

Chapter 9. Pharmacoeconomics and Economic Evaluation of Drug Therapies

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I. INTRODUCTORY REMARKS

Health care funders (governments, social security funds, insurance companies) are struggling to meet their rising costs. They make many efforts to contain drug costs, by price negotiation, patient co-payments or dedicated drug budgets. Expenditure on drug therapy is a particular target for their attention for several reasons: the size of the drug bill (10-15% of most national health care budgets, and usually the second largest item after salaries); the ease of measurement of pharmaceutical costs in isolation, in contrast to most other health care costs; evidence of wasteful prescribing; and a perception that many drugs are overpriced and that the profits of the pharmaceutical industry are excessive.

But this focuses on drug costs in isolation, when what should be of greater concern to decision makers, health care professionals and the public is the value of drug therapy, a function of its benefits as well as its costs (1). Payers acknowledge that spending on drugs, which may for instance reduce the need for hospitalisation or produce greater health gain for the same resources than other medical interventions, may be a very efficient use of scarce resources. They therefore respond by demanding evidence of value for money from drug therapy. Drug therapy is open to this simply because there are high quality trials to support most new drugs' licensing applications, in contrast to the poor evidence around most other health care interventions.

Health economics is the science of assessing cost and benefits, not to make decisions about resource use, but to inform those decisions. The aim is to identify what is most efficient, so that the greatest amount of benefit can be bought for a given amount of money or resources. But we must remember that in health care, efficiency may not be the most important objective -we might for instance prioritise caring for dying patients or treating patients with serious disease who have relatively little hope of surviving. Pharmacoeconomics is a branch of health economics that particularly considers drug therapy. It is of particular interest to pharmaceutical companies who in developing a new drug and after the traditional hurdles of efficacy, safety and tolerability must now jump over a fourth hurdle of cost effectiveness. It should also interest clinical pharmacologists, either in their roles assessing new drugs or in the conduct of clinical trials that now often include an economic component. In some areas, economic studies have become an accepted part of evaluations for reimbursement.

This chapter aims to explain the basic concepts and language of pharmacoeconomics, and of economic evaluation, and to introduce what for many clinical pharmacologists is a new area.

II. BASIC CONCEPTS AND TERMINOLOGY

Health economics is about making choices between options, when there is scarcity of resources. It is fundamentally comparative, weighing the costs and benefits of option 1 with those of option 2 (for instance, a new drug and the previous best therapy - traditional medical evaluation focused only on the benefits), to determine which is the most efficient way to use our limited resources. *Efficiency* is a key concept in economics, i.e. how to buy the greatest amount of benefit for a given resource use.

II.1. Opportunity cost

Another key concept is *opportunity cost*: this is defined as the “benefit foregone when selecting one therapy alternative over the next best alternative”. When we have limited money and we spend it on one health care intervention, we cannot spend the same money on something else. So we should be less concerned with how much a health care intervention costs, but rather with what other benefits we are giving up by using the money in that way. We need to be sure that spending money on the new therapy will buy more benefit than spending that money in some other part of the health care system.

The comparative nature of health economics means that we are interested in an *Incremental analysis* of costs and benefits. There is usually a current treatment for most conditions, with associated costs and benefits. We would not advocate stopping all existing treatment for the condition, so the question is not what are the costs and benefits of the new treatment, but what are its added costs and benefits, over and above those of the existing treatment.

II.2. Marginal cost

A related concept is *marginal costs*. For instance, if a new treatment enables patients to be discharged from hospital a day earlier than an older treatment, it might be tempting to count the average cost of a hospital bed day as a saving of resources. But all the fixed capital charges for a hospital bed, which go into the average cost, e.g. costs of laboratories, kitchens, and building maintenance, will be largely unchanged. The only costs which change may be those of having a patient physically occupy the bed - the costs of the patient's meals, treatment and perhaps nursing time. These are the marginal costs, where the resource use actually changes substantially. Incremental analysis is concerned with the marginal and not the average costs. Marginal costs are often very difficult to measure, and there is a temptation to use average costs instead. This may be justified if for instance, enough bed days are saved by the widespread adoption of a new treatment to actually reduce bed numbers and to close wards.

III. COSTS AND BENEFITS

These have broad definitions in health economics, which may depend in part on the *perspective* or viewpoint we choose to take. Perspective asks from whose point of view is the study conducted - from that of the health care payer, who is only interested in the direct costs of health care, or from society as a whole, where "indirect" costs (i.e. not directly on health care, such as lost of productivity etc) are also important. In general, the societal perspective is considered the most appropriate, but a health care manager with a limited budget might be tempted to ignore the societal view and consider only the costs that fall on his own budget. A study of migraine which took the health service perspective only might suggest that sumatriptan in migraine (an expensive drug in an area which previously cost the health service very little) was highly undesirable, but a study taking a societal perspective might come to the opposite conclusion (2).

III.1. Cost classification

Costs therefore can be classified as:

III.1.A. Direct – i.e. costs from the perspective of the healthcare funder: including staff costs, capital costs, drug acquisition costs. These should (in theory) be relatively easy to measure.

III.1.B. Indirect – i.e. costs from the perspective of society as a whole: for example, these might include loss of earnings, loss of productivity, loss of leisure time, due to the illness, and cost of travel to hospital etc. This would include not just the patient themselves but also their family and society as a whole. Many of these are difficult to measure, and there is some controversy over how to value these. (The UK National Institute for Clinical Excellence, NICE, adopts a limited societal perspective in its evaluations and considers the direct costs falling on the UK National Health Services, and those indirect costs funded by the state such as unemployment and sickness benefits (3)).

III.1.C. Intangible – i.e. the pain, worry or other distress which a patient or their family might suffer. These may be impossible to measure in monetary terms, but are sometimes captured in measures of quality of life.

III.2. Benefits

The benefits we expect from an intervention might be measured in:

III.2.A. “Natural” units - e.g. years of life saved, strokes prevented, peptic ulcers healed etc.

III.2.B. “Utility” units - utility is an economist’s word for satisfaction, or sense of well being, and is an attempt to evaluate the quality of a state of health, and not just its quantity. Utility estimates can be obtained through direct measurement (using techniques such as time trade off or standard gambles, or by imputing them from the literature or expert opinion. They are often informed by measures of quality of life in different disease states.

The Quality Adjusted Life Year (QALY) is one widely used measure, which attempts to integrate both quality and the quantity of life. Broadly, it assumes that if a treatment increases one’s life expectancy by 2 years, but causes adverse effects or inconvenience, such that one’s quality of life or utility are decreased by 25%, the net gain is $2 \times 0.75 = 1.5$ QALYs. QALYs are controversial for many reasons (4), not least that measuring patient utilities is difficult and preferences may change in the course of an illness (what seems an intolerable burden to a healthy individual may not seem so bad to someone who might otherwise be dead). Despite these criticisms, the concept of the QALY has advanced thinking on how to incorporate quality of life into economic evaluations.

Table 1.

Method of economic evaluation	Measurement of outcome (health benefits)	Synthesis of costs and benefits
Cost minimisation analysis	Assumed to be equivalent and can take any form (e.g. number of cases detected, reductions in cholesterol levels, years of life saved)	Additional costs of therapy A relative to B
Cost effectiveness analysis	Health benefits across therapies are measured in similar natural units	Cost per life year gained Cost per patient cured, Cost per life saved, etc.
Cost utility analysis	Health benefits across therapies are valued in similar units based on individual preferences	Cost per QALY gained Cost per HYE gained
Cost benefit analysis	Measured in similar or different units and are always valued in monetary units (e.g., amount willing to pay to prevent a death, amount willing to pay to reduce exposure to a hazard)	Net benefits = Benefits minus costs Benefit- cost ratio = benefits/costs

III.2.C. Associated Economic Benefit

This is usually measured in money, which is a useful common denominator allowing comparisons across different disciplines. This measure includes, for instance, the economic benefits of returning someone to work.

III.2.D. Methods of Economic Evaluation

Economic evaluation is the formal process of weighing benefits and costs in an incremental analysis. It is essentially a framework which draws up a balance sheet between costs and benefits to assist decision making.

Common Types of Study

The costs and benefits or outcome measures selected give rise to the four common types of economic evaluation (table 1). These studies are often complex and require use of economic models (a skill not dissimilar to pharmacokinetic modelling).

III.2.D.a. Cost minimisation analysis (CMA)

This involves measuring only costs, usually only to the health service, and is applicable only where the outcomes are identical and need not be considered separately. An example would be prescribing a generic preparation instead of the brand leader (lower cost but same health outcomes).

III.2.D.b. Cost effectiveness analysis (CEA)

The term cost effectiveness is often used loosely to refer to the whole of economic evaluation, but should properly refer to a particular type of evaluation, in which the health benefit can be defined and measured in natural units (eg years of life saved, ulcers healed) and the costs are measured in money. It therefore compares therapies with qualitatively similar outcomes in a particular therapeutic area. For instance, in severe reflux oesophagitis, we could consider the costs per patient relieved of symptoms using a proton pump inhibitor compared to those using H₂ blockers. CEA is the most commonly applied form of economic analysis in the literature, and especially in drug therapy. It does not allow comparisons to be made between two totally different areas of medicine with different outcomes. The broad form of these evaluations are shown in box 1, and the key measure is the incremental cost effectiveness ratio (ICER).

Box 1.

$$\text{Incremental Cost Effectiveness Ratio} = \frac{(\text{cost of drug A} - \text{cost of drug B})}{(\text{benefits of drug A} - \text{benefits of drug B})}$$
$$\text{ICER} = \frac{\text{difference in costs (A-B)}}{\text{difference in benefits (A-B)}}$$

III.2.D.c. Cost utility analysis (CUA):

This is similar to cost effectiveness in that the costs are measured in money and there is a defined outcome (box 2). But here the outcome is a unit of utility (e.g. a QALY). Since this endpoint is not directly dependent on the disease state, CUA can in theory look at more than one area of medicine, e.g. cost per QALY of coronary artery bypass grafting versus cost per QALY for erythropoietin in renal disease. In practice this is not so easy since the QALY is not a well defined fixed unit transferable from study to study. We should be particularly wary of attempts to draw up league tables of QALYs to allow comparisons between a range of therapies. The values in such tables have usually been derived at different times and in different ways and are not comparable.

Box 2. Calculating QALYs - a simple example

With treatment X

Estimated survival = 10 years

Estimated quality of life

(relative to 'perfect health') = 0.7

QALYs = (10 X 0.7) = 7.0

Without treatment X

Estimated survival = 5 years

Estimated quality of life

(relative to 'perfect health') = 0.5

QALYs = (5 X 0.5) = 2.5

QALY gain from treatment X = 7 - 2.5 = 4.5 QALYs

If the cost of treatment X is £18,000 then the cost per QALY is £4,000 per QALY
(£18,000 divided between 4.5 additional QALY's)

III.2.D.d. Cost benefit analysis (CBA)

Here, the benefit is measured as the associated economic benefit of an intervention (eg monetary value of returning a worker to employment earlier), and hence both costs and benefits are expressed in money. CBA may ignore many intangible but very important benefits not measurable in money terms, e.g. relief of anxiety. CBA may also seem to discriminate against those in whom a return to productive employment is unlikely, eg the elderly, or the unemployed.

However the virtue of this analysis is that it may allow comparisons to be made between very different areas, and not just medical, e.g. cost benefits of expanding university education (benefits of improved education and hence productivity) compared to establishing a back pain service (enhancing productivity by returning patients to work). This approach is not widely used in health economics, although many economists like it on theoretical grounds and because it removes some of the “sacred cow” protection which surrounds health care. They argue that health should be another commodity, and not necessarily valued more than other possible uses of the resources.

III.2.D.e. Cost consequences and other types of evaluation

Other forms of quasi-health economic evaluation may be seen in the literature but are not true economic evaluations because they do not weigh costs and benefits in an incremental manner. In some cases, often where studies consider multiple outcomes, costs and benefits are presented in a disaggregated form (e.g. health profiles). These evaluations are frequently referred to as cost consequences analyses. Burden of disease (also known as cost of illness) studies attempt to measure the health and resource implications arising to society from a particular disease.

III.3. Further Points

There are two further points for definition.

III.3.A. Discounting

There is often a difference in timing between the investment of health resources and gaining the benefits. Therefore we must discount future spending etc. to try to equalise the effects of inflation and health and financial preferences over a long period. In general, costs are discounted at an agreed rate (in the UK, currently 6% for costs). There is some debate over whether benefits can also be discounted (it is relatively easy to accept that £100 spent now is worth more than in five years time, but how does one compare a healthy year now to a healthy year in five years time?) NICE suggests discounting benefits at a rate of 1.5% (3).

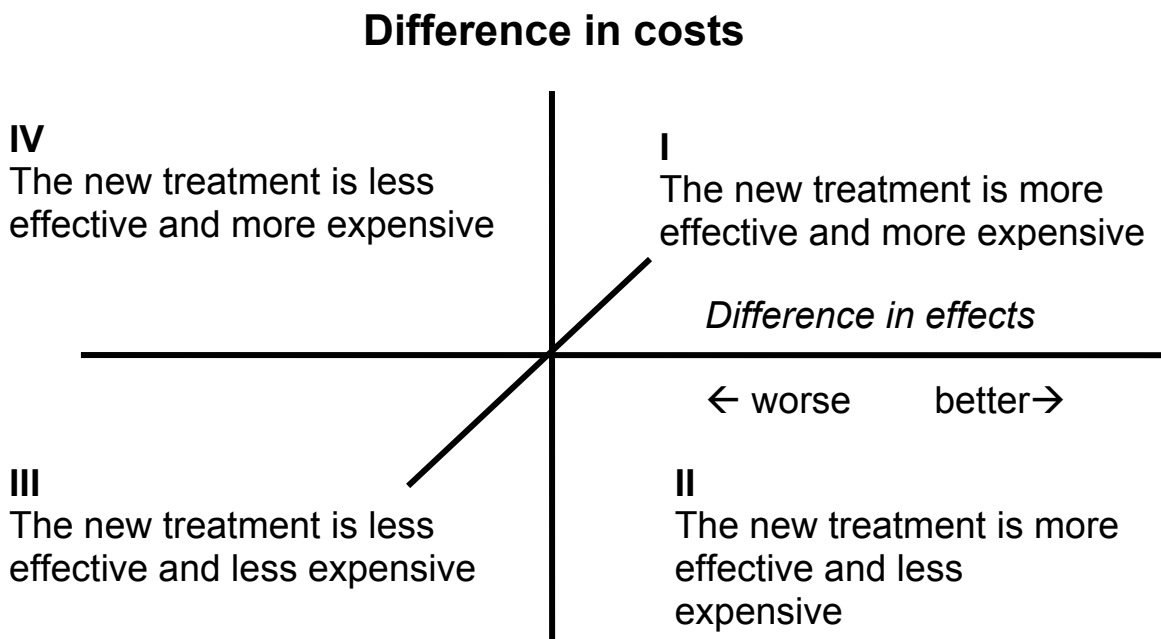
III.3.B. Handling uncertainty

The measures of benefit and cost in an economic evaluation come from the medical evidence, usually clinical trials. But clinical trials address efficacy whereas health economics is more interested in effectiveness – what benefits/costs are associated with a new therapy when it is used in the real world, where patients are less well defined or monitored and where the comparator may not be the one used in the clinical trial. There is often little evidence available about effectiveness, and we are forced to make *assumptions* to fill the gaps in our knowledge. These assumptions should be reasonable, and should be transparent, so that they can be challenged. Any good economic study will challenge these assumptions itself, by varying them in a *sensitivity analysis*. This explores the extent to which a conclusion is dependent on an assumption. For instance if a study assumes a rate of relapse of duodenal ulcers after treatment of 5% at one year, what happens if the relapse rate were to be actually 2.5%, or 10%? This might drastically affect the outcome of a study. A sensitivity analysis clarifies what are the critical assumptions and confirm that the results of the evaluation are robust, despite changes in the assumption.

IV. HANDLING THE RESULTS OF ECONOMIC EVALUATIONS

Consider the four possible results arising in a CEA (figure 1). First, if costs are lower and health benefits higher for one drug relative to another, the former is said to dominate and would be the preferred treatment (quadrant II). Second, the opposite applies, i.e. the new drug is more expensive and less effective, and thus is considered inferior and not recommended (quadrant IV). The third and most common case is where the new drug is both more effective and more expensive than the standard (quadrant I); on the basis of ICERs, a judgement must be made regarding whether the additional benefits are worth the extra costs of the new drug and, therefore, whether it is 'cost-effective'. This might be defined by a previously agreed ICER threshold value. The fourth case is similar to the third, with the roles of the new therapy and the standard reversed (quadrant III); the question now is whether the extra benefits provided by the standard justify the additional costs of retaining it as the preferred treatment when the option of a new, cheaper but less effective drug exists.

Figure 1.



Defining what is an acceptable maximum value or threshold for ICER is difficult and controversial, since it clearly carries an element of rationing of care. How much is an extra QALY or life year worth? This is a value judgment. It can be explored to some extent through techniques such as trying to identify what a patient or the public might be willing to pay to avoid an unfavourable outcome. There may be precedents—e.g. by common consent, we provide treatment in the form of coronary bypass grafting: we work out later that this cost £X per QALY, and so this establishes a baseline for our thinking about how much we value a QALY. In the UK, NICE seems to operate at a threshold of around £30,000 per QALY (5), although no formal threshold is declared and its existence has been formally denied. One might be more confident in setting a threshold if economic evaluations were more certain in their outcomes.

V. LIMITS OF PHARMACOECONOMIC EVALUATION

Many problems limit our use of health economics in practice (1). The whole process may be open to bias, in the choice of comparator drug, the assumptions made, or in the selective reporting of results. This suspicion arises because most studies are conducted or funded by pharmaceutical companies who

obviously are interested in the results, and there is a publication bias towards those studies favourable to sponsoring companies (6). Health economics is therefore sometimes misused as a marketing ploy. The same problems may however arise in studies funded by health care payers. To a specialist, this is not such a problem since the almost inevitable biases are usually clear. But since economic evaluation is less well understood by doctors and others, bias needs to be minimised.

Doctors may tend to equate health economics with rationing or cost cutting, and many therefore reject on principle the whole process as unethical. Since resources are limited within health services, wasting them by inefficiency is wrong, as it reduces the clinician's ability to give the best possible care to his patients. It therefore seems unethical not to consider the economics of a medical intervention.

A key problem is our ability to implement the results of a study. No matter how good a study is, and how cost effective a therapy compared to existing treatment, it may not be possible to achieve its potential benefits because of the existing cumbersome management structures. Three problems are common: first, a short term outlook which limits the application of economic evaluations showing long term savings for the health service in return for increased spending now. Second, many budgets operate in isolation, and it is not easy to move money between them: for instance, prescribing in primary care is often funded separately from hospital services, so any increased spending on drug therapy in primary care cannot be simply funded from a future reduction in hospital admissions. Third, a new intervention may simply not be affordable no matter how cost effective it might be.

Finally, health economics and pharmacoeconomics is a young science and is slowly developing and testing its methodologies. We do not have space to address all of these concerns here but many of the details of the methods described above are academically and practically controversial (2). There have been many guidelines developed (e.g. ref 3) for the conduct of economic evaluation, recognising the possibilities of bias and the poor understanding of many potential users about the whole process.

VI. THE FUTURE

Despite these problems, economic evaluations of drug therapy are increasingly important in decision making. Clinical pharmacologists should welcome this as a means to promote efficiency and effectiveness of prescribing, and aim to move the managers' debate away from pure cost to the question of value for money in prescribing.

VII. FURTHER READING

VII.1. Useful texts

1. Walley T, Haycox A, and Boland A (2004). Pharmacoeconomics. Churchill Livingstone, London
2. Drummond M, Stoddard G and Torrance G. (1988). Methods for the Economic Evaluation of Healthcare Programmes. Oxford: Oxford Medical Publications
3. Drummond M. (1994). Economic analysis alongside controlled trials: An introduction for clinical researchers. London: Dept of Health

VII.2. Useful introductory articles for nonspecialists

1. Eddy DM. Cost-effectiveness analysis: A conversation with my father. JAMA 1992;267: 1669-1675.
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3. Eddy DM. Cost-effectiveness analysis – will it be accepted? JAMA 1992;268:32-136.
4. Eddy DM. Applying cost-effectiveness analysis – The Inside Story. JAMA 1992;268: 2575 – 2582.

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<http://www.nice.org.uk/pdf/technicalguidanceformanufacturersandsponsors.pdf> (Accessed 18th November 2003).
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6. Hillman A, Eisenberg J, Pauly M et al. Avoiding bias in the conduct and reporting of cost effectiveness research sponsored by the pharmaceutical companies. *New Eng J Med* 1991;324: 1362-1365.