ECONOMIC EVALUATION in the DEVELOPMENT of MEDICINES

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PREFACE

In most countries the resources available for health care are increasingly stretched in the face of the competing demands for their use. Therefore health care policy makers, planners and managers have begun to scrutinize all health care procedures and treatments more closely, in order to ensure that they give good value for money. Medicines have not been exempt from this process and there is increased emphasis on demonstrating additional benefit or social value from new medicines that is commensurate with their costs.

The techniques of economic evaluation are well established as a method of comparing the costs and benefits of health care interventions. A number of evaluations of medicines have been undertaken and have contributed to the debate about their adoption within the health care system.

Nevertheless, many issues remain unresolved. What steps should be taken to generate more high quality evidence on the costs and benefits of medicines? How should such evidence be interpreted and used by health care decision makers? What methodological uncertainties remain and how are these likely to be resolved in the future?

This booklet is therefore for decision makers both within and outside the pharmaceutical industry. Written in a non-technical manner, it outlines the importance of economic evaluation of medicines, the achievements to date and the potential for the future.

JOHN BUTTERFIELD

Office of Health Economics

The Office of Health Economics was founded in 1962 by the Association of the British Pharmaceutical Industry. Its terms of reference are:

To undertake research on the economic aspects of medical care.

To investigate other health and social problems.

To collect data from other countries.

To publish results, data and conclusions relevant to the above.

The Office of Health Economics welcomes financial support and discussions on research problems with any persons or bodies interested in its work.

ISBN 047 3 88 37

Price £5.00

This Report has been prepared at the suggestion of and with the close co-operation of Medizinisch Pharmazeutische Studiengesellschaft (MPS) in the Federal Republic of Germany. OHE gratefully acknowledges their assistance.

1. THE CONTEXT FOR ECONOMIC EVALUATION

1.1 THE CHANGING ECONOMIC ENVIRONMENT IN HEALTH CARE

The economic environment for the provision of health care has changed dramatically over the last 10 years. In the 1960s expenditure on health care rose in most developed countries, in line with economic growth and improved living standards. However, since the mid-1970s economic growth has slowed in the majority of countries in Western Europe and North America. Although health care has received priority for government spending, the rate of increase in the resources made available has slowed. In some countries, the level of resources has remained roughly constant in real terms.

In addition there are other pressures on limited health care resources. First, most developed countries have an ageing population with the prospect that the economic burden of the health care for increasing numbers of elderly persons will be borne by people of working age. Secondly, the rapid pace of technological change in medicine means that the range of clinical possibilities continues to increase. Thirdly, there are changing public expectations about the range and quality of the health care provided. Individuals will increasingly voice their dissatisfaction with sub-standard service and a number of voluntary or charitable organizations have been formed to champion the cause of particular groups of patients. Taken together, these changes mean that health care budgets are increasingly stretched in the face of competing demands for their use.

Finally, the health care sector has now grown to such a size, around 6–10 per cent of gross domestic product in most developed countries, that it is continually in the public eye. Sizeable government expenditures are involved, even in countries with a large private sector in health care. In the USA, for example, the government provides in excess of 40 per cent of the funds for health care; in most other developed countries it provides around 80–90 per cent. The economic problems of the health care sector are now public property and health care expenditures are likely to come under increasing scrutiny in the quest for more value for money.

1.2 EFFICIENCY IN HEALTH CARE

There are not and never will be enough resources to achieve all the worthwhile objectives that can be identified. The extent to which the available resources fall short of the apparent demand for care varies from country to country, but even in the relatively rich countries one can identify areas of unmet need or point to examples where a rapid increase in health care costs has diverted resources from other beneficial uses.

Therefore, given *scarcity* of resources, the real problem with the overuse of new medical technology is not the financial expenditures themselves, but the more fundamental *cost* or sacrifice in that benefits in other programmes, such as community care for the elderly, are forgone. This is why economists refer to the notion of *opportunity* cost: that is, the cost of a resource is equal to the benefits that it would have generated in its best alternative use. Therefore, when economists argue that attention should be paid to *efficiency* in health care they are implying that health care programmes, treatments and procedures should be compared not only in terms of their relative benefits, but also in terms of their relative costs (ie, benefits forgone).

The issue of efficiency can be explored in choices of different levels of complexity. For example, the relative costs of two alternative ways of meeting the same treatment objective could be assessed. The more efficient approach would be the one having the lower costs, providing it achieved the objective to the same degree. However, this says nothing about whether the objective is worth attaining. A broader level of choice would therefore be between competing objectives. Here the assessment of efficiency would be based on the relative benefits resulting from attainment of the respective objectives and the relative costs of the programmes to achieve them. As will be seen later, the broader choices require more comprehensive and complex forms of analysis.

In many sectors of the economy, market forces encourage efficiency in the means of production and allocation of resources. If markets are functioning well, resources are automatically allocated to the most highly-valued wants and inefficient production processses are eliminated. However, in the case of health care there are reasons to believe that the nature of the commodity is such that efficiency is not automatically guaranteed. These include consumer ignorance about the product, uncertainty about future requirements, and the existence of externalities in consumption; for example if we vaccinate ourselves against an infectious disease we not only give protection to ourselves, but also to others. Economists disagree on the extent to which health care is 'different' from other commodities, but most acknowledge that some degree of government involvement in health care financing or provision is required. The methods of economic evaluation discussed in this booklet are therefore concerned with assessing the efficiency of different forms of health care provision, in the absence of efficiency being guaranteed by the market.

Another way in which health care differs from other goods and services is in the ethical issues its allocation raises. Although they accept in principle the arguments about scarcity and the need for efficiency, some clinicians are concerned that consideration of costs in clinical decision making is contrary to medical ethical principles. The first point to note is that the economic reasoning and the methods of analysis that are discussed below relate mainly to 'planning' decisions. That is, investment decisions about the kinds of facilities that should be provided, their location and the medical technologies (including medicines) that should be encouraged or discouraged from use. Against the background of the facilities made available, the clinician, in treating the individual patient, would still provide the best care at his or her disposal.

The way in which economic thinking should influence individual clinical decision making is less clear, although it should be pointed out that considering costs in decisions embodies an important ethical principle of its own; that resources should not be consumed in a given activity if they would generate greater benefits if used elsewhere. The extent to which the individual clinician considers costs in practice is likely to depend on whether he or she can identify the other uses to which the resources could be put. For example, if the clinician knows that other patients are waiting for care, he will tend to ration his time with a given patient or, in the case of inpatient care, discharge a patient earlier so that another can be admitted. Some of the initiatives discussed below encourage the clinical practitioner to take into account efficiency considerations when making decisions. Therefore it is likely that over time such mechanisms will have a profound impact on clinician behaviour and resource utilization.

1.3 MEASURES TO CONTROL COSTS AND TO INCREASE EFFICIENCY

The concern about health care costs and the need to improve efficiency has manifested itself in a number of measures taken by government or the health care sector (see Box 1). The precise forms of the measures vary from country to country depending on the nature of the health care system. For example, in countries with national health services it is often easier to lay down general guidelines about the location of specialist units, the nature of health care priorities, or the types of treatment technologies to be used. In more decentralized systems it may be more effective to use market forces or other kinds of incentives to influence the nature of health care provision. Haan and Rutten[1] have classified these mechanisms as *regulation by directive* and *regulation by incentive* (Table 1.1). Some are discussed further below.

BOX 1 THE DISTINCTION BETWEEN COST CONTAINMENT AND ECONOMIC EFFICIENCY

Some policy measures, such as cash limiting the expenditures of health authorities in the United Kingdom, may be very effective at controlling costs but may not necessarily lead to efficiency. For example, if faced with a budgetary constraint health authorities may not necessarily cut the treatments or programmes that give the lowest value for money; they may cut some highly valued programmes, either through political expediency or because they do not know which are their best investments. On occasions, authorities may deliberately threaten to cut their more highly valued programmes in order to draw attention to their case. Therefore aggregate expenditure control mechanisms should be viewed with caution. Economic evaluation seeks to provide some of the relevant data for assessing the relative value for money from health care programmes. It is concerned with maximising the total benefits, in terms of improved health status, from health care, given the resources available.

Because of its centralized nature, the UK National Health Service has the potential to employ a number of the regulatory mechanisms outlined by Haan and Rutten. For example, health authorities are 'cash limited', in that an annual budget is fixed in advance and any overspending is deducted from the budget in the following year. There are also attempts to secure a sensible geographical distribution of specialist services and expensive medical technologies, although often charitable funds have been used to purchase pieces of equipment that could not be afforded on the NHS budget. The more decentralized health care system in Germany does not lend itself so easily to such controls, although under the Hospital Cost Restriction Act of 1981 the purchase or utilization of large-scale technical equipment in hospitals must be carried out in co-ordination with the competent authority and with due regard being paid to regional needs for services.[2]

Some of the most interesting mechanisms are those that encourage more efficiency in health care through changing the incentives for the key institutions (eg, insurance companies, sickness funds and hospitals) or for the key health care professionals (eg, doctors). For example, there is a trend towards prospective reimbursement for hospitals. Under the old system, where hospitals in many countries were reimbursed retrospectively by a *per diem* rate based on the number of days of care provided, there were few incentives to search for more cost-effective treatment methods. Indeed, to some extent the hospital would be rewarded for inefficiency, if it unnecessarily prolonged patients' stays. With prospective reimbursement, either by a global budget agreed at the beginning of the year or by casemix-related payments, the hospital benefits from carefully reviewing its

Figure 1.1 **Possible mechanisms for encouraging a rational diffusion and use of health technology**

Regulation by **directive** *(central/regional government)*	*Regulation by* **incentive**
Planning of facilities, specialist departments or specific technologies	Reforming budgeting/ reimbursement schemes for health care institutions (especially hospitals)
Excluding technologies from public financing	Encouraging budgetary reform within health care institutions (eg, clinical budgeting schemes)
Developing settlement policies for health manpower	Changing payment systems for health care providers
Strengthening pre-marketing controls for medicines, devices (safety, efficacy)	Subsidizing specific technological developments
	Charging patients
	Encouraging competitive arrangements (eg, consumer choice health plans)
	Developing medical audit and utilization review systems

Adapted from Haan and Rutten[1]

expenditure and treatment methods. For example, under a casemix-related payment scheme, the agreed rate for a given surgical procedure may be $5,000. If the hospital can treat the case for $4,000, perhaps by the use of medicines that reduce infection post-surgery and avoid unnecessarily long inpatient stays, it will make a surplus. In a for-profit hospital this would be available for dividends or reinvestment. In a not-for-profit hospital it may be used to further other aims of the organization such as the promotion of research.

There are a number of variants on prospective reimbursement in different developed countries. In the USA the most famous is the payment by diagnosis-related groups (DRGs) pioneered by Medicare. Also, in a number of European countries, most notably Belgium and the Netherlands, there has been a movement towards global budgets with associated workload targets. There is evidence that this is having an impact within the hospitals, especially in increasing physician cost-consciousness.[1]

Another hospital based initiative is the reform of budgetary arrangements. In both the Netherlands and the United Kingdom there have been experiments concerned with increasing the budgetary accountability of departmental managers and clinical teams.[3] The experiments in clinical budgeting are of particular interest. Here clinical teams are given an incentive to consider the more careful use of resources by being able, after agreement with the hospital managers, to redeploy some of the savings to other beneficial activities. This initiative recognizes that clinicians are major allocators of resources, through the treatment decisions which they make on behalf of their patients. In the United Kingdom it was estimated in 1976 that each hospital consultant was responsible for resource allocation decisions involving the expenditure of £500,000 annually.[4] An equivalent figure today would be well in excess of £1 million.

There are also a number of important initiatives in the primary care sector. In Bavaria there was an experiment to ascertain whether doctors' treatment decisions would be influenced by the incentives given to them. It was decided that any savings made through the reductions in physical therapy, laboratory tests, hospital admissions and medicines prescribed would be given to the physicians concerned. A

preliminary analysis showed that many of these items were reduced, although interestingly the number of medicines prescribed rose slightly.[3] There is no detailed information on whether the physicians concerned viewed the increased use of medicines as an aid in reducing the other items of expenditure.

A related initiative is the growth of prepaid group practice in the USA, the most well-known version of which is the health maintenance organization (HMO). Here groups of physicians receive an annual payment, in return for which they accept all responsibility for the care required. Therefore, the costs of hospitalizations, diagnostic tests and other services consumed outside the HMO are a charge on the practice. The logic is that the physicians in the HMO will have the incentive to emphasize preventive care, to make good use of paramedical professionals such as nurse practitioners and to scrutinize carefully the use of all resources. The majority of the evidence suggests that HMOs reduce costs without serious reductions in quality, the largest savings being achieved through reductions in hospitalization.[6, 7]

In the United States the growth of HMOs has led to the birth of other forms of service delivery, such as preferred provider organizations (PPOs). Here patients are encouraged to use practitioners or institutions that have negotiated special rates with their insurance companies. In addition direct contract for service arrangements have been negotiated between major employers and service providers for workers' health care, thereby cutting out the insurance 'middle-man'.[8, 9] Indeed there has been a growth of a variety of competitive arrangements between both private and public providers. In the USA the HMOs compete for business with the traditional insurers such as Blue Cross and Blue Shield. In the United Kingdom, Canada and Sweden there has been interest in using contractual arrangements to increase the level of competition both within the public sector and between the public and private sectors.[10, 11, 12] This is therefore one way in which competitive forces can be harnessed to increase the efficiency of health care provision.

The initiatives discussed above have the common objective of making key decision makers, especially doctors, more aware of costs and giving them incentives to select the most cost-effective treatment practices. Although the initiatives are not specifically aimed at pharmaceuticals they are likely to have a profound impact in this area. A hospital director or head physician in a pre-paid group practice is more likely to scrutinize the cost of medicines, equipment, and consumables. On the other hand he or she may be more easily convinced that a new medicine or piece of equipment should be used, particularly if it leads to the saving of other resources. However, it would be wrong to suggest that cutting costs is all that is of interest. Efficiency in health care requires the consideration of both costs and effectiveness and many of the measures discussed above have led to as much discussion of the relative quality or effectiveness of procedures as of their cost. There is still an important place, therefore, for new medicines that provide higher quality care at an increase in cost. This in particular is why some of the more advanced methods of economic evaluation, discussed below, emphasise the impact that health care interventions have on the quality of life as well as on the overall cost of care. In economics jargon, *cost-utility analyses* are starting to replace the earlier cost-benefit analyses, which were often concerned with financial measurements alone. These and other forms of analysis are discussed in Chapter 2.

1.4 MEASURES TO INFLUENCE THE AVAILABILITY OR USE OF MEDICINES

As the demand for, and supply of, health care resources appear to become increasingly mismatched, there is no doubt that pharmaceuticals will be included in the search for efficiency. Indeed, health service managers may regard medicines as an easy target, since reductions in their availability or use do not lead to the industrial relations problems associated with some of the alternative policies. In the UK, the medicines bill at manufacturers' prices accounts for less than 10 per cent of total expenditure by the National Health Service. In cash terms, however, it represents a substantial amount of money – £1.9 billion in 1986 – and attempts have already been made to contain expenditure growth in this area. Similar developments have been experienced in other developed nations.

A number of measures have been used to influence the availability or use of medicines. Chew *et al*[13] note that of the seven developed countries they surveyed, only Japan had no 'limited list' of medicines. The United Kingdom and the Federal Republic of Germany are examples of countries operating a *negative list* to restrict prescribing. In the United Kingdom the government announced in 1984 that a smaller range of medicines would be available under the National Health Service in certain therapeutic categories: minor pain killers, cough and cold remedies, laxatives, indigestion remedies, vitamins and tonics, and sedatives. Similarly, in the Federal Republic of Germany a negative list is in existence for indications which could be treated with normal 'household necessities', such as cough and cold preparations and laxatives.

Other countries, such as France, Italy and Austria, employ a *positive list* of medicines that will be partially or fully reimbursed under the health service or health insurance scheme. In at least one case (Austria) the price of the medicine is a factor taken into account when deciding upon inclusion on the list. Also, in countries with a social security scheme it is common for the level of reimbursement of medicines to vary. For example, in France medicines on the positive list are reimbursed either 40 per cent, 70 per cent, 80 per cent or 100 per cent according to their therapeutic category. Patients frequently take out additional private insurance to cover any potential personal payments for medicines.

Finally, a number of measures have been employed to influence the use of medicines within health care systems. In many countries hospitals operate a formulary, where only a limited number of medicines are available routinely. Some countries publish comparisons of price and equivalence of medicines, known as 'transparency lists', in order to encourage selection of the cheapest available medicine for a given condition. Other countries give doctors routine feedback on the costs of their prescribing. The effectiveness of these measures seems to depend upon whether actions are taken against doctors who do not change their behaviour accordingly.

It follows from these observations that demands may be expected to increase in the future for more rigorous demonstration that medicines represent a good investment for health service resources. Failure to do so may be associated with policy initiatives whose ultimate effect will be to restrict the revenues which manufacturers obtain from the sales of their medicines. Such a development would clearly have extremely serious implications for research and development budgets and, in the final analysis, for continued pharmaceutical innovation.

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2. INTRODUCTION TO ECONOMIC EVALUATION METHODS

2.1 BASIC FORMS OF ECONOMIC EVALUATION

If it is to be argued that clinicians and other health care decision makers should take note of efficiency considerations, there is a need for evaluation methods that assess the relative costs and consequences of health care programmes and treatments.

There are a number of forms of economic evaluation, but they have the common feature that some combination of the inputs to a health care programme are compared with some combination of the outputs (Figure 2.1). The inputs include the direct costs of providing care (C1 in Figure 2.1), which fall mainly (though not exclusively) on the health care sector, and the indirect costs (in production losses) arising when individuals are withdrawn from the workforce to be given therapy (C2). Although not strictly an 'input', there may also be intangible costs, in pain or suffering, associated with therapy (C3).

The simplest form of analysis considers only costs. This approach is justified where it can be assumed, or has been previously shown, that the alternative programmes or therapies being compared produce equivalent medical results. This was the approach used by Lowson *et al* in their study of alternative methods of providing long-term domiciliary oxygen therapy.[1] Such a study is called a *cost analysis*. Some cost analyses confine themselves to consideration of direct costs only, others consider also the indirect costs (Figure 2.1).

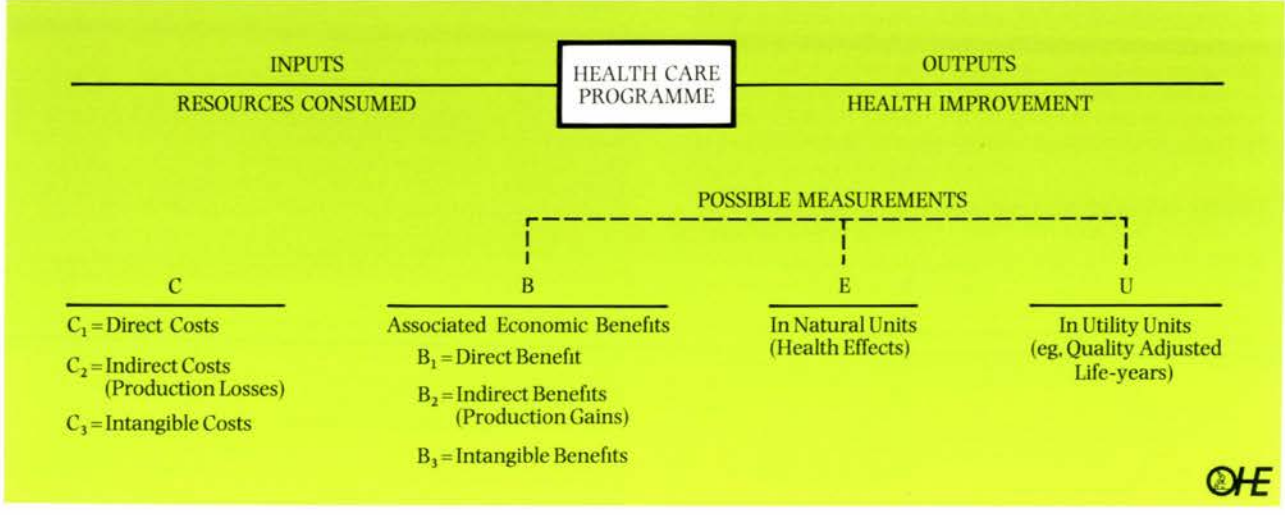
One particular form of cost analysis deserves further mention since it has had wide application. The *cost of illness* study calculates all the direct and indirect costs of a particular disease or illness, such as stroke or cancer.[2, 3, 4] These studies can serve two purposes, depending on how they are carried out. First, by providing an estimate of the economic impact of a given disease, they can alert policy makers to the importance of the problem and suggest that investments should be made in interventions to ameliorate its effect. Secondly, they can provide a baseline estimate of costs against which the potential economic impact of a new medicine can be judged.

However, most forms of economic evaluation require explicit measurement of the outputs of the programmes or therapies being compared. They differ mainly in the method of measuring the outputs. The earliest forms of analysis concentrated on the benefits of interventions in terms of the resulting savings in other direct medical care costs (direct benefits, B1), and the production gains from an earlier return to work (indirect benefits, B2). Typically, in a *cost-benefit analysis*, these benefits were expressed in money terms in order to make them commensurate with the costs of the intervention. However, other more intangible benefits, such as the value to patients of feeling healthier (B3), are obviously more difficult to express in money terms. Therefore cost-benefit analyses have often been criticised for ignoring important benefits from health care programmes and for concentrating on items that are easy to measure. Many of the early studies were therefore very narrow assessments, considering only direct and indirect costs and benefits. However, more recently there have been some good examples, such as the study by Weisbrod *et al*, which assessed a wide range of costs and benefits in a comparison of hospital-oriented and community-based care for mental illness patients.[5] The authors were able to demonstrate that the community-based service had higher net benefits than the hospital-oriented alternative.

Instead of attempting to measure outputs in money terms, other analysts have preferred to assess them in the most convenient natural units (health effects), such as 'cases successfully treated' or 'years of life gained'. For example, Hull *et al* compared objective diagnostic tests for deep-vein thrombosis in terms of their incremental cost per case detected, over and above normal clinical diagnosis.[6] Ludbrook compared treatment options for chronic renal failure in terms of their cost per life-year gained.[7] Such analyses are known as *cost-effectiveness analyses*.

Of course, much modern medicine is concerned with improving the *quality*, not quantity, of life. In addition, some therapies, such as cancer chemotherapy or hypertension

Figure 2.1 **Components of economic evaluation.**



Common forms of analysis

1. Cost Analysis: C_1, $C_1 + C_2$
2. Cost-benefit Analysis (CBA): $B_1 + B_2 - C_1 - C_2$; $(B_1 + B_2)/(C_1 + C_2)$
   Also sometimes includes consideration of C_3 and B_3
3. Cost-effectiveness Analysis (CEA): $(C_1 + C_2)/E$; $(C_1 - B_1)/E$; $(C_1 + c_2 - B_1 - B_2)/E$
4. Cost-utility Analysis (CUA): $(C_1 + C_2)/U$; $(C_1 - B_1)/U$; $(C_1 + C_2 - B_1 - B_2)/U$

BOX 2 MEASURING AND VALUING IMPROVEMENTS IN HEALTH-RELATED QUALITY OF LIFE

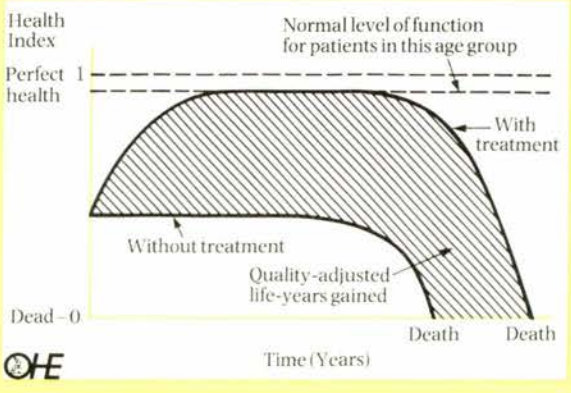
Since most modern medicine is concerned with improving the quality of life, rather than extending life, the measurement of health-related quality of life has gained particular importance of late. Of course, in everyday clinical practice the quality of life of the patient, as evidenced by the answer to the question 'how do you feel today?', is the clinician's main concern. However, formal clinical evaluations of therapies usually include more easily quantifiable measures, such as mm Hg blood pressure reduction.

The quantifiable clinical effects, that would typically be measured in a clinical evaluation and incorporated in a cost-effectiveness analysis, bear some relation to quality of life. For example, an evaluation of a surgical procedure may measure effectiveness in terms of the number of complications or recurrences, or an evaluation of a medicine may record the number and nature of side effects. It is implicit that it is not the side effects themselves that are important, but the impact that they have on the patient's functioning or psychological state. The economic evaluations incorporating a quality of life measure merely take this a stage further, by assessing the impact directly and explicitly, rather than implicitly. Indeed this is nothing particularly new. Rosser[21] pointed out that up until the start of the 20th Century, St Thomas's Hospital in London assessed outcomes of its patients in terms of 'relieved, unrelieved or dead'.

There are two main methods by which quality of life has been measured and valued in economic evaluations: by quality of life scales (or profiles) and by utility measurement. The **quality of life scales** consist of a range of attributes thought to affect the patient's quality of life, such as physical functioning, ability for self care, social functioning and psycho-social status. One example is the Nottingham Health Profile[22] illustrated here, which was used by Buxton *et al* in their economic evaluation of the heart transplant programme in the United Kingdom.[23] Other well-known examples of such general scales are the Karnofsky Index,[24] the Sickness Impact Profile,[25] the General Well-being Scale[26] and the Spitzer QL Index.[27] There is a growing number of evaluations of medicines incorporating such quality of life assessments, such as the comparison of anti-hypertensive agents carried out by Croog *et al*.[28] Although some of the quality of life scales embody scoring schemes, they usually do not generate a single quality of life score. This makes comparisons from one evaluation to another difficult, as does the fact that often disease-specific scales are used instead of the general scales referred to above. A disease-specific scale has the advantage that it focusses on those aspects of health-related quality of life most likely to be affected by the disease in question. This increases the sensitivity of the scale, at the expense of some loss of generalizability. Nevertheless, it is still possible to make comparisons of two medicines, or a medicine versus surgery, for a given condition using quality of life scales.

However, economists are interested in making broader comparisons and in assessing the relative value for money from a range of health care interventions. This has led them to search for a generalizable index of quality of life which can be used in programme evaluation. The method used is to measure health **utility values**, which can then be combined with survival data to calculate the **quality adjusted life years (QALYs)** gained from treatment. The utilities are relative valuations of states of health, standardized on a scale from 0 (dead) to 1 (perfect health). (However, it should be noted that some researchers have found states worse than death, with negative utility values.)

Quality-adjusted life-years added by treatment.



NOTTINGHAM HEALTH PROFILE: DIMENSIONS, STATEMENTS AND WEIGHTS

Physical Mobility	
I find it hard to reach for things	9.30
I find it hard to bend	10.57
I have trouble getting up and down stairs or steps	10.79
I find it hard to stand for long (eg, at the kitchen sink, waiting for a bus)	11.20
I can only walk about indoors	11.54
I find it hard to dress myself	12.61
I need help to walk about outside (eg, a walking aid or someone to support me)	12.69
I'm unable to walk at all	21.30
	100.00
Pain	
I'm in pain when going up and down stairs or steps	5.83
I'm in pain when I'm standing	8.96
I find it painful to change position	9.99
I'm in pain when I'm sitting	10.49
I'm in pain when I walk	11.22
I have pain at night	12.91
I have unbearable pain	19.74
I'm in constant pain	20.86
	100.00
Sleep	
I'm waking up in the early hours of the morning	12.57
It takes me a long time to get to sleep	16.10
I sleep badly at night	21.70
I take tablets to help me sleep	22.37
I lie awake for most of the night	27.26
	100.00
Energy	
I soon run out of energy	24.00
Everything is an effort	36.80
I am tired all the time	39.20
	100.00
Social Isolation	
I'm finding it hard to get on with people	15.97
I'm finding it hard to make contact with people	19.36
I feel there is nobody I am close to	20.13
I feel lonely	22.01
I feel I am a burden to people	22.53
	100.00
Emotional Reactions	
The days seem to drag	7.08
I'm feeling on edge	7.22
I have forgotten what it is like to enjoy myself	9.31
I lose my temper easily these days	9.76
Things are getting me down	10.47
I wake up feeling depressed	12.01
Worry is keeping me awake at night	13.95
I feel as if I'm losing control	13.99
I feel that life is not worth living	16.21
	100.00

Derived from: Hunt, McEwen and McKenna[22]

Whereas it is easy to accept that there is an ordinal ranking of health states, from better to worse, the methods of obtaining the health state valuations have generated considerable debate. In the United Kingdom the most widely used index is that developed by Kind, Rosser and Williams.[29] This classifies states of health by disability and distress, generating a 32 cell matrix for which relative valuations have been obtained from 70 respondents. The valuations were obtained by magnitude estimation.

In North America three main measurement methods have emerged, the rating scale, the time trade-off approach and the standard gamble.[8] A typical **rating scale** consists of a line on a page with clearly defined end points. The most preferred health state is placed at one end of the line and the least preferred at the other end. The remaining health states are placed on the line between these two, in order of their preference, and such that the intervals or spacing between the placements correspond to the differences in preference as perceived by the respondent. In some studies more sophisticated 'props' are now being used to aid the respondent, such as 'health thermometers'.

Under the **time trade-off** approach the respondent is asked to consider the relative amounts of time he would be willing to spend in various health states. For example, in order to value a chronic health state, the respondent would be offered a choice of remaining in this state for the rest of his life versus returning to complete health for a shorter period. The amount of time that the individual is willing to 'trade' to return to perfect health can be used to obtain a preference value for the chronic health state. A similar approach can be used to calculate the relative values of temporary health states.

The **standard gamble** is the classical method of measuring cardinal preferences, being based directly on the fundamental axioms of utility theory. In order to measure preferences for chronic states preferred to death the subject is offered two alternatives, either the gamble, a treatment with two possible outcomes (death or return to normal health for the remainder of his life), or the certain outcome of remaining in the chronic state for the rest of his life. The probability of a successful outcome to the gamble is varied until the respondent is indifferent between the gamble and the certainty. This probability can then be used to calculate the preference value for the health state. Slightly different approaches are used to assess states worse than death and temporary health states.

As was mentioned earlier, there is considerable debate about the methods of utility measurement; which method is to be preferred; whose values are the most relevant, those of patients, doctors, policy makers or members of the general public? The validity and reliability of the various methods are extensively discussed by Torrance[30] in a special issue of the *Journal of Chronic Diseases* dealing with quality of life measurement. (A general discussion of quality of life measurement can also be found in an earlier OHE publication.[31]) In addition, Buxton *et al*[32] have recently compared the Rosser index with the time trade-off approach. Many of the quality of life measurements discussed in this section were also used in the economic evaluation of oral gold therapy for rheumatoid arthritis discussed in Section 3.5. This study also included a direct measurement of patients' **willingness-to-pay** for a cure for their arthritis. Willingness-to-pay is the theoretically correct method of valuing the benefits of health treatments in money terms, but it has so far had limited applications.

Despite the advances in the measurement of health-related quality of life mentioned above, a number of questions remain. For example, how does one proceed in a situation where different quality of life measures give different results? After all, there is no 'gold standard' measure for quality of life. Also, how does one assess the clinical importance of a change in a quality of life score from 0.5 to 0.7? In the future there needs to be more assessment of the convergent validity of various quality of life and clinical measures.

treatment, may bring about slight reductions in the quality of life in order to extend life. Therefore, there has been a growth in interest in *cost-utility analysis*, where the life-years gained from treatment are adjusted by a series of utility weights reflecting the relative values individuals place on different states of health.[8] The output measure most frequently used in cost-utility analysis is known as the *quality adjusted life year* (QALY). An example of cost-utility analysis is the study by Boyle *et al*, who calculated the cost per quality-adjusted life-year gained from providing neonatal intensive care to very-low-birthweight infants.[9] Because of the growing importance of quality of life measurement and the complexity of measurement methods, this is discussed further in Box 2.

Economic evaluation has been widely applied in the health care field.[10, 11, 12] There is now a fair degree of agreement on the elements of a sound evaluation,[13] although there remain deficiencies in the published literature (see Box 3). A recent development has been the construction of 'league tables' of health care programmes in terms of their relative cost per quality-adjusted life-year (QALY). Hence, for the first time decision makers are formally being invited to compare alternative possibilities for health service investments in terms of their relative value for money.[14, 15] Obviously this approach raises important issues, not least that of the quality of the data and the analytical methods used to generate such estimates. However, this is clearly an important development which will be returned to, in the context of the evaluation of medicines, in Section 5.2.

2.2 IMPORTANT METHODOLOGICAL ISSUES

In undertaking an economic evaluation of health care programmes a number of important technical and value judgements need to be made. These are discussed in more detail elsewhere[3]. However, a few issues that are particularly pertinent to the evaluation of medicines are discussed below.

Viewpoint for the analysis

The broadest viewpoint for an economic evaluation is that of society, since it includes all costs and benefits no matter to whom they accrue. Therefore, it is recommended that, where possible, the societal viewpoint should always be investigated. This would involve consideration of all the costs and consequences set out in Figure 2.2. However, there are other more limited, but important, viewpoints that may require exploration, such as those of the government or

BOX 3 COMMON DEFICIENCIES IN ECONOMIC EVALUATIONS

Failure to specify clearly the viewpoint from which the appraisal was carried out (eg, health care sector, government, society);

Failure to base the economic study on good medical evidence, such as that generated by controlled clinical trials;

The inappropriate use of average costs, particularly in estimating the costs of hospitalization or the savings from shortening hospital stays;

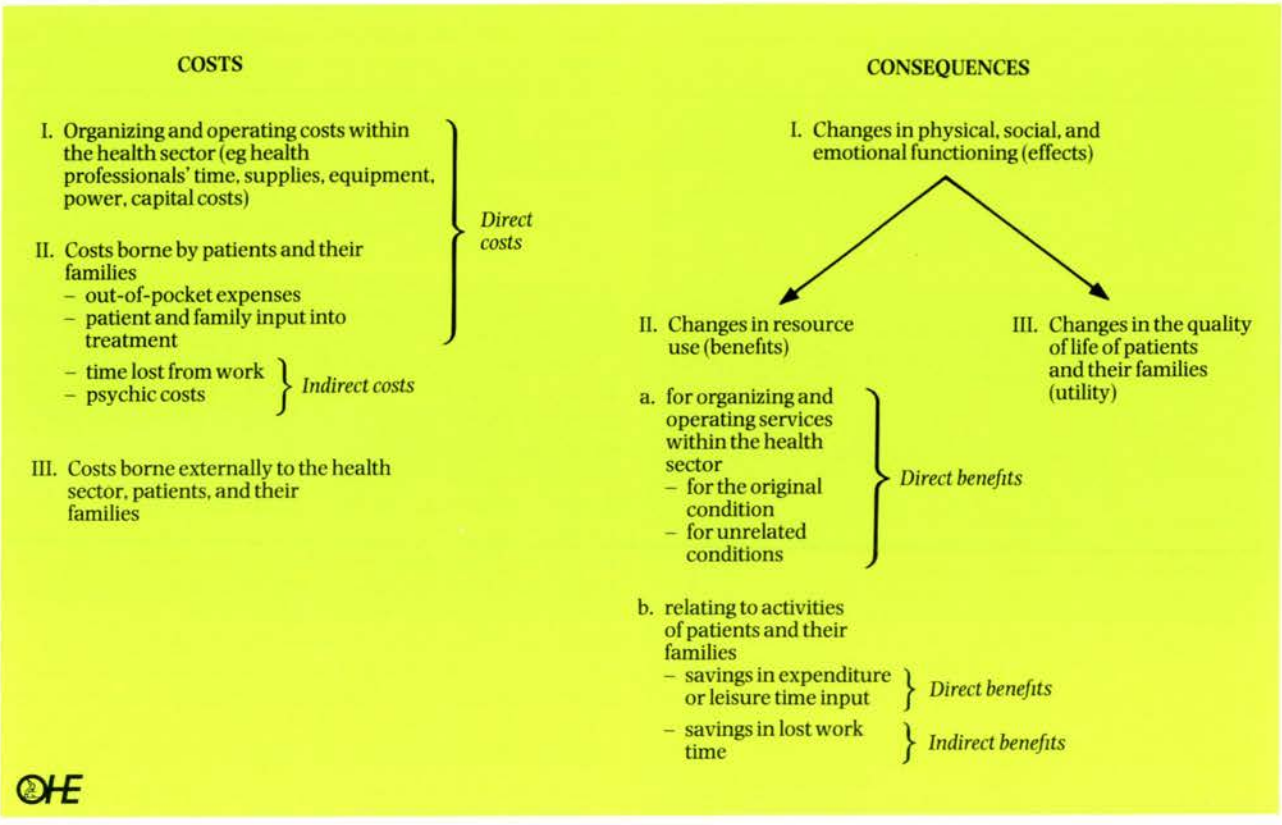
Failure to consider patient, family and volunteer costs where these were relevant;

Inadequate allowance for uncertainty in cost and benefit estimation;

Inadequate consideration of the link between evaluation results and the decisions, in health service planning and clinical practice, to which they pertain;

Failure to consider factors other than economic efficiency (including equity considerations and the managerial procedures required to bring about a change in policy).

Figure 2.2 **Types of costs and consequences of health services and programmes.**



Source Drummond *et al*[8]

other third-party payers, health care managers, clinicians and patients. It is important that economic analysts are clear about the viewpoint for their study and, in particular, do not confuse the government and societal viewpoints.

Governments are most concerned about the impact of health care programmes and treatments on their revenue and expenditure. Therefore, if the government is the third-party payer for health care, as in countries with a national health service or those with a sizeable government contribution to health care costs, it will no doubt be interested in the direct costs of medicines and any direct savings that result from their use. For example, from the government viewpoint it would be important to demonstrate that expensive antibiotics generate savings in reduced hospitalization, or that antihypertensives reduce the need for long-term care for those suffering non-fatal heart attacks and strokes. To a more limited extent the government may also be interested in the indirect costs and benefits, since these relate both to the productivity of the country and to the government's own revenue and expenditure in taxation and welfare payments. (These latter costs and benefits, known by economists as *transfer payments*, cancel out in a societal assessment. Nevertheless, they may be important to the government itself.)

Although the health care manager is also primarily interested in direct costs and benefits, he or she may have a slightly different viewpoint because of particular budgetary responsibilities. For example, the administrator of a hospital will be primarily interested in his own costs or profit margin and not necessarily in the savings that medicines bring about in other parts of the health service, or to patients themselves. Indeed the same may be true in primary care. In the United Kingdom, where family practitioner services and hospital services are financed separately, it may not immediately be recognized that an expensive medicine prescribed by family physicians could be economically justified because of the resource savings in the hospital sector. For example, reductions in the utilization of coronary care units may result from the use of medicines for heart disease, notwithstanding the obvious benefits from the gains in life expectancy.

Some of the measures discussed in Chapter 1 are aimed at solving this kind of problem. For example, under prepaid group practice the costs of hospitalization are charges against the annual premium paid in advance to the practice. Therefore it is in the primary health care physicians' interest to prevent expensive hospitalizations by the use of medicines or by other means.

The clinician's perspective is important given his or her key role in resource allocation in health care. It was mentioned earlier that under the new administrative arrangements the physician may have a financial interest in delivering efficient care. Incentives and disincentives operate in all systems, however. Under fee-for-service systems a physician's income may be affected by, for example, the number of physician visits required to administer, or monitor the use of, different medicines. He may also be influenced by the level of convenience or inconvenience associated with different therapies.

Finally, the patient's perspective is important since it may also affect the adoption of therapy. For example, in some countries patients pay a proportion of the costs of their medicines, although in others these costs are covered by insurance or are set at a flat rate. Also, it is well-known that side-effects influence patient compliance with therapy. In addition, the setting in which medicines are delivered may affect patients' costs. Logan *et al* found that the costs falling on patients were higher when antihypertensives were delivered by physicians in community care, rather than by nurse practitioners at the worksite.[16]

In summary, whilst the societal viewpoint should be the

main perspective from which to undertake economic evaluations in health care, the other subsidiary viewpoints should be considered since they may crucially affect the diffusion and use of health care programmes and treatments.

Marginal analysis

The concept of *the margin* is central in economics. That is, whereas efficiency requires that the total benefits of activities should exceed the total costs, it also requires that the marginal benefits (ie, those from the next unit of treatment) equal the marginal costs. This can be deduced by logic; if the marginal benefits are greater than the marginal costs then more benefit in total can be gained by further expansion of the programme; if the marginal benefits are less than the marginal costs there would be a net loss in expansion of the programme.

Most clinical practitioners would agree that one of the key questions in medicine is not whether procedures are totally worthless, but *the extent* to which diagnosis or treatment should be pursued. There are numerous examples: should C-T scans be given when headache is the only indication or should there also be associated neurological findings;[17] should skull X-rays be given routinely to patients admitted to hospital accident and emergency units with head injury, or only when indicated by clinical diagnosis;[18] should coronary artery bypass grafting be given only to patients with severe angina, or also to those suffering from mild angina with one or two vessel disease;[15] should hepatitis B vaccination be given to the whole population or only to high risk groups?[19] Therefore in evaluating the use of medicines from an economic perspective it is important to explore similar kinds of issues; for which indications should medicines be given; what is the appropriate frequency and level of dose; for how long should therapy be continued?

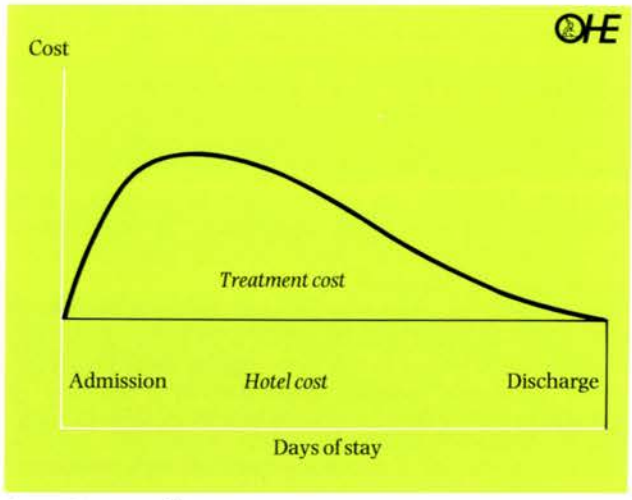
Another situation where marginal analysis is important is in the estimation of the savings in reduced hospitalization. For example, average hospital costs (per day) are sometimes used to calculate the savings from shortened stays brought about by antibiotic prophylaxis. This needs to be considered carefully, as often the later days of a patient's hospital stay are less resource intensive than the earlier days (Figure 2.3). Therefore the average costs may often overstate the real savings. Also, of course, the benefits of shortened stays are not necessarily translated into financial savings. (This is discussed further in Section 3.2.)

Discounting costs and benefits

In many cases the costs and benefits of the alternative health care interventions occur at the same point in time, such as in the comparison of two medicines for the same condition. However, on some occasions the time profile of costs and benefits may differ between the alternatives, such as in a comparison of long-term medical management versus surgery. Here the costs of surgery would all be incurred now, whereas the costs of medication would stretch far into the future. In the case of preventive measures, such as screening and treatment for hypertension, a conscious decision is being made to commit resources earlier in the disease process in order to avoid medical care costs, morbidity and mortality in the future.

It is usually argued that, as individuals and as a community, we are not indifferent to the timing of costs and benefits. We prefer to have benefits sooner rather than later and to postpone costs. (In economists' jargon we are said to have a positive rate of time preference.) Therefore there is a need, in economic evaluation, to reflect this preference in the analysis. This is achieved by a process known as *discounting* of costs and benefits *to present values*. It is not necessary to explain the mechanics of discounting here, as

Figure 2.3 **The variation of hospital cost with hospital in-patient stay.**



Source Drummond[20]

other sources are available.[6] However, it is important to note that the effect of discounting is to give costs and benefits occurring in the future less weight in the analysis. Therefore, discounting would make the long-term medical management of a condition more attractive, when compared to surgery. Conversely, it would make a preventive programme less attractive, because the averted future medical care costs would assume less numerical importance in the analysis.

Whilst most analysts acknowledge that costs and benefits occurring in the future should be discounted, there is still debate about the choice of discount rate. In some countries, such as the United Kingdom, the government advises the rate (currently 5 per cent per annum in real terms). Where no rate is advised, current practice is to discount by a range of rates from 2 to 10 per cent and to examine how sensitive the study conclusions are to the rate chosen. The other main debate centres around whether years of life or other health benefits should be discounted in the same way as costs. This issue is not fully resolved, but current practice is to treat all categories of benefit in the same way as costs, since inconsistencies emerge if this is not done. In addition the calculation of quality adjusted life years includes discounting.

Boundaries of the economic analysis

So far much of the discussion of economic evaluation in this booklet has centred on the comparison of alternative health programmes or treatments in clearly defined applications. The boundaries of the economic analysis are therefore drawn around the costs and benefits of the alternative programmes, treatments or procedures in question. However, another approach to economic evaluation would have as its focus the economic impact on the health care system in total. That is, instead of evaluating a medicine in one particular application, such a study would examine the total impact of its diffusion. This was the approach adopted by Bulthuis[33] in a retrospective analysis of the impact on hospital costs of cimetidine in the Netherlands. Jönsson[34] has pointed out that the same kind of analysis could be performed prospectively. Here one would consider not only the costs and benefits of a medicine in clearly defined clinical applications, but also those resulting from its use in other situations where effectiveness has not been proven. One would also consider the effects of changing epidemiology of the disease and the possible application of other new treatment technologies. Such studies are more complex and are rarely carried out.

Finally, one might choose to draw the boundaries of the study to include the impact on the economy as a whole. This would recognize that the economic impact of a new medicine is not restricted to the health care system, but that pharmaceutical industry profits and investments affect employment levels, national growth rates and the balance of trade. Whereas such considerations no doubt come into play when pricing and registration decisions are made, they have rarely been studied formally in the context of individual medicines. However, an earlier study by OHE and MPS documented the substantial contribution, in employment and international trade, made by the pharmaceutical industry in seven countries.[35]

This chapter has therefore outlined the main features of economic evaluation and identified a number of the key methodological issues. In the next chapter these points are further illustrated through discussion of a number of examples of the application of economic evaluation to medicines.

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3. EXAMPLES OF ECONOMIC EVALUATION APPLIED TO MEDICINES

3.1 A HISTORICAL PERSPECTIVE

Approaches to measuring the impact of new medicines have changed over time. This development has been an inevitable consequence of the shifting patterns of pharmaceutical innovation. In the main, new medicines coming onto the market today exert their principal influence on the quality of life. In contrast, many of those products which initially became available during the first pharmacological revolution tended to influence the quantity of life. It should be emphasised, however, that despite this process of transition heralding the need for more refined techniques of measurement, some of the measures traditionally employed to demonstrate the benefits of new medicines still occasionally have relevance today.

This latter point may be illustrated in the context of mortality. Three or more decades ago, the increasing availability of effective anti-infective medication made an important contribution to reductions in the annual fatalities from infectious diseases. Focusing on the classic example of respiratory tuberculosis, calculations based on mortality data for 1948 and 1984 suggest that without the improvements in death rates over the period, there might have been 22,000 more deaths from this cause in the latter year than was actually the case (376). This fall is largely due to medicines, although admittedly it is difficult to be certain about the precise magnitude of the part medicines have played.

Pharmaceutical benefits such as the drop in mortality from respiratory tuberculosis are largely of historical interest. It would, nevertheless, be misleading to imply that medicines are no longer associated with savings in mortality. Deaths from stroke and coronary heart disease, for example, are undoubtedly being avoided, or postponed, in people at the high extremes of the population distributions for blood pressure and serum cholesterol by the use of medicines for hypertension and hypercholesterolaemia. And there is evidence that the use of beta blockers following acute myocardial infarction reduces subsequent mortality by about 20 per cent. Yet in these and other areas of therapy, comprehensive data do not exist to show either the number of years of life being saved by medicines (let alone their quality) or at what expense these gains are being achieved.

Whilst the foregoing suggests that mortality might still occasionally have some, albeit limited, relevance in measuring the impact of pharmaceutical innovation, another traditional measure, reductions in incapacity for work, can no longer be applied in aggregate studies. In theory, medicines might still be expected to generate economic benefits by reducing sickness absence from work, either by cutting the number of spells of absence or by reducing their duration. However, with a shrinking data base – following a progressive shift in the responsibility for the payment of sickness benefit from State to employer – it has become increasingly difficult to discern the effect that the introduction of new medicines might have on trends in sickness absence. Therefore, data on sickness absence will have to be obtained through special surveys in the future.

In addition, numerous analyses in this area have demonstrated that decisions both to withdraw temporarily from the work-force through ill health and to return to work after such absences are, in reality, influenced by an extensive and diverse range of factors, very few of which are in any sense strictly of a 'medical' nature. As a result of these factors, 'sickness absence' is often increasing despite improvements in health.

The extent to which pharmaceutical innovation may give rise to savings in the hospital sector has also been employed as a measure of the gains from the development of new medicines. Analyses based on broad groupings of disease entities have suggested that pharmaceutical innovation may yield substantial financial benefits by reducing the number of hospital admissions and/or by cutting the duration of in-patient stay.

Inevitably, this approach is subject to a number of drawbacks. Setting aside the difficulties inherent in assessing the extent to which a change in hospital admission trends may be attributed to any one factor by itself, it should be recognised that potential savings are not generally realised in a purely financial sense. Instead, the benefit of pharmaceutical innovation may effectively lie in the release of hospital beds for alternative uses. Furthermore, if the latter involve individuals whose in-patient treatment is more expensive, then the innovation may in fact serve to increase the resource pressures experienced in the hospital sector. In addition, it is of course axiomatic that the results of analysis depend on the perspective that is taken. Focusing narrowly on the impact of a new medicine in a specific disease, it is still possible to show a financial saving effected through fewer hospital admissions and reduced lengths of stay. But elsewhere, new pharmaceuticals can also be cost-increasing for the hospital sector. For example, the development of immuno-suppressant agents has facilitated an expansion of expensive high technology surgical procedures. In addition, medicines promote the survival of some individuals who eventually may come to need hospital care. Consequently, the cost/benefit implications – in a strict financial sense – of pharmaceutical innovation may be expected to vary considerably.

The fundamental point is that gains in the various forms noted above have largely been superseded by benefits which are principally apparent in an improved quality of life. Consequently, a large element of contemporary health economics research is concerned with developing appropriate methodologies for measuring and quantitatively representing the gains from health care interventions that take the form, for example, of improved mobility and diminished pain.

It is clear that accurately quantifying these gains poses a considerable challenge. Attention has already been drawn to the changing nature of chemotherapy and the consequent need for measures that successfully reflect improvements in various aspects of day-to-day living. The latter embrace highly subjective items, such as pain sensation, and therefore demand much more sophisticated measurement techniques than those employed in, say, assessing productivity gains through reduced sickness absence.

In addition, despite consistency in the basic principles underlying the concept of evaluation, new methods of measurement will need to be sensitive to the highly differentiated nature of the pharmaceutical market. General practitioner prescribing statistics identify at least 15 major chemotherapeutic classes embracing such widely differing treatments as, for example, preparations acting on the cardiovascular system and those which are active in the central nervous system. Assessing the impact of diuretics and sedatives will therefore demand different outcome measures as, indeed, will single chemical entities which have multiple therapeutic applications. The beta blockers are an obvious example in this respect with treatment indications ranging from hypertension to glaucoma.

Further complications also stem from the fact that a given medicine may be associated with different outcomes according to various characteristics of the patients receiving

therapy (age, in particular).

The foregoing observations suggest that contemporary economic evaluation of medicines is confronted by two principal difficulties – devising measurement techniques that are sufficiently sensitive to register potentially small changes in highly subjective aspects of daily living and the need to be adaptable to the different outcomes associated with different types of therapy. Some of these issues are examined in more depth in the examples which follow.

3.2 ANTIBIOTIC PROPHYLAXIS IN SURGERY

One good example of a cost-benefit analysis which shows financial savings for the health services is the use of antibiotics to prevent post-operative infections. A recent estimate suggests that 5 per cent of all hospital cases are infected during their stay, giving a total cost for hospital infections in England and Wales of £76 million.[1] Turning to the United States, and taking post-operative infections alone, it was estimated in 1982 that the annual cost was between 200 and 800 million dollars.[2] Further evidence of very substantial costs of post-operative infection comes from a controlled clinical trial of antibiotic prophylaxis in high risk biliary operations in Southampton.[3] The surgeons in this study found that 16 per cent of a small series of cases were infected if antibiotics were not used prophylactically. In their text they suggested that in general between 5 and 10 per cent of surgical wounds might end up being infected – with a range from 0.2 per cent in 'clean' operations carried out with a high degree of surgical expertise to 100 per cent in 'contaminated' cases carried out with 'poor' surgical expertise (Table 3.1).

Based on the figure of 2.3 million operations carried out annually under the NHS and a recent estimate of an average of four extra days spent in hospital if an infection occurs,[3] a 5–10 per cent infection gives a cost for post-operative infections of between £40 million and £80 million a year.

The same surgeons in Southampton expressed the opinion – based on the results of their controlled trial – that antibiotic prophylaxis 'virtually eliminated' post-operative infection. However, perhaps a more realistic estimate comes from a French study which indicated that 80 per cent of infections were avoided by prophylaxis.[4] On this basis, the prophylactic use of antibiotics would save the NHS between £32 million and £64 million in reduced length of hospital stay. Incidentally, it is probably quite fair to use average total hospital costs to calculate this figure, as infected patients will require careful nursing and a full range of pathological and therapeutic services during their period of infection. They certainly do not incur 'hotel' costs alone. But even if the analysis were confined to hotel costs alone there would still be substantial savings in resources.

Table 3.1 **Approximate risk of septic complications, eg, wound sepsis, that may be expected in different areas of surgical practice, without the use of antibiotics, according to the technical expertise of the surgeon.**

	Sepsis rate according to degree of surgical expertise		
Type of surgery	*High*	*Average*	*Poor*
Clean			
Hernias, varicose veins, breast surgery, orthopaedics, vascular surgery	0.2	2	5
Potentially contaminated			
Low risk, Biliary, gastric surgery	3	10	20
High risk, Colorectal surgery (elective)	15	45	70
Contaminated			
Peritonitis, drainage of abcesses	75	85	100

Source Karran *et al*[3]

However, the statement of these very substantial figures does not automatically answer the question of whether or not antibiotic prophylaxis is cost effective. Antibiotic cover has to be provided for the 90–95 per cent of patients who would not be infected, as well as those who would. It would thus be possible that the cost of antibiotics themselves would outweigh the savings they achieved. Fortunately, from an economic point of view, this is a question which has been carefully studied in a number of different situations, and in each case the result shows an overall net saving. Some specific examples are given below, mainly from the United States. However, the conclusions are applicable internationally, as the relationships between pharmaceutical costs and overall hospital costs are similar in all countries.

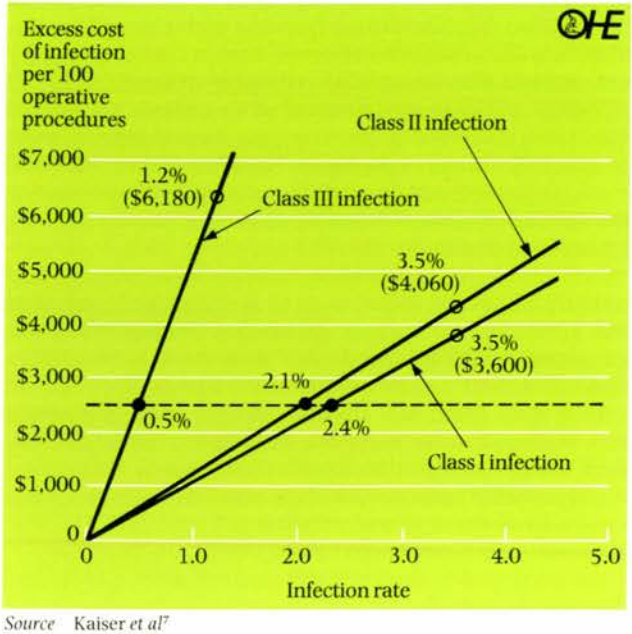
The first example relates to abdominal hysterectomy.[5] Cefazolin was used for prophylaxis in the treatment group in a controlled trial covering 429 patients. In this trial, patients in the treatment group each cost on average $102 less than those in the control group, after taking account of the cost of the antibiotic. The same paper, published in 1983, also reported on a small trial covering vaginal hysterectomy. In this case 44 patients received cefazolin prophylaxis and 42 received a placebo. The net saving was $492 per patient. The second study, also published in 1983, covered acute non-perforating appendicitis.[6] This was a prospective randomised double-blind trial in which 52 patients received the placebo and 51 received cefoxitin sodium. Post-operative wound infections occurred in 9.6 per cent of the placebo group, but in none of the treated group. It was calculated that prophylaxis in this case resulted in a net saving of $84 per patient.

Another brief communication in 1983 discussed the cost-effectiveness of antibiotic prophylaxis in clean vascular surgery.[7] In this case, the cost of five one-gram doses of perioperative cefazolin was $2,500 per 100 patients. Figure 3.1 shows that the excess costs associated with post-operative infections in untreated patients exceeded the costs of prophylaxis if 0.5 per cent of cases developed the most severe infections, if 2.1 per cent developed infection of the subcutaneous tissue, and if 2.4 per cent developed skin infections only. In the trial, the observed infection rate exceeded the 'break-even' infection rate for each of the classes of infection, and the authors therefore concluded that antibiotic prophylaxis was always justified for economic as well as for clinical reasons.

In 1984, a further study examined the economic consequences of prophylactic antibiotics in head and neck surgery.[8] The double-blind randomised trial covered 101 patients, who were assigned to one of three treatment groups or to a placebo group. Seventy-eight per cent of untreated patients developed an infection: but only 33 per cent of those on cefazolin and 10 per cent of those on cefoperazone or cefotaxime were infected. Table 3.2 shows the extra costs resulting from less than optimum prophylaxis. It is explained by the authors as follows:

> 'Extrapolation for a theoretical group of 100 patients is even more revealing. The third-generation cephalosporins serve as the standard of comparison. Theoretically, even with the best results and despite perioperative prophylaxis, nine patients (9 per cent) will develop wound infection. The Table compares the number of extra infections and costs with cefazolin. For example, in a group of 100 patients receiving cefazolin prophylactically, 33 will develop post-operative wound infection. The theoretical

Figure 3.1 **The cost effectiveness of antimicrobial prophylaxis in clean vascular surgery.**



Source Kaiser *et al*[7]

Legend The effect of the severity of infection and the infection rate on the excess cost of infection in vascular surgery involving the abdominal aorta. Wound infections were graded as Class I if only skin was involved. Class II if sc tissues were involved and Class III, or most severe, if the implanted graft was involved. The open circles denote the observed infection rate and the excess cost of infection per 100 operative procedures. The solid black lines define the relationship between the infection rate and the excess costs of infection. The dotted line represents the cost of cefazolin prophylaxis per 100 operations.

model would predict nine infections with the use of third-generation cephalosporin. Therefore, 24 infections could perhaps have been prevented.

'Each of the 24 additional infections results in 14.7 excess hospital days. This represents 352.8 days collectively. On the basis of our per diem costs of $697.62, these extra infections cost $246,120.33. The cost of cefazolin is $5,000 for 100 patients. Therefore the net increased hospital costs for the patients receiving cefazolin is $251,120.33. Obviously, the extra $6,800 spent on the third-generation cephalosporins is insignificant compared to the added expense of hospitalization for infected patients.'

Finally, the French study published in 1985, which has already been mentioned, examined the use of prophylactic cefoxitine in major surgery for cancer of the upper 'aero-digestive' tract.[4] Eighty per cent of controls developed post-operative infection, against 15 per cent of the treated group. This resulted in a net treatment cost of 1,002 French francs for the control group against 470 French francs for those treated prophylactically.

Although the individual experiences and results differ considerably, clearly all of these studies point in the same direction. Antibiotic prophylaxis does reduce costs, in addition to averting suffering and inconvenience for the patient. There appear to be no published studies which contradict this conclusion. This situation is confirmed by a recent article in the *New England Journal of Medicine*, which concluded that 'ample evidence suggests that in a broad range of surgical procedures – eg, caesarean section, colon resection and vascular surgery – it is more cost-effective to administer prophylactic anti-microbials than to treat the infections which occur in patients who have not received these agents'.[9] Even in the few cases where infections occurred extremely rarely, the author concluded that prophylaxis was justified by the benefit to the patient irrespective of relative costs.

It is therefore clear that studies in a number of settings have shown that antibiotic prophylaxis reduces length of hospital stay. The benefits can either be viewed in terms of freeing resources for the treatment of other patients or, in the longer term, rationalizing bed provision. However, these savings depend on the correct use of antibiotics on the appropriate patients and in the appropriate doses.

3.3 H_2 ANTAGONISTS FOR ULCER DISEASE

The H_2 antagonists, of which cimetidine was the first, represented a major breakthrough in the treatment of peptic ulcer disease. Early clinical trials demonstrated the potential of cimetidine in healing ulcers and further trials were launched to assess its efficacy in the longer term management of patients. Cimetidine appeared to offer an effective alternative to surgery in many cases and to provide superior therapy for those patients whose condition was inadequately controlled by diet or antacids.

However, the development of the H_2 antagonists raised a number of economic questions. Given the high prevalence of ulcer disease, what would be the total impact on the medicines budget? Would treatment with cimetidine be more cost-effective than surgery, both in the immediate treatment of ulcer and in the longer term? Given that the availability of the new treatment technology would have a 'demand generation' effect (ie, would be used for patients for whom surgery was contra-indicated), or may be used more widely (ie, for patients not having ulcers), would the total benefits exceed the total costs? Because of these and other concerns, the manufacturers commissioned a range of economic studies of cimetidine, such that it has been the subject of more economic evaluation than any other medicine.

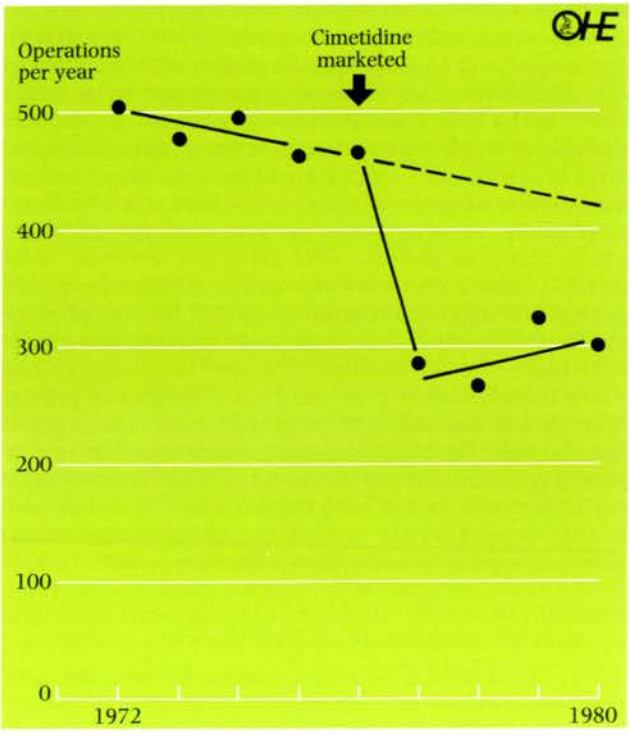
Paterson[10] chronicled the early economic analyses of cimetidine. He pointed out that the earliest studies were of the cost of illness type (see Chapter 2), where the total economic burden of ulcer disease (in medical care costs and lost production) was estimated. These studies confirmed the earlier forecasts of sales volume for the medicine but, more importantly, predicted where the savings from the introduction of cimetidine were likely to accrue. (These appeared to

Table 3.2 **Theoretical costs associated with development of wound infection of 100 patients according to prophylaxis given.**

Regimen	*Predicted infections*	*Infections in excess of ideal*	*Extra hospital days (14.7/patient)*	*Cost of extra hospitalisation*	*Cost of antibiotics (100 patients)*	*Net extra costs on 100 patients*
No drug	78	69	1,014.3	$707,606.10	—	$707,606.10
Cefazolin	33	24	352.8	$246,120.33	$5,000.00	$251,120.33
Third-generation cephalosporin	9	—	—	—	$11,800.00	$11,800.00

Source Mandell-Brown *et al*[8]

Figure 3.2 **Operations for duodenal ulcer by a group of six medical centres in the UK from 1972 to 1980.**



Source Paterson[10]

be mainly in reductions in hospitalization and reductions in lost work time.)

As with all medicines under development, a number of clinical trials were under way. However, none incorporated an economic component. Therefore it was suggested that researchers 'put a simple one-line item in the USA patients' case report forms: number of days of work missed last week because of ulcer disease'. It was thought that this was 'about all gastroenterologists would take time to ask'.[10] This showed that the cimetidine group was averaging about one day of missed work per week and the placebo group about two.[11] Another clinical trial, undertaken at around the same time, demonstrated that patients on cimetidine had fewer recurrences than those on placebo and that fewer went on to surgery within one year.

However, it was thought that the data from the clinical trials, though important in demonstrating cause and effect, may not necessarily be valid externally in the community. The trials considered the most severe categories of patient, their strict protocols ensured adherence to the regimen by doctors and patients, and the comparison was almost exclusively with placebo, whereas in the real world the alternative would be diet or antacids.[10] Therefore a number of studies were commissioned to ascertain whether, over time, cimetidine was bringing about a reduction in the costs of treating ulcer disease in the health care system more widely. These studies, which became known as 'macroeconomic studies of cimetidine'[12] were undertaken in a number of countries with similar results. The early studies concentrated on surgery rates and Figure 3.2 shows the reductions in the operations for duodenal ulcer in the UK following the marketing of cimetidine. Multivariate analyses were also performed in order to investigate other possible explanations for the reductions in surgery. The absence of other logical explanations, taken together with the evidence of cause and effect from the clinical trials, suggested that cimetidine was responsible for the reductions observed.

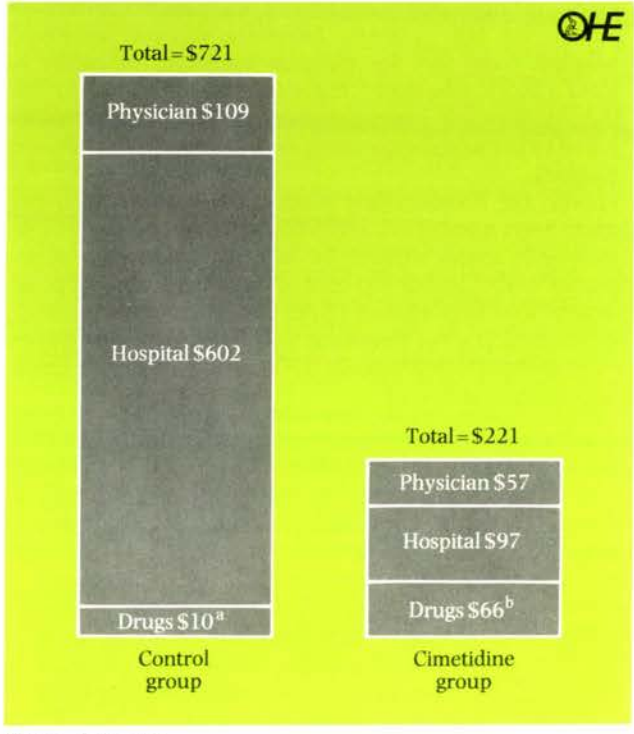
The next question was whether the cost of treatment by cimetidine was lower than that of surgery. In the Netherlands, Bulthuis[13] claimed that a reduction of 15.7 million Dutch guilders in hospital costs over the period 1972–80 was specifically attributable, with acceptable confidence, to the availability of cimetidine. In the USA, Geweke and Weisbrod[14] compared all ulcer-related costs of cimetidine patients with those of ulcer patients not treated with cimetidine, using the computerized reimbursement records of Medicaid in Michigan. They found that at the end of one year there was a cost differential of $500 per patient, due mainly to reduced hospitalization costs among the cimetidine patients (See Figure 3.3).

Such comparisons should be made in the knowledge that the two groups were identical, as in a randomized controlled trial. However, the authors did control retrospectively for the severity of cases and also undertook a sensitivity analysis of their results to different assumptions. Another point to note about this study is that the costs of antacids were excluded, since these are not eligible for reimbursement under Michigan Medicaid. (Inclusion of these costs would probably have increased the cost differential between conventional therapy and cimetidine by around $50, the additional costs being borne by the patients themselves.)

In a study undertaken in the United Kingdom, Culyer and Maynard[15] emphasized that there are a number of potential viewpoints for the cost comparison, the government or third party payer, the patient or society at large (see Chapter 2). In a comparison of cimetidine with surgery (proximal vagotomy) for duodenal ulcer, they found that from the perspective of society as a whole, cimetidine was the more cost-effective alternative. However, from the more limited perspective of the UK National Health Service, surgery would be preferred on cost grounds.

Culyer and Maynard's study also illustrates a number of other methodological issues. First, although a number of clinical trials of cimetidine had been carried out, none provided an adequate foundation for economic evaluation: they

Figure 3.3 **Average annual Michigan Medicaid expenditures per patient with duodenal ulcer. [a]Does not include antacids which are excluded from Michigan Medicaid; [b]includes cost of cimetidine therapy.**



Source Paterson[10]

were either too small, inadequately controlled, evaluated alternatives that were not the most relevant for economic assessment, or embraced too narrow a range of measurements. Therefore, in common with Weisbrod,[16] Culyer and Maynard make a plea for more consideration of these factors when clinical trials are being planned and designed. (This point is explored further in Chapter 4.) The main way in which the authors cope with uncertainties in the clinical (and other) estimates is to make assumptions which are conservative with respect to the hypothesis that cimetidine is the more cost-effective alternative. Therefore, their finding, that the *highest* estimate of the cost of cimetidine therapy (£1,240) exceeded by only £60 the *lowest* estimate of the cost of vagotomy (£1,180), is fairly strong evidence of the economic superiority of cimetidine.

Secondly, Culyer and Maynard note that a number of factors were omitted from their study, such as the pain associated with surgery and its aftermath, and inconvenience of permanent medication. Ideally one would want to develop evaluation methods which encompass these elements, such as those involving quality of life measurements. (One such example is discussed in Section 3.5 below.)

Thirdly, the time profile of costs differs between cimetidine and surgery, in that the costs of long-term therapeutic maintenance stretch into the future. Therefore the authors made different assumptions about the length of time on long-term medication (20, 25, 30 and 35 years) and discounted the costs to present values using discount rates of 5, 7 and 10 per cent. (See Chapter 2.) Of course, one of the results of discounting by rates of 5 per cent or more is that costs occurring more than 20 years or so into the future have very little numerical impact on the analysis. Therefore economic evaluations of new medicines are not necessarily greatly affected by our inability to predict far into the future.

Nevertheless there is a need to update economic evaluation results as new information becomes available. In the case of the H_2 antagonists a number of other research questions have emerged as time has passed. For example, there are now other H_2 antagonists on the market or under development; how do these compare with cimetidine in terms of cost, effectiveness and adverse effects? There are now longer term data on maintenance therapy, including recurrences of ulcer, losses in work time and early retirement.[17] There are also a number of trials of other therapies, such as those including tri-potassium di-citrato bismuthate, antacids, anticholinergics and therapeutic combinations. Miller and Faragher[18] claim that, although the results of individual trials conflict, the balance of evidence suggests that recurrence rates may be higher for patients treated initially with H_2 antagonists. In addition, one study from Canada suggests that it is important to give guidance to physicians on the appropriate use of H_2 antagonists, so that they are used in situations where they have been shown to be efficacious and where the benefits outweigh the costs.[19] On the other hand Bloom and Jacobs[20] argue that the small short-term savings of a closed pharmaceutical formulary may be negated by increased expenditures in the near future when sicker patients, previously denied peptic ulcer treatment with H_2 antagonist, require expensive hospital treatment. These examples illustrate the point made by Banta,[21] that the economic evaluation of medical technologies is not a one time event, but an iterative process where results are continually updated as new information becomes available and as new medicines come on the market, or other new techniques are developed.

3.4 ANTIHYPERTENSIVE MEDICINES

By the early 1970s, clinical trials had demonstrated the effectiveness of medicines in reducing blood pressure. This represented a considerable breakthrough, given the link between hypertension and cardiovascular disease, and an extensive range of medicines has now been developed. The most comprehensive economic evaluation of treatment options in hypertension is that carried out in the USA by Weinstein and Stason.[22, 23] Their study considered four main questions.

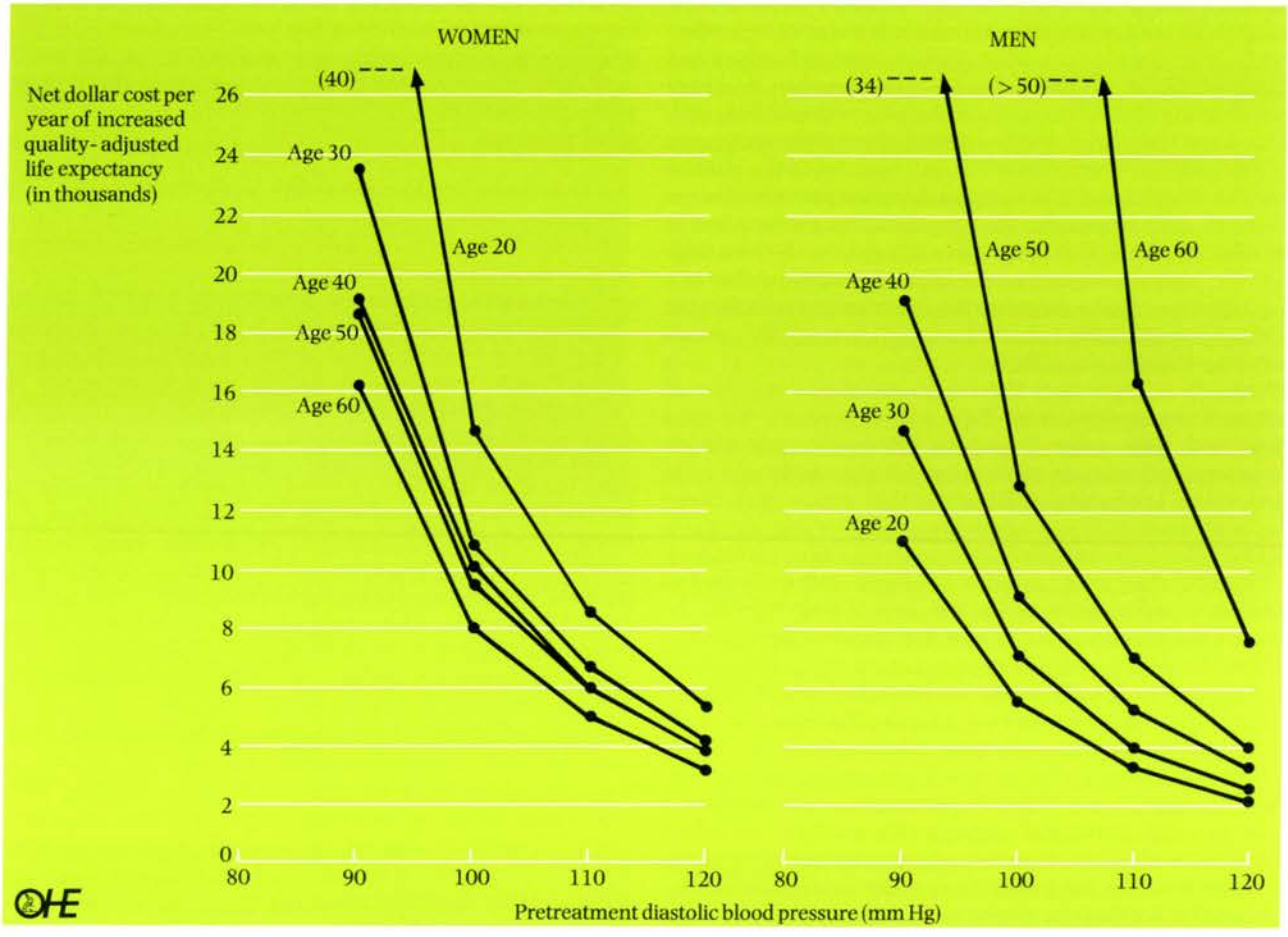
- to what extent does treatment for hypertension pay for itself?
- how efficient a use of health resources is the treatment of essential hypertension?
- what are the priorities for treatment?
- how should resources be allocated between screening programmes and efforts to improve continuity of care and adherence to prescribed medical regimens in patients known to have hypertension?

The study was not linked to a single prospective clinical trial, but drew data from a number of sources. It compared the additional costs and health effects of antihypertensive therapy with those arising from leaving hypertension untreated and treating, instead, the resulting disease. Specifically, the total costs of treating hypertension comprised the cost of treatment itself (including medicines, visits to the doctor and laboratory tests), plus the cost of treating the side effects of medicines, minus the saving in medical costs because disease is prevented, plus the cost of medical care in the years of life added by treatment. The inclusion of the last item has been a source of debate among economists,[24] as was the exclusion of the indirect benefits resulting from individuals living and working longer than they otherwise might. It could be argued, for example, that the decision whether or not to treat arthritis and cancer in added years of life is one that should be taken separately and not form part of the evaluation of antihypertensive medicines. Russell[24] points out that the inclusion or exclusion of various items in the economic evaluation depends on the perspective (viewpoint) adopted, a point made earlier in Chapter 2. Fortunately, in Weinstein and Stason's study the medical care costs in added years of life did not have a major quantitative impact on the results since, being in the future, they were heavily discounted. (See the discussion of discounting in Chapter 2.)

The total health effects of treatment comprised the added years of life from therapy, plus the improvements in quality of life through the prevention of nonfatal disease, minus any deterioration in health because of the side effects of treatment. The authors recognized that to amalgamate these effects in one index would require an assessment of the quality of life under antihypertensive therapy compared with normal healthy life. In the absence of any survey of patients, they decided arbitrarily that most people would value a year of life with side effects from hypertensive medication as worth just under 0.99 of a year of healthy life. That is, an average person would be willing to give up only about 1 per cent of his or her remaining life span, or about four days a year, to be free from side effects. Clearly it would have been desirable to obtain such valuations directly from individuals, using one of the methods outlined in Chapter 2; but at least Weinstein and Stason did estimate the sensitivity of their results to the assumptions made, as will be seen later. Similar judgements were made by experts of the quality of life of individuals suffering from nonfatal strokes or heart attacks.

The study produced a number of interesting results. First, it can be seen from Figure 3.4 that the cost-effectiveness of treating hypertension varies considerably, depending on the sex of the patient, the age at which treatment begins and the pretreatment diastolic blood pressure. The data suggested

Figure 3.4 **Cost effectiveness according to age and pretreatment level of diastolic blood pressure.**



Source Stason and Weinstein[23]

that it is more cost-effective to treat men of a given pretreatment level at an earlier age. Different results were obtained for women since hypertension seems to cause less damage, especially when they are young.

Table 3.3 shows that for 50-year olds the cost per year of healthy life gained was $6,900 for men and $6,000 for women in the reference case (1975 dollars). This estimate, for a reduction of diastolic pressure from 110 to 90 mm Hg, assumed that risk reduction is greater the earlier the age at which treatment is initiated and the longer it has been in effect, that treatment costs are $200 per year, that side effects are valued at 0.01 of a healthy year, that there is complete compliance with therapy and that the discount rate is 5 per cent per year. The authors pointed out that the key question was that of whether these were 'reasonable prices to pay'.[23] Subsequent analysis has shown that the cost per quality adjusted life year gained from treating severe and moderate hypertension in middle-aged males compares favourably with that from other health care investments.[25]

Table 3.3 **Cost-effectiveness of treating hypertension with medication in 50-year-olds, under alternative assumptions**

1975 dollars

	Cost per year of healthy life	
Assumption	*Men*	*Women*
Reference case	6,900	6,000
Change:		
Treatment confers full benefit	2,300	3,000
Treatment costs		
$100 a year	3,300	2,600
$300 a year	10,200	9,300
Side effects valued at .02	10,500	9,000
Incomplete compliance with treatment regimen		
Minimum cost	9,300	8,000
Maximum cost	14,900	13,200

Source Adapted from Weinstein and Stason[22] and Russell[24]

The table also demonstrates the impact of differing assumptions about the key variables. In particular, the level of compliance with therapy affects the cost-effectiveness results. If the patient continues to visit the doctor but does not take the full amount of medicine prescribed and reduces purchases accordingly (the 'minimum cost' assumption), the cost per year of healthy life is around 34 per cent higher. If, on the other hand, the patient continues to visit the doctor and buys all the medicine prescribed but does not take it all (the 'maximum cost' assumption), the cost per year of healthy life would be more than double that of the reference case. This finding led Weinstein and Stason to conclude that it may be a better use of limited resources to improve the compliance of known hypertensives than to make more efforts to detect further hypertensives. Other researchers have evaluated alternatives in the delivery of therapy. For example, in Canada Logan *et al*[26] found that care at the worksite by nurse practitioners was more cost-effective than care in the community by physicians, mainly because of higher compliance with therapy. In addition, Mitchell *et al*[27] demonstrated that a compliance-improving strategy was itself a cost-effective addition to therapy.

Table 3.4 **Changes in quality of life measures in the three treatment groups.**

Quality of life measure	*Change*			*P Value*†
	Improvement	*None*	*Worsening*	
	per cent of patients			
General well-being				
Captopril (n = 181)	51.4	17.7	30.9	
Methyldopa (n = 143)§	39.2	9.8	51.0	P<0.01
Propranolol (n = 161)§	39.1	15.5	45.4	
Physical symptoms				
Captopril (n = 181)	29.3	45.3	25.4	
Methyldopa (n = 142)§	19.7	43.4	36.6	P<0.05
Propranolol (n = 160)§	17.5	45.6	36.9	
Sexual dysfunction				
Captopril (n = 181)	18.2	63.0	18.8	
Methyldopa (n = 141)§	9.2	66.7	24.1	P<0.05
Propranolol (n = 160)§	8.8	65.6	25.6	

†P value based on chi-square test (3 by 3) for independence with 4 degrees of freedom.
§Variations in the numbers of subjects in the methyldopa and propranolol treatment groups are due to incomplete responses to the assessment measures.

Source Croog *et al*[28]

Now that there are many antihypertensive medicines, the interest has centred not on whether treatment itself is worthwhile, but on how the different medicines compare in terms of cost and effectiveness. There are as yet no full economic evaluations of this issue, although a recent study by Croog *et al*[28] tackles the important area of quality of life. They compared three well-known medicines in terms of their effects on patients' general wellbeing and satisfaction with life, physical state, emotional state, intellective functioning and ability to perform in social roles and the degree of satisfaction derived from those roles. (The series of scales and indices used is summarized in the paper.) It can be seen from Table 3.4 that patients taking captopril, as compared with patients taking methyldopa and propranolol, scored significantly higher on many of the measures of wellbeing, physical symptoms and sexual dysfunction. The question for economic analysis would then be that of whether these improvements justify any higher cost. (Indeed better control of side effects may also bring about reductions in other medical care costs.) In this case the economic question has not been answered formally, although the basic quality of life data from the study by Croog *et al* may help one come to a decision. Further economic analysis would include the calculation of costs and utility values, thereby enabling the calculation of cost per quality adjusted life year gained, and the estimation of willingness-to-pay for higher quality of life. The example discussed in the next section includes such assessments.

3.5 ORAL GOLD THERAPY FOR RHEUMATOID ARTHRITIS

Many modern medicines, such as those for rheumatoid arthritis, impact on the quality, not length, of life. In addition, therapies for the advanced stages of rheumatoid arthritis involve agents that are more toxic than non-steroidal anti-inflammatory medicines. Therefore, as well as providing relief to arthritis sufferers, there is a chance that such medicines will have some adverse effects.

During the premarketing review by the Food and Drug Administration of auranofin, the first oral form of gold therapy for rheumatoid arthritis, the manufacturers decided to undertake a major additional study aimed at defining more completely its effects on patients. Paterson[29] cites three reasons for the study. First, the traditional measures of efficacy, such as number of swollen joints, number of tender joints, grip strength, time to walk fifty feet and duration of morning stiffness, do not capture the effects of the pathologic process on the health of the patient. Secondly, traditional assessment separates beneficial effects (efficacy) from adverse effects. It would be better to try to measure the net effect of the medicine on quality of life. Thirdly, the need to control the costs of medical care is leading increasingly to the application of a cost-effectiveness criterion in the selection and reimbursement of medicines. As Paterson points out, 'the question then becomes one of "Does the improvement in health justify the added cost?" . . . . In an era of cost containment this had to be a relevant question in a full assessment of auranofin'.

The study therefore considered a wide range of variables, including data on resource use and quality of life. The alternatives compared were background therapy using non-steroidal anti-inflammatory medicines plus placebo, versus background therapy plus auranofin. Of course, the most relevant comparison for economic evaluation would be that of auranofin therapy with normal clinical practice, which would probably merely involve continuing with anti-inflammatories. Therefore, to the extent that there was a placebo effect among the controls in this instance, the therapeutic effect of auranofin would have been understated.

The conventional economic data considered were the costs of treatment, the additional medical costs incurred due to the treatment (eg, costs of monitoring and treating adverse effects), the medical costs averted, the costs of transportation for outpatient visits, the impacts on nonmedical expenses (such as paid and unpaid help in the home) and the changes in earned income.

The choice of the additional quality of life measures was not a straightforward matter. First, the traditional clinical measures were included since it was of interest to ascertain whether changes in these correlated with changes in the new measures being used. Secondly, a general quality of life measure, the Quality of Well Being Questionnaire[30, 31] was included because it would be expected to detect the adverse effects of therapy as well as the beneficial effects. This particular measure also had the advantage that its final score, derived through a set of 'preference weights', expresses a health state in relation to perfect health. This in turn allows the calculation of the quality adjusted life years (QALYs) added by treatment.

Thirdly, a number of arthritis-specific quality of life measures were included, since it was thought that the general quality of life measure might not be sufficiently sensitive to the improvements in functioning brought about by therapy. (One of the potential difficulties of the general measures is that they include many items that therapy could not be expected to affect and these may dilute the overall change score.) Finally, the patients' utility was measured using the Patient Utility Measurement Set and the standard gamble. Also, a direct measurement of willingness-to-pay to remove the arthritis was obtained from patients.[25]

One of the concerns at the beginning of the study was whether the preference weights used to calculate the scores in the Quality of Well Being (QWB) scale applied to the patients in the study. The preference weights had been derived earlier from interviews with thousands of persons, who were asked to rate and to compare various possible states of health. However, a study by Balaban *et al*[32] demonstrated that there was a close agreement (R = 0.937) between the weights obtained from the earlier general population sample and those obtained from the patients in the auranofin study.

Although it was conceivable that the costs of care for the auranofin group might be lower than those for the control, because of reduced hospitalizations and less use of hired

Table 3.5 **Economic outcome data: changes between baseline and 6-month assessment by treatment group**

Category	*Placebo (n = 147) Mean change (SE)*	*Auranofin (n = 146) Mean change (SE)*	*Auranofin – Placebo (SE)*	*Auranofin – Placebo p-value*
Annualized medical costs for rheumatoid arthritis ($/year)				
Outpatient expenses				
Visits	−105.5 (62.6)	47.9 (96.5)	153.3 (115.1)	0.03
Medications (excluding auranofin)	−2.3 (26.7)	−47.6 (20.8)	−45.4 (33.9)	0.05
Radiographs	−32.1 (18.3)	6.8 (32.4)	39.0 (37.2)	0.06
Laboratory tests	228.6 (16.4)	226.0* (25.2)	−2.7* (30.0)	0.31
Aids and devices	1.3 (9.6)	−0.5 (5.3)	−1.8 (11.0)	0.37
Treatments	−30.0 (15.4)	−5.5 (42.8)	24.5 (45.5)	0.23
Surgery	−7.6 (6.1)	5.3 (8.2)	13.0 (10.2)	0.11
Other	21.1 (36.4)	−10.9 (22.0)	−32.0 (42.5)	0.45
Hospitalizations	−587.1 (382.0)	−181.1 (430.3)	406.0 (575.4)	0.15
Nursing Home Care	−46.8 (46.8)	−74.8 (74.8)	−27.9 (88.2)	—
Nonmedical economic effects				
Paid help (hours/year)	−3.5 (13.3)	−1.8 (10.7)	1.8 (17.1)	0.70
Unpaid help (hours/year)	−47.9 (62.2)	−11.8 (42.1)	36.1 (75.1)	0.50
Own earned income ($/year)	−1,496 (707)	−881 (935)	615 (1,173)	0.46

*The figure $226 was taken to reflect the extra costs of laboratory tests with auranofin, since tests were required in the study for both groups in order to preserve the blinding of doctors and patients to therapy.

Source Thompson *et al*[30]

help, it was hypothesized that the costs of auranofin therapy would be higher because of the costs of the medicine itself and the associated monthly monitoring visits. The main question for economic evaluation would therefore be one of whether the benefits in improved quality of life or ability to remain at work justified this extra cost.

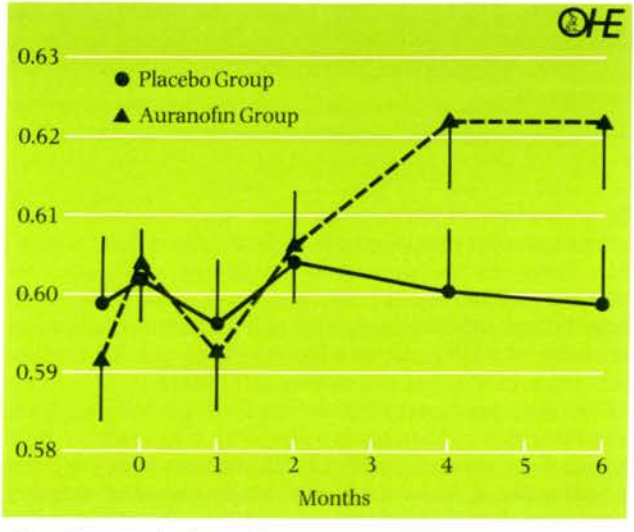
The changes in the economic variables over the study period for placebo and auranofin groups are shown in Table 3.5. (These are expressed as annual costs for ease of presentation, although the trial was terminated after six months on ethical grounds.) It can be seen that the major additional costs of auranofin therapy were those for the auranofin itself ($405.5), laboratory tests ($226), visits ($153.3) and radiographs ($39.0). On the other hand, the costs of other medications were lower, by $45.4. In addition the costs of hospitalizations were higher for the auranofin group ($406.0) and the costs of nursing home care lower (by $27.9). However, these events were so infrequent in either group that it is difficult to assess whether, in a much larger study, these differences would persist. Nevertheless, including all these data the total additional medical costs associated with auronofin usage were $1,160 per annum. Taking the broader societal perspective, including travel costs, the value of work lost by friends and relatives, the payments made for help in the home, the value of unpaid help and patients' earnings, the net additional cost of auranofin therapy can be seen to be $855.[33]

The changes in the clinical and quality of life measures are reported fully in Bombardier *et al.*[34] It can be seen from Figure 3.5 that after the two months required for the medicine to take effect, the quality of life of the auranofin patients, as measured by the QWB scale, was around 2 per cent higher. (This difference was statistically significant.) Auranofin was also superior to placebo in the clinical measures. Bombardier *et al* conclude that the 'results confirm the hypothesis that the favourable effect of auranofin on clinical synovitis is accompanied by improvements across a range of outcomes relevant to the patient's quality of life'.[34]

The improvement of 0.02 points on the QWB scale still needs to be interpreted in terms of its impact on the quality of life of patients. Thompson *et al*[33] argue that an overall gain across all components of the QWB scale of 0.02 points can be judged to be the approximate equivalent of all auranofin patients improving, identically, on the subscale of physical activity from moving one's own wheelchair without help to walking with physical limitations. Of course the improvements were spread over a number of subscales, and not just the one relating to physical activity.

The main question for economic evaluation is whether the improvements in quality of life observed justify the cost, when compared to alternative uses of resources. Thompson *et al* counsel against making broad comparisons of relative cost-effectiveness across programmes. Nevertheless, they do point out that a study by Liang *et al*[35] of total hip and knee replacement for patients with osteoarthritis was fairly comparable, since it dealt with a similar clinical problem and

Figure 3.5 **Changes in health status as measured by the quality of well being scale.**



(Adapted from Bombardier *et al*[31])

employed a similar methodology. In Liang's study an average health gain of 0.087 on the QWB scale was obtained at an incremental cost of $21,797 per patient. A simple comparison between the two studies shows that auranofin has a much superior cost-effectiveness ratio. However, Thompson *et al* argue that direct cost-effectiveness comparisons between the two studies can be superficial and misleading since the costs of auranofin therapy will be continuing, whilst surgery may not have to be performed again for a number of years. Rather they prefer to compare the incremental cost of auranofin therapy with the finding, from the willingness-to-pay estimations, that patients would be willing on average to pay 22 per cent of their household's income for a complete cure of their arthritis.

Paterson[29] also notes that in principle the improvement on the QWB scale could be used to calculate the cost per quality adjusted life year (QALY) gained from auranofin therapy for comparison with that of other interventions. However, he points out that there are a number of problems in making such comparisons. First, data relating to auranofin were based on only six months usage of the medicine and it would not be wise to extrapolate beyond that period. Secondly, the resource use observed during the clinical trial may be different from that observed in regular clinical practice. Thirdly, the comparisons of incremental cost per QALY would only be fair if the reference programme were the same in each case. That is, the most relevant reference programme for comparison with a new intervention would be existing care. However, it is not clear from the literature that such a comparison is being made on every occasion that an incremental cost per QALY has been calculated.

These and other methodological issues surrounding the incorporation of economic analysis in clinical trials and the interpretation of cost per QALY 'league tables' are discussed in Chapters 4 and 5 below. However, the economic evaluation of auranofin shows that many of the difficult measurement issues in the field of quality of life can be resolved, and that data can be obtained to inform difficult cost-quality trade-offs in medicine.

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4. ISSUES IN THE GENERATION OF ECONOMIC EVIDENCE ABOUT MEDICINES

4.1 LINKING ECONOMIC EVALUATION WITH OTHER FORMS OF EVALUATION

The examples cited in Chapter 3 demonstrate that it is feasible to undertake economic evaluations of medicines. In some cases the economic analysis was performed alongside clinical trials, in other cases it was performed retrospectively. Since new medicines undergo numerous clinical trials during their development, the clinical trial is an obvious vehicle for economic evaluation.

Drummond and Stoddart[1] have reviewed the arguments for and against undertaking economic analysis alongside clinical trials. They point out that there are a number of reasons why this approach should receive careful scrutiny. For example:

- the design and conduct of trials is already a time-consuming, complex and costly business, without having to incorporate yet another dimension:
- many trials, particularly those of new medicines, are not directly concerned with eventual implementation of the therapy, but with assessing the new therapy's efficacy under ideal conditions when compared with a placebo:
- even those trials that are directly concerned with assessing the performance of the new medicine in practice may be conducted under such experimental conditions that costs and outcomes in regular service use may be quite different from those experienced during the trial:
- many trials show the new medicine to be either ineffacious or no more effective than the old, and therefore it would be a waste of time assessing the economics of a regimen that is unlikely to be widely adopted.

Against this, the collection of economic data during clinical trials would mean that they are available when important decisions about the use of medicines are being made. Also, since they are based on real patient information, such data are more likely to be reliable than those assembled after the event. Finally, some of the relevant data may be more easily accessible during the trial. In an evaluation of a medicine thought to aid recovery following stroke, Drummond and Ward[2] were able to demonstrate the potential savings resulting from earlier discharge from hospital. (Fortunately, length of hospital inpatient stay was collected as part of the clinical trial.) However, because no information was available on the place to which patients were discharged, or, if discharged to home, the community care resources used, it was possible only to obtain a partial estimate of the costs of care with and without the new medicine. It was possible to make educated guesses about some of the missing data, but this was less satisfactory than having the true estimates.

In their paper, Drummond and Stoddart argue for a 'phasing policy' for the collection of economics data during trials, so as to minimise unnecessary work. (This is set out below in Box 4.) The objective would be to collect, during the trial, data that are thought to vary from patient to patient and that would be costly to collect retrospectively. Initially, resource data would be recorded in physical units only (eg, number of physician visits, number of days hospitalization) with a view to attaching money values later. Then, towards the end of, or after, the trial, additional economic analysis would be undertaken depending upon the policy issues arising.

Such an approach would be unlikely to impose a significant extra burden on clinical investigators. Indeed increasing numbers of clinicians are undertaking research jointly with economists since they realise that economic evidence is becoming more important in determining the appropriate use of medicines, given the scarcity of health care resources. In addition, in fields where medical research is funded by government, clinical researchers are sometimes asked to add an economic component to their study, so that data on

Box 4 ECONOMIC ANALYSIS ALONGSIDE CLINICAL TRIALS

During a selected trial

The object here would be to assemble the data base from which an economist could work should it become clear that, on medical grounds, the new therapy is likely to be preferred. These data are primarily those that are thought to vary from patient to patient, to relate to the economic questions and to be costly to collect retrospectively. They include:

- length of hospital inpatient stay;
- use of key resources essential to the treatment, such as medical time, nursing time, medicines and number and type of diagnostic tests – use in both hospital and community sectors should be recorded;
- use of other services that may be reduced as a result of treatment (eg, hospital readmission, use of medical and nursing services in the community);
- loss of work time by patient and family during treatment and corresponding savings of this resource resulting from improved health after treatment; and
- impact on other family resources.

Towards the end of the selected trial, if it becomes apparent that the economic issues are important

Here the objective would be to harvest the economic information relevant to the policy questions suggested by the medical results of the trial. If the trial suggests adoption of the new therapy then one might want to examine the wider costs and benefits of this change. If the trial shows no difference between therapies one might want to examine any changes in practice that might be suggested on cost, rather than medical, grounds. (That is, if there is no difference in medical effectiveness between the two therapies, why not adopt the lower cost one?)

Depending upon the policy questions arising, the economic analysis carried out at this stage might include:

- detailed costing of the alternative therapies, perhaps moving away from average hospital costs towards closer estimates based on actual resource use for the treatments concerned;
- estimation of the money value of any resource savings arising from adoption of a more effective therapy, perhaps to set against its higher cost;
- follow-up studies relating to key economic issues; for example, if it was thought that one therapy imposed higher costs on patients, one might like to perform more detailed analysis of these costs on (say) sub-samples of patients;
- extrapolation of the results of the trial to different settings; for example, the incremental or marginal cost of performing new treatments in a given location may depend on the scale of service envisaged and the anticipated level of utilization of facilities;
- preparation of a balance sheet of financial and non-financial costs and benefits relevant to the choice concerned for use by policy makers; and
- discussion of the merits and demerits of further quantification and valuation of some of the more intangible elements of treatment effects.

Source Drummond and Stoddart[1]

the relative costs of interventions are known as well as their relative effectiveness. For example, the Ontario Ministry of Health issues guidelines on this point to investigators seeking funding.[3] Also, in the United Kingdom an economic evaluation of the heart transplant programme was requested in order to inform the decision on whether it should be expanded.[4]

4.2 PRACTICAL ISSUES

Given that, in principle, it is considered desirable to undertake economic analysis alongside some clinical trials of medicines, there are still a number of practical issues to resolve. For example, **in which trials should economic analysis be included?** Drummond and Stoddart suggest three general indications for economic analysis: that resource allocation decisions about the therapy should be imminent; that large resource consequences will result from adoption of the new therapy, either because it will be applied to a large patient population or because it has a much higher unit cost than the existing therapy; or that there is an economic motivation for the trial (eg, it aims to demonstrate resource savings). In general terms these criteria would suggest that economic analysis is unlikely to be appropriate in many of the early trials in the development of a medicine, where efficacy under ideal conditions, dosage levels, toxicity, and pharmacological interactions are being determined. Neither is it likely to be appropriate where the medicine concerned is of similar therapeutic effect and similar cost to others already in regular use. Rather, economic analysis is likely to be indicated where:

- the medicine is nearing the end of its development phase and the trial (or group of trials) being carried out is likely to be influential in determining the medicine's appropriate use;
- the trial (or group of trials) compares the medicine with existing therapy (rather than a placebo). Existing therapy may be 'doing nothing' if no effective therapy currently exists for the disease in question;
- the medicine is currently (or potentially) indicated for use on a large patient population;
- it is likely that the negotiated price of the medicine and the consequent costs of care will be much higher than the costs of existing therapy;
- there are potential reductions in the use of other health service resources, owing to higher effectiveness of, or fewer side effects from, the new medicine (eg, avoidance of hospital admission, reduction in the length of inpatient stay, reduction in the number of general practitioner consultations);
- the benefits from the new medicine are unlikely to be captured by normal clinical measures and will therefore require direct assessment of quality of life.

The second practical issue concerns the **form of economic evaluation** and the complexity of the analysis. If the treatment objective itself is not being questioned and the comparison concerns two or more therapies for the same condition, certain simplifications in approach may be possible. For example, costs that are common to the alternative therapies may be excluded since they do not affect the choice. Also the benefit measure may be simply the effectiveness of therapy as typically assessed in clinical trials in the field of medicine concerned. However, if it is the case that decision makers are likely to question whether the particular therapy is worthwhile, when compared with the other potential uses of the same health care resources, then some degree of *valuation* of the benefits, in money terms or in utilities, may be justified. If the impact of the new medicine on quality of life is important, then undoubtedly one of the approaches to quality of life measurement discussed in Chapter 2 should be employed. Utility measurement will be necessary if it is intended to calculate the quality adjusted life years gained. Otherwise one of the general or disease-specific quality of life scales may be employed. Furthermore, although it would add to the cost of the study, it may be advisable, at this stage in the development of such measures, to use more than one approach to estimating quality of life.

Depending upon the audience for the study, particular viewpoints should be stressed. For example, the government is likely to be interested in the impact on its own costs, clinicians may be interested in their own costs and benefits, and those of their patients. Health service managers will be interested in the impact of therapies on their budgets.

As with all forms of scientific enquiry, further sophistications in economic evaluation can be achieved at increased cost. In Chapter 5 the main methodological issues are highlighted through a checklist of ten questions to ask about published studies. Probably the amount of detailed analysis required will depend upon the importance of the issue being investigated. Particularly expensive forms of analysis include the more sophisticated approaches to measuring quality of life (which frequently require trained interviewers) and detailed analyses of hospital costs. In the latter case it is fairly easy to obtain average hospital cost estimates, but those relating to a particular category of patients frequently require special surveys. In particular it should be noted that hospital billing figures, although they may have a spurious accuracy, do not necessarily reflect the opportunity costs of resources.[5] They also reflect in part the relative bargaining power of the parties setting the fee and billing schedules. Hull *et al*[6, 7] used an approach to estimating the costs of hospitalization that is somewhere between average costing and the more detailed approach. They identified those hospital costs unambiguously attributable to the treatment of interest (eg, physicians' fees, laboratory tests, medicines) and allocated these directly to the cost of the programme. Then they deducted, from total hospital operating expenses, the cost of departments already allocated above and departments known not to service the programme being costed. Finally, they allocated the remainder of hospital operating expenses to the programme according to its proportion of the annual patient days. Although imprecise, this approach may suffice, particularly if accompanied by a sensitivity analysis of the results of the study to different costing assumptions. (See Chapter 5 for more discussion of sensitivity analysis.)

Another practical issue arises out of the fact that many clinical trials of medicines are **multicentre trials**, often involving more than one country. Whereas it is normal to pool the clinical data in such trials, it is not clear that the economic data can be similarly pooled, or the cost data from one country can be interpreted in the context of another. Of course some methodological purists would also have concerns about pooling the clinical data since, although investigators may be following a strict protocol, trial data (strictly speaking) are only valid for the setting in which they are generated. However, the practical problems of recruiting enough patients in a reasonable amount of time often mean that multicentre trials are the only way forward.

Two main factors should be taken into account when pooling cost data or interpreting results from one setting to another. First, price levels and availability of resources will affect the costs reported. It is well-known that rentals and wage rates differ from location to location. In addition, the availability of (say) good community care services in a given location will make it easier to discharge patients from

hospital. (For example, it has recently been argued that the existence of a closely-knit gay community in San Francisco has made it relatively easy to promote home care for people with AIDS in that location.[8]) Secondly, the incentives or disincentives implicit in the organization and financing of health care in a given location are likely to affect resource use. For example, a hospital operating under a prospective reimbursement scheme is likely to discharge patients quicker than one that is not. Similarly, physicians in a prepaid group practice may treat their patients slightly differently from those operating under a fee-for-service system, within the general guidelines laid down by the trial protocol. This is likely to be particularly important in the treatment of side effects or complications, where the guidelines may be less tightly drawn. A close read of the trial protocol may give some indication of the scope for variations in approach given differences in resource availability or health care organization and financing from location to location. In addition, a general understanding of the incentives and disincentives operating in each country's health care system would be important in extrapolating from the trial to resource use in regular practice.

Given these problems the most sensible course in estimating costs alongside multicentre trials would be to:

- estimate resources in physical units, not financial amounts;
- note any differences in resource availability, organization or financing systems likely to affect resource use;
- report the overall economic results for the trial using the price data and institutional background of the most important trial setting;
- report, in addition, the cost results for different settings using the relevant price data for that setting and exploring the policy issues that are most important in that setting (eg, reductions in length of stay are likely to be more important to a hospital operating under a prospective reimbursement system or tight physical restrictions on the number of available beds.)

Finally, there are a few **logistical issues** in undertaking economic evaluations of medicines that merit more discussion. First, given the relative newness of this field of enquiry, there is a general need for clinical researchers and personnel within the pharmaceutical industry to familiarize themselves with the practice and potential of economic evaluation, so that they can recognize situations where economic evidence would be relevant and can monitor the quality of the research that is carried out. This booklet is intended to meet this need in part and in Chapter 5 issues in the interpretation and use of economic evidence are discussed. Secondly, it is important to integrate the economic analysis as closely as possible with the other forms of evaluation being carried out, perhaps by encouraging the economist to be part of the broader evaluation team. This would probably be beneficial even if it were decided to undertake economic analysis of the medicine retrospectively and not alongside a clinical trial (or group of trials) itself. Finally, as with other forms of evaluation of medicines, a decision has to be made on whether to carry out economic evaluation 'in-house' using industry personnel, or through contracts with independent researchers. Obviously work undertaken in-house can be more closely directed and monitored, although it is more likely to attract criticisms of bias, whether these are justified or not.

In summary, therefore, considerable progress has been made in recent years in the economic evaluation of medicines and there have been a number of pioneering studies. A number of the practical issues will only become resolved as more work is carried out. For example, should more efforts be made to undertake economic analysis alongside clinical trials, or will it be better to undertake such work retrospectively once the results of a series of trials are known? It seems that a sensible middle course can be steered, by collecting basic data on resource consumption during the trial, or series of trials, as a basis for subsequent economic analysis. Later, when it is clear that the clinical performance of the new medicine is satisfactory, it would then be possible to harvest the economic data. In doing so the economic analyst would obviously have to be conscious of any differences between the trial situation and the application of the therapy in practice. In addition it may be necessary to reappraise the situation after a time, when the indications for use of the therapy have changed and when it is being used by clinical practitioners of different levels of skill.

Another interesting issue concerns the **timing of the economist's involvement** – for example could economists make a useful contribution in the earlier stages of the development of medicines. For example, they may be able to estimate the potential social and economic benefits from the new medicine should it be efficacious, which may give an indication of the level of priority that should be assigned to its development. Economists may also be able to estimate the likely benefits arising from different features of the medicine eg, would it be worthwhile trying to develop a more convenient mode of administration, such as oral or subcutaneous use, as opposed to intravenous use? Which of the side effects are most important in economic terms and how much effort should be devoted to trying to ameliorate them? The answers to these kinds of questions are likely to have an impact on the overall research and development strategy for the medicine concerned and would represent a more fundamental contribution of economic analysis than that of merely assembling economic evidence about the medicine once it has been developed. However, the extent to which there would be 'added value' from economists turning their minds to these issues is currently unknown.

Given the increased interest in economic efficiency mentioned earlier, it is likely that more economic analysis will be carried out at a number of stages in the development of medicines. However, economic analysis, like all other forms of analysis, is not a costless activity. Therefore care needs to be taken to ensure that the maximum benefits are obtained from these efforts.

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5. INTERPRETATION AND USE OF ECONOMIC EVALUATION RESULTS

5.1 HOW TO ASSESS THE QUALITY OF AN ECONOMIC EVALUATION

Many groups of individuals may wish to use economic evaluation results for decision making purposes. For example, policy makers may wish to know which health care programmes give the best value for money and thereby should receive the highest priority. Health service managers may wish to know which treatment practices would be the most cost-effective when delivered in their hospital or clinic. Finally, groups of clinicians deciding upon local clinical policies may wish to know the diagnostic and therapeutic procedures that reflect a careful use of resources as well as delivering a satisfactory level of care to the patient.

In recent years there has been a rapid expansion in the publication of cost-benefit and cost-effectiveness analyses, particularly in medical journals, so that evaluations are now available for many choices in prevention, diagnosis, therapy, location of care and organization of services. A recent volume has reviewed 100 such studies.[1] In judging this literature the decision maker needs to answer two questions; 'is the study methodologically sound?' and 'does it apply to my setting?'. In order to help the decision maker resolve these issues a 10 point checklist of questions to ask about a published study has been developed[2] and applied in the assessment of studies in chronic bronchitis, treatment of hypertension, neonatal intensive care, prevention of pulmonary embolism and community care for mental illness.[3] The checklist is reproduced here in Box 5 and some of the main points are highlighted below.

As in all fields of scientific inquiry, it is important to *be clear on the study question*. In particular, it was stressed in Chapter 2 that the viewpoint(s) from which the alternatives are being compared should be clearly identified. Questions such as 'Is the new medicine worthwhile in the prevention of coronary heart disease?' beg the questions 'to whom?' and 'compared to what?'. A better specified question would be something like the following: 'From the viewpoint(s) of (a) the Ministry of Health (b) other agencies providing care and (c) patients and their families, would a preventive programme including the new medicine be preferable to the existing programme, which concentrates mainly on treating coronary heart disease as and when it occurs?'

It is important that studies include a *comprehensive description of the competing alternatives* so that the decision maker can assess the implications of study results for his own setting. In the case of the evaluation of medicines it would be important to specify the dosage levels, the mode of administration, the length of treatment, and the extent of monitoring of the patient's condition that is required.

Of course, given the need to consider both the costs and consequences of interventions in an economic evaluation, it is important that the *effectiveness of the programmes or treatments is established*. This further emphasizes the need, discussed in Chapter 4, to integrate the economic evaluation of medicines as fully as possible with their clinical evaluation.

The *identification, measurement and valuation of all relevant costs and consequences* was fully discussed in Chapter 2. Obviously the range included needs to match the breadth of the viewpoint(s) being considered and the study question being posed. In particular, broader questions demand that a wider range of costs and benefits is measured and valued, since frequently the issue of whether the treatment is worthwhile, when compared to the alternative uses of the same resources, is being explored.

As was discussed in Chapter 2, if the costs and consequences of the alternatives occur at different points in time they need to be adjusted for *differential timing*. Furthermore, *sensitivity analysis* should be performed, exploring the sensitivity of study conclusions to the values of those parameters about which there may be methodological controversy or imprecision in estimation. Typically, the factors varied in a sensitivity analysis include the discount rate, the costs of (or savings from reduced) hospitalization, the medical evidence on the success of therapy and the relative valuations of states of health. The precise selection of items for inclusion in a sensitivity analysis depends on particular circumstances, but users of evaluation results should be suspicious of a study that does not embody this general approach, as it is likely that many of the estimates used are more optimistic than would be found in practice.

Finally, in the *presentation of results*, it is normal that an *incremental analysis* be shown. That is, compared to the existing programme or treatment, what *extra* costs and *extra* benefits would result if the new intervention or medicine were used? It should be remembered that where the implicit existing programme is 'doing nothing', this rarely results in zero costs and zero benefits. In addition, the presentation of results should include a discussion of other concerns to users, such as the implications for other policy objectives (eg, equity), the managerial costs of changing to the recommended intervention and the extent to which the results of the particular study are confirmed by the results of other studies of the same topic.

Obviously few economic evaluations would pass such a stringent test of their methodology. Rather, the 10 question checklist should be regarded as a methodological 'gold standard' to which analysts should aspire. In the same way that we do not abandon medicine because it occasionally fails, we should not abandon economic evaluation as an aid to decision making because some of the studies have methodological imperfections.

5.2 PROBLEMS AND PROSPECTS OF COST PER QALY 'LEAGUE TABLES'

As was mentioned earlier, it has recently become fashionable to assess the relative value for money from health care interventions in terms of their cost per quality adjusted life year gained. In general terms this is a promising approach since the quality adjusted life year, as used in cost-utility analysis, addresses the issue of the relative value of states of health and the trade-off between quantity and quality of life, without raising the emotive question of valuing health benefits in money terms.

One example of a cost per QALY 'league table' is given in Table 5.1. Others have been calculated for health care interventions in North America and more recently health service researchers have begun comparing the results of their evaluations of other treatments or programmes with the existing published 'leagues'.[4, 5] The basic implication of the 'league tables' is that those interventions near the top of the league represent much better investments of health care resources. There is a strong temptation, therefore, to calculate the cost per QALY gained for new medicines and to use this as an argument for their extensive use.

However, despite their promise and apparent logical foundation, cost per QALY league tables have been the source of heated debate. The major features of the debate are summarized in Box 6. First, it has been argued that the mortality and morbidity data upon which QALY calculations are based are not sufficiently precise. However, the supporters of QALYs argue that, notwithstanding their

BOX 5 TEN QUESTIONS TO ASK OF ANY PUBLISHED STUDY

1. **Was a well-defined question posed in answerable form?**
   - 1.1 Did the study examine both costs and effects of the service(s) or programme(s)?
   - 1.2 Did the study involve a comparison of alternatives?
   - 1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. **Was a comprehensive description of the competing alternatives given? (ie, can you tell who? did what? to whom? where? and how often?)**
   - 2.1 Were any important alternatives omitted?
   - 2.2 Was (Should) a *do-nothing* alternative (be) considered?

3. **Was there evidence that the programmes' effectiveness had been established?**
   - 3.1 Has this been done through a randomized, controlled clinical trial? If not, how strong was the evidence of effectiveness?

4. **Were all the important and relevant costs and consequences for each alternative identified?**
   - 4.1 Was the range wide enough for the research question at hand?
   - 4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
   - 4.3 Were capital costs, as well as operating costs, included?

5. **Were costs and consequences measured accurately in appropriate physical units? (eg, hours of nursing time, number of physician visits, lost workdays, gained life-years)**
   - 5.1 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
   - 5.2 Were there any special circumstances (eg, joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. **Were costs and consequences valued credibly?**
   - 6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements.)
   - 6.2 Were market values employed for changes involving resources gained or depleted?
   - 6.3 Where market values were absent (eg, volunteer labour), or market values did not reflect actual values, (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
   - 6.4 Was the valuation of consequences appropriate for the question posed? (ie, Has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected?)

7. **Were costs and consequences adjusted for differential timing?**
   - 7.1 Were costs and consequences which occur in the future 'discounted' to their present values?
   - 7.2 Was any justification given for the discount rate used?

8. **Was an incremental analysis of costs and consequences of alternatives performed?**
   - 8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?

9. **Was a sensitivity analysis performed?**
   - 9.1 Was justification provided for the ranges of values (for key study parameters) employed in the sensitivity analysis?
   - 9.2 Were study results sensitive to changes in the values (within the assumed range)?

10. **Did the presentation and discussion of study results include all issues of concern to users?**
    - 10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (eg, cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
    - 10.2 Were the results compared with those of others who have investigated the same question?
    - 10.3 Did the study discuss the generalizability of the results to other settings and patient/client groups?
    - 10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (eg, distribution of costs and consequences, or relevant ethical issues)?

Source Department of Clinical Epidemiology and Biostatistics[2]

problems, these data are the best available for decision making and that their use in this way may stimulate epidemiologists and clinical researchers to improve upon them.

Secondly, it is pointed out that the different utility methods yield different results. As was mentioned earlier in Chapter 2, this issue merits further investigation. In the meantime it would be important to assess, through sensitivity analyses, whether health utility values *do* have a critical influence on study results. It may be that the results are just as sensitive to other estimates, such as those of costs. In situations where the utility values are critical, the analyst can only make this explicit and leave it to the decision maker to come to his or her own conclusions about the validity and reliability of the estimation methods used.

Thirdly, it has been noted that many of the cost per QALY values reported in the literature are average values, whereas the real choices are at the margins. For example, in considering Table 5.1 it can be seen that pacemaker implantation is near the top of the league and is therefore a strong candidate for expansion. However, the cost per QALY of the next stage

BOX 6 CRITICISMS OF COST/QALY 'LEAGUE TABLES'

There is now increasing interest in measuring the benefits of health care programmes in *quality adjusted life years (QALYs)* and in constructing 'league tables', where programmes are ranked in terms of their *cost per QALY gained*. However, a number of researchers have expressed concerns, the main ones being that:

- the mortality and morbidity data used for calculating QALYs are not sufficiently precise;
- the different methods of calculating health utilities yield different results;
- the cost per QALY values reported in the literature do not relate to choices at the margin;
- the highly summarized presentation suggests 'quick and easy' solutions to the decision maker;
- the broad comparisons, across widely different medical fields, are unwise;
- the strict application of cost per QALY logic would leave some groups in the population without any care;
- the comparisons ignore the possibilities of future medical research.

These points are discussed further in the text.

Table 5.1 **'League table' of costs and QALYs for selected health care interventions (1983–84 prices)**

Intervention	*Present value of extra cost per QALY gained (£)*
GP advice to stop smoking	170
Pacemaker implantation for heart block	700
Hip replacement	750
CABG for severe angina LMD	1,040
GP control of total serum cholesterol	1,700
CABG for severe angina with 2VD	2,280
Kidney transplantation (cadaver)	3,000
Breast cancer screening	3,500
Heart transplantation	5,000
CABG for mild angina 2VD	12,600
Hospital haemodialysis	14,000

CABG Coronary Artery Bypass Graft
LMD Left Main Disease
2VD Two Vessel Disease

Adapted from Williams[6, 19] and DHSS[4]

in the expansion of the pacemaker programme may not be the same as that reported in the table. For example, the pacemakers required for the extra patients may be more sophisticated in design and consequently more costly. Furthermore, it is likely that the patients that would be treated in the next expansion of the pacemaker programme are less seriously ill than those that have already been implanted. Therefore the benefits of treatment would be slightly lower. However, Williams' table, and some of the others reported, do embody margins to the extent that they consider the expansions in the indications for therapy (eg, as here from severe angina with left main disease, to moderate angina with two vessel disease). Consideration of these margins, and the resulting costs and QALYs, would be relevant for the clinicians working in the clinical fields concerned in deciding upon their treatment priorities, given limited resources.

Fourthly, it has been argued that the highly summarized presentation of data, in one cost per QALY estimate, is dangerous in that it suggests quick and easy solutions to the decision maker. This is a very important point and to the extent that these league tables encourage *less* thought by decision makers about the difficulty and complexity of health care choices they may be counterproductive. For example, is the decision maker happy to accept that a gain of one year of healthy life is equivalent to a gain of 0.1 in utility for each of 10 years? Are gains in length of life and quality of life different attributes that should be presented separately?[7] Because of these and other complexities, it is the responsibility of economic analysts to continue to stress that such estimates are only an *aid* to decision making, not a substitute for thought.

Fifthly, some commentators have suggested that the broad comparisons across widely different medical fields are unwise. Of course, these choices have to be made, indeed *are* made, through the policy process in health care. The question is therefore again one of whether such analysis helps those making the choices. In addition, it should be noted that many of the cost per QALY league tables also address choices *within* given clinical fields, such as open heart surgery and chronic renal failure, as well as between different branches of medicine. Another way forward would be to consider the costs and QALYs of different interventions for a given care group, such as the elderly or children, on the grounds that the allocation of a budget for the care of the group concerned would have already been made through the political process and that the main question is that of how best to use the budget.

A sixth objection is that the strict application of the cost per QALY league table would imply that some groups in society, with a low cost per QALY ranking, would receive no care. Of course it is true that the decision rule that is being applied is one that would maximise the total amount of health given the resources available. That is, it is concerned with economic efficiency (as discussed in Section 2.1), rather than with notions of equity or justice in the distribution of health care resources. Society may take the view that it wishes to give everyone an equal chance of receiving care no matter what condition they are suffering from. However, this view needs to be examined critically, since at the limit it would imply that two individuals, one suffering from an incurable condition and another suffering from one that is easily curable, should both receive equal treatment even though the chances of success are zero in one case and high in the other. Perhaps there are better ways in which society could exercise its moral duty, by giving access to palliative care and psychological help to those suffering from terminal illness, rather than engaging in heroic, unproven therapy. This does not deny the need for more medical research in such cases, however, providing this is carried out in accordance with a well-reasoned research protocol. Also it should be remembered that the cost per QALY league table does embody a kind of equality, in that a QALY is considered to be worth the same to every individual.

A final point, also linked to research, is that the cost per QALY estimates relate to treatment interventions at a particular stage in their development. Technological advances may make some of the interventions much more attractive in the future and these advances may never be realized if the treatments are discontinued. Certainly the cost per QALY estimates should be continually updated to take account of technological advances and research should continue to take place into all treatments. However, it is not wise to continue funding interventions that give poor value for money merely in the anticipation of future technological advances; equally, technological advances in other, competing fields may make them even less worthwhile in the future. Nevertheless, the calculation of costs and QALYs helps indicate situations where technological advances would potentially generate large benefits.

5.3 ECONOMIC EVALUATION AND HEALTH CARE DECISION MAKING

It should be apparent from the debate about cost per QALY league tables that economic evaluation incorporates a range of technical and value judgements. It is the responsibility of the analyst to make the value judgements as explicit as possible and to take the appropriate technical methodological decisions. However, economic evaluation is clearly an *aid* to decision making, not a substitute for thought, as health care resource allocation decisions are often made as a result of a complex interplay of social, economic and political factors.

Nevertheless it is possible to identify situations where economic evaluation has played an important part in decision making. For example, in the United Kingdom an *option appraisal*, using a methodology akin to economic appraisal, is required when large hospital building projects are being considered.[3] In addition, in the United States the results of economic evaluations have been influential in the development of Federal vaccination policies and of the recommendations of the American Cancer Society on screening for various types of cancer.[9] There is also a growing literature on the economic evaluation of particular medical procedures and, since the clinicians carrying out these procedures have been part of the evaluation team, the results have undoubtedly influenced practice. Occasionally, as in the

case of the evaluation of routine skull X-rays in the United Kingdom, professional bodies advise diagnostic or therapeutic protocols based on economic evaluation.[10] Also in the United Kingdom, the Department of Health and Social Security requested an economic evaluation to assist its decision on whether the heart transplant programme should be expanded.[11] So far there are few decisions concerning medicines that have been based on economic evaluation, although the work on cimetidine (discussed in Section 3.3) was important in putting the arguments about its cost into perspective.

However, considering new medical technologies in general, economic evaluation is becoming part of the accepted assessment process on both sides of the Atlantic.[9, 12] Therefore, although economic evidence is unlikely to be a formal requirement in pricing and registration decisions about medicines in many countries, questions about the economic justification for new medicines are more likely to be asked. In addition, if some of the measures discussed in Chapter 1 become more widespread, health care decision makers at the local level are more likely to consider economic factors when deciding which medicines to use in given clinical situations.

5.4 Economic evaluation and pricing and registration decisions about medicines

The US Kefauver Report in 1961, and the British Sainsbury Report in 1967 both concluded that price competition was largely absent in the prescription medicine market.[13, 14] This conclusion was based on the assumption that doctors were indifferent to the price of the medicines that they prescribed, because either the patient or the health service, and not the doctors, paid for their prescriptions. This assumption was strongly challenged by the Office of Health Economics in 'The Canberra Hypothesis' which was published in 1975.[15] Subsequent economic studies by Professor Duncan Reekie further demonstrated the existence of competitive pricing behaviour in the market in Britain, in the United States and in the Netherlands, in that medicines incorporating minor innovations were priced lower in relation to previously available treatments than were those incorporating major innovations.[16, 17, 18]

Nevertheless, the suspicion remains that competition has only a weak effect on prices in the prescription medicine market; hence most countries require pharmaceutical manufacturers to justify their prices in economic terms. This can be done either by showing that the manufacturers' profits are reasonable, or by showing that the medicines provide good value for money at the price actually charged for them. In so far as it is possible to demonstrate that medicines are cost-effective, it reduces the need to use other criteria to justify their price. In this sense, economic evaluation of medicines provides a substitute for the sort of market situation which exists for ordinary consumer goods. The examples given in Chapter 3 illustrate that it is possible to show that medicines give 'good value', in the same way that ordinary shoppers in the High Street expect 'good value' from their purchases.

No one expects a shoe manufacturer, for example, to disclose the cost of the leather, and his labour and overheads, or his profits, before a customer will buy his wares. All he must do is to establish a reputation for giving good value for money. Similarly, if excessively strict price control is to be shown to be unnecessary for medicines, the pharmaceutical manufacturers will probably be expected to show that they too give good value.

Hence economic evaluation is likely to become more important in the future in determining whether a pharmaceutical manufacturer's prices are 'reasonable'. This will be important to the manufacturer, who may otherwise be faced with unreasonable restrictions on his profits and costs. It will also be important to the health service administrators and to doctors, who will increasingly be expected to show that all types of health care expenditures are giving good value for money.

However, the economic value of a medicine should not be judged solely on the amount of money which it saves. 'Value for money' must now include the concept of improving patients' quality of life. Thus, if a more expensive treatment makes patients feel much better than a cheaper one, the higher cost may be fully justified. This aspect of 'good value' must be taken into account in judging the reasonableness of the price which is charged for a particular medicine.

The important point in using economic analysis to justify the price of a medicine is its *relative* value compared to alternative treatments. A higher price can be justified if economic evaluation – in addition to clinical trials – shows a medicine to be superior to its lower priced competitors. On the other hand if economic studies show that the medicine has only marginal advantages, perhaps for a minority of patients, it should then be priced more competitively. This is the principle which reimbursement agencies are likely to take into account in the future in making decisions about the reimbursement of medicines.

Already a number of countries such as Australia, Austria and France take the relative efficacy of a medicine into account in decisions on reimbursement under the national social security scheme. Price is also a factor which is taken into account in deciding whether a medicine is included in the 'limited list' of prescribable medicines in certain therapeutic categories in Britain. With the developments in economic evaluation discussed in this booklet, companies will increasingly be able to present economic as well as clinical evidence to influence the reimbursement decisions about a medicine.

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6. THE FUTURE

6.1 THE INCREASING USE OF ECONOMIC ANALYSIS

It is clear that the evaluation of medicines has become much more sophisticated over the past 50 years. In the 1930s doctors relied largely on clinical impressions to decide whether a new treatment was effective or not. Then in the 1940s and 50s the principle of the randomised controlled clinical trial was introduced; a classic example was the evaluation of different combinations of anti-tubercular compounds to find which was most effective. By the 1960s economic evaluation, initially in the form of cost-benefit analysis, was introduced. Early studies showed that medicines not only cured patients, but could also bring financial savings. These early cost-benefit studies were supplemented with cost-effectiveness studies in the 1970s. These compared different treatments to show which was the most efficient way to achieve a given outcome. Finally, in the 1980s the principle of measuring patients' quality of life before and after treatment has started to provide a measure of the human benefits achieved by medicines in quantitative terms.

However, none of these new developments have been introduced without discussion and resistance. Even such an historically obvious improvement as the controlled clinical trial was questioned when it was first developed. A classic paper in the *Lancet* in 1963 was entitled 'The feet of clay of the double-blind trial'.[1] It argued in favour of relying on clinical impressions rather than 'scientific' evaluation for many new medicines. Thus, it is necessary at every stage to demonstrate the benefits and the validity of new methods of evaluation. It is then necessary to 'sell' those benefits to everyone concerned with the use of medicines. More sophisticated methods of demonstrating the benefits of medicines are not automatically accepted when they are first introduced. In addition, more importantly, they usually go through a stage of refinement before they can be generally regarded as valid measures of benefit. Just as clinical trials needed to be developed and refined in the 1960s, so economic evaluation – and measures of the quality of life in particular – still need to be developed and refined in the 1980s.

Returning to the 1960s and 1970s, it soon became clear that cost-benefit analysis for new medicines was an important tool to help to put into perspective the steadily rising cost of health care in general, and of medicines in particular. It was possible to show, for example, that in Britain the use of the anti-tubercular medicines produced economic savings which equalled half the total cost of *all* medicines prescribed under the National Health Service.[2] Cost-benefit analysis is still valuable in showing how medicines often actually produce financial savings, and this paper has quoted examples. The approach must in the future be more widely applied in cases where it can show these savings in terms of money.

Similarly, cost-effectiveness analysis is now accepted as a valid management tool, and needs to be more widely introduced into the organization of health services. Like cost-benefit analysis, it can often show that a particular medicine is economically efficient. More generally, it can often demonstrate the cost-effectiveness of medicines as against surgery or prolonged bed-rest.

Turning to the newer techniques in connection with the measurement of the quality of life, they are already an essential tool, in trying to produce an objective balance between the benefits and risks of medicines. Up to the present, far too much public emphasis has been placed on the risks of medicines. These risks could often have been fully justified if quantitative evidence had been available on the benefits in terms of a better quality of life for the majority of patients. An obvious example is benoxaprofen. This was withdrawn from the market because of its risks. Immediately, a flood of anecdotal evidence appeared to indicate that many patients were prepared to accept even the risk of death because of the uniquely effective relief from pain which they obtained from that particular medicine. But without quantitative evidence of the extent of these benefits the risks alone were taken into account in deciding to bar the medicine.

In this connection, the 'Teeling Smith Risk Benefit Matrix' is relevant (Figure 6.1). On its two axes it shows the range of risk (vertically) and of benefit (horizontally). Any safe medicine is acceptable, but clearly a dangerous medicine with trivial benefits is unacceptable.

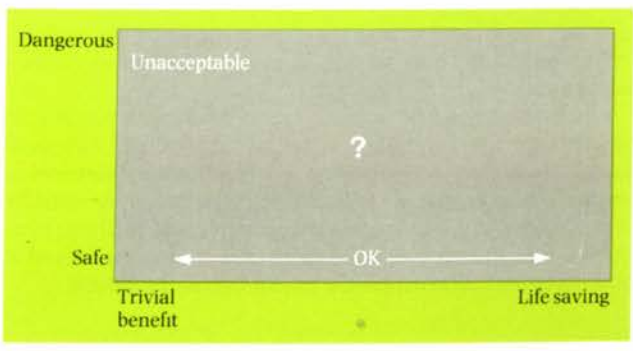
However, the important point about this matrix is that medicines do not have a fixed point on it. Chloramphenicol, for example, is in the top right-hand corner when used to treat typhoid. However, if it is used for a minor sore throat it shifts across to the top left-hand corner, and becomes unacceptable. Thus medicines in the future need to be evaluated in terms of their risk-benefit ratio according to the condition which they are used to treat. This is an urgent priority for many new medicines now.

The use of measurement of quality of life to justify the economic cost of a new medicine is still more in an early stage of development. Some economists have implied that the quality adjusted life year should already be taken into account in decisions about the allocation of scarce medical resources.[3] Certainly, individual studies of the effect of medicines on the quality of life have already proved valuable in arguing in favour of their use.[4, 5] There is no doubt that, more and more, pharmaceutical manufacturers are starting to employ health economists who will not only be concerned with traditional cost-benefit and cost-effectiveness analyses, but also with measurements of the effect of their company's medicines on the quality of patients' lives. The measurement of changes in quality of life is particularly important in evaluating the impact of the second, third or fourth medicine in a given category. Whereas it is often possible to demonstrate major net benefits for the first such medicine, its successors have to demonstrate further improvements in efficiency. These may be either through a lower price, or through a more favourable impact on quality of life.

6.2 FUTURE NEEDS AND TRENDS

Measurements of quality of life are still at a development stage. The Rosser index, for example, gave different values for the same state of health from the 'time-trade off' method in studies at Brunel University.[6] There is, at present, no 'gold

Figure 6.1 **'The Teeling Smith risk benefit matrix'**



standard' for the valuations put on different states of health. However, this must not prevent further work being done in this field. Nor does it prevent individual firms from arguing that their own medicines provide a better quality of life for patients than other treatments. However, at the present stage in development, it would be wrong for anyone to demand an economic evaluation for a new medicine, in the same way that controlled clinical trial evidence is demanded. The two approaches to evaluation are at different stages of development.

The sorts of problem which still exist not only concern different 'scores' for the quality of life using different methods of measurement. There are also at present problems about how the *length* of a patient's survival should be combined (or set against) the *quality* of their life during the period of survival. In other words, is the concept of the quality adjusted life year, which combines length of life and quality of life into a single measurement, a correct approach? These matters still need to be debated.

Even more controversially, is a year of life for a ten year old child of greater or lesser value than a year of life for a seventy year old? For which is it more 'valuable' to improve their quality of life? These are ethical as well as economic questions. Furthermore, should future years of life be discounted to present values, or is every year to be given the same value? This, too, is a matter of debate. However, the examples discussed in this booklet show that considerable methodological developments have been made in recent years. We expect further developments to take place in the future.

The fact that there are still both economic and ethical issues to be debated and researched in relation to the measurement of quality of life must not be allowed to justify a negative attitude to the subject. There is little doubt that by the year 2000 the evaluation of the effect of medicines on the quality of life will often be as routine as the use of controlled clinical trials in the 1980s. At that stage, it is possible that economic measures will be taken into account not only in relation to the reimbursement of medicines under health insurance schemes, but may also sometimes be considered in deciding whether a medicine should be allowed onto the market.

However, the major use of economic analysis is likely to be made by decision makers within the health care system. Hospital managers and pharmacists may wish to review the evidence on the cost and effectiveness of medicines in order to decide which should be included in their hospital formulary. Clinicians may take a greater interest in the cost as well as the effectiveness of medicines, especially when incentives change in such a way as to encourage more efficient medical practice.

With these possibilities in mind, it is important that progress is made as fast as possible to validate the methods of economic analysis which have been discussed in this booklet. Pharmaceutical companies and clinical researchers that remain ignorant of the techniques which are currently being developed are likely to find themselves at a considerable disadvantage in the future when economic evaluations may be considered alongside clinical evaluations. Indeed, more companies may decide to acquire 'in-house' economics expertise.

The underlying fact is that as more and more is spent on health care there is going to be an increasingly stringent approach in deciding whether any particular treatment is justified in economic (as well as clinical) terms. This must be regarded as a wise and rational approach, and all those concerned with the provision of health care must be prepared to accept more critical economic evaluation in the future.

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GLOSSARY OF TERMS

Average cost
The cost per unit of output (total costs divided by total number of units of output). Also known as unit cost.

Benefit – cost ratio
Total discounted benefits divided by total discounted costs. The outcome should be greater than 1 for an investment to be potentially worthwhile.

Cost
What has to be given up to achieve something. Either:

(a) the value of the benefits which are forgone in order to achieve something (the economic definition); or

(b) the total money expenditure required to achieve something (the accounting definition).

Cost-benefit analysis
A form of economic evaluation where all the costs and consequences are expressed in money terms. In principle, this form of analysis enables one to assess whether a particular objective is worth achieving. However, estimation difficulties often reduce cost-benefit analysis to a consideration of those costs and consequences that are most readily expressed in money terms.

Cost-effectiveness analysis
A form of economic evaluation where the costs are expressed in money terms but where some of the consequences are expressed in physical units (eg, life saving) and assumes the objective is worth achieving. If two programmes have consequences that are identical in all respects, the analysis is cometimes called a cost minimization analysis. If consequences are measured in quality adjusted life-years or 'utilities', the analysis is sometimes called cost-utility analysis.

Cost-utility analysis
A form of economic evaluation where the costs are expressed in money terms but where some of the consequences are expressed in utility units (eg, quality-adjusted life-years or healthy days of life).

Discounting
The treatment of time in the valuation of costs and benefits, requiring a choice of discount rate and time frame. This process estimates what something is worth today, given that it cannot be obtained or used until some time in the future (ie, its 'present value').

Discount rate
The annual rate at which the value of a future cost or consequence is reduced to find its present value. The discount rate expresses society's time preference rate. For example, at a discount rate of r, an event occurring in n years' time has a present value of $(1 + r)^{-n}$.

Economic evaluation
A process whereby the costs of programmes, alternatives or options are compared with their consequences, in terms of improved health or savings in resources. Also known as the cost-benefit approach or economic appraisal. It embodies a family of techniques including cost-effectiveness analysis, cost-benefit analysis and cost-utility analysis.

Efficiency
Relates to output per unit cost of the resources employed. Resources are being used efficiently if a given output is produced at minimum cost, or maximum output is produced at a given cost ('operational' efficiency). Economists also use the term in the wider sense of cost-benefit analysis ('allocative' efficiency).

Indirect costs
The productivity losses associated with illness, or the work-time taken up in medical treatment. Typically, these are valued by using earnings as a proxy.

Marginal cost
The change in total cost at a given scale of output when a little more or a little less output is produced. This concept of 'marginality' can also apply to benefit, value, income, production, etc.

Marginal product
The change in total production at a given scale of output resulting from an additional unit of input (eg, labour).

Opportunity cost
The benefits to be derived from using resources in their best alternative use. It is therefore a measure of the sacrifice made by using resources in a given programme. When economists use the term 'cost' they mean opportunity cost. This may not be the same as health care expenditures.

Present value
The value now of future costs or benefits discounted at a given rate.

Quality adjusted life year
A measure which reflects both the quality and quantity of life gained from health programmes. It is usually derived by making assessments of the relative value or 'utility' of defined states of health. These assessments can be made by professionals, patients or the general public and are obtained by interviews with individuals or through consensus-forming exercises.

Sensitivity analysis
A technique designed to allow for uncertainty by testing whether plausible changes in the values of the main variables would affect the conclusions of an analysis.

Source Mills A and Drummond M F (1985) *World Health Statistics Quarterly*; 38(4): 432–434.

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