Development of an economic model to assess the cost-effectiveness of treatment interventions for chronic obstructive pulmonary disease

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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 inhaled salmeterol plus fluticasone propionate (S/FP) in poorly reversible patients with chronic obstructive pulmonary disease (COPD). The dose examined was 50/500 microg S/FP twice daily.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of poorly reversible COPD patients with a history of exacerbations.

Setting
The setting was primary and secondary care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data came from studies published between 1981 and 2003. Some cost and resource use data were estimated from sources published between 1997 and 2002. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
A fully probabilistic decision model was constructed to assess the clinical and economic outcomes in a hypothetical cohort of patients with COPD. The four mutually exclusive health states considered were mild, moderate and severe COPD, and death. The cycle length of the model was set to 3 months and the time horizon was 25 years. Disease stages were defined on the basis of forced expiratory volume in one second (FEV1). For example, mild COPD was defined as an FEV1 $\geq$ 50%, moderate COPD as an FEV1 of 35 to 49%, and severe COPD as an FEV1 of less than 35%.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the transition probabilities across health states,
the rates of decline of FEV1 for smokers and ex-smokers,

the exacerbation frequency, and

the proportions of minor and major exacerbations,

**Study designs and other criteria for inclusion in the review**

It was not stated whether a systematic review of the literature was undertaken to identify primary studies. Efficacy evidence came from randomised clinical trials (RCTs), life expectancy came from US life tables, and utility values were estimated from groups of patients and physicians. Some information on the design and characteristics of the primary studies was provided.

**Sources searched to identify primary studies**

Not stated.

**Criteria used to ensure the validity of primary studies**

The authors did not report any criteria to ensure the validity of the primary studies. However, the use of RCTs to derive efficacy data ensured the robustness of the clinical evidence.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

The clinical inputs were derived from 12 primary studies.

**Methods of combining primary studies**

A narrative approach appears to have been used to combine the primary estimates.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The rate of decline in FEV1 was 62 mL/year for smokers and 31 mL/year for ex-smokers.

The exacerbation frequency was 0.79 (+/- 0.01) in the mild stage, 1.22 (+/- 0.01) in the moderate stage, and 1.47 (+/- 0.01) in the severe stage.

The proportion of minor exacerbations was 0.94 (+/- 0.01) in the mild stage, 0.93 (+/- 0.01) in the moderate stage, and 0.90 (+/- 0.01) in the severe stage.

The proportion of major exacerbations was 0.06 (+/- 0.02) in the mild stage, 0.07 (+/- 0.02) in the moderate stage, and 0.10 (+/- 0.02) in the severe stage.

The mean EuroQol (EQ-5D) tariff scores associated with mild, moderate, and severe stages of disease were, respectively:

0.81 (+/- 0.02) 0.72 (+/- 0.03) and 0.67 (+/- 0.05) at baseline;
0.61 (+/- 0.02), 0.61 (+/- 0.02), and 0.05 (+/- 0.05) at low point for minor exacerbation; and
-0.26 (+/- 0.07), -0.26 (+/- 0.07), and -0.26 (+/- 0.07) at low point for major exacerbation.

The mean modelled utility values associated with mild, moderate, and severe stages were, respectively:
0.72 (+/- 0.02), 0.658 (+/- 0.03), and 0.475 (+/- 0.05) with minor exacerbations; and
0.519 (+/- 0.02), 0.447 (+/- 0.07), and 0.408 (+/- 0.05) with major exacerbations.

The transition probabilities were not reported.

Methods used to derive estimates of effectiveness
Some assumptions were made to derive estimates of effectiveness.

Estimates of effectiveness and key assumptions
Transition probabilities were assumed to be unidirectional, as consistent with a progressive chronic disease.

The model assumed that smoking status influenced only the rate of FEV1 decline.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were estimated by combining life expectancy and utility weights in the decision model. An annual discount rate of 5% was applied. The mean life expectancy was also reported.

Direct costs
Discounting was relevant, owing to the long-term time horizon of the model, and a 5% annual discount rate was applied. Extensive information on resource use data was provided, but the unit costs were not reported for all items. The health services included in the economic evaluation were grouped into two main categories, routine/maintenance costs and exacerbation costs. The routine/maintenance costs (i.e. day-to-day maintenance of patients with COPD) included drug acquisition, oxygen therapy, laboratory and diagnostic tests, and clinic visits. The exacerbation costs included hospitalisations due to major exacerbations (e.g. laboratory tests and procedures, physician-related costs and additional medications at discharge), emergency department visits due to minor exacerbations (e.g. laboratory tests and procedures, and physician visits), study drugs and concomitant medications. All hospital and emergency department visits were assumed to be exacerbation related.

The cost/resource boundary of the Canadian health care system was adopted. The resource use data were mainly derived from authors' assumptions and published data. The costs came from the Ontario Case Costing Project 2000/2001, the London Health Science Centre 2001/2002, published Canadian data, and experts' opinions. All the costs were adjusted to 2002 values using the consumer health index.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not included in the economic evaluation because they were not relevant from the perspective of the study.

Currency
Canadian dollars (Can$).

Sensitivity analysis
Uncertainty in the model was handled probabilistically and all model inputs were assigned a stochastic distribution using a Monte Carlo simulation. While in the base-case scenario the benefit of S/FP was evident only in terms of its effects on exacerbations, two alternative scenarios were also considered. In scenario 1, S/FP had a positive effect on survival. In scenario 2, benefits in terms of a 133-mL improvement in FEV1 was assumed, leading to a higher starting lung function and hence a delayed progression between stages. Both scenarios relied on data from a RCT. In the base-case analysis, a univariate sensitivity analysis was carried out on the discount rate and exacerbation rates. Uncertainty in scenario 1 was addressed using cost-effectiveness acceptability curves, while a probabilistic sensitivity analysis was carried out in scenario 2.

Estimated benefits used in the economic analysis
In the base-case, the discounted QALYs were 4.08 (95% confidence interval, CI: 3.59 - 4.59) with UC and 4.21 (95% CI: 3.68 - 4.71) with S/FP.

Cost results
In the base-case, the lifetime discounted costs were Can$16,415 (95% CI: 14,102 - 19,290) with UC and Can$25,780 (95% CI: 23,748 - 26,633) with S/FP.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and benefits of the alternative treatment strategies.

The incremental cost per QALY gained with S/FP over UC was Can$74,887 (95% CI: 21,985 -128,671).

The sensitivity analysis showed that, if the decision-makers were willing to pay approximately Can$100,000 per QALY, S/FP had an 80% probability of being cost-effective. Applying a 6% discount rate for costs and 1.5% for benefits, the incremental cost per QALY fell to Can$56,454. Similarly, assuming an exacerbation rate of two per year for all severities of COPD led to a cost per QALY of Can$47,255.

The incremental cost per QALY was Can$11,125 in scenario 1 and Can$49,928 in scenario 2. Modest changes in cost-effectiveness estimates were observed in the sensitivity analysis.

Authors’ conclusions
For patients with poorly reversible chronic obstructive pulmonary disease (COPD) and a documented history of frequent COPD exacerbations, the addition of salmeterol (a long-acting beta2-agonist) to fluticasone propionate (an inhaled corticosteroid) was potentially cost-effective from the perspective of the Canadian health care payer.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (UC) was appropriate because it enables the clinical impact of S/FP to be assessed. However, it was unclear whether it represents an appropriate comparator in all contexts. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a synthesis of published studies. It would appear that the primary studies were identified selectively rather than from a systematic review of the literature. Details on study characteristics and patient samples were provided for most studies. The efficacy data were obtained only from RCTs. The estimation and calculation of some clinical inputs were extensively described in the appendix. Some assumptions were also made to
derive effectiveness data and to define the decision model. Extensive sensitivity analyses were carried out on clinical inputs in order to assess the robustness of the model results.

Validity of estimate of measure of benefit
The summary benefit measure (QALYs) was appropriate because it considers the impact of the interventions on both quality of life and survival. Discounting was applied, as usually recommended. Alternative discount rates were investigated in the sensitivity analysis. The source of the utility weights was reported.

Validity of estimate of costs
The categories of costs considered in the economic study appear to have been consistent with the perspective of a third-party payer. Details of resource use and treatment patterns were explicitly reported, which enhances the possibility of replicating the analysis in other settings. Limited information on the unit costs was given, although the sources used to obtain the economic data were reported. To address the issue of uncertainty, the costs were treated stochastically in the sensitivity analysis. The price year was provided, which aids reflation exercises in other settings. Some assumptions made to derive resource consumption were explicitly stated.

Other issues
The authors did not make extensive comparisons of their findings with those from published studies. In terms of the issue of the generalisability of the study results to other settings, the authors stated that Canadian data were used in the model. A possible shortcoming of the analysis, as the authors noted, could be that fact that the main RCT was a multinational trial, including few Canadian sites. The authors noted that a potential limitation of the current model was the reliance on factors such as FEV1 percentage predicted, and age, gender and smoking status as prime determinants of prognosis in COPD. Further, the model did not allow for smoking cessation. It was noted that the model has several potential applications. Finally, owing to the lack of data on lower dosages, the cost-effectiveness of a 50/250 microg S/FP dose was not assessed.

Implications of the study
The authors stated that the combination of S/FP may be more favourable if survival benefits seen in observational studies and suggested in a RCT are confirmed by the ongoing TORCH (TOwards a Revolution in COPD Health) study. The authors stressed that the incorporation of independent prognostic factors such as body mass index, health status, dyspnoea and prior exacerbation history into a validated prognostic index would be desirable.

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Other publications of related interest

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MeSH
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