Eur J Cancer, Vol. 29A, Suppl. 7, pp. S10–S14, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Economic Evaluation Alongside Cancer Trials: Methodological and Practical Aspects

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A recent extension of clinical evaluation is "economic evaluation", which seeks to characterise each relevant alternative health care strategy in terms of a summary measure incorporating the costs and benefits of such strategies. In an economic evaluation, separate measurements of resource volumina and resource prices on the cost side, and separate measurements of survival and quality of life effects and valuation of these outcome effects on the benefit side are required. From these effect parameters, which should be calculated for all competing strategies considered in the analysis, the relative cost-effectiveness of one strategy as against the other can be derived. The degree of generalisability of the study results determines the validity of economic evaluation in decision-making. This depends on the generalisability of the clinical findings, and in this respect the so-called "piggyback" economic evaluation, which is added to a clinical trial, has its limitations. In the field of cancer, specific attention should be given to costs and effects occurring after non-mortality endpoints, to patient and family costs and to variations in treatments between settings of care. It is argued that conventional clinical trials and economic evaluations will integrate further in the future.
Eur J Cancer, Vol. 29A, Suppl. 7, pp. S10–S14, 1993.

INTRODUCTION

CANCER NOT only accounts for a major burden of mortality and morbidity (about one third of all mortality in the Netherlands, for example), its economic impact is also considerable [1–3]. During the last few decades, fundamental and clinical research have provided a better understanding of cancer, and as a result improved prognosis (survival, quality of life) of patients can be observed. These results have been achieved through the development of refined diagnostics, new surgical techniques and new drugs, but also through rigorously carrying out clinical experiments and thoroughly analysing their results. One of the methodological innovations has been the introduction of quality of life outcome measures in clinical evaluation research, in addition to the use of standard fixed year survival rates. Moreover, the apparent trade-off between survival prolongation and quality of life improvement has urged the development of combined mortality–morbidity measures [4]. Economic evaluation is an even more recent development which broadens the scope of evaluation [5,6]. It has been induced by increased awareness of limited health care resources, and the consequent need for economically and medically sound choices. Particularly in the case of cancer, the economic issue is relevant [3,7,8] as the costs per case are usually high, and expected benefits are still small for large groups of patients [9]. This article describes some theoretical aspects of economic evaluation and some practical issues of economic evaluation are combined with a clinical trial [10]. Its application in oncology is illustrated.

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ECONOMIC EVALUATION — THEORY

Theoretical foundation

If costs have to be taken into account in clinical decision-making, the problem arises of how to incorporate this argument. Apparently, additional data and new definitions of the optimal choice are needed. To understand the pecularities of economic evaluation as more than merely an additional technique in epidemiology requires some notion of its theoretical background. From an economic point of view, health care resource allocation is rather inefficient. Policies directed to more efficiency appear to be necessary, and have to be guided by systematically collected and integrated information on the costs and benefits of health care. The traditional economic instrument for evaluating alternative public sector initiatives in this way is cost–benefit analysis (CBA), which is founded in Paretian welfare economics. This theory defines a situation as "efficient" if no potential Pareto improvement is possible, the latter implying that at least one person can be made better off and no one worse off if the losers are compensated from the beneficiaries' gains [11]. In this definition, the individual's own utility or willingness to pay is decisive, which poses some restrictions on the use of CBA when other values are deemed important, as is the case in health care[12]. Thus, a broader framework is needed in health care with the same goal in mind: the determination of a unique preferential ordering of (health care) programmes [13]. This broader framework again starts from quantification of all costs and benefits but the measurement of benefits is adapted. Instead of monetary units, such as the willingness to pay, non-monetary units may be used. In standard cost-effectiveness analysis (CEA), the benefits are expressed in one appropriate natural unit as, for instance, life-years saved. "CEA" is often used to describe this whole cluster of economic evaluation approaches. More recently, cost–utility analysis (CUA) has emerged, which applies so-called utility values which aggregate different dimensions of benefits. Note that the latter approach is particularly relevant in the case of oncology, where we often meet different arrays of effects

under different therapeutic options. Benefits measurement in economic evaluation in trying to cover all relevant outcome aspects is not new, but it specifically aims at summary values which can bear the claim that they represent overall societal preference values.

Choice of perspective

The preferred choice of perspective in CEA (as in CBA) is that of "society", as opposed to, for example, "patient" or "insurance company". This perspective implies that all costs and benefits for all parties in society should be accounted for. Some of the less obvious consequences of this perspective are listed below. First, patient costs (both out-of pocket expenses and time-investments) should be incuded. This theoretical point is relevant in patients with cancer as they, for example, frequently apply dietary measures and spend much time in diagnosis and treatment. For similar reasons, the care by close relatives or friends is not zero-priced, but appropriately valued. In oncology, we frequently observed the erroneous assumption that non-professional care of terminally ill patients by volunteers and close relatives is a preferable option because it is zero-priced. Second, the lost production due to illness or treatment is also a cost to society, and the associated indirect costs should be included in the analysis (for a description of techniques see [14]). Indirect costs in cancer are usually substantial. Third, accepting society's perspective implies that the real use of resources should be measured and valued rather than the charges paid by patients or third parties, as the latter may bear little resemblance to actual costs. This is, for example, relevant in the assignment of costs to days of hospitalisation, laboratory tests and medical services. An example in oncology of a more remote consequence is that economic evaluation uses the expected market price of a new chemotherapeutic drug, even if it may be temporarily zero-priced for research purposes.

Choice of approach

There are several pathways which arrive at the numerical values of the indicators for cost-effectiveness. In this paper, we will concentrate on the so-called "piggyback" design, particularly in oncological research. "Piggyback" indicates that the economic evaluation is added on to an established clinical trial as a prospective or retrospective supplement [10]. If the clinical trial provides insufficient data or a prospective experimental design is not feasible, some secondary options are usually feasible, particularly the synthesis of the major findings from literature within a mathematical model [15].

Below we discuss the "piggy back" approach and potential frictions arising from the reconciliation of the study requirements for clinical and economic evaluations. These frictions disclose the different perspectives of clinical versus economic evaluations: the clinical investigator generally seeks to demonstrate effectiveness in a well-defined patient group on the basis of a sensitive (clinical) outcome indicator, while the economist primarily wants to support a policy decision on an intervention or program by assessing its general cost-effectiveness in routine medical practice, comparing the best alternatives available.

ECONOMIC EVALUATION AS AN ADD-ON TO A CONTROLLED CLINICAL TRIAL

Controlled clinical trials (CCT) are increasingly considered as natural vehicles for economic evaluations [10]. The added costs of an economic evaluation are obviously relatively low, and the importance of economic evidence at an early phase of the health policy process is acknowledged by all health care parties involved [16]. With the resulting closer integration of economists within the clinical trial setting, the following issues have emerged.

Mode of comparison

As in a clinical trial, a randomised controlled comparison is preferred in an economic evaluation. However, in some cases the formation of a control group may be difficult for ethical or organisational reasons. For example, the course of disease under conventional treatment may be invariably lethal, making patients reluctant to participate on a randomised basis if a new potentially live-saving therapy is offered (e.g. an immune thereapy versus placebo trial in melanoma). In the absence of a control group, prognostic modelling of control group survival may be an option [17], but economic evaluation invariably requires a parallel prognostic model for information on the costs in the control situation. In selected cases, another option for obtaining control group estimations may be the extrapolation of waiting list data on survival, quality of life and costs [18].

Choice of alternatives

The choice of alternatives within a CCT determines the suitability of the trial for add-on economic evaluation. If the CCT does not include the usual or the best alternative treatment as a control, an economic evaluation is impossible. Placebo control, often essential in determining efficacy, is only suitable in economic evaluation if the no-treatment option reflects the best alternative action. However, in other cases, economic evaluation would sometimes require the placebo or no-treatment option in a CCT where it is not included. An example of the latter case might be an add-on economic evaluation comparing filgrastim versus placebo in the treatment of febrile neutropenic episodes. The economically relevant question is not only whether filgrastim decreases length of hospital stay given a set of criteria for discharge, i.e. if filgrastim increases efficiency within this context, but also what is the (cancer-specific) cost-effectiveness of the overall treatment protocol to which filgrastim is added. The same question will often apply to trials on salvage therapy.

Economic evaluation prefers the inclusion of preventive alternatives when considering diseases with a strong risk factor component (e.g. smoking in cancer of the lung, oesophagus and bladder). What seems efficient from a narrow perspective, may have an unfavourable cost-effectiveness from a broader view.

Choice of endpoints and follow-up times

This issue pertains both to the principal question of which outcome measure is at stake, and to the practical question of which endpoint results in a feasible sample size, given a reasonable time-frame and the usual values for precision and power. Theoretically, the primary outcome measures in economic evaluations are cumulative life-years gained and differential costs. The usual primary endpoints in cancer trials are fixed-time (e.g. 1 year or 5 years) survival rates and disease-free survival rates. From a clinical viewpoint, the choice of the analytical follow-up time (for example, 1 year or 5 years) may be difficult if the intervention has life-long influence on survival (e.g. breast cancer) or if the impact of alternatives on survival differs over time. Statistical methodology exists to deal with incomplete empirical follow-up (censoring of observations), enabling comparisons of survival rates. In economic evaluation, life-long follow-up is also preferred. Except for rare cases with either complete recovery or death within the empirical follow-up time,

life-long consequences cannot be observed. What happens after censoring should be explicitly estimated, which requires advanced statistical analysis. Usually mathematical modelling is applied, based on comprehensive data of patients at the time of censoring [17,18]. Systematic studies on patients with recurrent or terminal disease are rare, and cancer is no exception. Consequently, valid life-long estimates may be difficult to obtain.

Related to the endpoint definition and the empirical follow-up is the determination of the sample size. From a conceptual point of view, economic evaluation requires a separate sample size determination, based on distributions of costs and benefits in any of the alternatives distinguished. In practice, lack of reference values for costs and quality of life data may restrict sample size considerations to the clinical part of the trial. However, in economic evaluation, statistical significance of differences and the absolute magnitude of differences are equally important [19].

Determination of outcome

In economic evaluation, the determination of length of survival is straightforward, except for the modelling of incomplete observations. The measurement of health status/quality of life changes is more complex. Measurement instruments can be divided into two main categories: the generic instruments and illness-specific questionnaires. Generic instruments are developed to monitor changes in all health dimensions and allow comparison of outcomes across different disease categories. The Nottingham Health Profile, the RAND-MOS 20 and the related Short-Form 36 questionnaire seem to be suitable instruments. Illness-specific instruments measure health problems specific for an illness. These instruments are more sensitive for specific problems concerning a particular disease. Cancer-specific instruments often used are the Rotterdam Symptom Checklist, the EORTC Core Quality of Life Questionnaire, and the Cancer Rehabilitation Evaluation System–Short Form. So far, clinical and economic evaluations coincide.

As explained earlier, economic evaluation also tries to arrive at a summary value of the patient benefits. The following procedure applies. First, so-called utility values (a figure between 0 and 1 to indicate the preference value of a certain health state) have to be attached to outcomes. There are three dominant methods of acquiring utility values: direct rating, standard gamble (more convenient in surgical interventions) and time trade-off (more convenient in medical interventions). Utility values may be elicited from the general public (preferable within the societal perspective) and the patients themselves. Torrance provides an extensive description of these utility techniques [20]. If utility values for each characteristic health state have been acquired, the construction of quality-adjusted life-years (QALYs) becomes feasible, allowing the improvement in outcome to be expressed in terms of QALYs gained and, consequently, the construction of a cost–utility ratio.

Determination of costs

The first step is tabulation of resources in appropriate natural units [5], with an emphasis on the counting of variable cost items. *A priori* estimation of the relative importance of these cost items should guide the data collection [21]. Sometimes, costs per diagnosis-related group (DRG) may be readily available [22]. Case registry forms, as normally used in CCTs, provide insufficient information as tabulation of major cost items is usually incomplete. Contrary to these forms, hospital administration data are usually complete, but they contain only a few cost items which can be related to patients. As a result, enumeration of hospital cost volumina is performed using a mixture of appended case registry forms, patient questionnaires, hospital data, and occasionally, on-site observations. Additonally, hospital administrative data provide information on fixed costs (over-heads) and patient questionnaires are useful for obtaining information on direct patient's costs, indirect costs and costs related to outpatient care.

Next, prices are attached to these natural units. Frequently, prices differ substantially from the charges for a particular service (in both directions, see section on Economic Evaluation). In the last step, volumina and prices are multiplied. In addition to the empirical costs determination, economic evaluation includes estimates of future costs (disease-related and disease-unrelated) if follow-up of patients is incomplete. Particularly if the tail of the survival distribution is long — the usual case in cancer — these long-term estimates are of vital importance: average costs (as used in cost-effectiveness ratios) may largely exceed median costs [23].

Ethics

In our view, economic evaluation does not carry with it specific ethical issues regarding data collection. From an ethical point of view, people may judge separately whether or not to participate in an add-on economic evaluation. So far, we have never been confronted with a refusal for the economic part of the CCT, perhaps because most patients and their families face material and immaterial costs, which they are not compensated for, but which they feel are identified by economic evaluation. More frequently, we met with some reluctance from hospital administrators and doctors to cooperate in case a substantial departure of economic cost estimates from current charges and fees was likely to be determined.

Generalisation

From an economic perspective, the generalisability of CCT results is usually rather limited due to a variety of reasons. Clinical research attempts to demonstrate validly the effectiveness of a technology and, consequently, the design (patient selection, treatment allocation, treatment guidelines) is rigorous. Moreover, research patients are more compliant, clinical investigators are more competent, and the hospital setting offers more facilities than its counterparts in general practice. The better a CCT satisfies design criteria, the more easily the study results will be accepted for their reproducibility and scientific soundness. However, these criteria and the selective environment often drive a CCT far from the average clinical practice, and thus the role of CCT in health care decision-making outside the CCT environment may be limited.

For cross-country generalisation, the general level of a national health care system (quality, accessibility) requires attention, particularly in economic evaluation. What may be regarded as routine hospital care for any patient in one country, may be care which is restricted to special cases in another. Cultural differences may account for other patterns of care. For example, in the Netherlands, an important role of the general practitioner and close relatives in terminal care may be observed, whereas in other EC countries emphasis may be more on hospital care.

Two additional factors limit generalisability from the economic perspective. For the same health care services, prices between and even within [24] countries show differences to such an extent that cost-effectiveness ratios are usually incomparable [25]. Besides, the cross-cultural application of values attached to health care benefits requires more investigation.

SPECIFIC ISSUES IN ECONOMIC EVALUATION IN CANCER

Economic evaluation sometimes causes uneasiness in patients and doctors, and occasionally the introduction of economic considerations is even stated to be unethical. This is particularly true for disease groups with specific societal connotations like cancer and AIDS, and for the terminal stages of any disease [9]. We think that in view of the general scarcity of medical resources, all disease groups should be judged alike: a preterm painful death from systemic lupus or sclerosing cholangitis is not preferable to dying from cancer due to its pathophysiological base alone. The reluctance to apply economic evaluation in everyday practice may partially explain the current restriction of economic evaluation to screening programmes (breast cancer, colorectal cancer): less than 10% of the recent Medline literature on costs and cancer refers to non-screening topics.

A recurrent problem in the economic evaluation of cancer treatment is the complete definition of alternatives. As the perspective is life-time, it is important that the treatment protocols include details on long-term treatment. Generally, the highest costs in cancer are incurred after its detection (incidence costs, recurrence costs), and during the terminal phase (mortality costs) [19,26,27]. Thus, in the economic evaluation of primary therapies, significant differences may arise (particularly in quality of life and costs) due to uncontrolled variations in terminal treatment. If data on terminal stages are unavailable, combinations of trial data with "adjuvant" modelling using various "average" data [28] are required. Another problem encountered in cancer trials is the "minimal" change of a protocol during study. The cost impact of these changes is usually underestimated, if estimated at all, and trial data before and after the change may not be safely combined. The same argument applies to uncontrolled inter-centre variations in supportive treatment, particularly with antibiotics.

Three problems of outcome measurement deserve attention. First, the general lack of prognostic models for the more advanced stages of disease. Second, the understandable lack of knowledge on long-term effects of new life-saving approaches (e.g. bone marrow transplantation [29]). Both can only be dealt with through sensitivity analysis. Finally, the observed reluctance to apply comprehensive quality of life measurements because of the presumed burden on patients. If properly informed about the purpose and contents, few patients in our experience withdraw from completing extensive quality of life questionnaires: most of them express gratitude for the opportunity to communicate their feelings, abilities and general rating of life.

A specific issue in cost measurement is the appropriate measurement of costs incurred to the patient (waiting, travelling) and his or her family [26,30]. These are usually measured by way of a patient questionnaire, and in valuation, standardised methods are applied. Another problem to deal with is the fair assignment of costs to the diagnostic and therapeutic nucleus on the one side, and to costs which are induced by the research protocol on the other side. The latter may be considerable [31]. If the CCT is multicentred—the usual case—heterogeneity between hospitals on costs may be disturbing. Volume heterogeneity is generally caused by different policies not dealt with in the protocol (e.g. antibiotic prevention and curation, rehabilitative services). Price heterogeneity may be caused by incomparability of the cost structure of cancer treatment, even within one country. Even if the potential effect of policy heterogeneity on effectiveness is neglected, cost analysis may be cumbersome.

DISCUSSION

We believe that economic evaluation can play a valuable role in decisions on the adoption and utilisation of new technologies [32]. Economic evaluation in the field of medical research may take two forms, either as an add-on study or as a primary economic study. In both cases, specific economic features concern the mode of comparison, the defined alternatives, the primary endpoints (effects and costs), the perspective (society), the time period (life-time) and finally, the generalisability of results. The add-on study is the more familiar approach, and particularly in areas of clinical research with high methodological standards—as in oncology—the pros and cons of add-on economic evaluation disclose much of the underlying philosophies. In some features (comparative mode, to some extent the choice of alternatives, the perspective), the requirements of CCT and economic evaluations are similar. In others (costs, time period), economic evaluations require extension rather than change of a given CCT protocol, though the work load involved may exceed the clinical research part of the CCT. Good clinical practice standards are more established in hospitals than appropriate economic and administrative management, implying a major empirical task of cost measurement.

Apparently, some unresolved discrepancies remain: the width of the scope of alternatives, the role of quality of life and utility measurement, and the attitude towards generalisability. We believe that they will disappear with the further integration of evaluative methods, and also that these changes will be observed in clinical areas, like oncology, with a strong methodological tradition: the gradual change of medical services from a mythic event to a societal commodity is irreversible.

Acknowledgement—Amgen and Roche are gratefully acknowledged for their support during this study

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