Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined three treatments for patients with persistent asthma:

- budesonide-formoterol Symbiotic Maintenance and Reliever Therapy (SMART) (160/4.5 μg twice daily plus additional doses as required, one inhalation twice daily);
- budesonide-formoterol (BUD-FORM) (320/9 μg twice daily plus as-needed terbutaline, one inhalation twice daily); and
- salmeterol-fluticasone (SAL-FLU) (50/250 μg twice daily plus as-needed terbutaline, two inhalations twice daily).

All treatments were given to patients suffering with asthma uncontrolled by inhaled corticosteroids (ICS) alone.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis

Study population
The study population comprised patients aged 12 years or older with asthma for at least 6 months, who had been using ICS for at least 3 months and at a constant dose (≥500 μg/day) for 1 month or more.

Setting
The setting was primary care. The economic study was carried out in the UK and in Australia.

Dates to which data relate
Clinical data and information on resource consumption were derived from a study published in 2007. The price year was 2004.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the analysis of effectiveness.

Study sample
Of the 4,399 patients initially identified, 3,335 were eligible and were included in the final study sample. There were 1,123 patients (43% men) in the fixed-dose SAL-FLU group, 1,105 patients (41% men) in the BUD-FORM group and 1,107 patients (43% men) in the SMART group. The mean age of the patients was 38 years (age range: 12 to 83) in the fixed-dose SAL-FLU group, 38 years (age range: 12 to 83) in the BUD-FORM group and 38 years (age range: 11 to 79) in the SMART group. Other details about patient enrolment and selection were reported in the primary clinical study, but not in this economic analysis.

Study design
This was a prospective, double-blind, randomised clinical trial, which was carried out in 235 centres in 16 countries. The length of follow-up was 6 months. The loss to follow-up was not reported. Details about randomisation and other
characteristics of the study design were not reported in this paper, but the reader was referred to the primary publication.

**Analysis of effectiveness**

It was not stated whether all of the patients included in the study sample were accounted for in the analysis of effectiveness. The primary clinical end point used in the current analysis was the rate of severe asthma exacerbations (number of events/patient in 6 months in each treatment group). This was defined as deterioration in asthma requiring hospitalisation or emergency room treatment, or use of oral steroids for 3 days or more. This end point was compared among treatment groups using a Poisson regression model that allowed the calculation of rate ratios (RRs) and confidence intervals (CIs). Other clinical measures were the forced expiratory volume in 1 second, asthma control measured using the five-item Asthma Control Questionnaire, and quality of life assessed using the Standardized Asthma Quality of Life Questionnaire. The number of days with oral steroids for the treatments was also assessed. At baseline, the study groups were comparable in terms of their clinical and demographic factors, as well as their employment status.

**Effectiveness results**

The mean rate of severe exacerbations in a 6-month period was 0.12 events per patient in the SMART group, 0.16 in the fixed-dose BUD-FORM group and 0.19 in the fixed-dose SA-/FLU group.

The results suggested that SMART reduced the rate of severe asthma exacerbations by 28% compared with fixed-dose BUD-FORM (RR 0.72, 95% CI: 0.57 to 0.90; p=0.0048) and by 39% compared with fixed-dose SAL-FLU (RR 0.61, 95% CI: 0.49 to 0.76; p<0.001).

Other clinical outcomes were comparable between the groups. However, time to first severe asthma exacerbation was significantly longer in the SMART group than in the other two treatment groups. Similarly, the rate of exacerbations requiring hospitalisation or emergency room treatment was significantly reduced in the SMART group compared with the SAL-FLU group (39% reduction; p=0.0015). Finally, the numbers of days with oral steroids in the SMART group were reduced by 41% and 45%, respectively, compared with the fixed-dose BUD-FORM and SAL-FLU groups.

**Clinical conclusions**

The effectiveness analysis showed that SMART was more effective in reducing the rate of severe asthma exacerbations than the other conventional treatments for asthma.

**Measure of benefits used in the economic analysis**

The summary benefit measure used in the economic analysis was the rate of asthma exacerbations. This was derived directly from the effectiveness analysis.

**Direct costs**

The analysis of the direct costs was carried out from the perspective of the health care system. It included the costs associated with medications (study drugs and oral steroids) and other services such as ambulance transport, days in hospital (general or intensive care), visits to health care providers (emergency room, specialist, primary care physician or other health care professionals) and home visits (by physicians and other health care professionals). Scheduled visits and associated tests were not included. The unit costs were presented separately from the quantities of resources used. Resource use information was gathered prospectively using individual data for patients enrolled in the clinical trial. The patients were provided with a notebook to record all asthma-related costs. The costs were estimated using national registries and surveys. Discounting was not relevant as the time horizon of the analysis was 6 months. The price year was 2004.

**Statistical analysis of costs**

The costs and quantities were treated stochastically since CIs were calculated by means of a bootstrapping technique. The statistical significance of differences was tested using typical statistical tests.

**Indirect Costs**

Productivity costs were included in the analysis when the societal perspective was adopted. These costs included the
number of days on which patients were unable to perform their usual daily activities (i.e. school work, employment work or household work), plus the number of days when a person assisting the patient was unable to perform their usual daily activities as a result of the patient's asthma. Costing was applied only for employed patients and carers. Resource use and the unit costs were presented separately. Productivity costs were estimated using national average wage rates. Resource use was based on actual consumption observed in the clinical trial. The price year was 2004.

**Currency**

UK pounds sterling (£) and Australian dollars (AUD).

**Sensitivity analysis**

Two deterministic sensitivity analyses were carried out to deal with the issue of uncertainty. First, a subgroup analysis was performed to investigate whether the results from the pooled data set of resource use were comparable with those from patients in South Africa, Australia and those European countries with similar health care systems. Second, the cost of BUD-FORM was increased to assess the impact of changes in medication costs.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.

**Cost results**

In Australia, the total direct costs per patient over the 6-month study period were AUD 472 with fixed-dose SAL-FLU, AUD 353 with fixed-dose BUD-FORM and AUD 318 with SMART.

The total productivity costs per patient over the 6-month study period were AUD 177 with fixed-dose SAL-FLU, AUD 204 with fixed-dose BUD-FORM and AUD 170 with SMART.

The total costs per patient over the 6-month study period were AUD 649 with fixed-dose SAL-FLU, AUD 556 with fixed-dose BUD-FORM and AUD 486 with SMART.

In the UK, the total direct costs per patient over the 6-month study period were £287 with fixed-dose SAL-FLU, £278 with fixed-dose BUD-FORM and £205 with SMART.

The total productivity costs per patient over the 6-month study period were £92 with fixed-dose SAL-FLU, £105 with fixed-dose BUD-FORM and £88 with SMART.

The total costs per patient over the 6-month study period were £378 with fixed-dose SAL-FLU, £383 with fixed-dose BUD-FORM and £292 with SMART.

The statistical analysis showed that the total costs were significantly lower for SMART in comparison with SAL-FLU when both Australian and UK costs were used, \( p=0.0036 \) and \( p=0.0026 \), respectively) and in comparison with higher fixed-dose BUD-FORM when UK costs were used, \( p=0.0014 \).

The cost of the study drugs accounted for the majority of both the direct costs (78 to 87%) and total costs (50 to 63%) for all treatments.

**Synthesis of costs and benefits**

An incremental analysis was undertaken in order to combine the costs and benefits of the alternative treatments. However, cost-effectiveness ratios were not calculated as SMART dominated the other two treatments. Specifically, SMART was less expensive and more effective than SAL-FLU when using both Australian and UK data, and was also dominant compared with BUD-FORM when UK costs were used. When Australian economic data were applied, a weak dominance was observed as BUD-FORM was less effective than, but as expensive as SMART. These results held for both perspectives.

The results of the sensitivity analysis did not alter the conclusions of the base case analysis.
Authors' conclusions
The authors concluded that budesonide-formoterol Symbiotic Maintenance and Reliever Therapy (SMART) used for the treatment of asthma was more effective and less expensive than higher fixed-dose budesonide-formoterol and salmeterol-fluticasone combinations. Thus, SMART could be considered a cost-effective or dominant treatment.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear as they were selected in the primary clinical trial. They are commonly used medications for the treatment of asthma. The dosages were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was derived from a published study. The use of a clinical trial should have enhanced the internal validity of the analysis and the robustness of the clinical estimates. A positive feature of the clinical analysis was the use of a large sample of patients enrolled in several countries around the world. The use of double-blinding and the multi-centre nature of the study represent further strong features of the analysis. Further details of the design of the study were reported in the primary publication but not in this study.

Validity of estimate of measure of benefit
The benefit measure was derived directly from the effectiveness analysis and represents an intermediate end point. However, the number of exacerbations is commonly used in studies evaluating the impact of asthma treatment on patient health.

Validity of estimate of costs
The analysis of the costs was carried out satisfactorily. Two perspectives were adopted, which might be relevant for different payers. An extensive description of the unit costs and resource quantities was provided, which enhances the possibility of replicating the analysis in other settings. Resource use was pooled across centres and countries, which might be inadequate given that the economic analysis was performed in Australia and the UK. However, the impact of variations in resource use and some costs was investigated in the sensitivity analysis, and the subgroup analysis confirmed the results for the whole sample. Statistical analyses were performed on estimates of costs and resource use. The price year was reported, thus facilitating reflation exercises in other time periods.

Other issues
The authors reported the results from other studies which had shown similar findings to those achieved in the current economic evaluation. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analysis, in which the use of alternative values for some economic estimates was investigated. Although the use of a longer time horizon would have been more appropriate, the authors pointed out that the 6-month results used in the current study were comparable to the clinical improvements observed in studies with a longer timeframe.

Implications of the study
The study results agree with recent recommendations that support the use of SMART for asthma patients.

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Other publications of related interest
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**Indexing Status**
Subject indexing assigned by NLM

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Adolescent; Adult; Aged; Aged, 80 and over; Asthma /drug therapy /economics; Australia; Bronchodilator Agents /economics /therapeutic use; Budesonide /administration & dosage /economics; Child; Cost of Illness; Cost-Benefit Analysis; Dose-Response Relationship, Drug; Double-Blind Method; Drug Combinations; Drug Costs; Drug Therapy, Combination; Economics, Pharmaceutical; Ethanolamines /administration & dosage /economics; Female; Formoterol Fumarate; Great Britain; Humans; Male; Middle Aged

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