

Pharmacoeconomics: basic concepts and terminology

T. Walley & A. Haycox

Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

Introduction

Spending on drugs is a major target for savings in health care costs for governments around the world. Such a focus results from the size of the drug bill, the highly visible nature of drug utilization and the perception that the drug budget is currently not being used to best advantage. In addition the drugs bill is an area in which it is perceived that savings can be made without detriment to patients [1] and without having to address sensitive issues relating to staff redundancy. The total cost of the drug bill in 1994 was £3844 million which represented a cost of over £65 per capita and an average of 8.9 prescriptions were consumed per head of population [2]. Government attempts to contain the drug bill include increased patient copayments, encouragement of formularies, and the utilization of indicative or real drug budgets. The use of cost limited drug budgets to constrain the overall drugs bill has experienced some success in the UK [3].

The impact of placing severe constraints on the drugs bill needs to be evaluated to ensure that it does not lead to significant increased costs elsewhere in the health care system (e.g. increased inpatient episodes or diagnostic tests) or lead to a significant reduction in the level of benefits to patients. The focus of concern to decision makers, health care professionals and the public should be the value derived from drug therapy, rather than simply the level of the drugs bill. This wider focus requires a comparison of benefits derived and costs incurred [1, 4]. It is not after all the function of a health service to minimise costs but rather to use its available resources to achieve the greatest health gain for its population. By these criteria, increased spending on drugs which leads to a reduction in the need for hospitalisation or economises on the use of some other expensive resource can represent a cost-effective shift in resource utilization. The important issue concerns the optimum manner of investing health care resources to generate health gain and for this reason an increase in expenditure on drugs may be a highly efficient use of scarce health care resources. Such a comparison of the 'marginal productivity' (additional benefits derived from the application of additional resources) from different methods of using resources is difficult but essential for a health service determined to maximise patient benefit. Such assessments are essential, not to reduce costs, but rather to identify the benefits of alternative uses of resources in order to identify the structure of health care that best meets the needs of patients.

Pharmacoeconomics is a branch of health economics which particularly focuses upon the costs and benefits of drug therapy. A knowledge of pharmacoeconomics is therefore vital for clinical pharmacologists who are involved

in promoting rational prescribing [4] or in clinical trials which incorporate an economic component. In some areas (e.g. Australia) economic evaluations are now formally required prior to a drug being approved for reimbursement—the 'fourth hurdle' for a new drug after establishing safety, efficacy and tolerability [1]. Elsewhere, pharmaceutical companies are increasingly 'tagging' on economic evaluations to clinical trials primarily as a marketing strategy. The lack of scientific rigour in many such studies is in danger of bringing the entire process of economic evaluation into disrepute in the eyes of clinicians [5].

The concepts and terminology of health economics are likely to be new to most clinical pharmacologists but are becoming increasingly relevant to their professional role. In recognition of this growing importance this is the first in a series of three articles aimed at providing a non-technical introduction for clinical pharmacologists to pharmacoeconomics. This article introduces basic concepts and terminology, the second article provides a range of quality markers that will assist clinical pharmacologists in assessing the reliability of such evaluations while the third article analyses issues relating to the integration of economic evaluations into clinical trials. Excellent textbooks [6], articles [7–12] and courses are available for those who wish to develop their knowledge further.

Basic concepts and terminology

Health economics is fundamentally comparative and deals with choices between options. Thus when a study asserts that 'drug x is cost effective', our immediate response should be 'compared with what?' Currently there is debate about what the ideal comparator should be—should it be the drug and dose most widely used for a condition (which may vary from country to country), or a 'gold standard' comparator that is chosen on the basis of results obtained in clinical trials. One method by which the results of analyses can be biased is to choose a comparator (old generation drug or suboptimal dosage) that provides a patient benefit 'yardstick' that is relatively easy to beat. This raises further questions concerning the most appropriate sources of medical evidence to support economic studies. Where possible, such studies should be based on a balanced evaluation of the available medical evidence, but more importantly on the nature of clinical management in common medical practice rather than in a clinical trial. Frequently however little is known of the nature and impact of clinical management in practice and we are forced to make *assumptions* to fill the gaps in our knowledge. Such assumptions must be 'reasonable', and should be explicitly stated and therefore transparent so that they can be challenged. Indeed any good economic study will proactively challenge the impact of such assumptions, by varying them in a *sensitivity analysis*.

A sensitivity analysis explores the extent to which the conclusion derived from a study is dependent on the

Correspondence: Professor T. Walley, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

underlying assumptions or upon data that may be subject to measurement errors, e.g. resource use or clinical benefits. For instance if the results of a study are based upon a rate of relapse of duodenal ulcers after treatment of 5% at 1 year, what happens if the relapse rate is actually 10%? To what extent does such a change alter the conclusions that can be drawn from the study? A sensitivity analysis is essential in any good economic evaluation to confirm to the reader that the results of the evaluation are robust, and to clarify the nature and impact of the critical assumptions.

A number of other crucial concepts underlying pharmacoeconomic evaluations are defined below:

Efficiency Obtaining maximum benefit (i.e. health gain) from limited resources. Maximising clinical effectiveness is crucial in obtaining economic efficiency.

Opportunity cost This is defined as the 'benefit foregone when selecting one therapeutic alternative over the next best alternative'. The economist's approach to costs measures the true 'cost' of using resources in one manner in relation to what we are giving up to use that intervention. This is a concept familiar to all of us, though not perhaps in this terminology. For instance, suppose I can afford either to buy a new car or to take an expensive holiday but not to do both. The opportunity cost of buying one is my inability to enjoy the benefits that would arise from the other. In the health service, this concept requires us to analyse the level of health benefits that would arise if we used resources currently devoted to drugs in some other way (e.g. increased hospital services or social welfare). To emphasize the importance of 'opportunity cost', government ministers have discovered a new unit of currency—the total hip replacement (THR); Their objective is to develop a concrete example that succinctly describes the health benefits that could arise to patients as a consequence of diverting expenditure away from existing uses. For example—'If we spent x% less on the drug bill, we could afford y times more THRs!'

Incremental analysis Some form of treatment currently exists in most therapeutic areas even if such treatment is limited to 'best supportive care'. Economic evaluations focus on the costs and the benefits of a new intervention over and above those provided by the current therapy. As an example, effective treatments currently exist for the management of asthma, but perhaps they can be improved by the use of new anti-inflammatories. We would not be advocating stopping all existing treatment for asthma, so the question is not what are the 'average' costs and benefits exhibited by new anti-inflammatory drugs, but rather what 'additional' costs and benefits would arise as a consequence of using the new drugs in comparison to those obtained from existing drugs.

This gives rise to the related concept of incremental or marginal costs. For instance, if a new treatment enables patients to be discharged from hospital a day earlier than existing therapy, the actual resource savings resulting from such a change would be likely to be significantly lower than the average cost of a hospital bed day. All of the fixed support services required to support a hospital bed, e.g. costs

of laboratories, kitchens, and building maintenance (which are included in the calculation of average costs), will be largely unchanged. The only costs which would be likely to alter are those that are directly associated with having a patient physically occupy the bed—the cost of the patient's meals, treatment and some element of nursing time. These are the 'marginal costs' which measure how total resource use actually changes in response to a small increase or reduction in workload. Given that such costs are often very difficult to measure, studies frequently resort to applying average costs as a proxy measure for marginal costs. This may be justified if, for instance, enough bed days are saved by the widespread adoption of a new treatment to actually close a ward. However in all cases where average costs are used to approximate marginal costs, the extent of any potential distortions that may be introduced into the analysis should be explained.

Methods of economic evaluation

A range of methodologies are available for pharmacoeconomic evaluations but they all have a common structure requiring explicit measurement of inputs ('costs') and outcomes ('benefits') resulting from drug interventions. Economic evaluation therefore represents an essentially symmetrical framework which draws up a balance sheet to compare the costs and benefits of drug therapy. The 'cost' arising from drug therapy relates not to the price paid for a drug, nor even all monetary costs related to its use, but incorporates all the implications of drug therapy including time lost from work and distress [13]. Given such a wide definition of 'cost' it may be useful to define certain categories into which such costs may fall:

- **Direct**—paid directly by the health service, including staff costs, capital costs, drug acquisition costs. These should (in theory) be relatively easy to measure, but if one were to ask a GP fundholder how much a cholecystectomy costs, one would get a wide range of responses; the reality is that we are often not very good at costing medical interventions.
- **Indirect**—costs experienced by the patient (or family or friends) or society; for example, these might include loss of earnings, loss of productivity, loss of leisure time, cost of travel to hospital etc. Many of these are difficult to measure, but should be of concern to society as a whole.
- **Intangible**—these are the pain, worry or other distress which a patient or their family might suffer. These are difficult to measure in monetary terms but represent a considerable concern for both doctors and patients. The incorporation of 'quality of life' into economic evaluations represents one method by which such 'intangibles' can be effectively integrated into the analysis.

Table 1
Inputs ('costs')
↓
Medical interventions
↓
Outcomes ('benefits')

'Benefit' measurement aims to be equally comprehensive by incorporating all of the impacts upon the patient's life that arise as a consequence of drug therapy [14]. The benefits derived from an intervention might be measured in:

- 'Natural' units—e.g. years of life saved, strokes prevented, ulcers healed etc.
- 'Utility' units—measuring changes in a patient's satisfaction, or sense of well being in an attempt to evaluate the satisfaction derived from moving from one state of health to another as a consequence of the application of drug therapy.

Such utility measurements are frequently based upon some measurement of 'quality of life' [15]. Quality of life measures attempt to incorporate into the analysis the physical, social and emotional aspects of the patient's well-being, which are not directly measurable in clinical terms [16, 17]. Many different methods have been proposed to measure quality of life based upon widely different techniques and value systems [18–20]. The individual elements that interact to determine 'quality of life' tend to be divided between the physical dimension and the psycho-social dimension [21]. Physical measures concentrate on the presence or absence of physical symptoms such as pain and immobility. Equating quality of life with the absence of physical symptoms is too simplistic. The psycho-social dimension relates to the level of anxiety and depression experienced and hence the ability of the patient to cope with problems. Quality of life measures can take the form of 'health profiles' (e.g. the Nottingham Health Profile) which keeps different aspects of quality of life separate or single outcome measures (e.g. the Quality Adjusted Life Year) which attempts to construct a single summary measure of quality of life.

The Quality Adjusted Life Year (QALY) is a summary of quality and quantity of life [22, 23]. The original QALYs were heavily criticised for basing their analysis on the preferences of small numbers of healthy people, and for using insensitive descriptors of health, which may make it inappropriate to extrapolate QALYs to wider populations. Furthermore, the preferences of healthy people may not be an appropriate yardstick, since their experience of the states that they are being asked to evaluate is very limited and the preferences of people with illnesses may be quite different [24]. Despite these criticisms, the debate generated by the QALY has advanced thinking on the need to incorporate quality of life into economic evaluations. In particular it has emphasised the need for techniques used to evaluate quality of life to exhibit certain attributes including reproducibility, reliability and validity. In addition the method chosen must be sufficiently sensitive to identify the impact upon Quality of Life of the treatment being evaluated. Such measures are particularly important in the evaluation of drugs which improve a patient's quality of life or ameliorate the patient's condition rather than save lives or restore the patient to perfect health [25].

- *Associated economic benefit*: this is usually measured in monetary units (i.e. £s) because this is a useful common denominator that enables comparisons to be made across different disciplines. This concept includes, for example, the economic benefits that arise to society as a consequence of a patient's health improving sufficiently to facilitate a return to work.

Common types of study

The methodology for analysing costs and benefits outlined above gives rise to the four commonly encountered types of economic evaluation.

Cost minimisation analysis (CMA)

This is the most restrictive form of analysis and focuses entirely upon costs, usually only to the health service. As a consequence such analyses should only be used where the health benefits obtained from two alternative therapies are identical and therefore need not be considered separately. An example would be a decision to introduce generic prescribing rather than by brand name which would achieve the same level of benefit at a reduced cost. This form of evaluation is very easily understood and widely applied by doctors. However it cannot be used to evaluate programmes or therapies that lead to different outcomes.

Cost effectiveness analysis (CEA)

The term cost effectiveness analysis is often used loosely to refer to all forms of economic evaluation. The term however properly refers to a particular type of evaluation in which the health benefit can be defined and measured in natural units (e.g. years of life saved or ulcers healed) and the costs are measured in monetary terms. CEA therefore compares therapies which can be measured on a common scale of outcome but perhaps exhibit different success rates. For instance, if our desired outcome were symptomatic relief in severe reflux oesophagitis, we could compare the costs per patient relieved of symptoms through use of a proton pump inhibitor in relation to those using H₂-receptors blockers [26]. CEA is the most commonly applied form of economic analysis but it does not allow comparisons to be made between two totally different areas of medicine with different outcomes.

Cost utility analysis (CUA)

This is similar to CEA in that there is a defined outcome and the cost to reach that outcome is measured in monetary terms. However in this case the outcome does not have to be measured on a common natural scale. Outcome in CUA is measured in terms of changes in patient wellbeing (utility) and since such an outcome measure is not disease specific, CUA can in theory compare the 'value' of health interventions over more than one area of medicine (e.g. coronary artery bypass grafting versus the use of erythropoietin in treating anaemia in chronic renal failure). In practice this is not so easy since the utility measurements that have been proposed (such as the quality adjusted life year or QALY) are not well defined fixed units transferable from study to study. Measurements of quality of life may reflect different priorities and perspectives in different diseases. We should be particularly wary of attempts to draw up league [27] of QALYs to facilitate comparisons of the 'value for money' provided by a range of therapies. The values in such tables have usually been derived at different times by

different people using different methods and are not comparable [28].

Cost benefit analysis (CBA)

This approach is the most all-encompassing but also the most difficult to apply. In this case the analysis attempts to calculate the associated economic benefit of an intervention, and hence both costs and benefits are reduced to their monetary equivalents. Unfortunately CBA may ignore many intangible benefits which are difficult to measure in money terms, (e.g. relief of anxiety) but which are of fundamental importance to the patient. CBA may also seem to discriminate against those in whom a return to productive employment is unlikely, e.g. the elderly, or those that do not participate in the labour market.

Despite the difficulties underlying its practical application, the strength of this analysis is that it allows comparisons to be made of the costs and benefits arising in very different areas. Thus the 'value for money' arising from increased spending in education (benefits of improved education and hence increased productivity) can be directly compared with that obtained from establishing a back pain service (increasing productivity by reducing levels of absenteeism). Currently this approach is not widely applied in health economics as the theoretical and practical framework to reduce all aspects of the economic 'equation' to their monetary equivalent is not sufficiently well developed. The approach is valuable, however, as a 'system of thought' which reinforces the need to incorporate all of the consequences of change into an economic evaluation. Such an approach also widens the concept of opportunity cost in a manner that emphasises that resources consumed by the health service become necessarily unavailable to fund other public services.

Other issues of importance

Two further issues are crucial in understanding the approach utilised by health economics to evaluate drug use.

Perspective

The 'cost-effectiveness' of any health service intervention in large part depends upon from whose point of view the study is conducted. A range of potential perspectives can be adopted from the most limited (impact of changes on a single drug budget) to the societal where all indirect costs are studied as well. Given that the aim of economic analysis is to make the best use of all of society's resources, the societal perspective is considered the most appropriate, but a health care manager with a limited budget might be tempted to place increased emphasis upon costs that are imposed upon his area. A study of migraine from the perspective of the health service alone would be likely to find that the use of sumatriptan in migraine (a very high cost drug in an area which previously cost the health service very little) was highly undesirable. In contrast a study taking a societal perspective, that incorporates all of the additional costs imposed upon the migraine sufferer, might come to the opposite conclusion [29].

Timing of costs and benefits

Frequently the investment of health service resources occurs over a different time scale to the period during which patients experience the health benefits. For example a surgical intervention to improve cardiovascular functioning represents an investment of resources. Now to achieve health benefits over a number of years. In comparison pharmacological interventions, to achieve the same benefit, create continuous costs and benefits into the future. Therefore in order to compare two such interventions with different profiles of costs and benefits, it is necessary to 'discount' them to their Net Present Value. In general, costs incurred in the future are discounted at an annual rate set by the Treasury (currently 6%). The extent to which future health benefits should also be discounted remains an area of controversy within health economics. While it is relatively easy to accept that £100 spent now is 'worth' more than £100 spent in 5 years time, the theoretical basis for comparing the value of a healthy year now with a healthy year in 5 years time is not as obvious. Given such controversy, the most sensible approach is to analyse the sensitivity of the results obtained from the economics analysis to the discounting of future health benefits by presenting future health benefits both in a discounted and an undiscounted form.

Applying pharmacoeconomics to the Health Service

Many practical difficulties may limit our ability to apply pharmacoeconomic approaches to the health service. The whole process may be perceived by clinicians to be open to bias either through the choice of comparator, the nature of the assumptions made, the selective use of medical evidence or in the selective reporting of results [30]. To a health economist, this is not such a problem since the presence or absence of such biases is usually clear. Given that economic evaluation is less well understood by clinicians and others at whom such studies are aimed, it is important that the independence and scientific validity of such studies is ensured.

Concerns about bias normally arise because most studies are conducted or funded by pharmaceutical companies who obviously have a commercial interest in ensuring that their products are viewed in a favourable light. The suspicion is that 'in-house' health economists or commercial consultancy firms will be under immense pressure to come up with the 'right' result. At the very least this is perceived as biasing publications towards economic evaluation that are favourable to sponsoring companies. The extent to which such 'bias' actually exists in practice is immaterial since its very perception is sufficient to destroy the credibility of such studies. This problem needs to be addressed over the long term by utilising scientific criteria to establish explicit standards in health economics and by improving the understanding of health economics and hence the scientific expectations of customers for such studies. In the short term the establishment of a central NHS unit that could be responsible for assessing and validating the results of studies on behalf of the NHS [31] would greatly assist clinicians to distinguish the pharmacoeconomic 'wheat' from the 'chaff'.

Clinicians frequently equate health economics with rationing or cost cutting and fail to perceive its potential value in improving patient care and exposing areas of underfunding. Many doctors therefore reject as a matter of principle the whole process and condemn its application as being 'unethical'. While such an approach does not stand up to serious analysis [1], it must be recognised that there is a potential conflict between the traditional Hippocratic medical ethic (what is best for the individual patient) and utilitarian ethics (what is best for any given population of patients) [32]. The tensions between the two approaches must not be allowed to stifle debate but rather can be constructive in advancing our thinking on the future of health services. Ultimately decisions concerning the 'optimum' level and configuration of health services should be taken by society in general. Unfortunately, little of this discussion gets into the broader public domain, and in the UK a full public discussion concerning the implications of constraints in service provision as a consequence of limited resources in the health service has yet to take place [33]. The reality of life within a resource constrained NHS is that it is the refusal to ensure efficient resource use that is inherently unethical. The inefficient use of resources reduces the clinician's ability to provide the best possible care to his patients. Far from being unethical to consider the economics of a medical intervention, the implications of ignoring potentially beneficial options make it unethical not to.

The savings identified in economic evaluations are putative. As such it is necessary to assess the extent to which such savings can be realised in practice. The health service is faced with budgetary constraints which limits the application of pharmacoeconomic evaluations that identify significant long term benefits as a consequence of increased investment in drug use during the current period. Such analyses must recognise that it may not be feasible to immediately free up resources in order to finance the necessary investment. Furthermore the strict separation of funding for drugs at the primary and secondary care level can lead to problems in implementing a more cost-effective structure of prescribing. For example in attempting to persuade hospitals to avoid the use of drugs whose price is artificially low in the hospital environment ('loss leaders') cost savings in primary care cannot automatically be used to recompense hospital prescribers for any increased level of cost that they incur. Therefore no matter how effective a therapy or policy may be in achieving a more cost-effective pattern of prescribing it may not be possible to achieve its potential benefits simply because of the existing cumbersome budgetary restrictions currently imposed upon the NHS.

A final important point is that health economics in general and pharmacoeconomics in particular is a young science and is slowly developing and testing its methodologies. Some would argue that in such circumstances it is not yet ready for practical applicability. The counterargument is that the science will only be refined by application and that as the science improves, so too will the value of the analyses to clinicians. Clinicians are acutely aware that there has to be a more sensible method by which to evaluate the money spent on drugs than concentrating upon the simple acquisition costs. We need to move the focus of the debate away from the acquisition cost and towards the value for

money obtained from prescribing. Clinical pharmacologists should be key protagonists in this [34].

One of the key elements in improving the acceptability of economic evaluations by clinicians is to improve the validity, reliability and robustness exhibited by such studies. Methods by which this can be achieved [35–38] are discussed more fully in the next article in this series.

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