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
Four treatments for patients with persistent symptoms of asthma were examined:

- low-dose budesonide (total daily dose 200 microg) plus placebo;
- low-dose budesonide plus formoterol (total daily dose 24 microg);
- moderate-dose budesonide (total daily dose 800 microg) plus placebo; and
- moderate-dose budesonide plus formoterol (total daily dose 24 microg).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 to 70 years who had had asthma for at least 6 months, had been treated with an inhaled corticosteroid for at least 3 months, and had a daily pre-run in corticosteroid dose of less than 1,600 microg or 800 microg.

Setting
The setting was primary and secondary care. The economic study was carried out in the UK, Sweden and Spain.

Dates to which data relate
The effectiveness data and some resource use data were derived from a study published in 1997. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was, in part, carried out prospectively on the same sample of patients as that used in the effectiveness study.
Study sample
Limited information on the sample selection was reported since the trial had been published already. A sample of 852 patients was included in the study. The number of patients in each group was not reported.

Study design
This was a prospective, double-blind, randomised clinical trial, which was carried out in 9 countries over a 1-year follow-up period. Of the randomised patients, 81% completed the study. Reasons for withdrawal were the recurrence of severe exacerbations (if patients experienced three severe exacerbations within 3 months, or five during the 12-month period), adverse events, non-compliance with study procedures, incorrect randomisation and lost to follow-up.

Analysis of effectiveness
The outcome measures used in the effectiveness analysis were the numbers of mild and severe exacerbations, the number of symptom-free days (SFDs) and the number of episode-free days (EFDs).

A mild exacerbation was defined as 2 consecutive days with any combination of the following: a peak expiratory flow (PEF) in the morning that was more than 20% below the baseline value; the use of more than three additional inhalations of terbutaline per 24 hours in comparison with the baseline period; awakening at night due to asthma.

A severe exacerbation was defined as requiring treatment with oral glucocorticoids, as judged by the investigator; and/or a decrease in PEF as measured in the morning, on 2 consecutive days, of more than 30% below the baseline value.

An EFD was defined as a day that satisfied all of the following criteria: a morning PEF greater than 80% of baseline, no inhalation of a beta-2-agonist, no asthma symptoms, no awakenings at night due to asthma and no adverse events.

An SFD was defined as a day with no symptoms.

There was no information on the comparability of the study groups at baseline.

Effectiveness results
The number of mild exacerbations was:

- 19.5 with budesonide 200 microg only and 11.6 with formoterol 24 microg added, (p<0.001);
- 13.6 with budesonide 800 microg only and 7.9 with formoterol 24 microg added, (p<0.01).

The number of severe exacerbations was:

- 1.8 with budesonide 200 microg only and 1.3 with formoterol 24 microg added, (p<0.01);
- 0.9 with budesonide 800 microg only and 0.5 with formoterol 24 microg added, (p<0.01).

The number of SFDs was:

- 209 with budesonide 200 microg only and 247 with formoterol 24 microg added, (p<0.01);
- 222 with budesonide 800 microg only and 263 with formoterol 24 microg added, (p<0.01).

The number of EFDs was:

- 152 with budesonide 200 microg only and 186 with formoterol 24 microg added, (p<0.01);
- 167 with budesonide 800 microg only and 200 with formoterol 24 microg added, (p<0.05).
Clinical conclusions
The effectiveness analysis showed that the addition of formoterol to budesonide treatment for patients with persistent asthma significantly reduced the frequency of mild and severe exacerbations. It also increased the number of SFDs and EFDs.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of SFDs. This was derived directly from the clinical study.

Direct costs
Discounting was not relevant since the costs were incurred during a short timeframe. The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were medication, visit to a general practitioner (GP), a specialist or a nurse, house-call by physician and nurse, phone-call to physician or nurse, emergency unit visit and admission to hospital. The cost/resource boundary of the third-party payer was adopted in the analysis of the direct costs. Resource use was estimated using data derived from a panel of experts (including specialists in pulmonary medicine and GPs), which were contacted in the three countries. Data on medication use were derived from the FACET study. The costs were derived from official price lists for the three countries. All the costs were adjusted to 1999 values using the local consumer price index.

Statistical analysis of costs
The costs were presented as average values with confidence intervals.

Indirect Costs
The indirect costs (i.e. productivity losses due to days absent from work) were included in a secondary analysis where a societal perspective was adopted. Data on resource use were derived from the panel of experts. The source of the costs was not reported, but was available from the authors. The unit costs were presented separately from the quantities of resources used. The issues of discounting and the price year were similar to those in the analysis of the direct costs.

Currency
UK pounds sterling (£), Swedish kroner (SEK), and Spanish pesetas (PES). These converted to Euros (Euro) at the rate for September 2000: Euro 1 = 0.613 = SEK 8.39 = PES 166.39.

Sensitivity analysis
A sensitivity analysis was carried out by adopting a societal perspective and including the indirect costs associated with the treatment strategies. A threshold analysis was also performed to examine the percentage by which the physicians’ estimates of costs for a mild and severe exacerbation would have to be changed to reverse the results.

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

Cost results
In the UK, the total direct costs were Euro 1,159 with budesonide 200 plus formoterol, Euro 968 with budesonide 200, Euro 1,218 with budesonide 800 plus formoterol, and Euro 947 with budesonide 800.

In Sweden, the total direct costs were Euro 2,161 with budesonide 200 plus formoterol, Euro 2,710 with budesonide 200, Euro 1,638 with budesonide 800 plus formoterol, and Euro 1,924 with budesonide 800.

In Spain, the total direct costs were Euro 1,310 with budesonide 200 plus formoterol, Euro 1,336 with budesonide 200,
Euro 1,143 with budesonide 800 plus formoterol, and Euro 1,040 with budesonide 800.

The additional cost of formoterol was completely offset by the reduction in other direct costs (mainly associated with the treatment of mild and severe exacerbations) in Sweden and in Spain (when added to budesonide 200), and partially offset in the UK and Spain (when added to budesonide 800).

**Synthesis of costs and benefits**

An incremental cost-effectiveness ratio (ICER; i.e. the additional cost per SFD avoided) was calculated to combine the costs and benefits of the alternative strategies.

In the UK, the ICER with budesonide 200 plus formoterol over budesonide 200 alone was Euro 4.67. The ICER with budesonide 800 plus formoterol 800 over budesonide 800 alone was Euro 6.60.

In Sweden, formoterol plus budesonide treatments dominated budesonide alone.

In Spain, budesonide 200 plus formoterol dominated budesonide 200 alone. The ICER with budesonide 800 plus formoterol over budesonide 800 was Euro 2.51.

The cost offsets were larger in all three countries when adding formoterol to the low dose of budesonide. However, in all three countries the combination of the moderate dose of budesonide and formoterol was the most cost-effective alternative.

The sensitivity analysis showed that from a societal perspective, the addition of formoterol led to cost-savings in all countries (the cost of formoterol was totally offset by the reduction in indirect costs).

The threshold analysis showed that the direct costs of exacerbations would need to increase by 69% (low-dose budesonide plus formoterol) and 135% (moderate-dose budesonide plus formoterol) over the base-case estimates for the formoterol costs to be completely offset in the UK.

In Sweden, the exacerbation costs would need to be reduced by 58% (low-dose budesonide plus formoterol) and 41% (moderate-dose budesonide plus formoterol) to reverse the outcome (i.e. negate the cost-savings).

To reverse the outcome in Spain, the cost estimate would need to decrease by 6% for low-dose budesonide, or increase by 31% for moderate-dose budesonide.

**Authors’ conclusions**

In general, the higher costs of adding formoterol to budesonide in patients with persistent asthma were partially or totally offset by a reduction in the use of health care services, owing to the higher efficacy of formoterol. In Sweden and Spain (low-dose budesonide), the extra cost of adding formoterol was more than offset. In the UK and Spain (high-dose budesonide), the extra cost of formoterol was only partially offset. The adoption of a societal perspective when adding formoterol generated a potential for net savings.

**CRD COMMENTARY - Selection of comparators**

The comparators were selected on the basis of the interventions compared in the FACET study, which was used as the source of evidence. The authors highlighted that the use of high-dose inhaled corticosteroids as an alternative treatment option to adding long-acting beta-2-antagonists was not considered because it was not investigated in the FACET study. Different dosages were considered. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from a published study. Limited information on the design of the study was provided, but it would appear that the trial had a high internal validity because of the robust design. Indeed, the study was randomised and double-blinded, and was carried out in several countries. A substantial proportion of the patients...
withdrew from the study, although the results were reported for both treatment completers only and on an intention to treat basis.

**Validity of estimate of measure of benefit**
The summary benefit measure used in the economic analysis was specific to the disease considered in the study and represents a common measure for influenza vaccination programmes. However, such a measure is not comparable with the benefits of other health care interventions.

**Validity of estimate of costs**
The methods used to estimate the costs were explicitly reported. Resource use was mainly derived from a panel of experts in each of the countries. The sample of expert (17-18) was very high for all countries, which enhanced the validity of the analysis. With the exception of costs, the source of which was not reported, other data came from the clinical trial. The costs were gathered using local currencies and were then converted into euros. The price year was reported, as were the unit costs and quantities of resources used. This enhances the possibility of replicating the analysis and reflating the results in other settings. The selection of the third-party payer perspective was appropriate for decision-makers. However, a broader perspective (i.e. that of society) was also adopted and the indirect costs were included in the sensitivity analysis.

**Other issues**
The authors compared their findings with those from two other published studies and found contrasting results. The issue of the generalisability of the study results was not explicitly addressed, but the authors noted that the three countries selected for the analysis reflected three different treatment patterns which could be extrapolated to similar countries. The authors pointed out that the use of experts' opinions to derive resource use data was common when validated prospective data were not available. Further, a threshold analysis was carried out to examine the impact of changes in such assumptions. However, it was noted that such estimates could have been inaccurate or might change over time.

**Implications of the study**
The study results supported the option of adding the inhaled long-acting beta-2-agonist formoterol to low to moderate doses of the inhaled corticosteroid budesonide in patients with persistent asthma.

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Astra Draco A B, Lund, Sweden, funded the FACET study.

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**Other publications of related interest**


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