Measuring costs and consequences in economic evaluation in asthma

M. J. SCULPHER* AND M. PRICE†

*Centre for Health Economics, University of York, York, U.K., †Global Health Outcomes, GlaxoSmithKline Research and Development, Greenford, Middlesex, U.K.

Abstract Formal economic evaluation is playing an increasingly important role in health-care decision-making. This is shown by the requirement to present economic data to support applications for public reimbursement for new pharmaceuticals in Australia and the provinces of Canada, and by the appraisal process initiated by the National Institute for Clinical Excellence in the U.K. This growing role of economic analysis applies as much to the field of asthma as anywhere. This paper provides a detailed review of applied economic studies in asthma. The review is used to explore a range of methodological issues in the field including the choice of perspective and maximand, whether to use disease-specific or generic measures of outcome and whether decision-makers should receive disaggregated cost and consequence data or results that focus on an incremental cost-effectiveness ratio. It is concluded that, given the heterogeneity in decision-makers' objectives and constraints, economic studies should be planned and executed in such a way as to maximize flexibility in how results are presented.

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INTRODUCTION

Given the limited resources available for health care and a policy decision, in most developed countries, to remove the unregulated market from the role of resource allocation, priorities need to be set in terms of which health-care interventions and programmes should be funded. Economic evaluation is a set of formal analytical techniques to establish the efficiency of alternative policy options and thereby assist with priority-setting. These methods fulfil an increasingly important role in health service decision-making. In some countries this is imposed at a central level; for example, the need for formal economic analysis to demonstrate the value for money of new pharmaceutical products prior to public reimbursement in Canada (1) and Australia (2). In the U.K. this 'macro' regulatory use of economic evaluation is developing with the National Institute of Clinical Excellence (3). Economic methods also have an important role in local health service decision-making — for example, in the development of hospital formularies.

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Correspondence should be to: Prof. Mark J. Sculpher, Centre for Health Economics, University of York, Heslington, York, YO10 5DD, UK.
Fax: 01904 433644; E-mail: mjs23@york.ac.uk

The importance of formal economic analysis in asthma care is, in part, a reflection of the burden of the disease in terms of resource cost and health. Weiss *et al*. estimated that the total cost of asthma in the US was $US6.2 billion in 1990, with the cost to the health-care system contributing 59% of this total (4). In the U.K., asthma was estimated to cost society £843 million per year at 1988 prices, with total health-care costs for asthma running at £344 million per annum (5). Whilst the costs of asthma are related to severity of disease, and the most severe asthmatics contribute a disproportionately high amount to the total economic burden of disease, significant costs are also incurred by the health-care system as a result of poor management of milder patients (6).

Economic evaluation is also needed as a result of the development of new forms of management, such as pharmaceutical therapies, which often impose extra costs on the health-care system but promise additional health benefits to patients. Despite the activity in economic analysis in asthma, the methods that have been employed have been inconsistent (7), and there is little evidence that their results have yet to impact on decision-making. The variability in choice of methods is a reflection of the general uncertainty regarding appropriate analytical tools in economic health care and, in particular, the choice of costs and outcomes to incorporate.

This paper describes the methods of economic evaluation in asthma and critically assesses the published literature in this field. It focuses on the choice of costs and outcomes in published studies and assesses whether these endpoints are sufficient given the alternative objectives underlying the use of economic evaluation. An important objective of the paper is to suggest ways in which economic evaluation in asthma may improve decision-making.

PRINCIPLES OF ECONOMIC EVALUATION IN HEALTH CARE

Defining economic evaluation

Economic evaluation in health care is defined as the comparison of alternative options in terms of their costs and consequences (8). Alternative options refer to the range of ways in which health-care resources can be deployed to generate improved health in a given patient or population group; for example, pharmaceutical and surgical interventions, screening and health promotion programmes.

Health-care costs refer to the value of physical resources at the disposal of the health-care system; for example, clinical and other staff, capital equipment and buildings, and consumables such as drugs. In addition, non-health service resources are frequently deployed as part of the process of producing health-care, such as the time of patients and their families. Consequences represent all the effects of health care programmes other than those on resources. Typically, these would include the implications of options for individuals' health, and these can be positive or negative. However, consequences also include other effects that individuals may value, such as reassurance and information provision (9).

Establishing value for money

Establishing the value for money of interventions involves aggregation of the various costs and consequences of alternative options within a comparative framework and relating the differential cost between options to their differential benefits. There are two alternative approaches to aggregation: cost–effectiveness analysis (CEA) and cost–benefit analysis (CBA). Three types of CEA are used: standard CEA, cost-utility analysis (CUA) and cost-minimization analysis (CMA) (Table 1). The process of aggregating costs is essentially identical in each form of analysis and straightforward given that all costs are expressed on a single monetary scale. The four forms of analysis differ in how they aggregate consequences. Standard CEA and CMA can only be used in specific circumstances: CEA is used when only one measure of consequence is considered important or differs between the options; CMA is used when evidence indicates that there are no important differences between options in any non-resource consequence.

CUA and CBA are more flexible in that they offer methods of combining various consequences of interventions in a single benefit scale (Table 1). CUA usually focuses on the various health effects of options (e.g. pain, physical function, mental health) and synthesizes these, with any implications for life expectancy, onto a single scale, typically in the form of the quality-adjusted life-year (QALY). CBA also values multi-dimensional consequences onto a single scale but differs from CUA in that the scale is represented in monetary units. In practice, CBA is rarely used in health care evaluations (10), in part due to the difficulties of valuing health in monetary terms.

Published economic evaluations in asthma

A literature search was undertaken using Medline, the Office for Health Economics (OHE) Health Economic Evaluations Database (HEED), the NHS Economic Evaluation Database and the Current Contents on-line databases from 1985 to June 2002, with the purpose of capturing all economic evaluations that have been published to date in asthma. Studies which failed to conduct a full economic evaluation were excluded as were studies which failed to measure both costs and consequences of treatment. Thus, studies that considered only costs with no evidence of equivalent outcomes between competing interventions were not included.

The results of this search are presented in Table 2. It is clear that health economic terminology has been subject to much misuse in the asthma literature. Some studies claim to be cost-effectiveness analyses, but in practice only consider costs (11). Others evaluate effectiveness in terms of a reduction in the use of health-care resources, which are also included in the cost component of the analysis (12). Similarly, some studies claim to be cost-benefit analyses but do not explicitly value consequences and are essentially cost analyses (13,14). Only one published study has used a true cost–benefit approach in the economic evaluation of asthma (15). In this study, consequences of therapy were valued using a willingness to pay approach (16), and the authors were able to demonstrate that budesonide was more cost–beneficial than placebo in patients with mild asthma.

Table 2 shows a total of 33 studies published between 1985 and 2002 that met the inclusion criteria. Of these, 27 were standard CEAs, four took a disaggregated approach to costs and consequences, whilst there was one example each of CMA and CBA. Despite some methodological work in asthma (17–19) and its importance for some decision-makers, there were only two examples of CUA. Given the preponderance of CEA,

Table I. Methods for aggregating costs and benefits in economic evaluation

Type of analysis	Aggregation of benefits	Establishing value for money
Cost-effectiveness analysis (CEA)		
Three variants		
Standard CEA	Benefits expressed on a natural scale that represents (a) the only important consequence of the options or (b) the only consequence on which the options differ e.g. symptom-free day in asthma	If one option is less costly and generates at least as much benefit (or produces greater benefit and is no more costly) than its comparators, it is dominant and considered cost-effective. If a more costly option is also more effective, its incremental cost per extra unit of benefit (ICER) is presented (relative to the other options being evaluated) and compared with other uses of health service resources usually in the same clinical area
Cost–utility analysis	A full range of health effects of options are expressed on a single scale, usually the QALY	Same process as for standard CEA, but the ICER takes the form of the incremental cost per additional QALY which facilitates comparison across programmes and specialties
Cost–minimization analysis	Used when evidence indicates that there are no important differences between the options in any non-resource consequence	The less or least costly option dominates its comparator(s) and can be considered more cost-effective
Cost–benefit analysis	The full range of health (and other non-resource) consequences are valued in monetary terms and aggregated to generate a single estimate of benefit	Costs and benefits are both on a single (monetary) scale, the net benefit (benefits minus costs) is presented. A negative net benefit is not good value or money. Positive net benefits are compared with other uses of health-care resources

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

the remainder of this paper focuses on this form of analysis.

DECISION RULES IN CEA

Within the framework of CEA, identifying a preferred option from among those being compared ('decision rules') involves relating differences in costs to differences in benefits. In the case of an option being dominant (costing less and generating at least as much benefit, or producing greater benefit and being no more costly than its comparators), it is unequivocally cost-effective. However, if an option generates additional benefits it can still be considered cost-effective even if it also increases costs. In such a situation, the option's incremental cost per additional unit of benefit is calculated and compared with other uses of health service resources. For example, if an incremental cost-effectiveness ratio (ICER) was calculated for a new asthma drug relative to standard practice, the only way in which an assessment could be made regarding whether the additional cost of the new drug is worth incurring to reap its extra benefit is to compare its ICER with those of asthma treatment options not considered in the evaluation (e.g. implement a new asthma treatment or fund an asthma self-management programme). This sort of comparison can establish whether, in a resource-limited system, the independent options with a higher ICER should be scaled-down or stopped to fund the new asthma drug, with the health-care system generating a net gain in benefits. Recently, it has been argued that the ICER should be replaced due to its statistical intractability and replaced by the concept of net benefit (20). However, the main principles of CEA remain largely unchanged.

MEASURING COSTS AND CONSEQUENCES IN ASTHMA

Although the principles of CEA are clear, there are no firm implications regarding the most appropriate measures of costs and consequences to incorporate into an analysis. In the context of economic evaluation in asthma,

Table 2. Summary of published health economic studies in asthma 1985–2002

Study description	Design	Measures of effectiveness	Costs measured	Key messages
(i) *Treatment comparisons*				
Andersson *et al.* (34). Cost-effectiveness of adding FORM to BUD in moderate asthma	CEA using data from a 12-month RCT plus survey of experts	Symptom-free days	Direct and indirect (productivity) costs for three European countries	Adding FORM to low -doses of BUD is cost-effective
Barnes *et al.* (35). Economic meta-analysis of FP *vs.* BUD	CEA using a meta-analysis of RCTs	Improvement in PEF, symptom-free days, episode-free days	Direct heath-care costs	At half the dose, FP more cost-effective than BUD
Berggren and Ekstrom (36). Cost-effectiveness of FORM compared to terbutaline in moderate-to-severe asthma	CEA alongside 12-week RCT	Severe exacerbations	Drug costs, physician visits and productivity costs	FORM is more effective and generates cost savings
Bisgaard *et al* (37). Cost-effectiveness of FP via MDI *vs.* standard therapy with bronchodilators in pre-school children	CEA alongside 12-week RCT	Exacerbations, symptom-free days	Direct health service costs	FP via MDI is more cost-effective than standard therapy with bronchodilators
Booth *et al.* (38). A comparative CEA of ICS in asthma	CEA using data from an 8-week RCT	Improvement in morning PEF	All asthma-related medication costs	FP more cost-effective than BUD
Booth *et al.* (39). A comparative CEA of FP *vs.* SCG in paediatric asthma	CEA using data from an 8-week RCT	Multiple measures of effectiveness addressing symptoms, sleep disturbance and PEF	All asthma-related medication costs	FP more cost-effective than SCG
Van den Boom *et al.* (29). Cost-effectiveness of early treatment with FP in obstructive airway disease	CUA and CEA using data from a 12-month RCT	QALYs, FEV_1	Direct and indirect (productivity) costs	Incremental cost per additional QALY of fluticasone US$13 016 for early treatment, and US$33 921 for detection and treatment
Campbell *et al.* (40). Comparison of the cost-effectiveness of BUD 400 μg and 800 μg in mild-moderate asthma	CEA using-data from a 12-week RCT	PEF and symptoms	Not clear	BUD 400 μg more cost-effective than BUD 800 μg
Connett *et al.* (41). Cost-effectiveness of BUD in children aged 1–3 years	CEA using data from a 6-month RCT	Symptom-free days	Direct and indirect costs	BUD reduced overall health-care costs, productivity loss, and increased symptom-free days
Everden *et al.* (42). Cost-effectiveness of eformoterol Turbohaler *vs.* SALM in children with symptomatic asthma	CEA using data on proportion of patients in a 12-week RCT	Symptom-free days	Direct health-care costs	Eformoterol was found to be more effective and less costly
Lundback *et al.* (43). CEA of three studies comparing SFC (50/100, 50/250 and 50/500 μg) with an equivalent dose of FP alone	CEA using data from three 12-week RCTs	Improvement in PEF, ymptom-free days, episode-free days	Direct health-care costs	SFC associated with improved outcomes at a small increase in costs compared with FP alone

Table 2. (Continued)

Study description	Design	Measures of effectiveness	Costs measured	Key messages
Lundback *et al.* (44). Cost-effectiveness of SFC compared to BUD in moderate-to-severe asthma	CEA using data from a 24-week RCT	Improvement in PEF, Symptom-free days, episode-free days	Direct health-care costs (Swedish Krona)	Incremental cost per successfully treated week (based on improvement in PEF) SEK 31.6; incremental cost per episode-free day SEK 7.7; incremental cost per symptom-free day SEK 9.2
Menendez *et al.* (45). Cost-effectiveness of FP *vs.* zafirlukast in patients with persistent asthma	CEA using data from a 12-week RCT	Symptom-free days, FEV_1	Direct health service costs	Treatment with FP was more cost-effective than zafirlukast, being less costly and more effective
O'Byrne *et al.* (15). Efficacy and CBA of BUD 400 and 800 μg in mild asthma	CBA (willingness to pay) over 4 months	Benefits valued in monetary units	Direct costs	BUD 400 and 800 μg are cost-beneficial *vs.* placebo
Paltiel *et al.* (28). Cost-effectiveness of inhaled corticosteroids plus short-acting B-agonists compared to short-acting B-agonists alone	CUA and CEA based on decision model and synthesis of published data	QALYs, symptom-free days	Direct health-care costs	The incremental cost per additional QALY of inhaled corticosteroids is US$ 13 500. The results are sensitive to assumed efficacy and side effects with inhaled corticosteroids
Perera (46). Cost-effectiveness of ICS in children in developing countries	CEA. Before and after study over 4 years of BDP and BUD	Parental satisfaction	Direct medical, non-medical and indirect costs	Implementation of ICS therapy reduced overall costs and improved parental satisfaction ratings
Price and Appleby (47). Primary care audit of outcomes and cost-effectiveness of FP in primary care	Non-randomized 'before and after' cost and outcomes analysis in clinical practice	PEF	All direct medical costs	Switching symptomatic asthma patients to FP improved outcomes for a similar overall cost
Rutten-van Molken *et al.* (48). Cost-effectiveness comparison of SALM and FORM	CEA using data from 6-month RCT	Episode-free days and improvement in disease-specific QoL	Comprehensive collection of direct, direct non-medical and indirect costs	No cost-effectiveness difference between the treatments
Rutten-van Molken *et al.* (49). Cost-effectiveness of ICS and bronchodilators in asthma and COPD	CEA using data from a randomized 3-year trial	Symptom-free days, FEV_1	Direct and indirect costs	ICS plus a bronchodilator is cost-effective *vs* a bronchodilator alone
Rutten-van Molken *et al.* (50). Cost-effectiveness of ICS and bronchodilators *vs* bronchodilators alone in asthma	CEA using data from a randomized 2.5-year trial	Symptom-free days, FEV_1	Direct costs	Incremental cost per symptom-free day with ICS of US$ 5
Sculpher and Buxton (51). Cost-effectiveness of FORM *vs.* salbutamol in asthma	CEA using data from a 12-week trial	Episode-free day	Drug costs	Incremental cost per episode-free day of formoterol Can $ 5.67–7.29
Stanford *et al.* (52). Cost-effectiveness of FP compared to inhaled triamcinolone acetonide	CEA using data from two 24-week RCTs	Symptom-free days, FEV_1	Direct costs	Incremental cost per symptom-free day for FP US$ 1.70

Steinmetz *et al.* (53). Cost-effectiveness of FP and BUD in moderate asthma	CEA using data from 6-week RCT	Symptom-free days, improvement in PEF, overall treatment effectiveness	All direct medical costs	FP cheaper and more effective than BUD
Stempel *et al.* (54). Comparative cost-effectiveness of FP and BUD	Meta-analysis of RCTs	Symptom-free and episode-free days	Direct costs to the health-care payer	FP more effective and less costly than BUD
Venables *et al.* (55). Cost-effectiveness of BUD and FP in adult asthma	CEA using data from 8-week open-label RCT	Symptom-free days, improvement in PEF	Drug costs	BUD more cost-effective than FP
Williams and Richards (56). Economic analysis of FP and BUD in paediatric asthma	CEA using data from 4-week clinical trial	Improvement in PEF	Direct medication costs	FP more cost-effective than BUD
(ii) *Device comparisons*				
Liljas *et al.* (57). Cost-efffectiveness of DPI *vs.* MDI	CEA using data from a 1-year RCT	Asthma exacerbations (effectively measured by PEF)	Direct and indirect costs	Better outcomes and lower costs with the DPI
Turner *et al.* (58). Economic evaluation of nebulizer *vs.* MDI in secondary care	CMA from a prospective 6-week audit	None (equivalent outcomes)	Direct secondary care costs	Administration of bronchodilators via MDI is cheaper
(iii) *Educational or guideline evaluations*				
Bolton *et al.* (59). Costs and effectiveness of an asthma self-management plan	Analysis of costs and consequences over a 12-month period	Activity-limited days	Direct health-care costs	Decreased utilization of health-care resources in study group
Gallefoss and Bakke (60). Cost-effectiveness of self-management in asthma	CEA using data from a 12-month RCT	FEV_1, St Georges Respiratory Questionnaire	Direct health-care costs, direct costs to patients, productivity costs (Norwegian Krone)	Including productivity costs, self-management reduces costs and improves outcomes; with direct costs, the incremental cost per unit of effect is NOK 9.4–301
McFadden *et al.* (61). Evaluation of a protocol for the management of acute exacerbations in hospital emergency rooms	Costs and outcomes evaluation over 1 year	Time to resolution of symptoms	Direct hospital costs, direct non-medical costs	Adherence to the treatment protocol reduced costs to patient and hospital, and improved time to resolution of symptoms
Sondergaard *et al.* (62). Economics of an asthma education programme	Prospective cost–consequence analysis	Avoidance of productivity loss, QoL and health status	Direct costs (indirect costs avoided were used as an effectiveness measure)	Improved health status and QoL. Some costs were off-set. Few cost differences
Windsor *et al.* (63). Cost-effectiveness of a health education programme	Prospective CEA	Adherence score	Staff time costs in implementing the programme	Costs were increased, and there were improvements in adherence scores

BUD: budesonide; CBA: cost–benefit analysis;
CEA: cost–effectiveness analysis; CMA: cost–minimization analysis;
CUA: cost–utility analysis; DP: dry powder inhaler; FEV_1: forced expiratory volume in 1 s; FORM: formoterol; FP: fluticasone propionate;
ICS: inhaled corticosteroid; MDI: metered dose inhaler;
PEF: peak expiratory flow; QALY: quality-adjusted life-years;
QoL: quality of life; RCT: randomized controlled trial; SALM: salmeterol; SCG: sodium cromoglycate; SFC: salmeterol/fluticasone propionate combination therapy.

the variety of costs that have been considered in studies is shown in Table 2. A range of perspectives have been taken in the literature and include studies which consider only asthma drug costs through to adoption of a full societal perspective by, for example, including productivity costs. By far, the most common costs included in asthma economic evaluations are direct health-care costs. Regardless of the types of costs included, one common failing illustrated in the literature is that the perspective taken for the analysis is rarely explicitly stated, even when the types of costs included are clearly presented.

As well as a wide range of costs included in these studies, there has been an equally large variation in measures of consequence within asthma cost-effectiveness analyses (Table 3). Even where there is some agreement across studies about the desired outcome of asthma management, there is still a considerable degree of heterogeneity in how benefits are expressed.

PERSPECTIVE AND MAXIMAND

As mentioned above, any assessment of published studies with respect to their choices regarding costs and consequences needs to be clear about the appropriateness of a study's perspective (i.e. whose costs and benefits are we interested in?) and its maximand (i.e. what benefits are we trying to maximize from limited resources when we

Table 3. Summary of endpoints used in economic evaluations in asthma

Consequence	Variation	References
QALYs	Based on direct elicitation of utilities from patients based on standard gamble exercise	(29)
	Based on direct elicitation of utilities from patients based on time trade-off exercise; other methods used in sensitivity analysis	(28)
Improvement in PEF	≥5% Weekly improvement in morning PEF compared with baseline predicted value	(35, 38, 44)
	Improvement in PEF from baseline to end of treatment[a]	(35, 40, 47, 53, 55, 56)
	Attainment of desired predicted PEF[a]	(38, 40)
	Days with PEF <80% predicted	(57)
Improvement in FEV_1	10% Improvement in predicted value from baseline	(49, 50, 60)
	12% Improvement from baseline	(45)
	Change from baseline	(60)
	100 ml gain relative to comparator	(29)
Symptom-free day	Not defined in paper	(40, 52)
	Total symptom score of zero, although unclear if only daytime or 24-h symptoms considered	(41, 44, 49, 50, 53, 54)
	Total symptom score of zero over 24-h period	(35, 42, 55)
	No daytime symptoms	(28, 34, 37, 39, 44)
	No night-time symptoms	(28, 37, 39, 44, 45)
	Time to resolution of acute symptoms	(61)
Episode-free day	As defined by Sculpher and Buxton (51): absence of asthma attack, need for rescue medication or sleep disturbance	(35, 44, 45, 48, 49, 54)
Monetary values	Benefits value in monetary terms using willingness to pay methodology	(15)
Patient satisfaction	Mean satisfaction score	(46)
Health-related quality of life	Achieving a clinically important improvement in St George's Respiratory Questionnaire score	(48, 60)
	Improvement in asthma quality of life questionnaire and psychosomatic discomfort scale	(62)
Activity limitation/impact on activities	School absenteeism	(50)
	Activity-limited days	(59)
Exacerbations	Need for oral corticosteroids, PEF	(36)
	Change in medication, medical contact	(37)
Treatment adherence score	Percentage improvement in adherence score	(63)

[a]Level of desired improvement constituting a 'success' was variable between studies.
FEV_1: forced expiratory flow in 1 s; PEF: peak expiratory flow; QALYs: quality-adjusted life-years.

undertake an economic evaluation?). In essence, these are normative questions to which there is no correct technical answer. There appear to be strong arguments in favour of the health-care system seeking to maximize some measure of population health; however, individual decision-makers may have quite different ideas about the most appropriate objective of resource allocation.

The choice of perspective in an analysis is also one over which the various stakeholders in an evaluation (analysts, patients, potential patients, clinicians, managers) may have different views. There are strong arguments in favour of considering the costs and consequences of health care for all groups and individuals (societal perspective) (21,22). Perhaps the strongest of these arguments is that a societal perspective avoids the risk that an option is deemed cost-effective despite a sub-group of the population or an organization experiencing significant negative consequences or additional costs. For example, an education programme for asthmatics may appear cost-effective when only health service costs are considered, but perhaps only because the costs to patients (in terms of, for example, the time costs of attending a education sessions) are ignored. However, as with the choice of maximand, the individual decision-maker may have a very narrow perspective. For example, on the cost side, they may only be interested in the impact of a new drug on the pharmacy budget.

Measuring consequences

Consequence measures in asthma

Table 3 shows that there is consistency in economic studies in asthma regarding the perspective they have employed: the individual with asthma is always the focus; however, the table shows considerable variation in the measures used including symptoms, exacerbations and more formal health-related quality of life (QoL) measures. Table 3 identifies 11 different groups of consequence measures used in economic evaluation is asthma and, even within these groups, there remains variation in the specific measures used. For example, although the majority of cost-effectiveness studies chose to focus on symptoms as their main measure of consequence, the process of weighting and aggregation differed markedly between studies. Variants included symptom-free days (with the actual definition of a day unclear), symptom-free 24-h periods and time to successful control.

The variability in consequence measure probably partially reflects the fact that the objectives of asthma interventions differ or have multiple objectives. For example, bronchodilators have a mode of action that is more focused on short-term alleviation of symptoms and improvement in lung function, so it would seem appropriate for endpoints measuring these facets to predominate in evaluations of these interventions. On the other hand, measures such as reduction in exacerbations, improvement in health-related QoL and longer term improvements in lung function and symptoms tend to be more important for prophylactic therapies such as inhaled corticosteroids.

Asthma-specific measures of consequence

The lack of consistency in consequence measures used in studies has important implications for the usefulness of economic data to decision-makers. As described above, when a new therapy is more costly but also more beneficial than its comparator, an incremental cost per additional unit of benefit is calculated to provide a decision-maker with an indication of how much more patients are getting for the additional cost involved. To help in the decision-making process, the ICER should be compared with the same ratio calculated in other (i.e. independent) evaluations.

For decision-makers to be able to make full use of the data generated by such studies, there needs to be agreement on the appropriate perspective and maximand, and each study has to employ a common measure of consequence that relates clearly to the maximand. If it is assumed, for example, that the objective of caring for all asthma patients is to maximize, from the limited resources available in that area, the proportion of patients' lives without symptoms, and if it is also agreed that the a symptom-free day (SFD) could be defined and used in all CEA in asthma, then each study would compare its alternative treatments in terms of their costs and rates of SFD. A dominant treatment (e.g. one which is less costly than its comparator(s) and generates at least as many SFDs) would clearly be cost-effective and worth funding. If the more costly therapy also achieved more SFDs, its ICER would be calculated (the incremental cost per additional SFD). If a number of studies in asthma had already reported similar ratios, it would be possible for decision-makers to compare ICERs and assess whether resources should be re-allocated in the area.

There are limitations to this focus on an asthma-specific maximand and measure of consequence. The first is the relevance of a single measure of consequence to all patients with asthma. As noted above, different types of therapy for different sub-groups of asthmatics are likely to have a variety of clinical objectives. It may be the case, for example, that minimizing symptoms and the use of an SFD as the measure of consequence is not appropriate for all sub-groups of asthmatics. Furthermore, an SFD may be interpreted differently between individuals: for example, a severe asthmatic may define a SFD in quite a different way to a mild asthmatic. In other words, it may be very difficult to identify a single maximand and common measure of consequence in CEA in asthma.

A generic measure of health

A second limitation of an asthma-specific maximand is that there may be good reason to fund more costly but more beneficial therapies for asthma by re-allocating budgets from outside of that particular clinical area. This cross-programme resource allocation is more clearly related to a broader maximand than symptoms in asthma. If the cost-effectiveness of new asthma treatments is to be compared with that of interventions in a range of different specialties and disease areas, it is necessary to agree on a broad maximand, such as health in general.

With such a maximand, a new drug for asthma (which is more costly and more beneficial than standard therapy) would be considered cost-effective if its incremental cost per extra unit of health gain compared favourably with health-care interventions inside or outside asthma. In order to facilitate cross-programme resource allocation of this sort using a maximand of overall health, it is necessary to incorporate generic measures of health gain into CEA. The use of the QALY as a measure of consequence, as described earlier and in Table 1, represents the branch of CEA which focuses on supporting the broader maximand of health. The process of estimating QALYs in a given study is not a subject for detailed consideration here and is covered elsewhere (8, 23, 24). In brief, a popular approach to measuring QALYs involves measuring patients' health-related quality of life (HRQoL) (within a trial or observational study) using a generic measure that describes health in terms that are not associated with a specific disease or intervention. It would then be necessary to score this instrument in such a way that a single index (often called a value or utility) is derived to reflect a patient's HRQoL at any point in time running from 0 (equivalent to death) to 1 (equivalent to good health). This scoring process involves weighting the relative importance of different dimensions of HRQoL, and of different items within each dimension, using utilities or preference scores,. This is inherently subjective and will reflect the different preferences of individuals.

A number of generic 'utility instruments' now exist in health care including the EuroQol (EQ) 5D (25), Health Utilities Index (HUI) III (26), and Quality of Wellbeing (QWB) Scale (24). Each of these instruments uses the preferences of the general public to derive utility weights for different domains and items in the HRQoL scale, based on the view that, as the ultimate payers for health care, it is societal views that should count in this respect (21). An alternative way to measure QALYs is to elicit utilities directly from patients relating to their own state of health at a given time point. In a recent authoritative review of good methodology in economic evaluation (21), the use of societal utilities was preferred, and this has been mirrored in NICE's technical guidance on economic evaluation (27).

As Table 2 shows, there are two examples of the use of QALYs as a measure of consequence in economic evaluations in asthma (28,29). In both cases, utilities were elicited directly from patients, although Paltiel *et al.* (28) also used the HUI as a sensitivity analysis. The limited use of CUA in asthma is, in part, likely to be due to the fact that QALY-based measures of consequence are inevitably less sensitive to clinical change than asthma-specific measures. Generic classifications of HRQoL are by their nature not as focused on the specific impact of a disease or its treatments from the patient's perspective as a disease-specific measure. For this reason, most studies have focused on asthma-specific measures of consequence in the hope of reflecting clinically important changes, despite the fact that this is of limited value for cross-programme resource allocation.

A second reason why the use of QALYs has been rare in asthma studies is the lack of consensus, on the part of decision-makers, that health is the appropriate maximand and that the QALY is the relevant measure of health in applied studies. Decisions need to be taken at the 'top of the service' regarding resource allocation between specialties and programmes, and here a health maximand, with QALYs as the best currently available expression of that in evaluative studies, would seem appropriate. This explains NICE's preference for the QALY (27). However, decisions on different types of resource allocation need to be made lower down in the system, and QALYs may be less relevant here. For example, there is evidence that currently general practitioners do not value the QALY as an ideal maximand in health-care decision-making (30).

A third reason for the limited use of QALYs in asthma may be the limited opportunities to evaluate QALY endpoints within the framework of traditional drug development. The majority of published economic analyses to date have been conducted as part of clinical trials, whose primary aim is regulatory approval or demonstration of superior clinical efficacy. From Table 2, it is clear that many of these trials are of relatively short duration and this, coupled with the perceived lack of sensitivity of generic QALYs, may have resulted in the limited use of QALYs in applied studies in asthma. If there is to be an increase in the use of this measure of benefit, it will require greater investment in longer term, properly powered studies that have economic evaluation as a primary aim.

Given the heterogeneity in the type of decisions that need to be taken in health care systems, there appears to be a strong argument for economic studies in asthma to take a pragmatic approach and offer a range of consequence measures and, where appropriate, generate ICERs using each of these. In other words, for cross-programme resource allocation, the presentation of cost-effectiveness using QALYs is desirable and ideally should be factored into studies. However, this should be undertaken in parallel with asthma-specific measures of conse-

quence like SFDs, the use of which may support decision-making within specialties and programmes.

Furthermore, if decision-makers are unwilling to be explicit about a maximand for CEA, then it is important for one of the outputs of studies to be a disaggregated description of costs and all consequences. Often referred to as cost-consequences analysis (8), this form of evaluation essentially presents a balance sheet of the costs and consequences of the two or more interventions under comparison.

Measuring costs

Compared to the issues associated with the measurement of consequences in economic evaluation, cost measurement is less contentious. However, some important methodological uncertainties exist including how to estimate accurate unit costs and the appropriate vehicle for resource allocation measurement. These are discussed fully elsewhere (8,21). Some methodological issues in costing are particularly relevant to the economic appraisal of asthma interventions. These include the choice of perspective, valuation of time costs and the appropriate time horizon.

Cost perspective

As noted above, there are strong reasons to take a societal perspective on costs. Of those economic studies in asthma (Table2), 12 studies included costs of lost productivity and could be argued to have adopted a broad societal perspective. One reason why some studies took a narrower perspective than societal is probably the perception that all or a sub-group of health-care decision-makers are not interested in costs other than those falling on the health-care system. As with consequences, it is likely that decision-makers at the various levels within the system have different attitudes to the appropriate cost perspective.

Given the variety of cost implications that are likely to be of interest to decision-makers and the importance of checking that a health-care intervention is not deemed cost-effective because not all its resource cost implications have been included, a variety of perspectives should be adopted in economic studies in asthma. There is again a strong case to present decision-makers with disaggregated information on the resource implications of interventions and the cost of those resources within a cost–consequences analysis. This allows decision-makers to include those costs they think appropriate in reaching a decision. However, it is also important for data on all costs to be made public and for the decisions that are ultimately taken to be assessed against a societal perspective on costs.

Valuing time costs

If, as argued above, a societal perspective should be part of economic studies in asthma, an important non-health-care cost is the value of the time of patients and carers that is affected by asthma and interventions to treat it. Four time costs are relevant here: patients' healthy time that is lost due to the morbidity and mortality associated with asthma; the time patients put into the process of receiving health care (e.g. visiting a clinic); and the time carers put into caring for friends and relatives with asthma.

In principle, measuring these time inputs can be undertaken in clinical trials and observational studies. It is their valuation which raises difficult methodological problems. These issues have been discussed fully elsewhere (21, 31). The key ones relating to economic evaluation in asthma would be:

- Whether time away from usual activities as a result of asthma should be valued in monetary terms or as part of a QALY.
- Whether time away from school in paediatric asthma should be valued in monetary terms and, if so, what basis of valuation should be employed.
- How should carers' time be valued: on the basis of a shadow wage (i.e. the wage rate of someone who would be formally employed caring for the sick), average wage rates or the carer's actual loss of income.

Appropriate methodology in this area is currently unclear and considerable research is required. In an applied study in asthma, therefore, it would be appropriate to use as many valuation techniques as possible and to compare their implications for the conclusions of a study.

Appropriate time horizon

The choice of time horizon is important in any study. In a CEA, appropriateness should be judged according to the time-point at which the options under consideration can be expected not to differ in terms of their costs and consequences. Inevitably, there will be marked uncertainty about this time-point, especially in the context of a chronic disease such as asthma, where symptoms and treatment may continue for many years. The problem is accentuated in asthma by the short-term duration of many of the clinical trials that provide the data for CEA. As shown in Table2, the duration of trial-based studies ranges from just 4 weeks to 4 years. Unless it can be assumed that, after these points, differential costs and benefits do not alter, shorter time horizons are likely to be inappropriate, although the minimum acceptable time frame for economic analysis in asthma is somewhat unclear.

In future, economic analysis of asthma interventions will have to include alternative or complementary methods to short-term regulatory trials. These will include long-term pragmatic trials, decision modelling to extrapolate trial results over a longer time horizon and the use of large longitudinal databases to generate long-term resource use and consequence data to populate models. Longer term pragmatic trials probably offer the best opportunity of measuring QALY benefits of asthma treatments as there is likely to be a favourable time horizon and the more naturalistic setting may reduce 'noise' associated with trial effects.

CONCLUSIONS

National guidelines for economic evaluation in Canada and Australia are spreading across Europe with initiatives established or in development in countries such as The Netherlands, Ireland and the U.K. Following increasing national requirements, economic evidence is also becoming key data for health-care providers such as HMOs (32). It is clear that the importance of formal economic analyses will only increase.

Economic evaluations of health-care technologies should ideally facilitate better health-care decision-making by explicitly identifying, measuring and valuing the costs, consequences and trade-offs between competing interventions. However, to enable competing interventions to be compared and evaluated, there is a need for a level of comparability across methodologies which is currently lacking in the asthma literature. This is particularly evident in the choice of consequences reported. Even when similar measures of effectiveness are used there is a lack of consistency over definition as well as over the methodology used to collect the evidence.

Given the objective of satisfying the needs of different decision-makers at alternative levels in the health-care system, but also the normative strength of health maximization as the primary objective of the system, it is important to develop an economic analysis with a range of measures of consequence. The first step, however, should be to take a disaggregated cost-consequence approach, with a 'balance sheet' of all relevant costs and a full range of consequences reported.

Finally, an issue that will require further consideration is who should be undertaking and funding economic evaluation studies. Manufacturers of health-care technologies, such as pharmaceutical companies, represent an important source of economic studies (either directly or through the funding of other groups). Furthermore, the decisions of reimbursement authorities, such as those in Canada and Australia, are largely based on submissions from manufacturers. It has been argued that economic evaluations are more susceptible to bias than clinical studies (33). Although this point is open to debate, reimbursement authorities are likely to have to fund independent groups either to undertake new economic studies or to critically appraise submissions.

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