An economic evaluation of adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthma patients: the ASSURE study

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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 use of the Symbicort Turbohaler, a budesonide/formoterol combination, for the treatment of patients with asthma in primary care. The drug combination was administered as either an adjustable maintenance dosing plan (SAMDP) or as a fixed dose. Under the SAMDP, the drug combination was administered in 1, 2 or 4 inhalations twice daily according to symptoms, following a simple plan. Under the fixed-dose plan, the drug combination was administered according to need, 2 inhalations twice daily. The doses administered (budenoside/formoterol) appear to have been either 80/4.5 microg (metered-dose equivalent 100/6 microg) or 160/4.5 microg (metered-dose equivalent 200/6 microg). Further details of the adjustable dosing strategy were reported in the paper.

Type of intervention
Treatment

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years or older with asthma.

Setting
The setting was primary care. The economic analysis was conducted in the UK.

Dates to which data relate
The dates to which the effectiveness data and some of the resource data related were not reported. Data on most items of resources used were collected between 1999 and 2001. The unit costs related to the period between 1999 and 2001. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a single study.

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

Study sample
Although sample size calculations were not reported, the authors commented that the study was adequately powered to detect differences in the primary outcome considered in the effectiveness analysis. Patients were included in the study...
if they had at least 6 months' history of asthma prior to their first visit, and were maintained on a dose of 400 to 2,000 microg/day of inhaled corticosteroid at the time of recruitment. A total of 1,719 patients from 365 general practices and hospital centres in the UK were enrolled in the study. From this total, 1,553 were randomised to either the SAMDP group (782 patients in total) or to the fixed-dose group (771 patients). Details of those patients who withdrew prematurely were not reported in the study, but the authors stated they were reported elsewhere (Ind et al. 2004, see 'Other Publications of Related Interest' for bibliographic details).

The patients had a mean age of 48.8 (standard deviation, SD=14.9) years in the SAMDP group and 48.0 (SD=14.8) years in the fixed-dose group. The proportion of females was 62% (SAMDP group) versus 59% (fixed-dose group). The mean height of the patients was 166 (SD=10) cm in the SAMDP group and 167 (SD=10) cm in the fixed-dose, while the mean weights were 77.5 (SD=17.0) kg and 78.4 (SD=16.7) kg, respectively. The mean duration of asthma was 16.3 (SD=13.5) years for SAMDP patients and 16.0 (SD 13.6) for fixed-dose patients.

Study design
This was a multi-centred, pragmatic randomised, open-label, parallel-group study that was carried out in 365 general practices and hospital centres in the UK. The method used to randomly allocate patients was not reported, although the authors stated that further information about treatment allocation was reported in a related study (Ind et al. 2004, see 'Other Publications of Related Interest' for bibliographic details). The patients were followed up over 16 weeks. This 16-week period comprised a 4-week run-in period before randomisation was performed, and a further 12-week period after randomisation. The authors reported that some patients withdrew from the study during the follow-up period, leaving 1,291 evaluable patients (653 in the SAMDP group and 636 in the fixed-dosing group; note, this totals 1,289 patients).

Analysis of effectiveness
It appears that the basis for the effectiveness analysis was treatment completers only. The primary health outcome used in the analysis was the net proportion of patients experiencing clinically significant improvement in quality of life (QoL) during the randomisation period in comparison with the run-in period. The improvement in QoL was defined as an increase in the mini-Asthma Quality of Life Questionnaire summary score of greater than 0.5. The secondary effectiveness outcomes used were symptom-free days (SFDs) and SFDs without a short-acting beta-agonist (SABA; i.e. day without symptoms, without asthma-related night-time awakenings, and without the use of a SABA). The study groups were comparable at baseline in terms of their demographics and disease characteristics (i.e. age, gender, height, weight and duration of asthma).

Effectiveness results
During the first 4 weeks, a net benefit in QoL was reported by 54.3% of the patients (95% confidence interval, CI: 48.9 - 58.2). During the following 12 weeks, an additional net benefit was reported by 1% of the patients in the SAMDP group (95% CI: -3.7 - 6.3) and by 5.7% of patients in the fixed-dose group (95% CI: 0.4 - 10.9). No statistically significant differences between the study arms were detected, (p>0.05).

The mean percentage of SFDs with no SABA use was 48% in the SAMDP group (95% CI: 45 - 50) versus 49% in the fixed-dose group (95% CI: 47 - 52). The mean percentage of SFDs was 59% in the SAMDP group (95% CI: 57 - 62) versus 58% in the fixed-dose group (95% CI: 55 - 61). No statistically significant differences were found in the secondary effectiveness end points.

Clinical conclusions
No statistically significant difference in effectiveness was found between groups during the study period. Therefore, there was no evidence that self-management led to a deterioration in asthma control.

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic evaluation since there was no evidence of differences in the
effectives between the study groups. Consequently, the authors reported that a cost-minimisation analysis was performed.

**Direct costs**
The cost/resource boundary of the study was that of the UK NHS. The costs of the health services included in the economic evaluation referred to the following categories:

- study medication;
- SABA usage;
- the number and type of health care contacts (including diagnostic investigations);
- asthma-related hospitalisations; and
- relevant concomitant and asthma-related medications.

The unit costs were derived from actual data, mainly from published sources (e.g. the 2001 British National Formulary), a hospital source (2000) and the Royal London Trust Tariff (1999). Resource use was derived from patient diary cards, while patient data related to medication were derived from case report forms. The costs of study visits and investigations were not included in the analysis as they did not reflect the normal treatment of asthma in the UK. The unit costs were reported separately from the quantities of resources used. The unit costs were reflated to 2001 costs by using HCHS indices when required. Discounting was not relevant on account of the short timeframe of the analysis. The costs reported were the expected daily and annual costs per patient, and the estimated annual NHS expenditure for patients treated with either SAMDP or a fixed-dose strategy.

**Statistical analysis of costs**
A non-parametric bootstrap analysis was performed to generate CIs around the estimated costs per patient, taking the distribution presented by the cost data into consideration.

**Indirect Costs**
The indirect costs were not considered in the economic analysis.

**Currency**
UK pounds sterling ( £ ).

**Sensitivity analysis**
One-way sensitivity analyses were conducted to assess the uncertainty related to variability in the data. The variables investigated were the percentage of asthma patients treated at Step 3, the percentage of the Step 3 asthma patients currently self-managed, and the inclusion of the education costs to estimate the costs associated with the SAMDP treatment group. The ranges of sensitivity analyses were derived from published literature and from authors' assumptions.

**Estimated benefits used in the economic analysis**
See the Effectiveness Results section.

**Cost results**
The total per patient daily cost was 1.13 (95% CI: 1.08 - 1.18) in the SAMDP group and 1.31 (95% CI: 1.27 - 1.34) in the fixed-dose group. The difference between the groups was statistically significant, (p<0.001).
The mean per patient daily cost of study medication, which was the largest component of daily cost, was 0.93 in the SAMDP group and 1.08 in the fixed-dose group.

Based on the estimate that 40,000 asthma patients might be switched to an adjustable dosing regimen, this study suggested potential annual savings to the NHS of over 2.6 million.

One-way sensitivity analyses indicated that the potential saving was between 1.2 and 3.9 million.

**Synthesis of costs and benefits**
The costs and benefits were not combined as a cost-minimisation analysis was carried out.

**Authors’ conclusions**
Compared with fixed dosing, adjustable dosing with the budesonide/formoterol combination was associated with equivalent quality of life (QoL) and significantly reduced costs in adults with Step 3 asthma.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. Fixed dosing was selected as the comparator because it represented common practice in the authors' setting. You should decide whether it represents a valid option in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness was based on an apparently well-designed clinical trial, which was appropriate for the study question. The study sample appears to have been representative of the study population, although the methods of sample selection and randomisation were not reported in the paper but in another published study. The groups were shown to have been comparable at analysis in terms of the baseline patient characteristics.

**Validity of estimate of measure of benefit**
No summary measure of benefit was used in the study as a cost-minimisation analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**
The perspective adopted in the cost analysis was that of the UK NHS. Most of the costs relevant to this perspective were included in the analysis, although some relevant costs were excluded. For instance, the costs of protocol-driven visits and those associated with the required clinician or nurse time to educate the patient about adjusted dosing and to train them in the use of self-management plans were excluded. These omissions might have led to an underestimation of the true costs associated with the SAMDP strategy. The indirect costs were not estimated because of the perspective adopted. No discounting was performed, which was appropriate as the time horizon was shorter than 2 years. The price year was specified. The resource quantities were reported separately from the unit costs, and sufficient details of items of resource use and unit cost were given. The costs were treated stochastically and statistical comparisons were carried out. The above factors enhanced the validity of the cost results and would make future reflation exercises in other settings easier to perform. Sensitivity analyses on the costs were performed, which will enhance the generalisability of the cost results to other settings.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies, showing that other studies reported better results in terms of effectiveness for the adjusted-dose strategy. They commented that these differences may have arisen on account of the longer time horizon considered in the studies compared. The authors do not appear to have presented their results selectively and the conclusions reflected the scope of the analysis. The authors
acknowledged certain limitations in relation to the generalisability of the results. First, diary data were based on patient recall, the validity of which has yet to be established for medication usage. Second, given that asthma is a chronic disease and the timescale was limited to a 12-week period following randomisation, a longer time period would have been preferable for capturing the nature of asthma.

**Implications of the study**
The study results suggested that adjustable maintenance dosing with budesonide/formoterol can provide equivalent QoL to fixed dosing at significantly lower cost. The widespread adoption of adjustable dosing could result in significant cost-savings across the NHS.

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**Other publications of related interest**


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