EUROPEAN JOURNAL OF CANCER 42 (2006) 2867–2875

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

# Methodological issues in the economic analysis of cancer treatments

*Paul Tappenden*, Jim Chilcott, Sue Ward, Simon Eggington, Daniel Hind, Silvia Hummel*

*School of Health and Related Research (ScHARR), The University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK*

ARTICLE INFO

*Article history:*
Received 7 August 2006
Accepted 7 August 2006
Available online 4 October 2006

*Keywords:*
Costs and cost analysis
Cost-effectiveness analysis
Economics
Neoplasms

ABSTRACT

Cost-effectiveness analysis may be applied to the full range of interventions that make up a cancer service, including screening programmes and early treatments, diagnostic test and referral processes, surgery, radiotherapy, chemotherapy and palliative care. Numerous methodologies have been employed within existing models of cancer interventions. However, not all methodologies are equal; inappropriate modelling approaches may bias cost-effectiveness results. Generic guidelines for good practice in decision-analytic modelling provide a useful basis for critically appraising cost-effectiveness models, yet explicit consideration of a range of cancer-specific issues is required to avoid bias in cost-effectiveness results. These cancer-specific issues include the appropriate representation of relevant costs and health effects associated with unplanned treatments for metastatic disease administered beyond disease progression, the appropriate extrapolation of long-term outcomes and resources from clinical trials, assumptions concerning the nature of the event hazard function beyond the duration of the trial, and relationships between surrogate outcomes and final outcomes.



## 1. Introduction

Cost-effectiveness analysis addresses questions concerning whether health care interventions represent value for money for budget-holders. Typically, such analyses require the estimation of the additional costs, resources and health consequences resulting from the use of a novel intervention compared to management of the disease under usual clinical practice. The use of economic evaluation to inform health care resource allocation decisions is not new.[1] The rationale for the economic evaluation of therapies used to treat cancer is clear, as health care resources are scarce, and humans are increasingly demanding.[2] Questions concerning whether cancer interventions represent value for money require an explicit, coherent and rational approach to the prioritisation of scarce healthcare resources. Cost-effectiveness analysis provides such an approach through explicitly considering the opportunity costs associated with the provision of cancer interventions in terms of the benefits that could have been achieved if the money had been spent on the next best alternative intervention.[3] Cost-effectiveness results are typically interpreted with respect to some previously determined threshold (or range) of acceptability, whereby technologies which have a cost-effectiveness ratio below that threshold may be considered to represent good value for money and may be adopted, whilst technologies which appear less economically attractive would not be purchased.

Economic analysis may be applied to the full range of interventions that make up a cancer service, including cancer screening programmes and early treatments, diagnostic test and referral processes, surgical procedures, radiotherapy, chemotherapy and palliative care. Typically economic evaluations focus on one specific intervention within this broad pathway of care. However it should be noted that the applica-

* *Corresponding author:* Tel.: +44 114 2220855; fax: +44 114 2220785.
E-mail address: p.tappenden@Sheffield.ac.uk (P. Tappenden).
0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2006.08.010

tion of mathematical modelling techniques also allows questions concerning the balance of care and organisation of the broader service to be evaluated.

More often than not, empirical evidence collected within clinical trials and observational studies of competing cancer therapies is insufficient to enable the rigorous assessment of all direct and indirect costs and consequences over the lifetime of patients for whom the intervention is targeted. Consequently, the use of mathematical modelling may be required to help describe the relationship between the novel technology and the clinical condition it is intended to affect, and to predict how the use of that technology will affect medically important outcomes such as overall survival and quality of life.[4] An illustration of the need for modelling to support decision making is the fact that to date, none of the technology appraisals of cancer treatments undertaken by the National Institute for Health and Clinical Excellence (NICE) have relied solely on direct trial-based economic evidence; rather, all of these economic assessments have been augmented with some element of mathematical modelling. Common modelling methodologies include decision analysis, state transition modelling, discrete event simulation (DES), and survival modelling.[5] The potential role of mathematical modelling techniques within cost-effectiveness analysis is broad, ranging from the translation of surrogate to final outcomes, adjusting for prognostic factors within clinical trials and observational studies, extrapolating final outcomes beyond trial durations, generalising from different countries and populations, and informing the design and prioritisation of future research.[4–6]

By their very nature, mathematical models are abstractions or simplifications of reality, based on both explicit and implicit assumptions and value judgements. As such, two models comparing the same technology using similar data sources may generate distinctly different cost-effectiveness results depending on the assumptions used and the modelling methodology employed.[7] The authors' experience in the critical appraisal of cost-effectiveness models of therapies for colorectal, breast and pancreatic cancer highlights considerable variation in the quality and validity of many cost-effectiveness models.[8–13] These problems include the poor scoping of the decision problem to be addressed, inappropriate methods for extrapolating beyond the duration of clinical trials, the omission of relevant costs and health effects, the use of problematic outcome measures, and limitations in approaches employed to explore parametric, methodological and structural uncertainty surrounding the incremental costs and health effects of the novel intervention compared to usual clinical practice. This paper examines these key issues in the modelling of cancer treatments to assist readers to critically appraise and judge the reliability of published economic modelling papers. Current methodological problems are highlighted, and some potentially appropriate modelling approaches are suggested.

## 2. Scoping the decision problem

The objective of health economic modelling is to support or influence decision-making, rather than to purely describe the system under consideration. Consequently, mismatches between the scope of the decision problem and the health economic model severely limit the interpretation of the cost-effectiveness results. This is perhaps the most common weakness encountered in economic modelling, with numerous existing cost-effectiveness models suffering from the inclusion of inappropriate patient populations which do not directly relate to the decision under consideration, the absence of relevant comparators, the use of inappropriate health economic outcomes, and the omission of relevant costs and effects.

In order for cost-effectiveness estimates to be meaningful, it is usual to compare the incremental costs imposed by the new health technology over the current standard treatment against the incremental effects it delivers, typically over the lifetime of the patient.[14] In practice, direct incremental comparisons may be problematic, particularly in instances where trials have evaluated the benefits of a novel therapy against a non-standard comparator, or whereby perceptions of standard current therapy change prior to the completion of the trial. As such, incremental comparisons of the costs and effects of interventions may be reliant on comparisons across clinical trials, and may be prone to numerous potential biases. For example differences in the costs and health effects resulting from the use of two technologies sourced from disparate and discrete clinical trials may not be solely due to the treatment received; differences in observed health outcomes may also be a result of differences between the clinical trials in terms of heterogeneity of the underlying patient populations, unbalanced protocol-driven intensity biases, such as the frequency of clinical follow-up, or other random or non-random differences between underlying health service delivery systems.

This problem may be illustrated by the recent NICE assessment of chemotherapies for advanced colorectal cancer,[9] within which two key trials of alternative sequences of these therapies were identified.[15,16] The French trial reported by Tournigand and colleagues[15] observed a substantially better overall survival rate than the UK-based FOCUS trial,[16] yet a statistically significant improvement between treatment groups was not observed within either study. Consequently, it was unclear whether these survival differences, which led to a clear cost-effectiveness advantage for the trial arms included in the French trial,[15] were due to the more intensive use of the cytotoxic agents under consideration (i.e. the effectiveness of the treatment sequence), differences between UK and French healthcare systems, inherent differences in the patient groups, some other bias, or a combination of all of the above.

It is thus crucial that explicit consideration is given to potential heterogeneities in terms of patient populations specified within the inclusion criteria and observed across clinical trials, inconsistencies in the administration of the current standard treatment, as well as other potential differences between health service delivery systems. It is highly important that such indirect incremental comparisons should be accompanied by caveats; specifically this should include a discussion of potential heterogeneities between trials and whether any decisions or recommendations are crucially reliant on the assumptions made within the model.

The perspective of the analysis (e.g. societal, direct, third-party payer) is also an important consideration during the

scoping phase of the modelling assessment. The appropriateness of the perspective adopted is determined by the requirements of the funding body or commissioner, and by the nature of the decision problem to be addressed. Whilst in the UK it is usual practice to present analyses in terms of those costs and effects directly affecting the NHS and Personal Social Services (PSS), the inclusion of indirect health effects, such as impacts of patient carers, or indirect costs, such as transportation costs incurred by patients may provide additional information if these influence cost-effectiveness results.

## 3. Choice of health outcome(s)

Benefit measures employed within economic evaluations of cancer therapies commonly include overall survival, quality-adjusted survival, progression-free survival, quality-adjusted progression-free survival, tumour response and adverse events avoided. A discussion of the advantages and disadvantages of these benefit measures is presented below; these issues should be borne in mind when interpreting the results of any cost-effectiveness analysis of cancer treatments.

### 3.1. *Overall survival*

Overall survival is an unambiguous measure of clinical benefit which is directly relevant to the economic evaluation of cancer treatments. Within randomised controlled trials (RCTs) overall survival refers to the time from randomisation to the death of the patient, with the median survival duration commonly reported as the primary or secondary endpoint within clinical trials of competing cancer therapies. However, there exist problems associated with the use of overall survival as a measure of clinical benefit. The true survival benefit of one intervention compared to another relates to the area between two survival curves; the *mean* survival difference. Median improvements in survival have the benefit of avoiding assumptions regarding long-term survival patterns beyond the follow-up period of a clinical trial; however, this may not reflect the actual survival difference between treatments. Mean survival within the trial duration may be estimated by calculating the area under the empirical survival curve using the trapezium rule. However, survival curves are typically incomplete (right-censored) as the duration of clinical trials is rarely sufficient to follow up all patients until death. The final portion of the survival curve may be extrapolated using parametric models such as Weibull, exponential, or Gompertz distributions.[17] However, the process of fitting survival curves to empirical survival data requires assumptions concerning the shape of the final portion of the curve, and a degree of error between the fitted and empirical curves is inevitable.

A further problem for cost-effectiveness analyses of cancer treatments derives from the intentionally ethical and externally valid design of clinical trials. With respect to the majority of advanced cancers, it is often considered unethical not to offer a patient further treatment using an alternative therapy regimen following disease progression. The central difficulty in interpreting overall survival data from many existing cancer trials concerns the number of patients who crossover to alternative therapies following disease progression or treatment failure. As a result, the effect of subsequent-line therapies on overall survival is unknown, thus the survival of these patients cannot be uniquely related to the allocated therapy. In such cases, estimates of overall survival are confounded as it is unclear how much of the observed benefit is attributable to the first-line therapy or subsequent-line therapies. The implication for clinical effectiveness is that outcomes observed within the comparator treatment group may be exaggerated, leading to the underestimation of the incremental treatment benefit, whilst the implication for cost-effectiveness analyses is that the cost of achieving such benefits within the comparator arm will also be underestimated if these are omitted from the model. Such considerations should be incorporated into cost-effectiveness analyses in order to avoid biases against the novel treatment. The necessary implication here is that the true survival benefit of individual treatment regimens can only be reliably estimated whereby patients receive planned sequences of treatment.

A final problem with the use of life years gained as the measure of clinical benefit is that it neglects to account for differential impact of the treatment on the health-related quality of life (HRQoL) of the patient. For example, two cancer therapies may be equivalent in terms of their overall survival, but one may have a substantially better adverse event profile and may thus confer quality of life benefits.

### 3.2. *Quality-adjusted survival*

The role of many cancer therapies, in particular those used in the treatment of metastatic disease, is as much for the palliation of symptoms as for the relatively modest survival benefits they confer.[8] It is essential that toxicities resulting from treatment do not negate these benefits. This is a particularly relevant consideration for the assessment of newer orally administered 5-FU analogues, which may confer additional improvements in HRQoL.[11] However, the interpretation of HRQoL data collected within many clinical trials is difficult. Most commonly, the impact of new technologies on quality of life has been evaluated within clinical trials using the cancer-specific questionnaires such as the EORTC QLQ C-30 or the FACT. However, there currently exists no preference-scaling method through which to translate such data into an index utility score; as a result, much existing quality of life data cannot be used in the context of comparative economic evaluation.

The timing of the administration of the quality of life instrument and the time horizon posed by the questionnaire may lead to further problems in the interpretation of HRQoL outcomes. The EORTC QLQ-C30 quality of life instrument asks patients to assess their wellbeing over the previous week, whereas the EQ-5D asks patients about their state of health on the day the questionnaire is administered. The time at which the questionnaire is administered may influence the results; if the time profiles of the toxic effects of treatment or recovery durations following treatment are very different, quality of life data may be further difficult to interpret. In addition, censoring of quality of life data may not be random, an effect known as 'informative censoring.'[17] This means that completion rates are not independent of the quality of life of

the patient, and quality of life data for very ill patients may not be represented within the results of the study. Such non-random censoring may bias HRQoL results. In addition, for trials in which patients are allowed to crossover to alternative treatments following disease progression, quality of life outcomes cannot be uniquely related to the allocated therapy.

### 3.3. *Progression-free survival*

Progression-free survival relates to the time from randomisation to the documented progression of disease. The WHO criteria define disease progression as an increase in the size of the primary tumour of $>25\%$ and/or the appearance of new lesions,[18] whilst the more recent RECIST criteria define progressive disease as $\geqslant 20\%$ increase in the sum of the longest diameters of the target lesions, or unequivocal progression of non-target lesions, or the appearance of new lesions.[19] The clinical relevance of progression-free survival as a benefit measure derives from the notion that patients who do not respond to treatment, but whose disease is stabilised derive benefit from treatment.[8] Progression-free survival is commonly reported as either a primary or secondary endpoint within most clinical trials of chemotherapy for advanced cancer.

Whilst progression-free survival avoids problems of confounding due to treatment crossovers, there exist problems in interpreting progression-free survival results from existing clinical trials. Disease progression results reported within the clinical trials relates to the documented time of progression; confirmation of disease progression is thus dependent on the frequency of checkups received. The true progression-free survival benefit relates to the area between two progression-free survival curves; as with overall survival, the use of median estimates of progression-free survival may not reflect the actual benefits attributable to therapy. Furthermore, from a policy-making perspective, it may be difficult to determine an acceptable range of cost-effectiveness for health technologies valued in terms of cost per progression-free life year avoided.

### 3.4. *Tumour response*

Tumour response may be either complete or partial. Complete response is defined by both the WHO response evaluation criteria and RECIST response evaluation criteria as the disappearance of all detectable tumours.[18,19] The WHO criteria defines partial response as a decrease of 50% or more in the tumour surface area without the appearance of new lesions,[18] whereas the more recent RECIST criteria defines this as a decrease of 30% or more in the surface area of the tumour.[19] Tumour response in itself is an inadequate measure of clinical benefit for economic analysis; its main role is as a predictor of HRQoL and/or survival benefits for patients. However, tumour response may be only a weak predictor of overall survival, and as such is of limited use in cost-effectiveness analysis. Where tumour response is used as the measure of clinical benefit within health economic models, it is imperative that the link between tumour response and final outcomes is explicitly quantified and preferably validated alongside adequate exploration of the uncertainty surrounding this relationship.

### 3.5. *Adverse events avoided*

The avoidance of adverse events may be considered a relevant measure of the benefits attributable to alternative cancer treatments. Whereby survival benefits between alternative treatments are modest, the toxicity profile of individual therapies may be an important factor which may influence patient and clinician choice. However, the avoidance of adverse events is not an ideal benefit measure for use in cost-effectiveness analysis. Whilst the avoidance adverse events is a clinically relevant endpoint, the central issue concerns the HRQoL impact associated with alternative technologies; it is unlikely that the full breadth of treatment effects on HRQoL will be captured by consideration of this endpoint alone. Similar to the problems in evaluating overall survival and quality-adjusted survival benefits attributable to individual technologies, existing clinical trials of cancer treatments usually report adverse events according to the intention-to-treat (ITT) principle. It may thus be unclear which and how many adverse events are attributable to the allocated therapy, and how many are attributable to unplanned alternative therapies received following disease progression.

## 4. Modelling the effectiveness of cancer therapies using direct evidence from clinical trials

### 4.1. *Modelling the effectiveness of treatments for advanced disease*

RCTs of cancer treatments commonly report median Kaplan–Meier survival durations within each treatment group, whereby the relative impact of the novel treatment is described by a hazard ratio. However, the length of follow-up within RCTs is rarely sufficient to observe the event of interest over the entire survival duration. Consequently, the tails of the survival curves are censored according to the proportion of patients whose final outcomes were unknown at the end of the follow-up period. Mean survival (the AUC) can be estimated by fitting parametric curves to empirical Kaplan–Meier survival curves in order to predict the survival of patients beyond the termination of the trial (as shown in Fig. 1).

A variety of parametric functions may be used to project survival data into the future; these functions differ in terms of the assumptions that are made concerning the nature of the hazard of the event, e.g. time-dependency (Weibull, Gompertz) time-independency (exponential).[17] Parametric curves can be fitted to empirical KM data using simple regression analyses by transforming the survivor function $S(t)$ to a linear function with time $t$. Examples of more common parametric functions and their respective regression counterparts are shown in Table 1.

One approach is to compare the effect of the intervention against the baseline treatment option through the application of the hazard ratio to the baseline survival estimate. Numerous approaches are available for this type of analysis, typically varying in terms of whether the parametric function is fitted to the entire Kaplan–Meier curve or to a portion of the

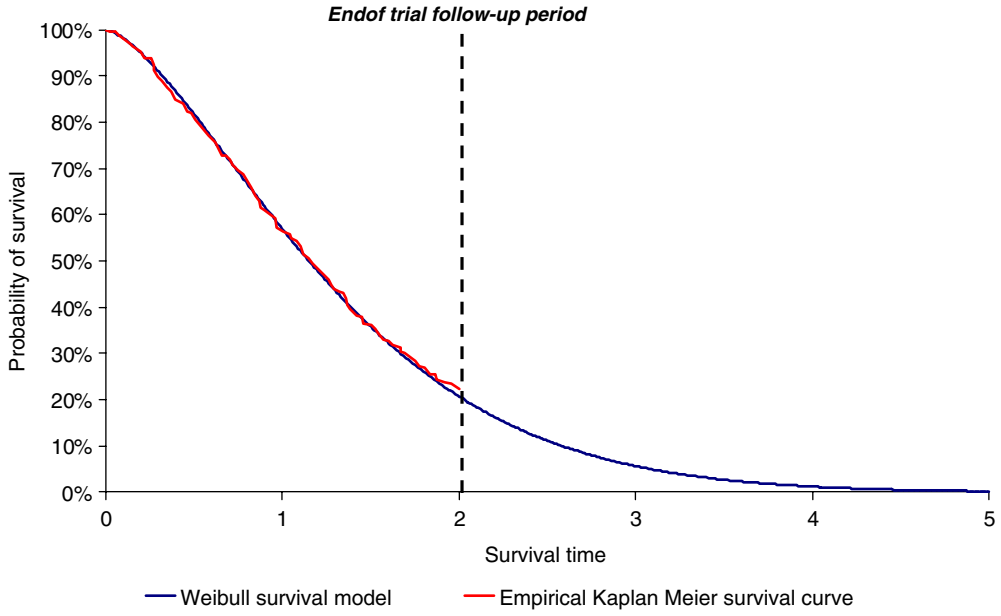


**Fig. 1 – Use of survival modelling to extrapolate final outcomes beyond the trial duration.**

**Table 1 – Some common parametric distributions for survival modelling**

| | Exponential | Weibull | Gompertz |
|---|---|---|---|
| Nature of hazard of survival | Constant | Time-dependent | Time-dependent |
| Survivor function | $S(t) = e^{-\lambda t}$ | $S(t) = e^{-\lambda t^{\gamma}}$ | $S(t) = e^{\left[\frac{\alpha}{\beta}(1-e^{\beta t})\right]}$ |
| Corresponding hazard function | $h(t) = \lambda$ | $h(t) = \gamma\lambda t^{\gamma-1}$ | $h(t) = \alpha e^{\beta_Z}$ |
| Independent variables | $t$ | Log(t) | $t$ |
| Dependent variables | Log(S) | Log(-Log(S)) | Log($h(t)$) |

tail of the curve. The appropriateness of these alternative extrapolation methods has not been the subject of rigorous assessment; further research is indicated to explore the validity of these alternative extrapolation methods.

### 4.2. *Modelling treatment effects from RCTs in which treatment crossovers occur*

Particularly with respect to clinical trials of alternative chemotherapies, it is commonplace for patients to crossover to other therapies following disease progression, which consequently leads to confounding of effectiveness estimates. It is possible to adjust for the effect of subsequent-line therapies on survival outcomes through adjusting patient-level survival estimates, although in the authors' experience, this is rarely accounted for. However, if treatment crossovers occur in usual clinical practice, one could argue that the effects of subsequent-line therapies should be included in the effectiveness estimate in order to maintain the external validity of the model. Whilst this is essentially a problem to be addressed by the scope of the economic evaluation, there is an associated problem in that RCTs rarely collect resource use data beyond disease progression. This is particularly important as the absence of such cost information from the model will inevitably bias cost-effectiveness results. Irrespective of whether such confounding should be included in models of chemotherapies, it is imperative that the costs of treatment reflect the actual resources consumed and the observed level of benefit for each treatment option in order to obtain a reliable estimate of the additional costs of the additional benefits attributable to the novel technology as compared to the comparator treatment option.

### 4.3. *Modelling the effectiveness of curative treatments*

Modelling the cost-effectiveness of curative therapies represents a different type of problem to the assessment of palliative therapies in that the long-term survival of cured patients cannot be feasibly measured within the duration of the trial. Unlike therapies used to manage advanced cancers, the primary endpoint used within trials is typically relapse-free survival (RFS) or disease-free survival (DFS). Crucially, the event of relapse following resection of the primary tumour may not be inevitable; patients who are cured will never experience the event. As a result, key assumptions are required concerning the nature of the hazard of relapse over time, and the expected survival duration for those patients who relapse and those who do not. For example, for some types of cancer it may be reasonable to assume that all relapses occur within a specified period of time following resection of the primary tumour, e.g. the hazard rate for relapse in colorectal cancer is very low beyond 5 years,[20] whilst for other types of cancer, e.g. breast cancer, such assumptions may be markedly less reasonable. Such assumptions should be used only following

the elicitation of advice from clinical experts. There is further uncertainty concerning the expected survival duration of patients who do not relapse, which could be modelled using a variety of optimistic assumptions, e.g. modelling subsequent survival using age-matched life tables, or pessimistic assumptions, e.g. no additional survival benefit beyond the duration of the trial. As these assumptions cannot usually be supported by empirical evidence, their impact on estimates of effectiveness and cost-effectiveness should be tested extensively within the sensitivity analysis.

### 4.4. *Modelling HRQoL associated with cancer treatments*

Within cost-effectiveness/cost-utility analysis, HRQoL is described by a single index utility score whereby 0 represents '*dead*' and 1 represents a state of '*perfect health*.'[14] Utility scores which are less than 0 may be used to describe states of health which are worse than death, which may be justified for certain cancer states. Such utility estimates are then combined with estimates of overall survival in order to estimate quality-adjusted life years (QALYs) gained. Fig. 2 shows a hypothetical model of overall survival (whereby the mean number of life years gained relates to the area under the upper curve) and the corresponding estimate of QALYs gained assuming a constant health utility of 0.50 (whereby the mean number of life years gained relates to the area under the lower curve).

Utility data for inclusion in the model may be obtained using a variety of methods, often including the direct valuation of the preferences of patients or the general public, using visual analogue scales, standard gamble or time-trade-off techniques, or through the use of a generic health status measurement questionnaire such as the EQ-5D, the Health Utilities Index (HUI) or the SF-36. A detailed review of the use, reliability and validity of these approaches has been reported by Brazier and colleagues.[21] However, RCTs of cancer treatments rarely use preference-based methods to measure HRQoL, hence modelling studies typically use indirect sources of evidence to describe the HRQoL associated with different states of health. The reliability of such studies should be explicitly stated within any health economic modelling analysis.

### 4.5. *Modelling resource use and costs of care*

The types of costs and resource use to be included in the model should be led by the objective of the analysis, the appropriate perspective of the economic evaluation, and the nature of intervention. It should be noted that the collection of full and accurate cost data within clinical trials is often severely limited on account of short-term follow-up of patients; trials of adjuvant therapies typically collect resource use data during the period for which patients receive adjuvant therapy and thus do not include the costs of patients who relapse, whilst for advanced cancer therapies, RCTs typically collect detailed resource use data relating to the line of therapy only, and thus exclude resources consumed post-progression. In order to obtain a balanced estimate of the true costs of the therapy, modelling is usually required to capture those costs associated with resources consumed beyond the scope of the trial.

Cost estimates included in the model should ideally relate to the number of treatments received, their relative dose intensity or mean dose received, the duration of treatment, and should account for patients who are withdrawn from treatment. Cost estimates should also include estimates of resource use associated with administration and resources used to manage treatment-related adverse events, as well as non-treatment related resource use such as clinical consultations. Many of these data are not routinely collected within clinical trials and as such must be sourced from the literature (for example time and motion studies) or using clinical advice. For the purpose of improving the consistency of cost assumptions, cost estimates should be uplifted to a formal

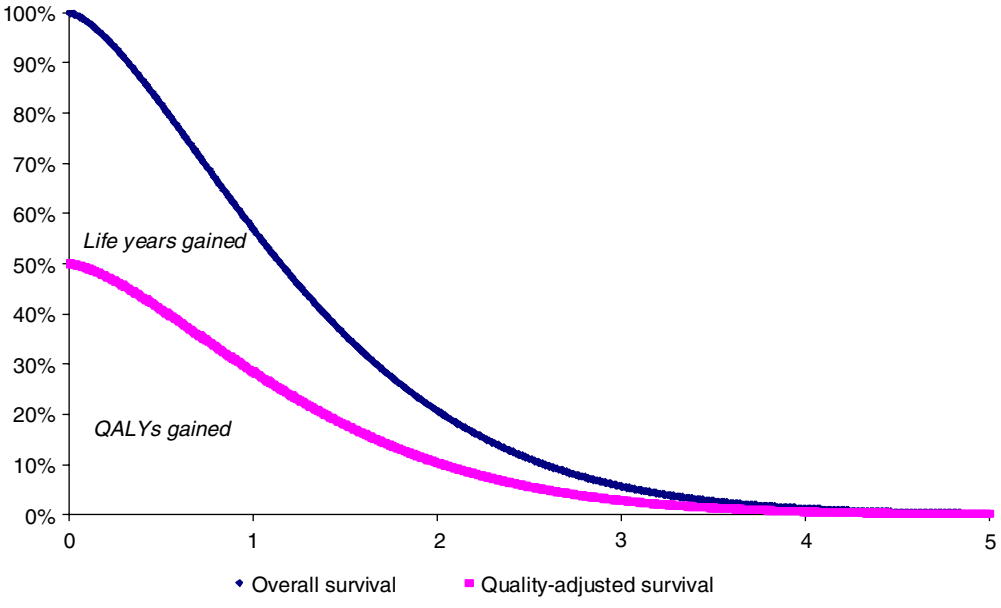


**Fig. 2 – Example of modelled survival curves and quality-adjusted survival curves.**

cost year using inflation indices, such as the Hospital and Community Health Services.[22]

### 4.6. *Time preference and discounting*

Patients (and society in general) prefer to reap the benefits of a new technology immediately, whilst deferring the associated costs into the future. In health economics, this principle is incorporated through differential weighting of health effects enjoyed and health care costs incurred through a process known as discounting.[23] This ensures that health benefits and costs incurred in the future are given less weight than those which are observed immediately. Any economic evaluation in which the costs and health benefits of a programme are observed over a period of several years should incorporate discounting. Suitable discount rates are often recommended or prescribed by budget-holders (e.g. the UK Treasury). The impact of alternative discount rates upon the cost-effectiveness analysis can be assessed using simple one-way sensitivity analysis. Debate surrounding whether costs and health outcomes should be discounted at equivalent or differential rates remain unresolved.[24] The omission of discounting from cost-effectiveness of therapies for advanced cancer is unlikely to bias cost-effectiveness results significantly for advanced cancers due to the limited survival durations; such omissions from analyses of adjuvant and neo-adjuvant treatments may however represent an important bias.

### 4.7. *Handling uncertainty surrounding incremental costs and benefits*

The true costs and effects resulting from the use of health technologies within a particular patient population cannot be known with absolute certainty;[25] consequently, the propagation of uncertainty surrounding model parameters leads to uncertainty in cost-effectiveness results. Traditionally, such uncertainties have been dealt with through extensive use of one-way sensitivity analyses, to explore the impact of changing the value of individual model parameters in order to identify the key determinants of cost-effectiveness. Whilst one-way sensitivity analysis does have some value, such analyses are commonly undertaken without consideration or justification of the alternative parameter ranges used and, by definition, are restricted to the consideration of the uncertainty surrounding a single model parameter. These approaches represent at best, a minimum requirement for the competent health economic evaluation of a novel health technology.

In recent years, considerable research has been afforded to the development of methods to describe uncertainty within health economic models, particularly with reference to the impact of such uncertainty on the decision the model is intended to inform.[5,25–27] The main focus of such research has focussed on the description of the uncertainty surrounding all model parameters simultaneously, rather than on a parameter-by-parameter basis. The impact of this joint uncertainty in all model parameters on the resulting cost-effectiveness estimate can be evaluated through the use of probabilistic sensitivity analysis, whereby each model parameter is described by a probability distribution (e.g. Normal, Lognormal, Beta, Gamma, Dirichlet, Poisson) rather than a single mean value. Monte Carlo sampling, in which each model parameter is randomly sampled simultaneously a large number of times and propagated through the model, can be used to produce a distribution of costs and health outcomes for each modelled treatment option to generate information on the likelihood that each treatment option is optimal. The results of such probabilistic analyses may be represented graphically using cost-effectiveness planes, distributions of net benefit or cost-effectiveness acceptability curves (CEAC).

Fig. 3 shows a cost-effectiveness plane, whereby the treatment option which represents current practice is held at the origin, whilst each of the scatter points describe the incremental cost and effect of the novel technology based upon the sampled set of model inputs.

These planes are particularly useful to describe the likelihood that the novel technology is more or less expensive than the current treatment, the likelihood that the novel technology confers additional benefits over the current treatment, as well as the likelihood that the cost-effectiveness of the

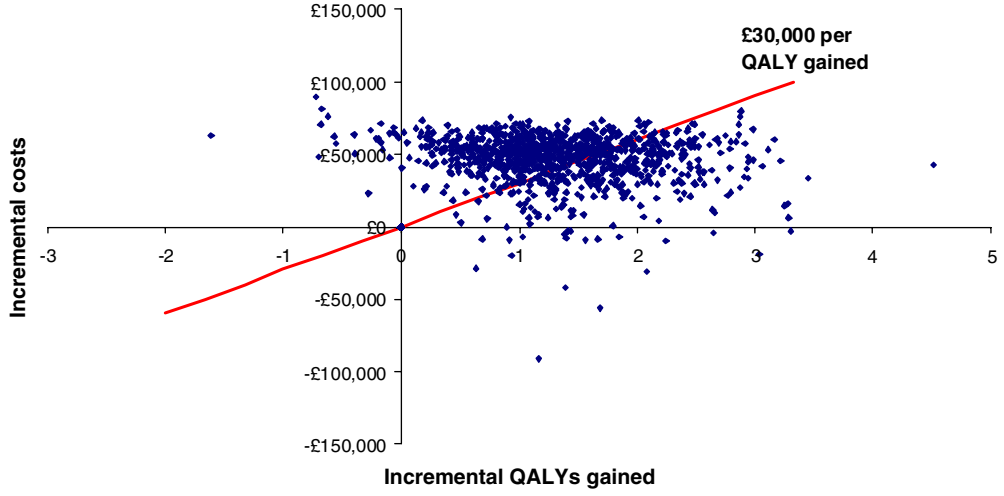


**Fig. 3 – Example cost-effectiveness plane.**

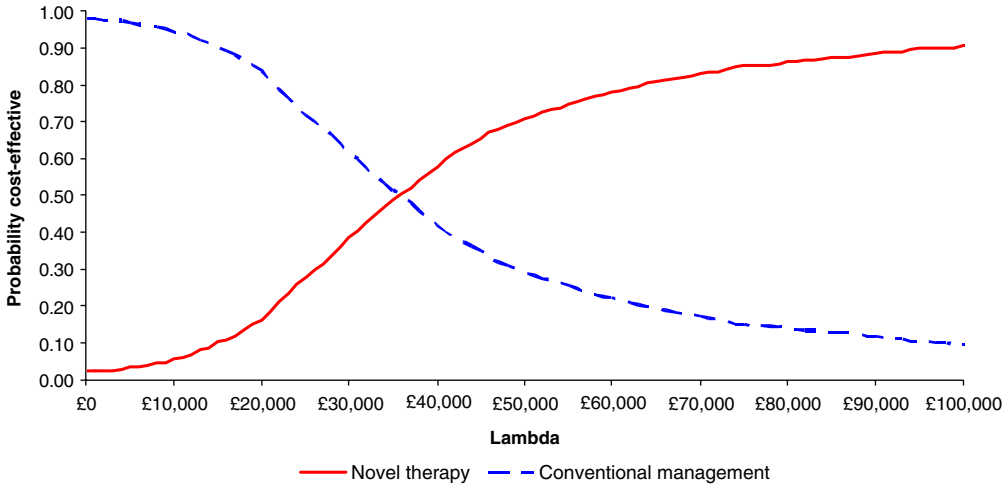


**Fig. 4 – Example cost-effectiveness acceptability curves.**

technology is better than some pre-determined acceptability threshold. However, for the comparison of more than two treatment options, the correct interpretation of cost-effectiveness planes becomes impossible.[28] A natural extension of the cost-effectiveness plane is the CEAC, which uses the concept of the net benefit of alternative interventions, whereby the health gains resulting from the use of the technology are valued in monetary terms after adjusting for any cost consequences (See Fig. 4).

The use of CEACs to represent parametric uncertainty has recently been recommended as part of NICE's Reference Case for cost-effectiveness analyses.[29] These curves describe the probability that each technology results in the greatest level of net benefit according to the amount the decision-maker is willing to pay for each additional unit of health gain. The use of CEACs may be particularly helpful in enabling decision-makers to consider the implications of adopting cancer treatments alongside decisions concerning the commissioning of further research.

## 5. Summary

This paper has highlighted some of the key methodological issues surrounding the role of cost-effectiveness analysis for cancer treatments and services, as well as outlining potential considerations relating to the interpretation of such analyses. The reader is invited to note however that the issues presented here are by no means an exhaustive list; our primary intention is to highlight some of the major pitfalls identified within previous cost-effectiveness models of cancer therapies. Whilst the development of guidelines for cost-effectiveness modelling in cancer therapies would indeed be an invaluable resource, this is beyond the scope of this paper. For the time being, the interpretation of existing cost-effectiveness analyses may be adequately undertaken via consultation with clinical experts, generic guidelines for the critical appraisal of modelling studies,[4,14,30] together with a detailed appreciation of the disease-specific issues relevant to the economic analysis of cancer treatments. In particular, this review has highlighted several cancer-specific issues which are relevant to the evaluation of any cancer treatment; these include:

1. 'Where patients receive unplanned therapies beyond treatment progression or failure, have all relevant costs and health effects been appropriately represented?'
2. 'Can health outcomes (favourable or adverse) be attributed to the planned therapy?'
3. 'Has the nature of the hazard of relapse and death been extrapolated on the basis of current clinical understanding of the natural history of the cancer?'
4. 'Where surrogate outcomes have been employed as the measure of clinical benefit, has its relationship with final outcomes been established empirically?'

Perhaps the most important generic question to be considered when assessing the reliability of a health economic model concerns whether the model itself makes sense to those individuals who know about the disease.[4]

The problems observed within previous economic models of cancer treatments lead directly to the indication of several areas for future research; these include further investigation of the reliability and validity of alternative extrapolation methods for modelling long-term survival data, exploration of the relationship between the numerous surrogate outcomes commonly measured within clinical trials against outcomes which are required for decision-makers using cost-effectiveness information across cancer types, and in particular the *a priori* consideration of the types of information required for cost-effectiveness as part of the design phase in the development of future clinical trials.

## Conflict of interest statement

None declared.

REFERENCES


1. Hutton J, Maynard A. A NICE challenge for health economics. *Health Econ* 2000;**9**:89–93.
2. Fuchs VR. Who shall live? Health economics and social choice. London: World Scientific; 1998.
3. Palmer S, Raftery J. Economics notes: Opportunity cost. *BMJ* 1999;**318**:1551–2.
4. Eddy DM. *Technology assessment: The role of mathematical modeling. In Assessing medical technology.* Washington DC: National Academy Press; 1985.
5. Chilcott JB, Brennan A, Karnon J, Booth A, Tappenden P. The role of modelling in prioritising and planning clinical trials. *Health Technol Assess* 2003;**7**(23):i-138.
6. Brennan A, Akehurst RL. Modelling in health economic evaluation: What is its place? What is its value? *Pharmacoeconomics* 2000;**17**:445–59.
7. Miners AH, Garau M, Fidan D, Fischer AJ. Comparing estimates of cost effectiveness submitted to the National Institute for Clinical Excellence (NICE) by different organisations: retrospective study. *BMJ* 2005;**330**(65).
8. Lloyd-Jones M, Hummel S, Bansback N, Orr B, Seymour M. A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. *Health Technol Assess* 2001;**5**(25):i-137.
9. Hind D, Tappenden P, Tumur I, Eggington S , Sutcliffe P, Ryan A. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation (Review of Guidance No. 33). Technology assessment report submitted to The National Institute for Clinical Excellence. London: NICE; 2005.
10. Ward S, Bansback N, Morris E, Calvert N. A review of the clinical and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer. Technology assessment report submitted to the National Institute for Clinical Excellence. London: NICE; 2000.
11. Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P. The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer. Technology assessment report submitted to the National Institute for Health and Clinical Excellence. London: NICE; 2005.
12. Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. Technology assessment report submitted to the National Institute for Health and Clinical Excellence. London: NICE; 2006.
13. Tappenden P, Jones R, Paisley S, Jones R. The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Technology assessment report submitted to the National Institute for Health and Clinical Excellence. London: NICE; 2006.
14. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the economic evaluation of health care programmes*. New York: Oxford University Press; 1997.
15. Tournigand C, Thierry A, Achille E, et al. FOLFIRI Followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol* 2004;**22**:229–37.
16. Maughan T, on behalf of the NCRI Colorectal Clinical Studies Group and FOCUS Trial Investigators. Fluorouracil (FU), oxaliplatin (Ox), CPT-11 (irinotecan, Ir), use and sequencing, in advanced colorectal cancer (ACRC): the UK MRC FOCUS (CR08) trial. Proc ASCO; 2005.
17. Collett D. *Modelling survival data in medical research*. London: Chapman and Hall; 1994.
18. World Health Organization. Tumour response criteria: WHO handbook for reporting results of cancer treatment. World Health Organization Offset Publication No. 48. Geneva: WHO, 1979.
19. Therasse P, Arbuck SG, Eisenhauer E, Wanders J, Kaplan R, Rubinstein L. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;**92**:205–16.
20. Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil plus levimasole as effective adjuvant therapy after resection of stage III colon carcinoma. *Ann Intern Med* 1995;**122**:321–6.
21. Brazier J, Deverill M, Green C, Harper R, Booth A. A review of the use of health status measures in economic evaluation. *Health Technol Assess* 1999;**3**(9):i-165.
22. Curtis L, Netten A. *Unit costs of health and social care*. Kent: Personal Social Services Research Unit; 2004.
23. Lipscomb J, Weinstein MC, Torrance G. Time preference. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996.
24. Severens J, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. *Value in Health* 2004;**7**:397–401.
25. Briggs AH, Gray A. Handling uncertainty when performing economic evaluation of healthcare interventions. *Health Technol Assess* 1999;**3**(2):i-134.
26. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *Journal of Health Economics* 1999;**18**:341–64.
27. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: The role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87.
28. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ* 2005;**14**:339–47.
29. National Institute for Health and Clinical Excellence. Guide to the methods for technology appraisal. London: NICE, 2004.
30. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36):i-172.