteroids improves outcomes in mild, persistent asthma (11–13). However, there is a clear need for reliable data relating to the resource implications of this treatment strategy in children. An economic evaluation was therefore prospectively integrated as part of the inhaled

Steroid Treatment As Regular Therapy in early asthma (START) trial, a long-term international, double-blind, randomized study designed to assess the efficacy of early intervention with the inhaled corticosteroid budesonide in asthma patients with recent-onset mild persistent asthma. The results of this economic evaluation have been reported previously (14, 15). However, given the importance of asthma in children, a sub-group analysis of the health economic results was conducted for children <11 yr of age. The results of this analysis will be presented here.

Methods

As previously reported, the START trial consisted of an initial 3-year, double-blind phase in which once-daily budesonide was compared with placebo, and a 2-year open-label extension during which time all patients received budesonide. The 3-year phase, for which efficacy results pertaining to the total study population have already been published (16), included 1974 children aged 5–10 yr, 1000 of whom received budesonide 200 μ g once daily via TurbuhalerTM and 974 of whom received placebo (lactose) via TurbuhalerTM, in addition to their usual asthma medication and clinical care. The efficacy results for the double-blind period show a significantly decreased risk of a severe asthma-related exacerbation and improved asthma control in patients randomized to budesonide for both the entire study population of 7165 individuals (16) and the subpopulation of children aged from 5 to 10 yr (17).

Economic analysis of clinical findings has been driven by the ever-increasing need for efficient use of scarce health service resources. Accordingly, in addition to comparing the clinical efficacy and effect on bronchial function of budesonide with those of placebo, the START trial was prospectively designed to examine asthma-related costs so that economic factors linked to budesonide use could be objectively assessed. Thus, the objective of the economic analysis was to relate costs associated with healthcare utilization and loss of work and school time to the primary health outcome of cumulative number of SFDs. This enabled the researchers to determine whether the costs of adding budesonide via TurbuhalerTM to regular treatment in recently diagnosed mild asthma would be offset by reductions in other costs of asthma-related care, and, if not, whether the additional costs were likely to be acceptable in terms of the improvement in health outcomes as measured by the additional number of SFDs. SFD was defined as a 24-hr period with no

asthma symptoms (18). The economics of budesonide usage was analyzed from two perspectives: the *healthcare provider's perspective* which includes all direct healthcare costs incurred over the study period, and the *societal perspective* which includes both healthcare and indirect costs such as those associated with absence from work or school.

Symptoms were measured by 2-wk recall at each clinic visit, and patients and/or their caregivers recorded asthma-related events and asthma control details in notebooks between visits. Collection of these data allowed for estimation of the annual number of SFDs experienced during the 3-year study period. SFD and resource utilization data were pooled for children across the 32 countries involved in START, and cost-effectiveness calculated as the incremental cost incurred for each additional SFD gained (18).

Resource use

Medical resource utilization details were reported by patients and their caregivers after having been collected prospectively during the study. Healthcare resource items captured included days spent in hospital, number of emergency room visits, physician or nurse contacts, telephone contacts, and use of drugs to treat asthma (including study medication). Concomitant medication use as recorded in each patient's Case Report Form was classified as asthma- or non-asthma-related, with the latter group not included within the analysis. Asthma drugs were grouped as follows:

- (i) Short-acting β_2 -agonists
- (ii) Long-acting β_2 -agonists
- (iii) Methylxanthines
- (iv) Cromoglycate and derivatives
- (v) Inhaled corticosteroids (including combination products)
- (vi) Leukotriene antagonists
- (vii) Systemic corticosteroids
- (viii) Other medications (e.g. ipratropium bromide; over-the-counter preparations).

Numbers of days on which school was missed or on which a caregiver had to take time off to look after their sick child (because of asthma) were recorded at follow-up visits.

Unit costs

Unit costs for the US (at 1999 price levels) were applied to the entire dataset because of the large numbers of American patients recruited and because of the availability of reliable and readily

accessible price data (18). The unit cost of a physician visit was derived from the weighted average of the first and a follow-up visit. Costs for visits to nurses or other professionals were calculated on the assumption that such costs would be proportional to the average annual salary for ambulatory care nurses relative to that for family physicians. Cost estimates for drugs were based on US average wholesale prices, reduced by 15% to account for discounting. Costs of infrequently used drugs and medicines not available in the US were derived from the weighted average costs of the most commonly used drugs from within the eight therapeutic classifications (as outlined above).

The cost of a day's absence from school was taken to be the same as that of a day's work lost, and was estimated via the human capital approach. The reason for valuing absence from school in this way is twofold; to be consistent [as this was also carried out in Sullivan et al. (14) and Buxton et al. (15)] and to ensure that the cost-effectiveness results are not biased against children. Mean daily wage rates were estimated by the method of Rice and Max for the US workforce (19). In the main analysis, discounting at an annual rate of 3% was applied to total costs and SFDs.

In sensitivity analyses, results with different discount rates and unit costs were studied. Furthermore, in a sensitivity analysis estimates of cost and SFDs were adjusted for overall mean gross national product (GNP) per capita and for pre-specified baseline socioeconomic and clinical variables by regression analysis. The reason to include GNP per capita was to try to control for differences in treatment patterns between countries (18).

Statistical analysis

Estimates of arithmetic means and variances of SFDs and costs, and covariances between them, were calculated for children aged 5–10 yr by treatment group, with cost data logarithmically transformed (to account for skewed cost distributions) and then back-transformed for presentation (18). For presentation of cost components, costs were computed on the raw data scale to maintain additivity. Statistical analyses were carried out with SAS software version 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

Children constituted 27.6% of the overall study population; the mean age of children was slightly

above 8 yr. Approximately, 60% of children were male. The mean duration of asthma in children was just under 1 yr, and around 40% of children were being exposed to tobacco smoke in the home [see also Chen et al. (17)]. Further details on baseline characteristics are given in Table 1.

Over the 3 yr of the double-blind study period, children receiving once-daily budesonide experienced a mean of 16 additional SFDs compared with those randomized to placebo ($p < 0.001$). In addition, budesonide therapy was associated with a substantial reduction (50%) in the mean number of days spent in hospital, and with the reduced frequency of emergency room visits and missed school and caregiver work days (Fig. 1). The mean of 5.6 SFDs per year (undiscounted) gained by children using budesonide was reduced only marginally when discounting (at 3% yearly discount rate) was applied. Unit costs and 3-year resource use are summarized in Table 2, and 3-yr changes in resource use are illustrated in Fig. 1.

As summarized in Fig. 2, the major cost components in children in both groups were concomitant medication and loss of days at school (children) or work (caregivers). Figure 2 also shows the relative cost contribution of budesonide therapy. Use of budesonide resulted in an increase in mean direct cost over 3 yr of \$169. So, from the healthcare provider's perspective (direct costs), the mean daily net cost to the healthcare system of these benefits translated into an incremental cost-effectiveness ratio of \$10.50 (95% CI \$1.20–33.30) per SFD gained (Table 3). From the societal perspective, however, there was a cost reduction of \$192, related mainly to reductions in concomitant medication usage and school and work days lost (Fig. 2). In terms of

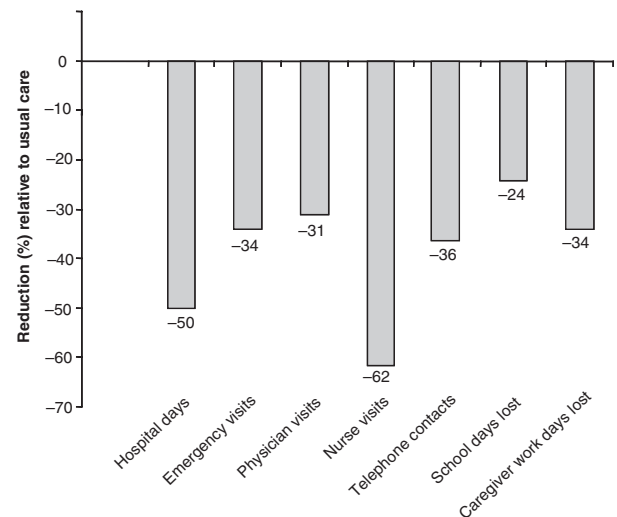


Fig. 1. Reduction in resource consumption over 3 yr in children receiving budesonide. Figures shown are percentages relative to resource use recorded in children receiving the usual care. The reductions in physician visits, nurse visits, telephone contacts and schooldays lost attained statistical significance at $p < 0.05$, and the reduction in hospital days was borderline significant, $p = 0.06$.

Table 2. Unit costs (in \$ at 1999 price levels) and mean resource consumption (in units) over 3 yr by treatment group for children aged 5–10 yr

Item	Unit cost (\$)	3-year consumption	
		Budesonide added to usual care (n = 1000)	Usual care (n = 974)
Direct costs			
Hospital days	694.00	0.20	0.39
Emergency visits	89.00	0.03	0.05
Physician visits	47.00	1.73	2.53
Nurse visits	36.00	0.06	0.17
Telephone contacts	8.00	0.57	0.89
Indirect (non-medical) costs			
School days lost	162.50	4.30	5.67
Caregiver work days lost	162.50	1.45	2.19

Table 1. Baseline characteristics for children aged 5–10 yr at study entry

Characteristic	Budesonide added to usual care group (n = 1000)	Usual care group (n = 974)
Mean age (years) $\pm$ s.d.	8.3 $\pm$ 1.5	8.4 $\pm$ 1.4
Gender (%)		
Male	60.6	59.3
Female	39.4	40.7
Mean duration of asthma before study entry (years) $\pm$ s.d.	0.8 $\pm$ 0.7	0.8 $\pm$ 0.6
Mean proportion of symptom-free days (SFDs) (%) over the 2 wk preceding visit 1	64.8	67.1
Passive smoker (%)	37.9	43.1
Mean FEV ₁ (% predicted) $\pm$ s.d.		
Pre-bronchodilator	85.0 $\pm$ 13.4	85.5 $\pm$ 12.9
Post-bronchodilator	95.8 $\pm$ 14.4	95.9 $\pm$ 13.3

FEV₁ = forced expiratory volume in 1 s; s.d. = standard deviation.

cost-effectiveness from the societal perspective, budesonide was a dominant treatment.

Regression analysis of SFDs and costs showed statistically significant ($p < 0.001$) dependence on per capita GNP and percentage SFD at baseline for children (and all other age groups). Incremental cost-effectiveness was only marginally reduced when calculations were performed with regression-adjusted estimates. Alteration of discount rates had no relevant effect on the incremental cost-effectiveness of budesonide.

Discussion

The START study has shown for the first time, from a long-term and multinational perspective,

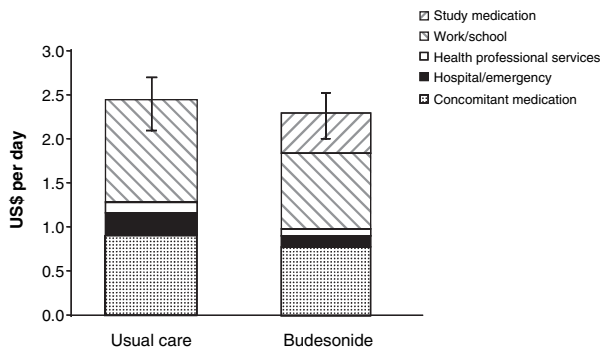


Fig. 2. Components of daily cost of asthma treatment in children aged 5–10 yr. Error bars show 95% CI.

Table 3. Mean 3-year symptom-free days (SFDs) and cost parameters (in \$ at 1999 price levels)

Parameter	Usual care group (n = 974)	Budesonide added to usual care group (n = 1000)
SFDs ± s.e.	948 ± 3.4	964 ± 3.2
Direct (health care) costs (\$) ± s.e.	1347 ± 60	1516 ± 45
Total (societal) costs (\$) ± s.e.	2581 ± 149	2389 ± 108
Direct cost (\$) per additional SFD (95% CI)		10.50 (1.2–33.3)
Societal cost (\$) per additional SFD (95% CI)		Dominant (–38.1–13.7)

CI = confidence interval; s.e. = standard error; SFD = symptom-free day.

that patients with mild persistent asthma benefit from very early intervention with inhaled budesonide. Furthermore, the 'real-world' setting of the trial, whereby restrictions on enrolment were few and study treatment could be added to existing therapy, enhanced the applicability of the study's findings to the daily clinic situation and provided a valuable opportunity to characterize the likely consequences of the widespread use of this type of intervention.

The economic results of START have already shown that early intervention with inhaled budesonide is cost effective across the broad range of ages of patients with asthma (14) and in several different countries (15); the present findings show the particular benefits accrued in young children. In children, the number of school days lost was reduced by 24% ($p < 0.05$) in the budesonide group, relative to the usual care group. Also, the reductions in physician visits, nurse visits and telephone contacts attained statistical significance at $p < 0.05$, and the reduction in hospital days was borderline significant, $p = 0.06$. However, some of the reductions in resource consumption in children aged 5–10 yr were not as marked as in older patients: 50% and 34% reductions in

hospital days and emergency room visits, respectively, when compared with corresponding reductions of close to 70% in the overall population. Patient recall of symptoms and medication use over 2 wk is likely to be an issue with children in particular, although the involvement of motivated caregivers may have helped lessen this effect.

Despite these factors, the cost per additional SFD gained of \$10.50 was less than the global figure of \$11.30 for all ages (14) when direct costs only were considered (healthcare provider's perspective). When indirect costs were included, however, the 5- to 10-yr age group provided the strongest evidence among all subpopulations of the benefit of addition of inhaled budesonide therapy in early asthma. The reductions in numbers of lost school days for children and work days for caregivers showed the early addition of budesonide to usual therapy to be a dominant strategy: cost saving over 3 yr from the societal perspective, in addition to increasing SFDs. This is the most compelling evidence to date of the value of inhaled corticosteroid therapy for children in the early stages of asthma. The cost saving appeared to stem chiefly from the lower dosage of budesonide necessary for this age group relative to adolescents and adults together with the beneficial effect on work time lost by those who care for these children. It is worth highlighting that these results may vary slightly when adopting the unit costs from other countries (15).

As for all treatments, the translation of these benefits from this study to the everyday clinic setting is dependent to a large extent on the maintenance of good rates of adherence to prescribed treatment. This is always a concern when attempting to reproduce encouraging trial findings in the general community, and applies particularly to the use of inhaled asthma therapy (20). It should be reiterated here that TurbuhalerTM was used for the delivery of budesonide in START, and that this device is associated with good adherence and inhaler technique (20), and high levels of patient acceptability and preference relative to pressurized metered dose inhalers (21). Although compliance was not measured in the trial, there were no indications of a reduction in clinical effect with time. This indirectly lends support to an acceptable compliance during all 3 yr in the study.

Furthermore, our results mirror earlier findings in children with asthma, although previous studies have focused on individuals with more pronounced symptoms than those treated in START. A study in 40 patients aged 1–3 yr with

persistent and severe symptoms showed a significant increase in number of SFDs when budesonide was given via a pressurized metered dose inhaler via a spacer device, with a reduction in overall treatment costs relative to placebo of \$9.50 per additional SFD gained (22). In 138 children, aged 5–11 yr, with initially unstable asthma that was stabilized during 4–6 wk treatment with budesonide 200–400 μ g twice daily, the clinical and health outcomes of 12 months' treatment with budesonide 400 μ g/day was compared with sodium cromoglycate 60 mg/day. Total annual cost per patient was 24% (Swedish kronor 4195; \$487; €485) lower in the budesonide than the cromoglycate group, mainly because of a lower cost for asthma medication (23). It is noteworthy that a large proportion of the cromoglycate group switched to budesonide treatment because of poor effect, and despite this cost savings were still found in the budesonide group. In addition, a study in 86 children with troublesome wheezing in Sri Lanka showed a reduction of around 83% in direct and indirect costs when inhaled therapy with budesonide or beclomethasone dipropionate was introduced (24). In this analysis, the mean cost per unit of satisfaction with treatment was reduced from Rs. 255.54 to 5.42.

The economic implications of addition of inhaled budesonide to β_2 -agonist therapy have been assessed in 116 children and teenagers aged from 7 to 16 yr with moderate asthma (25). After a median follow-up of 22 months, frequencies of asthma symptoms and absence from school were significantly lower with budesonide than with placebo, with an incremental cost-effectiveness ratio of 175 Netherlands guilders (NLG) per 10% increase in FEV₁. The cost per SFD gained was estimated to be NLG 10.00. These costs were reduced when the effect of patient drop-outs was accounted for and indirect costs were included. A cohort of patients of age closer to the paediatric subpopulation in START was studied by Ager-toft and Pedersen (26) in a trial in which 216 of 278 children aged 3–11 yr were switched to inhaled budesonide from cromones, theophylline and β_2 -agonists. After follow-up for 2–5 yr, there was an 85% reduction in the rate of hospitalization and an 80% reduction in numbers of exacerbations and unscheduled outpatient treatments. These benefits were accompanied by a 58% reduction in total healthcare costs.

In conclusion, the health economic findings of START are the first to emerge from a controlled study of inhaled budesonide therapy in patients with mild persistent asthma of recent onset. They show early intervention with once-daily

budesonide added to usual asthma care in children with mild persistent asthma saves costs from a societal perspective and is acceptably cost-effective when viewed from a healthcare payer perspective, the clinical benefits being achieved at increased annual costs of \$56 per patient. These results also show concordance with other findings in children with asthma treated with budesonide. These children formed a subpopulation of the START study, and further work to build on these findings could be carried out in larger numbers of patients in a dedicated trial in young children with early disease. The present findings suggest that budesonide delivered via Turbuhaler™ might also confer benefit in terms of patient quality of life and reduction of disease burden in such children, and future research should ideally also focus on these issues. The significance of the findings of this analysis is underlined by the fact that patients randomized to placebo in the START trial continued to receive their regular asthma medication and hence would have been expected to maintain a reasonable degree of asthma control at the very least.

References

1. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention: NHLBI/WHO Workshop report. Bethesda, MD: National Heart, Lung and Blood Institute. National Institutes of Health, Publication no. 95-3659, 1995.
2. BARNES PJ, JONSSON B, KLIM JB. The costs of asthma. *Eur Respir J* 1996; 9: 636–42.
3. WEISS KB, SULLIVAN SD, LYTTLE CS. Trends in the cost of illness for asthma in the United States, 1985–1994. *J Allergy Clin Immunol* 2000; 106: 493–9.
4. Boston Consulting Group. The Cost of Adult Asthma in Canada. Princeton, NJ: Communications Media for Education, Inc., 1993.
5. O'BYRNE PM, CUDDY L, TAYLOR DW, BIRCH S, MORRIS J, SYROTIUK J. Efficacy and cost benefit of inhaled corticosteroids in patients considered to have mild asthma in primary care practice. *Can Respir J* 1996; 3: 169–75.
6. DONAHUE JG, FUHLBRIGGE AL, FINKELSTEIN JA, et al. Asthma pharmacotherapy and utilization by children in 3 managed care organizations. The Pediatric Asthma Care Patient Outcomes Research team. *J Allergy Clin Immunol* 2000; 106: 1108–14.
7. ANIS AH, LYND LD, WANG XH, et al. Double trouble: impact of inappropriate use of asthma medication on the use of healthcare resources. *Can Med Assoc J* 2001; 164: 625–31.
8. National Asthma Education and Prevention Program (NAEPP). Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute. Bethesda, MD: National Institutes of Health, 1997.
9. National Asthma Education Prevention Program (NAEPP). Expert Panel Report: guidelines for the

- diagnosis and management of asthma – update on selected topics. *J Allergy Clin Immunol* 2002; 110: S141–S219.
10. GlaxoSmithKline. Asthma in America: a landmark survey, 1998. Available from: <http://asthmainamerica.com> [accessed 3 March 2006].
11. HAAHTELA T, JÄRVINEN M, KAVA T, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991; 325: 388–92.
12. AGERTOFT L, PEDERSEN S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; 88: 373–81.
13. SELROOS O, PIETINALHO A, LÖFROOS A-B, RISKÄ H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995; 108: 1228–34.
14. SULLIVAN SD, BUXTON M, ANDERSSON LF, et al. Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 2003; 112: 1229–36.
15. BUXTON M, SULLIVAN SD, ANDERSSON FL, et al. Country-specific cost-effectiveness of early intervention with budesonide in mild asthma. *Eur Respir J* 2004; 24: 568–74.
16. PAUWELS RA, PEDERSEN S, BUSSE WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; 361: 1071–6.
17. CHEN Y-Z, BUSSE W, PEDERSEN S, TAN W, LAMM C-J, O'BYRNE PM. Early intervention of recent onset mild persistent asthma in children aged under 11 years: the Steroid Treatment As Regular Therapy in early asthma (START) trial. *Pediatr Allergy Immunol* 2006; 17 (Suppl. 17): 7–13.
18. 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; 22: 420–37.
19. HADDIX AC, TEUTSCH SM, SHAFFER PA, DUNNET DO. *Prevention Effectiveness: A Guide to Decision Analysis and Prevention Effectiveness*. Oxford, UK: Oxford University Press, 1996.
20. COCHRANE MG, BALA MV, DOWNS KE, MAUSKOPF J, BEN-JOSEPH RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices and inhalation technique. *Chest* 2000; 117: 542–50.
21. JADAD AR, SULLIVAN C, LUO D, ALLEN IE, ROSS SD, SHEINHART IA. Patient preferences for Turbuhaler or pressurized metered dose inhalers (pMDIs) in the treatment of obstructive airways disease: a systematic review. *J Allergy Clin Immunol* 2000; 105: S17.
22. CONNETT GJ, LENNEY W, MCCONCHIE SM. The cost effectiveness of budesonide in severe asthmatics aged one to three years. *Br J Med Econ* 1993; 6: 127–34.
23. ANDERSSON F, KJELLMAN M, FORSBERG G, MÖLLER C, ARHEDEN L. Comparison of the cost-effectiveness of budesonide and sodium cromoglycate in the management of childhood asthma in everyday clinical practice. *Ann Allergy Asthma Immunol* 2001; 86: 537–44.
24. PERERA BJ. Efficacy and cost effectiveness of inhaled steroids in asthma in a developing country. *Arch Dis Child* 1995; 72: 312–5.
25. RUTTEN-VAN MÖLKEN MP, VAN DOORSLAER EK, JANSSEN MC, VAN ESSEN-ZANDVLIET EE, RUTTEN FF. Cost effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator monotherapy in children with asthma. *Pharmacoeconomics* 1993; 4: 257–70.
26. AGERTOFT L, PEDERSEN S. Cost-effectiveness of inhaled budesonide in children with chronic asthma. *Am J Respir Crit Care Med* 1997; 155: A351.