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Economic Evaluation of Cancer Treatment Strategies

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Economic constraints are a reality in the European healthcare environment. Because it is impossible to adopt all potentially effective treatments without destabilising national welfare systems, the costs of different treatments have been considered when making decisions in hospitals and healthcare administrations. However, this has often been done implicitly, intuitively, or with suboptimal information. Today, economic evaluations are attracting increasing attention. Their aim is to consider the overall picture of costs and effectiveness associated with different treatments. The essential parts of an economic evaluation are an estimate of the additional costs incurred by one treatment over another and the formal comparison of these additional costs with the corresponding gain in effectiveness. Information on effectiveness should preferably come from large, prospective, randomised trials with sufficient external validity. Cost information is usually retrieved from various secondary data sources. A cost equals the amount of a resource used, multiplied by its unit price. Ideally, key data on resource use should be collected from the clinical trials providing effectiveness data. This approach requires close collaboration among clinicians, statisticians, and health economists in all phases of the trial process, including the design of the protocol. When economic evaluations result from a multidisciplinary approach and are systematically integrated into the whole clinical research process for all important new treatments, they become a powerful tool. They may assist decision makers on all levels to allocate scarce healthcare resources in a rational and optimal way, thereby allowing optimal gains in life expectancy and quality of life within budgetary limits. © **1997 Published by Elsevier Science Ltd.**

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INTRODUCTION

'CLASSIC' STUDY designs in cancer research are concerned with the assessment of outcomes. They focus on the clinical outcomes of efficacy or effectiveness and, increasingly, on quality-of-life outcomes. Information about these outcomes is aimed at helping clinicians and other decision makers at various levels of health policy administration to adopt the most appropriate treatment strategies for specific patient groups.

However, economic constraints are a reality in today's European healthcare environment. At any one time, it has become impossible to adopt, on a large scale, all potentially effective treatment options without seriously destabilising national welfare systems. In practice, this fact has been recognised and the costs associated with different treatments have been taken into account in daily decision making in hospitals and in healthcare administrations. However, this has often been done implicitly, intuitively, or on the basis of suboptimal information.

Economic evaluations are an explicit, formal way to simultaneously assess both the effectiveness and the costs of treatments. Given that the aim of healthcare is to maximise the total health of a population within a democratically decided budget, economic evaluations deliver crucial information to achieve this goal. It can be shown that allocating limited healthcare budgets on the basis of the sound and formal consideration of both costs and the effectiveness of treatments leads to more gains in health, measured in terms of life expectancy or quality of life, than allocating budgets on the basis of any other considerations, such as effectiveness data only.

PRINCIPLES OF ECONOMIC EVALUATIONS

In contrast with traditional clinical research which deals with efficacy or effectiveness, economic evaluations deal with efficiency (Table 1). Efficiency is the relationship between costs and outcomes and can be expressed as the ratio of incremental cost over incremental effectiveness. The incremental cost associated with a new treatment is the difference in cost between the new treatment and the standard treatment to which it has been compared.

The incremental effectiveness is the difference in effectiveness between the new and the standard treatment. If life

Table 1. Some basic concepts in health economics

Concept	Relevant questions
Efficacy	Does the treatment have the potential to work?
Effectiveness	Does the treatment also work in a less controlled environment? Will patients comply with the treatment?
Efficiency	Is the treatment worthwhile compared with other things that could be done with the same amount of money? Could we invest the money in other treatments that would be more beneficial?

expectancy is the main outcome measure, then incremental effectiveness is ideally expressed as the area between two survival curves. The ratio of incremental cost over incremental effectiveness, the incremental cost-effectiveness ratio, expresses the cost per unit of effectiveness gained by the adoption of a new treatment compared with an existing standard treatment (e.g. the cost per extra life-year gained). In the process of allocating healthcare budgets, treatments with a favourable incremental cost-effectiveness ratio should be preferred over treatments with a less favourable incremental cost-effectiveness ratio.

Economic evaluations that express their results in terms of an incremental cost-effectiveness ratio are called cost-effectiveness studies. They are the most widely applied type of economic evaluation in healthcare.

A hypothetical example of a cost-effectiveness study

The example given in Table 2 illustrates the main principle of cost-effectiveness studies. The first row shows the costs, while the second row shows the effectiveness of five possible cancer screening strategies. The first strategy contains only one test. The other strategies contain the same test, but performed up to five times. When more tests are performed, the total cost increases and the effectiveness, in terms of detected cancers, improves.

If the average cost per detected cancer is calculated for each strategy (third row), it can be seen that this increases with the number of tests performed, but not spectacularly. Many specialists would be inclined to recommend that all five tests be performed. This approach leads to the optimal outcome for an average cost, which does not seem exceptional. However, the average cost per detected cancer is not the relevant piece of information for a recommendation about allocation of scarce resources.

The fourth row of Table 2 shows the incremental cost for each screening strategy; that is, the additional cost of each strategy compared with the next best strategy. Similarly, the incremental effectiveness is shown in the fifth row. What one should ultimately look at when making a recommendation about which strategy to adopt is the incremental cost per detected cancer, shown in the last row. It can then be seen that adopting, for example, four tests instead of three tests will induce an extra cost of 600 000 to detect three more cancers, with a ratio of 200 000 per extra detected cancer. Deciding to adopt the five-test strategy would give an incremental cost-effectiveness ratio of 400 000 per extra detected cancer. The difference between the average cost per detected cancer with the two last strategies and the incremental cost per detected cancer is dramatic. Nevertheless, many decisions are based on an 'average cost per effectiveness' basis. The only valid criterion is the incremental cost-effectiveness ratio.

Whether 400 000 for one extra detected cancer is 'much' and whether society should pay for it is a different question, which is not the responsibility of the economic evaluator alone to answer. Given that the objective of the economic evaluation is to optimise healthcare outcomes within limited budgets, the relevant question is whether the 400 000 can lead to more potential benefit when spent on an alternative healthcare intervention, instead of on the fifth screening test. If the answer is yes, then any rational decision maker would transfer the 400 000 to the other, more beneficial action.

Of course, in order to compare the cost-effectiveness of competing treatments, a common denominator is needed. In the above example, the outcome measure, the number of detected cancers, has to be translated into life expectancy gained. One can then compare the incremental cost per life-year gained of the various screening strategies with the incremental cost per life-year gained by adopting new treatments in lung cancer, prostate cancer, or another type of cancer, or even by adopting new treatments in diseases outside the cancer field.

CONSIDERATION OF ALL OUTCOMES AND COSTS

The number of life-years gained is indeed the most commonly used denominator in cost-effectiveness studies, since it allows broad comparisons between treatments, even for different diseases. However, this measure denies the impact on quality of life that makes many treatments, especially in cancer, very valuable. Impact on quality of life can be taken into account in the denominator of a cost-effectiveness study by applying utility weights to the time periods patients spend

Table 2. Five alternative strategies for screening for cancer X

Variable	1 Test	2 Tests	3 Tests	4 Tests	5 Tests
Screening costs for entire population	1 000 000	1 800 000	2 400 000	3 000 000	3 400 000
Number of detected cancers	50	80	95	98	99
Average cost per detected cancer	20 000	22 500	25 263	30 612	34 343
Additional costs for entire population	1 000 000	800 000	600 000	600 000	400 000
Extra number of detected cancers	50	30	15	3	1
Additional cost per extra detected cancer	20 000	27 000	40 000	200 000	400 000

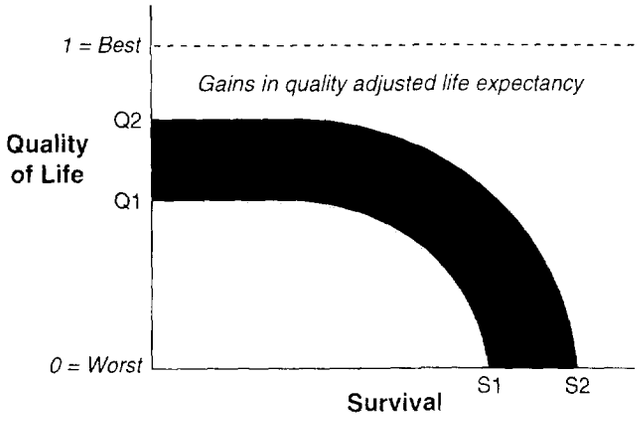

Figure 1. Illustration of the concept of combining quality of life and length of life into one outcome measure. The increase in survival obtained by treatment is shown on the *x*-axis, while the improvement in quality of life is shown on the *y*-axis. The shaded area gives the total gain in 'quality-adjusted survival'.

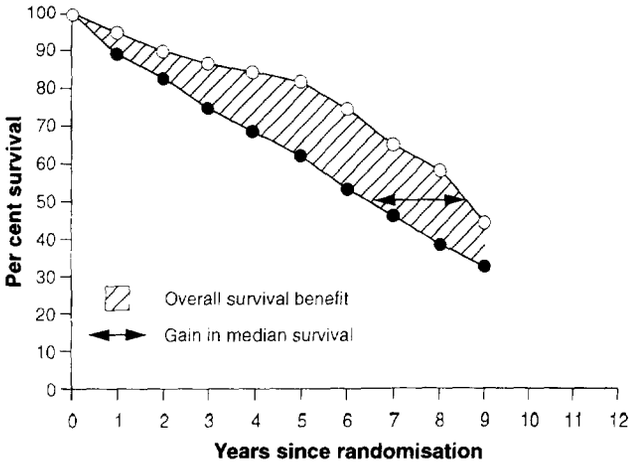

Figure 2. Survival benefit in an economic evaluation. The area between two survival curves is the effectiveness measure of interest for the economic evaluation.

in different health states. These utility weights are numbers between 0 and 1 that represent the preference of patients, or alternatively, of random individuals representing society, for the various health states, compared with worst and best health. A number of methods exist for eliciting these preferences either from patients or the general population [1, 2].

Figure 1 illustrates the concept of combining quality of life and length of life into one outcome measure. The increase in survival obtained by treatment is shown on the *x*-axis, while the improvement in quality of life is shown on the *y*-axis. The shaded area gives the total gain in 'quality adjusted survival'. When economic evaluations adjust life expectancy for the quality of life in the denominator of the incremental cost-effectiveness ratio, they are often called cost-utility studies.

At the cost side of the economic evaluation, one can expand the scope towards expenditures other than direct medical costs, depending on the perspective of the study and the particular research question. If one takes, for example, a societal perspective, information on lost productivity (i.e. indirect costs) might sometimes be relevant. Other costs that might be relevant would include the various types of paid and unpaid costs incurred by patients, caregivers, and relatives, such as travel to and from the hospital and voluntary care.

Apart from deciding which costs to include in the cost estimations, one should, especially in cancer therapy, look beyond the pure acquisition prices of the compared treatments and consider cost differences that might occur as a result of side-effects and cost differences that might occur during the follow-up time after the initial treatment. For example, supportive care that permits optimal chemotherapy might add to the short-term hospital bill, but might also postpone or even reduce future costs due to treatment failures.

INFORMATION REQUIRED FOR AN ECONOMIC EVALUATION AND THE ROLE OF CLINICAL TRIALS

Clearly, reliable information is needed on both effectiveness and costs. Cancer clinical trials usually have life expectancy as their primary endpoint. The area between two survival curves is, therefore, the effectiveness measure of interest for the economic evaluation (Figure 2). Ideally, in order to enhance comparison between different economic evaluations, life expectancy should be adjusted for quality of life. However, this requires estimates of the relative utility of the various health states that may occur during the course of the disease and that can be affected by the compared treatments. Instruments for utility estimation are not routinely included in clinical trials, but their inclusion is recommended for trials with an important economic component, comparing treatments for which overall quality of life is expected to be substantially different, or for which overall quality of life is an important endpoint.

Effectiveness data are readily available from cancer clinical trials, but this is seldom the case for cost data. Retrieving cost data prospectively through the clinical trial process greatly improves the reliability of the economic evaluation, but has to be balanced against the additional workload caused by the collection of more extensive data. However, most economic evaluations will benefit substantially if only a few key economic variables are integrated in the Case Report Forms. Such integration of economic parameters in clinical trials has recently been advocated in an Advisory Report of the European School of Oncology to the European Commission [3].

Within the European Organization for Research and Treatment of Cancer, economic parameters, ranging from a few simple questions to the inclusion of specific modules, have been incorporated in 11 clinical trials as of October 1996. These trials deal with divergent subjects such as the comparison of various induction chemotherapy schedules and inpatient versus outpatient consolidation therapy in the treatment of acute myeloid leukaemia; the use of prophylactic antibiotics and haematopoietic growth factors with intensified chemotherapy in lung cancer; the use of postoperative interferon in high-risk melanoma; larynx preservation in head and neck cancers; short-term versus long-term androgen blockade in locally advanced prostate cancer; the comparison of various 5-fluorouracil/folinic acid schedules in advanced colorectal cancer; and the use of paclitaxel in advanced epithelial ovarian cancer. The common rationale for prospective integration of economic parameters in all these studies was the perceived or expected 'economic' difficulties for turning the experimental treatments into daily practice, given that their superiority could be proven. Reliable data on the economic consequences of the treatment strategies compared in each

Table 3. Considerations when integrating economics in clinical trials

A multidisciplinary approach is necessary.
An economic chapter should be included in the protocol.
Key resource utilisation should be counted through the Case Report Forms.
Costing (finding unit prices of resources) should be done separately, taking into account the perspective of the study.

trial were considered essential for assessing their 'value for money'.

The idea that pharmaco-economic claims should be based on sound clinical trials has also been expressed by the United States Food and Drug Administration (FDA)[4]. The draft guidelines that were issued by the FDA in 1995 state that comparative pharmaco-economic claims must be substantiated by adequate and well-controlled studies, and that these studies should have both internal validity, which can be found only in randomised clinical trials, and external validity, meaning that the approach should be relevant to current norms of clinical practice. The guidelines explicitly discourage secondary data analysis, or 'data dredging', which now serves as the basis for most economic evaluations. Basic principles for integrating economics into clinical trials are summarised in Table 3.

When it is decided to collect economic data prospectively, it is important to distinguish clearly between resource utilisation data and data regarding unit prices of these resources. Only data on the amounts of resource utilisation, such as the number of hospital days for various causes or the number of blood transfusions, should be collected prospectively. These resource utilisation amounts can, at the time of the analysis, be multiplied by specific sets of unit prices (e.g. the price of one hospital day or the price of one blood transfusion) to obtain total costs from a specific perspective, such as that of a particular country or a specific health insurance organization.

ANALYSIS TOOLS

Theoretically, by using the appropriate instruments, it is possible to collect all relevant information on resource utilisation through the clinical trial. Multiplying the amounts of resource utilisation by their relevant prices and then summing all the obtained products provides an estimate of total costs in the compared treatment arms. These total costs can then be compared directly with the effectiveness in both arms through the incremental cost-effectiveness ratios. Methods for estimating confidence intervals around these cost-effectiveness ratios have recently been proposed and discussed in the literature [5].

In practice, however, one will rarely be able to collect all cost information within a clinical trial. Moreover, some substantial costs will only occur with a low probability (e.g. costs related to rare but severe side-effects). Inclusion of these costs would render the overall cost estimates highly subject to random error. Finally, unit prices can hardly be considered as fixed and yet differ according to the perspective of the study.

Uncertainty about essential data is very often inherent in an economic evaluation. Therefore, a modelling approach is usually the most appropriate way to analyse the data, whether or not the data have been collected prospectively. The modelling approach consists of the combination of probabilities of clinical events (e.g. by means of a decision tree) affected by the compared treatments, with costs and outcomes associated with each of these events.

Even if an economic evaluation is not integrated prospectively, cancer clinical trials can deliver good information on the probabilities of the occurrence of certain events that can be included in such a model (e.g. incidences of side-effects, cure and relapse). The challenge is to obtain good estimates of the outcomes and costs associated with the various clinical events. Ideally, these estimates should come from the same clinical trial as the one that delivers the clinical information. Alternatively, they can be collected from different sources, such as a literature search, expert interviews, or retrospective examination of patient files. Finally, given the uncertainty surrounding each economic evaluation, it is crucial to perform univariate and multivariate sensitivity analyses on all the important parameters in the evaluation, on the basis of reasonable lower boundary and higher boundary estimations (e.g. 95% confidence interval limits, or lowest and highest estimates by experts).

CONCLUSION

Economic evaluations are a powerful tool for assessing the efficiency of competing treatments and providing insight to their relative 'value for money'. By adopting and prioritising the treatments with the best 'value for money', that is, with the most favourable cost-effectiveness ratio, one maximises the health outcomes that can be obtained within a limited budget [6]. In practice, economic evaluations are, above all, a multidisciplinary effort requiring input from clinicians, economists, statisticians and other professionals. A good understanding of the clinical background of the treatment alternatives evaluated is crucial, as is a rigorous application of economic and statistical techniques. To ensure that economic evaluations are reliable and comparable, a number of scientific principles should be adhered to. Although there is considerable disagreement among health economists with respect to specific concepts and methods, several publications are now available to offer guidance on these principles to those who wish to carry out or assess economic evaluations [3, 7–14]. In summary, the inclusion of economic evaluations in prospective clinical studies is a major challenge today, but an important step towards more efficient healthcare tomorrow.

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