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Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

Pharmacoeconomics – what do I need to know?

The assessment of pharmaceuticals has, in recent years, expanded beyond considerations of efficacy and safety to cover economic implications and other consequences. The incorporation of an economic perspective into the decision-making process as to what therapies can be made available by the NHS has aroused much discussion and debate. Newspaper headlines about people having to remortgage their houses to pay for "life-saving" therapies and media coverage of instances when "effective" treatments are denied to desperate patients are common occurrences.

This bulletin explores some of the concepts that underpin the economic assessment of medicines. It discusses the rationale for economic considerations and how the approaches and instruments used in undertaking economic assessments can be applied to everyday decision-making processes.

The rationale for pharmacoeconomic evaluation

As individuals we are constantly making choices as to how we allocate our time, into which activities we channel our energies, and on what we spend our available funds. The fundamental economic problem is that while we all have unlimited wants and desires, we only have limited resources (time, energy, expertise, and money) at our disposal to satisfy them. In spending time on one activity or purchasing a certain commodity, that period of time and those funds are not available for other activities and for other purchases.

This situation has become particularly evident in health care. It has been compounded by factors such as the increasing expectations of the population as to what can be delivered by healthcare services, the continuing advancements in health technology and medical science, and the increasing health needs of an ageing population.

Which patients to treat, when, and with what therapies?

The answers do not lie simply in spending more money — how do we know whether spending more will produce additional benefits?

It is these issues that health economic evaluation seeks to address and, specifically in relation to pharmaceutical products, provides the underlying premise on which pharmacoeconomics is based. What is required is information that guides decision-makers as to which medicine provides the greatest "bang per buck". Is it worth paying more for the potential additional benefits that a new medicine offers compared with existing treatments that are currently available?

What is a pharmacoeconomic evaluation?

Pharmacoeconomic evaluations employ the same techniques that are used to assess all healthcare interventions (preventative, diagnostic, or therapeutic). The term **cost-effectiveness** has become synonymous with health economic evaluation and has been used (and misused) to depict the extent to which interventions measure up to what is considered to represent value for money. Strictly speaking, however, cost-effectiveness analysis is one of a number of techniques.

The choice of evaluation technique depends on the nature of the benefits specified. **Cost-effectiveness analysis (CEA)** has been defined as an economic study design in which the consequences of different interventions are measured using a single outcome, usually in "natural" units (e.g. life-years gained, deaths avoided, heart attacks prevented, or cases detected) and the interventions are compared in terms of cost per unit of effectiveness.[1]

This material was developed in collaboration with Ceri Phillips, Professor of Health Economics and Head of the Institute for Health Research, Swansea University

Welsh Medicines Resource Centre
Academic Centre, University Hospital Llandough,
Penarth, Vale of Glamorgan CF64 2XX

Tel: 029 2071 6117 Web: www.wemerec.org
Email: wemerec@cardiffandvale.wales.nhs.uk

Outcomes are very specific and differ according to the nature of the condition being treated. In order to compare the cost-effectiveness of an intervention in one therapeutic area with that of an intervention in a different area (e.g. outcomes in obstetrics and gynaecology compared with those in renal disease, care of the elderly, or musculoskeletal disorders, etc.) it is necessary to utilise "common currencies". The usual currency that is employed is the **quality-adjusted life-year (QALY)**, which is derived from the combination of the impact of an intervention on both quantity and quality of life. The derivation and use of QALYs is discussed in more detail later. The specific type of cost-effectiveness analysis that is undertaken when using QALYs is referred to as **cost-utility analysis (CUA)**.

There may be occasions when the outcomes generated by interventions are virtually equal or at least very similar. In such circumstances it might be possible for a **cost-minimisation analysis (CMA)** to be undertaken, where only the cost differences between the interventions are needed to establish which of them provides the best value for money. However, caution should be exercised in relation to what is meant by equivalence or similarity in outcomes – for example, while both oral and intravenous delivery of a drug can provide equivalent therapeutic effects, outcomes from a patient's perspective might be very different. Rarely used, a **cost–benefit analysis (CBA)** compares outcomes of interventions expressed solely in monetary terms.

With all economic evaluation techniques, the aim is to maximise the level of benefits – health effects – relative to the resources available. Complexities relating to assigning monetary valuations to healthcare outcomes have meant that CUA is the primary technique used in pharmacoeconomic evaluations. This is advocated by the organisations appraising medicines for the NHS: the All Wales Medicines Strategy Group (AWMSG), the National Institute for Health and Clinical Excellence (NICE), and the Scottish Medicines Consortium (SMC).

Which comparator should be used?

In undertaking an economic appraisal of a medicine, the appropriate comparator is the therapy or care package, and not necessarily just a medicine, that is most likely to be displaced. In some cases, it may be appropriate to consider more than one comparator. For others, the comparator may relate to a care package that varies between locations. It is also important to distinguish between care packages in which the medicine forms an element, and those that are clear alternatives that would be displaced if the medicine were adopted.

It needs to be recognised that comparators used in clinical trials may not be those that are used in everyday practice. In such circumstances, some form of bridging assessment to an appropriate comparator is necessary. This should be accompanied with sensitivity analyses to assess the impact of assumptions about comparators, and a discussion of possible biases.

The two main components of economic evaluations relate to the costs associated with a new therapy and the benefits (or outcomes or effects) that it generates.

What constitutes a cost?

Costs are seen differently from different points of view. Reference was made earlier to the need to make choices, because resources are limited in relation to the demands placed on them. Making a choice to commit resources to one treatment or patient means that they are not available for others. As a result, the benefits that would have been derived are sacrificed. These sacrifices are referred to as **opportunity cost**. It is usual, in practice, to assume that the price paid for a medicine reflects the opportunity cost and to adopt a pragmatic approach to costing by using market prices wherever possible.

In undertaking pharmacoeconomic appraisals the conventional approach is to include costs and outcomes from the perspective of the NHS and personal social services. This approach has been criticised when it fails to encompass costs that impinge on other sectors of society. For example, the manufacturers of donepezil, galantamine, and rivastigmine (for Alzheimer's disease) brought a court case against NICE as its decision process regarding these medicines did not take into account the benefits to carers.

In principle, pharmacoeconomic evaluation should aim to assess, comprehensively, the changes in health states and associated changes in cost that arise from using a medicine. The main analysis should focus on changes that affect the healthcare system, patients, and their families/carers, where these are thought to differ significantly between options. However, an indication of the nature and likely magnitude of any further benefits and costs that would arise from adopting a wider societal perspective, and the effect of including these in the analysis, should also be

provided, even where these are difficult to quantify. Every effort should be made to reduce the risk of a partial and potentially misleading assessment of the balance of gains and losses.

In developing a cost profile, the resource implications associated with a therapy (including any essential and specific resources necessary to provide it) are considered. Its comparator(s) should ideally be identified, measured, and valued within a relevant context. If local data are not available, a comment on the validity of using resource data from elsewhere should be included. The appraisal should present resource usage for the therapy and its comparator(s) separately and in natural units, such as hospital days or dosage and duration of treatment, with data sources cited.

Patient resource use in accessing treatment should also be included where considered to be significant, particularly where there are major differences between the options. Other resource use may also be presented separately where differences arise between the medicine and its comparator(s), e.g. direct non-healthcare resource use by other agencies. Productivity losses attributable to changes in health outcomes might also warrant discussion.

Total costs should be calculated for the therapy and its comparator(s) by the application of standardised unit costs to the resources used. The date of the study or reference time period spanning the collection of cost data should be clearly stated.

How are outcomes measured?

In any given healthcare situation there is a multiplicity of possible outcomes, the significance of which are dependent on the perspective being considered – that of the patient, the professional, the manager, the funding agency, or any other stakeholder. As discussed earlier, outcomes generated in one therapeutic area are not comparable with those generated in other areas, so it is necessary to use "common currencies" to compare outcomes across areas. One such currency is the QALY.

QALYs

A QALY is the arithmetic product of life expectancy and a measure of the quality of the life-years. NICE define a QALY as a "measure of a person's length of life weighted by a valuation of their health-related quality of life".[1]

The **quantity of life,** expressed in terms of survival or life expectancy, is a measure that is widely accepted and has few problems of comparison – people are either alive or not. **Quality of life,** on the other hand, embraces a whole range of different facets of people's lives, not just their health status. Even restricting the focus to a person's health-related quality of life will result in a number of dimensions relating to both physical and mental capacity.

A number of approaches have been used to generate these quality-of-life valuations, referred to as **health utilities** –- for example, "standard gamble", "time trade-off", and the use of rating scales. The utilities that are produced represent the valuations attached to each health state on a continuum between 0 and 1, where 0 is equivalent to being dead and 1 represents the best possible health state (although some health states are regarded as being worse than death and have negative valuations).

The preferred instrument for the measurement and valuation of health-related quality of life in NICE appraisals is the EQ-5D (see Box 1).

Box 1. Using the EQ-5D.

Scores for the EQ-5D are generated from the ability of the individual to function in five dimensions. These are:

Mobility
- No problems walking about.
- Some problems walking about.
- Confined to bed.

Pain/discomfort
- No pain or discomfort.
- Moderate pain or discomfort.
- Extreme pain or discomfort.

Self-care
- No problems with self-care.
- Some problems washing or dressing.
- Unable to wash or dress self.

Anxiety/depression
- Not anxious or depressed.
- Moderately anxious or depressed.
- Extremely anxious or depressed.

Usual activities
(work, study, housework, leisure activities)
- No problems in performing usual activities.
- Some problems in performing usual activities.
- Unable to perform usual activities.

Each of the five dimensions used has three levels – no problem, some problems, and major problems – constituting 243 possible health states, to which 'unconscious' and 'dead' are added to total 245.

The EQ-5D is widely used and has been validated in many different patient populations. It has been designed so that people can describe the extent to which they have a problem in five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. For each of the 245 possible health states, utility scores were constructed from responses to a random sample of 3000 people in the UK, using a choice-based method of valuation (the time trade-off method). The utility scores for some of the health states are shown in Table 1.

If data using the EQ-5D instrument are not available, mapping utility scores from other health-related quality-of-life measures included in the relevant clinical trial(s) can be employed, or other standardised and validated measures (e.g. SF6D, Health Utilities Index) included in the relevant trial(s) may be used.

How are QALYs calculated?

The amount of **time spent** in a health state is *weighted* by the **utility score** given to that health state. It takes one year of perfect health (utility score of 1) to be one QALY. One year in a health state valued at 0.5 is equivalent to half a QALY. Thus an intervention that generates four years in a health state valued at 0.75 will generate one more QALY than an intervention that generates four years in a health state valued at 0.5.

With data relating to both health-related quality of life and survival, it is then possible to chart the impact of an intervention on an individual patient. For example, it is possible to compare the health profile of a patient receiving the intervention with that of a patient who is not. Figure 1 shows a situation where a therapy provides a consistently greater area under the QALY-time curve than current practice.

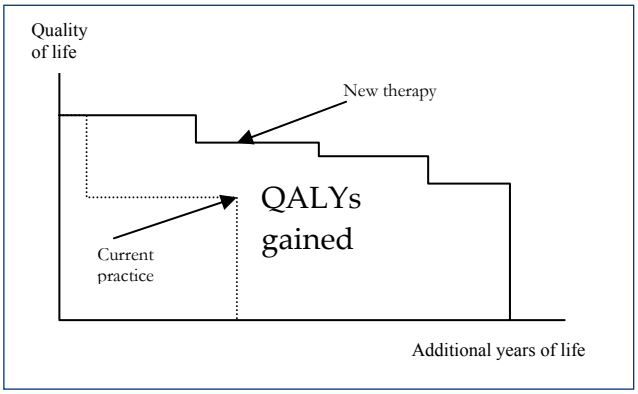

Figure 1. QALYs gained with a new therapy.

Limitations of QALYs

While QALYs provide an indication of the benefits gained from interventions, they are far from a perfect measure of outcome as they may exclude important health consequences. Criticisms have surrounded the inadequate weight attached to emotional and mental health problems, and the lack of consideration of the impact of health problems on carers and other family members. Much debate surrounds who should be involved in placing values on health states. QALYs also suffer from a lack of sensitivity when comparing the efficacy of two competing but similar drugs, and when assessing the treatment of less severe health problems.

Nevertheless, the use of QALYs combined with associated costs helps to assess the relative worth of interventions and allows choices between patient groups competing for medical care to be made explicit. It provides decision-makers with a "benchmark" as they grapple with addressing the dilemma of where to allocate resources in order to generate the maximum health benefits for their communities and society as a whole.

Table 1. EQ-5D health state valuations.

Health state	Description	Valuation
11111	No problems	1.000
11221	No problems walking about; no problems with self-care; some problems with performing usual activities; some pain or discomfort; not anxious or depressed	0.760
22222	Some problems walking about; some problems washing or dressing self; some problems with performing usual activities; moderate pain or discomfort; moderately anxious or depressed	0.516
12321	No problems walking about; some problems washing or dressing self; unable to perform usual activities; some pain or discomfort; not anxious or depressed	0.329
21123	Some problems walking about; no problems with self-care; no problems with performing usual activities; moderate pain or discomfort; extremely anxious or depressed	0.222
23322	Some problems walking about; unable to wash or dress self; unable to perform usual activities; moderate pain or discomfort; moderately anxious or depressed	0.079
33332	Confined to bed; unable to wash or dress self; unable to perform usual activities; extreme pain or discomfort; moderately anxious or depressed	–0.429

Understanding a pharmacoeconomic analysis

A distinction must be made between those interventions that are completely **independent** – that is, where the costs and effects of one intervention are not affected by the introduction of other interventions – and those that are **mutually exclusive** – that is, where implementing one intervention means that another cannot be implemented, or where the implementation of one intervention results in changes to the costs and effects of another.

Appraisals of independent programmes require that **cost-effectiveness ratios (CERs)** are calculated for each programme and placed in rank order:

$$\text{CER} = \frac{\text{Costs of intervention}}{\text{Health effects produced (e.g. QALYs)}}$$

Usually however, choices will have to be made between different treatment regimens for the same condition, different dosages, or treatment versus prophylaxis – that is, between mutually exclusive interventions.

The key question is: what are the additional benefits to be gained from the new therapeutic intervention and at how much greater cost?

In order to answer such a question, **incremental cost-effectiveness ratios (ICERs)** are used.

$$\text{ICER} = \frac{\text{Difference in costs between intervention A and B}}{\text{Difference in health effects between intervention A and B}}$$ as shown in Table 2:

Table 2. Calculation of an ICER.

Therapy	Costs (C) (£)	Effects (E) (QALYs gained)	Incremental cost (ΔC)	Incremental effect (ΔE)	ICER (ΔC/ΔE)
A	100,000	60			
B	125,000	75	25,000	15	1,667

The cost of generating an additional QALY by using a new therapy (B) rather than the conventional medication (A) is £1,667, i.e. an additional 15 QALYs result from using medication B as opposed to medication A, but there is also an additional cost of £25,000.

The results from such analyses can be placed on a cost-effectiveness plane (Figure 2). In the above example the ICER would be located in the north-east quadrant, since B is more effective but also more expensive.

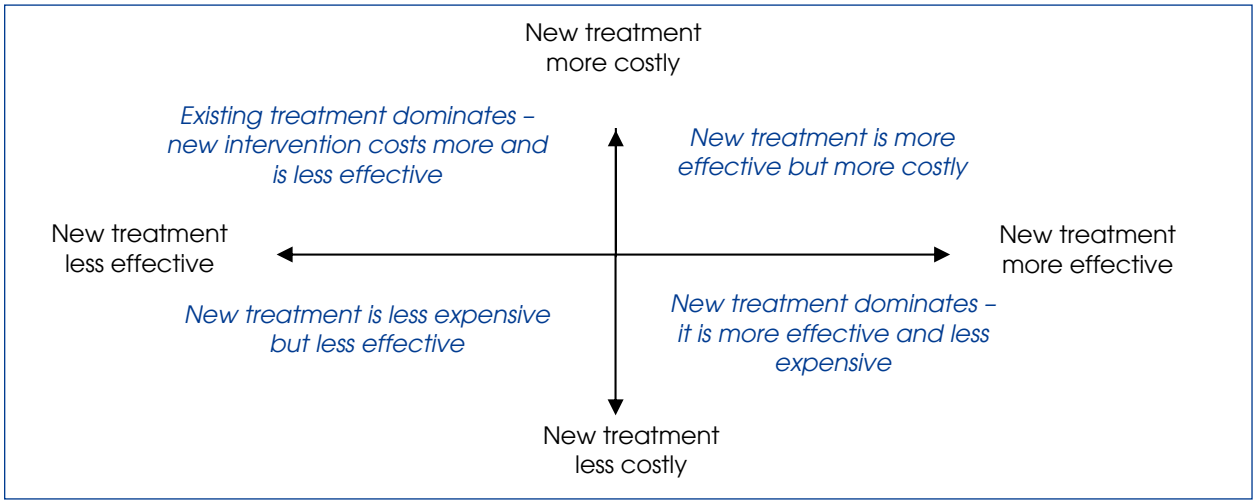

Figure 2. Cost-effectiveness plane.

Interventions that have ICERs located in the north-west quadrant should not be provided. Those interventions with ICERs located in the south-west quadrant are often termed 'questionable', i.e. they raise questions as to whether, and to what extent, resources can be withdrawn for smaller health gains. Interventions with ICERs in the south-east quadrant are termed dominant, i.e. they more effective and less expensive; a win-win situation. Interventions with ICERs in the north-east quadrant require some consideration.

The decision whether or not to choose a treatment that is more effective but more costly should be based on the level of additional resources available, or by viewing the ICER in the light of a specific acceptable threshold. It is this threshold that is the source of much contention when recommendations are made by appraisal groups. In the UK it is currently thought that an intervention whose cost per QALY gained is less than £20,000 to £30,000 could be regarded as being cost-effective when there is good evidence of its effectiveness. However, there has been considerable pressure on the assessment agencies to value QALYs differently for different classes of therapies, e.g. ultra-orphan drugs, and end-of-life treatments.

Pharmacoeconomics is far from a precise science and the findings emerging from such evaluations should be treated with a degree of caution. There is often considerable uncertainty associated with the findings with wide variation surrounding the ICERs generated. For example, one of the early technology appraisals undertaken by NICE was on beta interferon and glatiramer acetate for the treatment of multiple sclerosis: estimates of the cost-effectiveness varied enormously due to differing assumptions relating to the duration of treatment; the number, severity and impact on quality of life of relapses that occurred; and the extent to which progression was compromised by the interventions. ICERs, therefore, require some indication of the confidence that can be placed in them. It is imperative that an assessment of cost-effectiveness should be subjected to a sensitivity analysis.

Sensitivity analysis

The need for sensitivity analysis arises because of:

- methodological issues arising from different approaches employed in the evaluation;
- potential variation in the estimates of costs and benefits used in the evaluation;
- extrapolation from observed events over time or from intermediate to final health outcomes;
- the transferring of results and the validity of results from different populations/patient groups.

What would happen, for example, if the 'true cost' of one of the treatment strategies was somewhat higher or lower than the estimate used in the investigation, or if there were significant changes in the life-years gained or other parameters used? Sensitivity analysis tests all the assumptions used in the model and enables the impact of changes on baseline estimates to be assessed.

The use of probabilistic sensitivity analysis is now recognised as the appropriate format for undertaking and reporting sensitivity analysis, with the production of a cost-effectiveness acceptability curve (see Figure 3) being particularly helpful for the decision-maker.

The curve is generated by costs and effects data being simulated repeatedly (usually 1000 times) to generate a vector of cost-effectiveness ratios which are plotted on the cost-effectiveness plane. Decision-makers can determine how much they are prepared to pay for the production of one QALY and the curve indicates the likelihood that the cost-effectiveness ratio lies below that threshold.

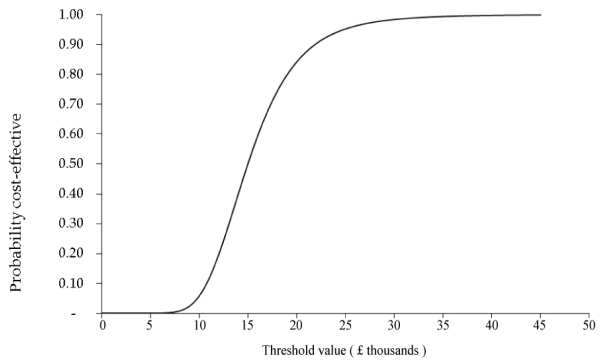

Figure 3. Cost-effectiveness acceptability curve.

Summary

Determining which healthcare services and treatments should be provided is highly complex and involves a number of different, often conflicting, factors. Pharmacoeconomic evaluations can help decision makers to use the information relating to the effectiveness and efficiency of an intervention. They can also contribute to the process of determining priorities and seeking to ensure that the most efficient use is made of resources available within limited healthcare budgets.

Further reading

- Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes.* Oxford: Oxford University Press, 2005.
- Phillips CJ. *Health Economics: An introduction for health professionals.* Oxford: Blackwell Publishing, 2005.

Reference 1. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf