COST BENEFIT ANALYSIS OF MEDICINES – A GUIDE FOR INDUSTRY

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Preface

The objectives of this booklet are twofold. First, to describe in simple terms the state of the art in undertaking economic studies to demonstrate the benefits of new and existing medicines. Second, to remind readers why such analyses are of increasing importance both to individual pharmaceutical companies and to the industry as a whole.

The text of the booklet has been prepared in consultation with the newly formed 'Pharmaceutical Industry Health Economics Group' (PIHEG) chaired by Nicholas Wells of Glaxo, as well as with the Editorial Board of the Office of Health Economics. However – as with all OHE Reports – it has tried to avoid the pitfalls of 'Committee drafting' and its ultimate style and presentation remain the responsibility of myself as author.

It is hoped that pharmaceutical executives, and medical and research directors in particular, will read the booklet, in order to understand better how health economists can help to achieve an improved awareness, in economic terms, of the benefits of the medicines which their companies develop, manufacture and market.

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Why economic studies are important

If the resources available for medical care were unlimited, economic analysis would be irrelevant. Essentially, economics is about the allocation of scarce or limited resources. In a market where the individual customers themselves pay for what they receive, formal cost benefit analysis is unnecessary. The customers subjectively decide whether to use a sum of their own money to buy particular goods or services. But this sort of 'private' market is inequitable in the health care field.

Cost benefit analysis, in systems such as health care where the 'customer' pays through taxation or insurance, attempts to mimic the private purchasing process by weighing up the costs and benefits of using limited collective funds to buy one thing rather than another. It extends the framework for making the decision by assembling as full information as possible and by taking account of long-term costs and benefits as well as those which occur in the short-term. The aim is to get good value from public funds in the same way as the individual seeks good value from his own spending.

Health care resources will always be limited in all countries and under all varieties of system of financing. Thus every time a medical procedure is undertaken, either a doctor or an administrator has taken a decision to use some of the limited nationally available pool of resources for that purpose. Those resources are then no longer available for any alternative use. As a result, the way in which health care resources are used is being critically examined. Furthermore, governments and health authorities everywhere are attempting to restrict the growth in the total resources devoted to medical care. Thus, for two reasons there is downward pressure on the cost of health care, and this is most obvious in the pharmaceutical sector.

In Britain this has led to restrictions on which medicines a doctor can prescribe (the 'limited list'), to pressures to prescribe cheaper generic medicines, and soon it will lead to practice formularies and prescribing budgets. In West Germany, costs have been contained by introducing 'reference prices' which limit what the health insurance organisations will pay for branded medicines. In France, there are well established price controls which have resulted in some of the lowest prices in Europe. In Italy, the patient pays a 'ticket' for prescribed medicines, and the ticket is priced in such a way as to favour generic products and cheaper medicines. Similar methods of ensuring downward pressure on prescribing costs exist in other European countries. In the 'free market' situation in the United States, on the other hand, pharmacists are permitted to substitute cheap generics for the original brands prescribed by the doctors, thus creating strong price competition.

As a result of all this, there is considerable urgency for pharmaceutical firms to demonstrate that their medicines give good value for money as well as being clinically effective. In Britain, for example, medicines may

be excluded from formularies unless they are cost-effective. Nor will budget-conscious doctors prescribe particular medicines unless they represent good value. The extreme situation already exists in Norway, where medicines may not even be licenced for sale unless a 'need' for them has been proved, and this will often entail economic considerations.

In summary, the era when it has been sufficient merely to show that a medicine was effective and relatively safe is coming to an end. It will very soon also be necessary to show that medicines are cost-effective, either in comparison to other forms of treatment or in comparison to other medicines. Incidentally, this will soon also be true for all other forms of medical and surgical treatment. Pharmaceuticals have simply come into the economic limelight a little ahead of other forms of therapy.

Introduction to the terminology

The title of this short booklet uses the phrase 'cost-benefit analysis' because that is the longest established and most generally recognised term for studies which attempt to relate the cost of a procedure to the benefits which it yields. The term has been used to describe many types of study – for example, to assess the desirability of investment in transport, education, urban development and environmental programmes, as well as health care.

Within the broad category of cost benefit analysis, several studies of a more specific nature have been undertaken in health care. These include:

cost-effectiveness analysis
cost-utility analysis
quality of life studies

Unfortunately, although these terms are intended to differentiate studies with different objectives they are not always used by different authors or economists in a consistent way. But a fairly general set of definitions are as follows:

Cost-effectiveness analyses compare the costs of achieving the same outcome by a variety of different methods. Thus, they show how to spend resources most effectively given a particular desired objective;

Cost-utility analyses relate the costs of different procedures to the increased 'utility' which they produce. Utility is a term of economic jargon to mean the amount of well-being, independent of what it actually costs or whether it produces any financial gain. Thus the basic life of an old age pensioner can be said to have much the same 'utility' in economic terms as the basic life of a young productive worker. The latter, of course, also yields a further economic benefit related to the goods or services which are produced;

Quality of life studies relate the use of health care resources to various measures of the improved well-being of the patients. The techniques involved will be discussed in a later section;

Cost-benefit analysis (although widely used as a generic term to cover all these economic studies) is often more strictly confined to studies where both the resources used in an activity and the benefits which it yields can be expressed in monetary terms. That is, both sides of the 'cost-benefit equation' are set out as pounds, dollars, etc. In medical care, this is most easily done where the cost of using a medicine, for example, produces a clear financial saving in other health care costs – eg, when the cost of surgery or hospitalisation is avoided. However, more sophisticated studies have attempted to convert 'utility' (that is, well-being) into monetary terms, so that a strict 'cost-benefit' analysis can be undertaken relating the cost of medical care to improved well-being, which is given a cash value. The techniques for this will be referred to later. In the text of this booklet (unlike its title) the phrase 'cost-benefit analysis' will be used in its narrower sense.

Thus, it can be seen that cost-benefit, cost utility and quality of life studies all in principle allow a comparison between the economic effectiveness of different uses of the same scarce resources. If procedure A produces a greater economic gain (however measured) than procedure B, there is an *economic* argument for putting more resources into A and less into B. However, economists are the first to agree that economic considerations are not the only ones to be taken into account. Political or ethical factors may be equally or more important. But it is necessary to recognise that *clinical* considerations alone can often no longer be the criteria for deciding on the most desirable pattern of medical care.

Scope of the analysis

The economic benefits of medicines can be looked at from three points of view. First, do they reduce *total* health care costs? Second, do they contribute to the wealth of the nation as a whole? And third, do they increase the well-being of the individual patients and their family and friends?

The answer to the first question depends on whether savings, for example, in surgical or hospital costs outweigh the cost of the medicine. This question must, however, be answered honestly. For example, if a patient with schizophrenia is treated with a medicine in the community rather than in hospital, the costs of community care must be taken fully into account. It is wrong simply to measure the savings in hospitals costs without looking at the whole picture. There are many cases, however, when a cost-benefit equation will indeed show a positive saving from the use of a new medicine to replace more expensive alternative therapies – or where a new expensive medicine can be administered at less total cost than a cheaper old one.

The answer to the second question depends, in addition, on whether the use of the medicine reduces sickness absence or premature

mortality. If it enables a person to remain a productive member of society for longer, the medicine does, at least in theory, add to national wealth. However, once again caution is necessary. If the sick person remaining at work simply keeps another person unemployed, there may be no real benefit for the economy. Thus, in an era of unemployment, the economic contribution of reduced sickness absence or the avoidance of premature mortality may be more notional than real. Furthermore, if premature mortality is reduced, it may also *increase* the number of dependant elderly in the community (because the individuals concerned are unlikely to die exactly when they reach retirement age). However, interestingly at least one study has shown that the reduction in cardiovascular deaths, for example, adds more through increased production than it costs through increased pension payments.[1]

Finally, improved quality of life, independant of any financial contribution, has an economic value in terms of 'utility'. This can be measured in ways which are discussed later.

Thus, medicines can make an economic contribution to the community in three ways. It must be recognised, however, that it may only be the first of these – savings for the health service itself – which at present really impresses health service managers, Treasury officials and politicians. Thus, cost-benefit studies to show savings for the health service may at present be more convincing to politicians and others than more broadly based economic analyses. However, it is important to encourage a broader economic perspective, taking account of economic benefits in the widest possible way.

The epidemiological approach

The actual economic analyses can be approached in either of two broad ways. The first is through an epidemiological study, which examines the economic effect of a medicine on a group or cohort of patients as a whole. It can be a retrospective analysis, a prospective study of the use of the medicine in practice, or a placebo (or comparator) controlled study during phase two, phase three or phase four clinical trials.

In each case, the objective is to compare the economic benefits of the treatment against the cost of using the medicine. On one side of the equation, the cost of the medicine is easy to measure – although at a pre-marketing stage it may still be flexible if the price of the treatment has not yet been fixed. The benefits – using the epidemiological approach – are measured by comparing what happens to patients receiving the medicine against what happens to patients who do not receive it (and may instead receive a comparator medicine or a placebo).

In a retrospective analysis, it will be necessary to look through patient records to establish, for example, how often they were admitted to hospital and for how long, what other treatments they received, whether they lost time from work through sickness, and whether they died prematurely. It is, however, impossible to capture 'quality of life' data retrospectively. In a prospective study, each of these parameters (including, if

necessary, quality of life) can be recorded for the treatment group and the control group as the study progresses.

The various measurements can then be converted into monetary terms using, for example, average hospital bed-day costs for the appropriate type of patient, or estimated costs for surgery and other procedures. This will give a total average cost for the group receiving the medication and for the control group. The difference between the two costs gives a measure of the economic benefit in monetary terms to set against the cost of medication.

This epidemiological approach can never give exact costs. To some extent almost all the costings will be based on estimates, and they must be as realistic as possible. For example, if a patient in the control group is being kept in hospital for largely social reasons, receiving minimal medical care, it would be unfair to cost such a stay as if full medical care and intensive nursing were required. In other words, 'marginal costs' may often be more appropriate than 'average costs'. Expert advice will often be required from economists at this stage to make the costings realistic.

Nevertheless, this approach can often give a clearcut indication that a new medicine will indeed reduce total health service costs. Depending on the extent of such savings, they may be apparent from only a small number of patients over a short period. (This was true of cimetidine against surgical treatment for ulcers). On the other hand, if the savings are less obvious, a study on fairly large numbers of patients over a year or more may be required to show up significant economic differences. This situation is not unlike the one which has for many years existed with traditional clinical trials.

Similar costings can be produced for the added value for the national economy. The extra contribution of those kept at work can be calculated either from their average earnings or from the average value of their production. The former is a more conservative figure, and generally to be preferred, as the value of production depends on capital investment as well as human resources. Male and female patients, and juveniles, will all have different rates of earnings.*

Measurements made on the patients' quality of life are generally expressed separately, although methods (to be discussed later) do exist for turning improved quality of life into financial terms. Overall, therefore a cost-benefit equation can be produced through an epidemiological approach balancing the cost of the medication either against its savings to the health service or its financial contribution to the economy, or

*Savings occurring in future years, both for the health service and the national economy, should be 'discounted' to give their present value. The usual discount rate is between 5 per cent and 10 per cent per year, and the actual rate chosen can substantially affect the present value. If costs of treatment also relate to future years they too must be 'discounted' in the same way. This is standard economic practice as future costs and benefits have less 'value' than those incurred today.

both. This can be done either retrospectively or prospectively, although clearly the latter will give more accurate figures.

The measurements made in a controlled trial may be the most precise that are available. However, on the other hand, they may relate to an artificial situation which differs substantially from the use of the treatment in normal practice. Thus, both clinical trial evaluations and 'normal practice' evaluations can each have advantages. Ideally, both should be undertaken to show as conclusively as possible that there are economic benefits from the therapy.

Identifying specific costs and benefits

The epidemiological approach is perfectly valid, but another method which has been used in other cases is to identify precisely the resources used for each patient in a specially constructed study, and then to produce average costs and benefits from these exact measurements. This basically uses a 'work study' approach with (at least ideally) independent observers with stop watches recording every event which occurs in both the treatment group under examination and the control group. The observations can be made in normal clinical conditions, reflecting what actually happens in practice. This was done, for example, in order to produce exact costings for heart transplant patients in a major study financed by the Department of Health.[2]

When this approach is used, exact costings are generally also available, such as the individual doctors' and nurses' salaries and the actual price of all medical and surgical materials used for the patients. Whereas the epidemiological approach would usually rely (at best) on the total cost of an operating theatre divided by the number of operations in order to obtain a surgical cost, the alternative method would, for example, be to measure the exact time spent in the theatre by each member of staff, and assess the full cost of employing them for that length of time.

Once the cost for the treatment group and the control group have been established, these costs are compared in the same way as in the epidemiological approach. A much more accurate assessment is possible when it is based on exact costings, but this method is usually a very great deal more complicated and costly than the epidemiological method. However, where epidemiological data are not generally available, it can be the only practical method. This was the case, for example, in a study to evaluate the economic benefit of using a glycerol trinitrate patch to reduce the rate of failures with intravenous infusions.[3] This study involved a limited number of observations over a short period of time and was a model of the circumstances in which it is preferable to obtain specific costs rather than to try to collect epidemiological data.

Measuring the quality of life

There are two basic approaches to measuring the quality of life in groups of patients. The first in the 'health profile' and the second is the 'health index'.

A **health profile**, such as the Nottingham Health Profile developed in Britain or the Sickness Impact Profile from the United States, essentially measures the degree of disability and distress which an individual is suffering for a number of different parameters, such as pain, immobility, sleeplessness, social isolation and so on. There is no attempt to add together the scores for the individual characteristics, and the results are generally presented as a series of bar charts showing the different scores for the treatment and control groups for each characteristic.

The measurements in each case are derived from the answers to a series of questions, put in random order, and given weights according to their importance. Thus, under the heading of mobility a positive answer to 'I'm unable to walk at all' gets a higher weighting than a positive answer to the question 'I can only walk indoors'.

The questionnaires used in these profiles have been painstakingly constructed and evaluated, and variations or translations of them should not be used without equally careful preparation. This is work for a professional health economist. However, the well tried and tested questionnaires already available such as the Nottingham Health Profile can easily be used either by interviewers with a minimum of training or even for self-completion by the patients. The average scores for the different answers, appropriately weighted, are combined to construct the bar charts for the two groups being compared – or for the same groups being compared over time, in order to evaluate their improvement from a baseline measurement.

A **health index**, on the other hand, gives a single value for each of a range of specifically described states of health. The best known example was developed in the 1970s by Professor Rachel Rosser. It consists of 29 health states defined in a matrix consisting of four degrees of distress and eight degrees of disability. (Three of the 32 squares in the matrix are invalid, because they would define degrees of 'distress' when the patient was unconscious). On Rosser's scale, perfect health scores one, and death scores zero.[4]

The values for each of the 29 states were established by the technique of asking samples of different individuals to rank each pair of states as better or worse than each other, and then analysing these answers on a computer.

Two other ways of valuing the different states of health are called the 'standard gamble' and the 'time trade-off' methods. The first involves asking people to rate the states, according to the relative risk of suffering the particular state of illhealth which they would accept against a variable chance of either perfect health or death; in the second case the states are rated according to the length of extra survival which people would 'trade off' in each state of imperfect health against a shorter fixed period in perfect fitness.

The important point here is not to understand exactly how to apply these methods, but to recognise that they each give different values for the same health states (although generally in the same rank order).

Thus, in the present state of the art any attempt to use health indices to give specific valuations for different states of health should be approached with caution.

This is also true of a technique which has been used to put financial values on different states of health, or on improvements from one state to another. This is the so-called 'willingness to pay' approach, in which individuals are asked to say how much they would be willing to spend to achieve a particular improvement in health. It is an interesting technique, and gives high financial values for improvements in health. However, it is not a universally accepted method of establishing how much a particular treatment is 'worth' in terms of the improvement in health which it achieves.

In general, practical quality of life studies should at present probably be confined to the use of well tried health profiles. Nevertheless, it is important for economic research to continue into refining health indices and the measurement of 'willingness to pay' as a means of financial valuation for the avoidance of illhealth.

Finally, in this section, many readers will have heard of the term 'Quality adjusted life year' or (QALY) in connection with the economic evaluation of medicines. This is an economists' unit derived by multiplying a patients' years of life by factors depending on their *quality* of life in each year. Thus a person whose treatment extends their life by 10 years, but has only 50 per cent 'well-being' during each of those years, would have gained on five QALY's. Some interesting debates have arisen from discussion of the extra QALY's derived from different treatments at different costs. However, it must be clear from the discussion above that the use of the unit of QALY's is still somewhat speculative. This is because the value of each year of life can be discounted at different rates according to the method used to calculate the health index which measures the degree of a patient's 'well-being'. Until a generally accepted health index has been established discussion related to numbers of QALY's must take the form of a debate rather than definitive statements.

When, by whom and where?

Although companies are now starting to carry out an economic evaluation during Phase 2 and Phase 3 clinical trials, it remains true that in many cases the full economic benefits of a new medicine will be difficult to demonstrate until it has been marketed and is in generally accepted use. Thus the decision at what stage to undertake the first economic evaluation must still be a matter of individual judgment.

In a number of countries, where price approval (at least approval for reimbursement) has to be granted before marketing, there are good arguments for having economic evidence about the new medicine before it is launched. However, in other cases, arguments over the level of prices will only arise once the medicine is clearly going to be a success.

There is, after all, little concern about the price of a medicine which has negligible sales.

Another argument for early economic evidence about a medicine is that it may actually influence the price which is set for it. Clearly a higher price can be justified if the medicine is still very cost-effective at that price. It may be difficult to raise the price when strongly favourable economic evidence only becomes available after the medicine is already on the market.

Perhaps, as one economist suggests: 'it is always too soon to carry out a cost-benefit study until it suddenly becomes too late'. Certainly, there can be no hard and fast rule as to when during a medicine's life history is the universally 'correct' time to undertake an economic analysis. But generally, it seems the tendency now is to do so earlier rather than later.

The other question is who should be responsible for the analysis. Of course, independent academic or contract reseach economists will often be involved. However, this begs the question of who within the company should be responsible for initiating and supervising the studies. The marketing department, for example, may be too inclined to think of cost-benefit studies as a sort of magic wand which can produce quick results to demonstrate added value for their products. Absolute objectivity is required if economic studies are to be credible. Certainly from some countries there have been reports of inadequately qualified free-lance economists applying less than acceptable methodologies. This must be avoided at all costs if economic analyses are to be generally trusted.

In many companies the responsibility for economic evaluation has devolved onto the medical department. In other cases, a specific health economist has been appointed, who may be attached either to the commercial development department or to the central research facility. The latter arrangement assumes that most evaluation will be initiated at the pre-marketing stage. It seems likely that 'in-house' health economists will play a larger part in future in the organisation and supervision of academic cost-benefit studies, cost utility studies and measurement of the quality of life. These economists will, of course, also be able to undertake studies themselves although – as with clinical trials – there will always be added kudos for a study undertaken by a well-known academic centre.

The final question is whether an economic analysis carried out in one country will convince the authorities in another. Once again there is a parallel with clinical trials. If a well conducted study is reported from an internationally respected centre and published in a refereed journal it will carry great weight in other countries also. There are, of course, possible variations in clinical practice and in actual costs which may reduce the applicability of a national study to other parts of the world. But once the core study has been undertaken it will often be possible to replicate it more easily in other places, or even to extrapolate from it to show corresponding benefits in different national situations. Widespread international studies have not generally so far been attempted.

Table 1 **Some recent company sponsored economic analyses**

Company	*Type of Product*	*Date*	*Country*	*Type of Study*
Smith Kline & French	Ulcer therapy	1970s	Various	Cost benefit
Smith Kline & French	Oral antirheumatic	1986	USA	Quality of life
Ciba Geigy	Avoidance of infusion failure	1988	UK	Cost benefit
Lilly	Antidepressant	1989	Belgium	Cost benefit
Pfizer	Antihypertensive	1989	Sweden	Cost benefit
Searle	Ulcer therapy	1989/90	UK/International	Cost effective/benefit
Roussel	Antibiotic prophylaxis in surgery	1989	UK	Cost benefit
Pfizer	Antimycotic	1990	UK	Cost benefit
Fisons	Asthma prophylaxis	1990	UK	Cost benefit

but may become more common in the future. Here again, the differences in local practices and costs would have to be taken into careful account. In conclusion, in this section, it appears that Britain is well up with the leaders internationally in understanding the need for economic studies and in having started to conduct them.

Some practical experience to date

Table I shows a summary of some of the economic analyses which have been sponsored by pharmaceutical companies recently. It is far from exhaustive, but indicates that a number of economic studies are indeed already being undertaken. The Office of Health Economics has been involved with most of these studies. It is pleased to advise individual companies on what sort of study might be appropriate and to put companies in touch with academic centres or contract agencies which are equipped to undertake such studies and are already experienced in this work.

As a concluding note, it is worth emphasising once again that cost-benefit analyses or other similar investigations must be conducted with the same degree of objectivity and quality which already applies to clinical investigations. The newly formed Pharmaceutical Industry Health Economics Group has, as one of its most important objectives, the remit to ensure that studies carried out on behalf of pharmaceutical companies are invariably of a good academic standard. Provided that this is achieved, the economic analyses will reliably demonstrate that pharmaceutical products are very often cost-effective as well as being of proven medical value.

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