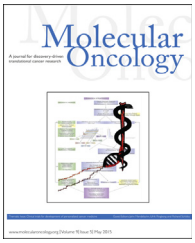
MOLECULAR ONCOLOGY 9 (2015) 1025–1033

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/molonc



Review

Bringing in health technology assessment and cost-effectiveness considerations at an early stage of drug development

Bengt Jönsson

Department of Economics, Stockholm School of Economics, Sweden

ARTICLE INFO

Article history:
Received 16 September 2014
Received in revised form
16 October 2014
Accepted 20 October 2014
Available online 23 October 2014

Keywords:
Health technology assessment
Cost-effectiveness
Clinical trials
Outcome research
Early development
Relative effectiveness

ABSTRACT

This paper reviews the issues involved in undertaking HTA studies early in the development of new cancer therapies, and discusses the data and methods for estimating the cost-effectiveness of new diagnostics and treatments. The value for patients of new cancer therapies is based on access to the treatment and optimal use. Realising potential value depends on successful completion of a series of steps, from the initial economic evaluations based on clinical trial data, to the reimbursement decisions based on the evaluations and the implementation of these decisions in clinical practice. Considerable resources have been devoted to the study of the cost-effectiveness of new cancer drugs as a basis for decisions about payment and use. Such resources could be used much more effectively if industry and HTA agencies were to collaborate at an early stage in the development process. The traditional clinical trial approach of using progression-free survival and cross-overs has serious shortcomings, producing data that cannot be used to determine outcomes and, so, cost-effectiveness. A new standard is needed; both regulatory and HTA authorities should be involved in its development.

1. Introduction

Clinical trials conducted during the drug development process provide the most important information for predicting value at the time a new medicine is introduced into medical practice. Regulatory approval long has been one indication of value, now supplemented by economic assessments of clinical value that provide the basis for decisions about reimbursement. Such evaluations use health technology assessment (HTA) methods; formal cost-effectiveness studies are an important part of HTA intended to help decisions makers optimize health care spending by basing decisions on value for money.

This paper reviews the issues involved in undertaking HTA studies early in the development of new cancer therapies, and discusses the data and methods for estimating the cost-effectiveness of new diagnostics and treatments.

The general methodology of technology assessment, including calculations of cost-effectiveness, is applicable in principle to cancer treatments. In practice, however, oncology presents its own set of challenges, most of which are linked to the specific need to do assessments very early in the product

http://dx.doi.org/10.1016/j.molonc.2014.10.009

development process. Technology assessment requires estimates of gains in mean survival, whereas clinical trials are designed to study differences in progression-free or overall median survival. The inclusion of data on resource use and patient-reported outcomes, such as quality of life, also suffers from lack of power to provide evidence on differences between treatments due to the small number of patients included in the trials.

The development of targeted therapies and personalized cancer medicine increases the complexity of the assessment. Smaller and shorter trials may give safer and faster evidence about which treatment works for different types of patients, but they will not provide enough information for assessment of outcome and cost-effectiveness. Assessing a diagnostic and a new treatment together, in addition, increases the number of intervention strategies that must be considered and also requires data for the combined assessment of the biomarker and the treatment. The usefulness of efficacy data from clinical trials to predict relative effectiveness in clinical practice must also be considered.

The close link between the pricing of new oncology drugs and their cost-effectiveness makes the use of technology assessment for policy decisions complicated for all stakeholders involved. Ability and willingness to pay differ across countries, as do the administrative and political frameworks for decision-making. The role of HTA and cost-effectiveness studies, then, will differ across jurisdictions, and studies need to be adapted to fit the requirements of different decision-makers.

Without an obviously superior alternative, HTA, including economic evaluation, likely will play an increasing role in the future in informing policy decisions aimed at providing evidence-based and cost-effective cancer care. The main reason for this is the decisive role third-party payment, primarily public payment, plays in determining patients' access to new cancer treatments.

2. Clinical trials, HTA and cost-effectiveness

While data from clinical trials form the basis for HTA studies and cost-effectiveness calculations, it is important to remember that the purpose of most clinical trials is to test hypotheses about the efficacy and side effects of diagnostic and therapeutic medical interventions. Health technology assessments, in contrast, aim at answering questions about how these interventions work in clinical practice; estimates of cost-effectiveness aim at informing decisions intended to ensure value for money.

Clinical trials and HTA studies are aimed at different decision-makers. Scientific clinical studies are mainly directed towards satisfying regulatory authorities and the physicians who make decisions about treatments for individual patients. HTA studies have a wider audience and are directed primarily at policy making in a broad sense. Economic evaluations are intended primarily to inform the decisions by third-party payers about reimbursement, including whether and how to pay for a new intervention for different groups of patients that may benefit from it to varying degrees. Despite the fact that out-of-pocket payments account for only ten per cent of total health care expenditure in Europe and the US, HTA studies may also be relevant for doctors and patients in discussions about the economic consequences of alternative treatment options (Shih et al., 2014).

Data and study results that may be very useful for one decision, then, may not have the same value for another. Introducing HTA and cost-effectiveness early in the development process traditionally has been done by augmenting scientific clinical studies with collection of data on resource allocation and costs, known as "piggy-back studies". However, an increasing number of clinical trials now are undertaken primarily, or partly, to provide information for HTA and cost-effectiveness analyses. Thus, the design of trials is increasingly influenced by the requirements for HTA and cost-effectiveness studies. The methods and data needs for undertaking economic evaluations within or alongside clinical trials, as well as the potential and limitations of such studies, have been well described and discussed (Drummond and Davies, 1991; Bonsel et al., 1993). The typical conclusion is that although clinical trials can be an opportunity to efficiently collect data for economic evaluation, obtaining rigorous results requires careful consideration of the suitability of the study design and use of appropriate analytical methods.

Methodological issues involved in analysing data and reporting results are similar regardless of the type of disease or intervention under study. With this in mind, we focus below on what must be incorporated in the design of innovative clinical trials for personalized cancer medicine to make them as useful as possible for HTA and cost-effectiveness analysis. We also will address specific analytical issues related to calculation of cost-effectiveness based on data from clinical trials in cancer.

3. Clinical trial design issues

Table 1 shows the clinical trial design issues and the recommendations for addressing them that are identified in two key references (Ramsey et al., 2005; Glick et al., 2007).

The summary above of relevant design issues for collecting cost-effectiveness data alongside clinical trials points out specific issues that must be addressed in designing innovative clinical trials for personalized cancer medicine.

The first issue is the selection of study population. The use of biomarkers to identify the relevant patient population can help create a close link between the population in the clinical trial and the use of the drug once it reaches the market.

Box: Definition of HTA and cost-effectiveness
Health Technology Assessment (HTA) is the assessment of all relevant aspects of a technology, including clinical effectiveness and safety as well as its economic, social, and ethical implications.
Cost-effectiveness analysis compares the relative costs and outcome (effectiveness) of two or more alternative interventions for a defined indication or population.

Table 1 – Recommendations for clinical trial design.

ISPOR Taskforce on cost-effectiveness alongside clinical trials (Ramsey et al., 2005)	Economic evaluation in clinical trials (Glick et al., 2007)
Trial design should reflect effectiveness rather than only efficacy when possible	Preplanning • Identify an appropriate length of follow-up time for economic endpoints • Estimate Specify arithmetic means, variances, and correlations for costs, health-related quality of life and preference • Identify the types of health services used by study participants
Full follow up of all patients is encouraged	Resource use measurement • Limit data collection to disease related services • Limit settings in which data on used of medical service is collected • Limit participants from whom economic data are collected
Determine and describe the power and ability to test hypotheses, given the trial sample size	Level of aggregation of resource use • Outpatient visits, tests, treatments, etc. • Hospital discharges according to diagnosis, LOS or DRG
Clinical endpoints used in economic evaluations should be disaggregated	Price weights for costing • Hospital charges, fee schedules • Trial specific costing
Direct measures of outcome are preferable to use of intermediate endpoints	Naturalistic study design • Representativeness of sample • Intention-to-treat analysis • Minimize loss to follow up • Protocol-induced costs and effect
Obtain information to derive health state utilities directly from the study population	Modelling consequences beyond what is observed in the trial • Disease analytic modelling
Collect all resources that may substantially influence overall costs; these include those related and unrelated to the intervention	

However, this requires that the testing methods and strategies are harmonized between clinical trials and clinical practice. Other factors also may influence the outcome of treatment—for example, the patients' age, co-morbidities, and any earlier treatments. Patients in the clinical trials as well as clinical practice must be properly characterized on these factors as well. It is common practice in developing new cancer drugs to start assessing efficacy and safety in patients with advanced disease. Testing patients in earlier disease stages may take more time and produce a different outcome; for example tamoxifen and herceptin were shown to be more effective, and cost-effective, in early breast cancer than in later stages. Moreover, given the nature of cancer, randomized studies of all possible treatment strategies may not be possible, which means that economic evaluations based on modelling must supplement those based on data obtained directly from a clinical trial.

A second issue is the choice of comparator in evaluating a new treatment option. In some cases, a placebo-controlled trial may make the most sense, but this can raise questions of relevance to clinical practice if the placebo arm of the trial differs substantially from what happens in actual clinical practice. The recommendation to use standard clinical practice as the comparator may not be helpful in cases there is no 'gold standard' in clinical practice; in addition, clinical practice may differ both within and between countries. Such differences may decrease over time as basing treatment on evidence becomes more common, encouraging greater similarity in therapeutic approach.

Ensuring the relevance of HTA and cost-effectiveness analysis to decisions about treatment of patients in clinical practice is a third challenge. Data on outcome in terms of overall or disease specific mortality are the most relevant for policy and clinical practice decisions, but it may not be feasible to power a clinical study to capture the effect of treatment on mortality. Most cancer clinical trials use a surrogate endpoint—progression-free survival—as the measure of effectiveness, which presents a challenge in making clinical trial results relevant to patient outcomes. Criticism of using this surrogate outcome measure in clinical trials is extensive as a result (Booth and Eisenhauer, 2012; Hotte and Bjarnason, 2011). Surrogate endpoints may be useful nevertheless if a clear link can be established between them and final outcomes. To use an example in cardiology, early models that used the surrogate endpoints of reducing blood pressure or lowering lipid levels proved accurate in predicting final outcomes and were useful for economic evaluation. But it was only when those models were validated by studies that showed a reduction in cardiovascular events that they became more widely accepted by decision-makers.

The development of targeted therapies in cancer, and the possibilities of following and assessing the impact of interventions using molecular diagnostics, may provide opportunities for developing new models useful for assessing cost-effectiveness. Those later can be validated with outcome studies based on clinical practice. Such outcome studies would be facilitated by the collection of data on clinical practice patterns and outcome before and parallel to the clinical trials to establish a baseline for assessing changes in costs and improvements in outcome. Observational data on resource use and outcome can also be very useful for early modelling of potential cost-effectiveness for different development strategies. The

headroom for innovation will differ for the various possible applications of any new technology, and early modelling may improve the chance of selecting high value development strategies.

Studies should have an appropriately long follow-up time to allow the inclusion of all costs and effects. This may be possible in cases where the treatment cures the cancer, or where the effects are mainly on symptoms and quality of life. But in an increasing number of cases, the new intervention will change the progression of the disease, not cure it. This makes it necessary to follow patients for the rest of their lives, and also consider subsequent treatment and its impact on quality of life and survival. It is thus not possible to limit the analysis to the clinical trial period alone. In these cases, modelling will be necessary to gain insights into longer-term cost-effectiveness.

Resource utilization and costs in clinical trials may not be relevant for clinical practice because costs specific to the trial will not be incurred outside the trial. If such resource use has no impact on outcome, it can be excluded from the analysis. Data on quality of life and other patient-reported outcomes may be less of a problem, but the clinical trial design also can affect these measures.

4. Analysis and reporting of results

It is important that a study of cost-effectiveness has a clearly defined question and that the analysis is guided by a data analysis plan. A set plan is particularly important if formal tests of hypotheses are to be performed. There are several possible approaches for analysing resource use, cost, outcome, and cost-effectiveness, but the following recommendations are common to all analyses of economic data derived from clinical trials (Ramsey et al., 2005):

- The intention-to-treat population should be used for the primary analysis
- A common time horizon(s) should be used for accumulating costs and outcomes; a within-trial assessment of costs and outcomes should be conducted, even when modelling or projecting beyond the time horizon of the trial
- An assessment of uncertainty is necessary for each measure (standard errors or confidence intervals for point estimates; *p* values for hypothesis tests)
- A (common) real discount rate should be applied to future costs and, when used in a cost-effectiveness analysis, to future outcomes
- If data for some subjects are missing and/or censored, the analytic approach should address this issue consistently in the various analyses affected by missing data.

4.1. *Survival analysis in an economic evaluation*

It is common practice to calculate gain in terms of median survival in oncology clinical trials. For HTA and cost-effectiveness analysis, it is the gain in mean survival time that is relevant. The problem is that estimates of the latter are more difficult and less certain and the difference can be considerable. This is illustrated in a comparison of the two measures based on a trial of ipilimumab for the treatment of metastatic melanoma (Davies et al., 2012). The median survival benefit is estimated (in second-line treatment at a dose of 3 mg/kg) to be just short of four months, which means that the cost of one life-year gained would be 350 000 USD. If the analysis is based instead on mean survival gain, the cost per life-year gained is reduced by more than half.

Generally, trial data must be extrapolated, and many models are available for this purpose. The choice of extrapolation model is critical because different models can lead to very different cost-effectiveness results. A review of the survival analysis component of 45 HTAs undertaken for the UK National Institute for Health and Care Excellence (NICE) in the cancer disease area concludes that survival analysis has not been conducted systematically in HTAs (Latimer, 2013). While it is important to have a systematic model selection process, the need for follow-up studies to validate the predictions still remains.

4.2. *Predictions beyond the clinical trial*

The choice of extrapolation methodology can have an important impact on calculations of comparative efficacy, costs, and cost-effectiveness. This is illustrated in an example using data from a pivotal phase III trial in the US comparing sunitinib to IFN-a as first-line treatment for metastatic renal cell carcinoma (mRCC) (Ekman et al., 2011). Cost-effectiveness results varied quite substantially depending on assumptions made. A short time horizon (one year) resulted in an incremental cost-effectiveness ratio (ICER) of 120 304 USD versus an ICER of 52 571 USD for the lifetime horizon assumption. Depending on choice of survival distribution, ICERs varied between 50 000 and 150 000 USD. The pessimistic ('stop and drop') scenario and the optimistic (continued benefit) assumption produced large differences in ICERs: 114 000 USD vs. 50 000 USD, respectively.

4.3. *The problem of cross-over in clinical trials*

Patients in cancer trials may be offered the opportunity to 'cross over' to active treatment as their disease progresses or when sufficient evidence about the efficacy of the new treatment is achieved. This is a common approach to addressing the ethical issues associated with use of placebo controls, but may lead to statistical challenges in the analysis of overall survival and cost-effectiveness as cross-over leads to loss of information and dilution of data on comparative clinical efficacy. Methods for analysing overall survival data in the presence of cross-over include simple methods (intent-to-treat analysis and censoring data at cross-over) and advanced statistical methods (the inverse probability of censoring weighting [IPCW] and the rank-preserving structural failure time [RPSFT] models) (Ishak et al., 2014). Methods to adjust for switching have been used inconsistently in HTAs, according to one review (Latimer et al., 2014). RPSFT models and IPCW are appropriate in different scenarios. In some scenarios, both methods may be prone to bias; intent-to-treat analyses may sometimes produce the least bias. Table 2 shows recommendations for choice of method from a recent study (Jönsson

Table 2 – Considerations for selecting method to analyse overall survival in the presence of cross-over according to trial type and availability of data (Jönsson et at., 2014).

	Cross-over at random[a]	Cross-over not at random
Few patients cross over	ITT	IPCW
Many patients cross over	ITT or RPSFT	RPSFT
Small trial	ITT or RPSFT	RPSFT
Large trial	ITT or RPSFT	IPCW
Little information on confounding factors	ITT or RPSFT	RPSFT
Abundant information on confounding factors	ITT or RPSFT	IPCW

IPCW = inverse probability of censoring weighting; ITT = intent-to-treat; RPSFT = rank-preserving structural failure time.
a Cross-over at random means that cross-over is independent of patient characteristics and prognostic factors that are correlated with survival.

et al., 2014). Note that the data requirements of adjustment methods also have important implications for clinical trial design.

5. Outcome research – follow-up studies in clinical practice

While clinical trial data are an important part of the evidence base for both patient-doctor and policy decisions, their usefulness has limits for all decision-makers. Recently, regulatory authorities, the primary customer for clinical trial data, have recognized the limitations and introduced new initiatives to address issues such as adaptive licencing and post-authorisation efficacy studies. This brings regulatory and HTA data requirements closer together.

Outcomes research is well established in oncology (Lee et al., 2000). Its focus is on assessing patient-relevant outcomes for a wide range of both clinical and policy decisions. Economic evaluation, often included in outcomes research, does not have a prominent role in the US in the design of policy decisions aimed at improving quality of care for cancer patients (Shih et al., 2014). In Europe, the role of economic data and systematic analysis of cost-effectiveness in outcome studies of cancer treatment also is limited and controversial.

The increasing importance of comparative effectiveness research in the US, and relative effectiveness research in Europe, is changing what evidence is considered in clinical and policy decisions (Luce et al., 2012). Evidence from early clinical trials and follow-up studies in clinical practice are complementary. Both types of studies, then, must be considered in the development of a new technology. An important issue will be to decide what data should be collected during the early clinical trials, and what should be collected in follow-up studies when the outcome can be studied in clinical practice.

5.1. *What are the data needs?*

The data needs for HTA are basically the same whether collected during clinical trials or in follow-up studies. Data on resource utilisation and patient-reported outcomes are particularly important in the development of treatment guidelines and for decisions about reimbursement and funding. Epidemiological data and data collected through patient registries, combined with data from patient records and administrative data bases, also are used in outcome studies. These data sources, however, are often short on information about resource use and patient outcomes.

5.2. *What are the methods for the analysis and reporting of results?*

Ideally, outcome studies, like clinical trails, should be designed using randomization to ensure enough variation to allow assessments with high internal validity. Many examples of using randomization in clinical practice exist—for example in follow up of patients in registries (Lauer and D'Agostino, 2013). The cost per patient for this is only a fraction of the cost of collecting data in a study set up specifically to collect such data. This allows a significant increase in the number of patients included in the study, which is particularly important for identification of differences in resource use and outcome between different groups of patients.

For chronic progressive diseases, randomization is not possible for all relevant and important study questions because the final outcome is determined by a number of actions during the treatment process, diagnostic as well as therapeutic. Statistical methods, such as propensity score and instrumental variable techniques are available to analyse variation in treatment patterns as a basis for assessing effectiveness and cost-effectiveness.

The study results required for HTA and cost-effectiveness analyses are an account of which patients have been treated, and the outcome and cost-effectiveness of alternative treatments. The results of outcome studies are particularly important for clinical decision-makers, which means that patients and clinicians in particular have an important stake in reliable and complete data.

6. Economic evaluation alongside clinical trials versus modelling- a case study

Economic evaluations alongside clinical trials are rather rare in oncology. Ramsey et al. performed an economic analysis alongside Southwest Oncology Group Trial (SWOG) to estimate the cost-effectiveness of cisplatin plus vinorelbine versus carboplatin plus paclitaxel for patients with advanced non-small-cell lung cancer (NSCLC) (Ramsey et al., 2002). There were no statistically significant differences in survival or cancer-related quality of life between the treatment arms.

The analysis thus focuses on cost differences. Use of both protocol and non-protocol lung cancer-related health care was tracked for 24 months from the initiation of therapy. To determine expenditures, nationally standardized costs were applied to each type of health care service used, and these were summed over time. Lifetime expenditures and 95% confidence intervals (CIs) for each arm of the trial were calculated using a multivariate regression technique that accounts for censoring.

Cancer-related health care costs over the period of observation averaged 40 292 USD (95% CI = 36 226 USD to 44 359 USD) for patients in the cisplatin plus vinorelbine arm versus 48 940 USD (95% CI = 44 674 USD to 53 208 USD) for patients in the carboplatin plus paclitaxel arm ($P = .004$), with a mean difference of 8648 USD (95% CI = 2634 USD to 14 662 USD). Protocol chemotherapy drugs and medical procedures costs were statistically significantly higher in the paclitaxel arm ($P = .0003$ and $P < .0001$, respectively), whereas protocol chemotherapy delivery costs were statistically significantly higher in the vinorelbine arm ($P < .0001$). There was no difference between the arms in costs for blood products, supportive care medications, non-protocol-related inpatient or outpatient care, and non-protocol chemotherapy.

Treatment with carboplatin plus paclitaxel is substantially and statistically significantly more expensive than treatment with cisplatin plus vinorelbine. The majority of the cost difference is due to the additional cost of the protocol chemotherapy (approximately 12 000 USD). The study shows that it is possible to undertake relevant cost estimates within a clinical trial with a total of about 400 patients. However, the SWOG study was undertaken 1996–98 and the economic evaluation was published in 2002; 10 years after launch of the newest of the drugs (paclitaxel) included in the study.

6.1. Modeling the cost-effectiveness of testing and treatment for patients with advanced NSCLC

In a recent study the cost-effectiveness of EML4-ALK fusion testing in combination with targeted first-line crizotinib treatment was estimated for Ontario, Canada (Djalalov et al., 2014). This is a modelling study based on diagnostic pathway (decision tree) and registry data (Markov model). The model combines data from several sources. Effectiveness of treatment is based on data from three clinical studies in phases I–III. In patients with advanced NSCLC, EML4-ALK fusion molecular testing for all patients and targeted crizotinib treatment for patients with EML4-ALK fusion–positive NSCLC is compared with standard care. In the standard care strategy, patients receive conventional treatment for NSCLC, which includes platinum doublet (cisplatin and gemcitabine) as first-line therapy, pemetrexed as second-line therapy, and erlotinib as third-line therapy. Lifetime costs and outcome in terms of quality-adjusted life-years (QALY) are calculated in the model.

Molecular testing with first-line targeted crizotinib treatment in the population with advanced non-squamous NSCLC resulted in a gain of 0.011 quality-adjusted life-years (QALY) compared with standard care. The incremental cost was 2725 Canadian dollars (CAD) per patient, and the incremental cost-effectiveness ratio (ICER) was 255,970 USD per QALY gained. Testing adds to the costs of treatment. However, only 60 USD was attributed to the cost of molecular testing out of a total extra cost per patient tested of 2725 USD. Assuming that you need to test 25 patients for each patient treated, the upfront testing cost is 1500 USD. This can be compared with the extra treatment costs of 95,043 USD. The testing costs have only a minor impact on the cost-effectiveness of the intervention in this case. Even if the cost of testing were included in the price of the drug, the ICER would only drop from 255,970 USD to 250,632 USD. The key determinant of cost-effectiveness is the extra cost of crizotinib, determined by relative price per cycle in relation to other chemotherapy and best supportive care, and length of treatment. A sensitivity analysis performed showed that price per cycle is close to proportional to the incremental cost-effectiveness ratio; reducing the price by 50% reduces the ICER by approximately the same.

6.2. Lessons for early assessment of HTA and cost-effectiveness

It is rarely possible to perform a full economic evaluation alongside a clinical trial during early development. However, the inclusion of data on resource use, in particular related to the intervention, is possible as is data on patients' quality of life on the experiential treatment. Such data can be included at low extra cost. Modelling is necessary for early assessment for HTA and cost-effectiveness, and will be facilitated by collection of observational data parallel to the development process. Such data should include both resources and outcome for alternative treatment strategies.

The inclusion of testing strategies complicates the assessment of HTA and cost-effectiveness, but the assessment of clinical outcome of the treatment is still the driver of the results. It is possible to model the cost-effectiveness of different testing and treatment strategies, for local decision-making needs, when a basic model of treatment outcome and cost-effectiveness is available.

While the case study shows that cost-effectiveness is driven by the price of the new treatment, in the future further use of drugs in combination and sequence will lead to a demand for more detailed models of the costs and outcome of different strategies for intervention. Outcome research is needed to provide relevant data for these models.

7. HTA, cost-effectiveness and decision-making

The *raison d'être* for bringing HTA and cost-effectiveness considerations into the development of drugs early in the process is to improve decision-making. Even though such studies provide important evidence that can guide resource allocation, quality of cancer care and outcomes will be affected positively only if this produces changes in clinical practice.

Interpreting studies and implementing change based on them is not always straightforward. A decision based on cost-effectiveness is obvious only when one alternative clearly is both better and less expensive. Even so, the best alternative may not be selected and implemented if the choice is not compatible with decision-makers' incentives.

When an alternative is both better and more expensive, which is the most common situation when new and better treatment alternatives are introduced, the cost-effectiveness ratio needs to be interpreted and a decision about whether it represent "good value for money". While it seems logical to direct more resources to interventions with lower cost-effectiveness ratios, such decisions make sense only if the ratios are comparable. The frequent use of cost per QALY to express the results of cost-effectiveness studies facilitates comparison, but it does not determine what the cut-off value should be. The 50 000 USD/GBP or EUR per QALY gained has been used as a benchmark value for a long time (Neumann et al., 2014), but observations of decisions on resource use in practice indicate that, at best, this is a rough calculation of value.

Studies of the decisions by NICE in the UK show a strong correlation between cost per QALY and the decision to recommend a new drug for use in the NHS. Studies also show a willingness to pay more for cancer drugs—about 1000 GBP per QALY. Determining the impact of cost per QALY is complicated further by the use of such studies to negotiate prices for new cancer drugs. The increasing use of specific market access agreements, including confidential rebates and complicated payment schedules, makes it even more difficult to study the impact of cost-effectiveness estimates on decision-making.

An alternative is to rely on studies of whether and how much use in clinical practice reflects evidence of cost-effectiveness. This is even more complicated given that cost-effectiveness does not always determine decisions. Studies will find the use of treatments that are not proven cost-effective as well as the failure to use interventions that have been proven cost-effective.

It is not surprising that formal cost-effectiveness estimates have a limited impact on decisions to reimburse or not reimburse because the uncertainty surrounding ICERs is high. Decision-makers may use the data and the models in these studies, however, to recommend restrictions in use while further data are gathered, for example, through an observational study or a pragmatic trial. Value-of-information analysis can determine whether the investment in further research will yield enough reduction in uncertainty to warrant the cost and delay in access that another trial would entail. Cost-effectiveness studies may provide the basis for market access agreements, including those that may result in a reduction in the price of a drug.

While it is possible to demonstrate the probability of a cost-effectiveness ratio leading to a positive reimbursement decision (see above), it is seldom possible to assess the effect on individual decisions. One reason for this is that evidence on clinical efficacy, probably the most important factor in reimbursement decisions, is correlated to estimates of effectiveness, and thus cost-effectiveness. The impact of cost-effectiveness also is more obvious in a choice between two drugs with similar effectiveness, such sunitinib and pazopanib for first-line treatment of mRCC. Prices then will be the primary determinant of cost-effectiveness and, since prices can easily be changed, the impact of cost-effectiveness should be assessed based on data on use, rather than decisions about reimbursement.

Economic evaluations appear to have had little impact on the worldwide diffusion of targeted therapies in clinical practice. Data on international variations in use indicate that other factors, mainly from the supply side, account for most of the variation across countries. The most important demand-side factor is the economic status of the country measured as income or health care expenditure per capita. Since prices of new drugs vary less than per capita income, affordability may be more important than cost-effectiveness in countries with low per capita income. Data also indicate that how drugs are paid for in the health care system is important. Comparatively high uptake of new cancer drugs in France, for example, can be explained in large part by France's price-volume agreements and its practice of reimbursing hospitals for new drugs outside DRG-based hospital funding.

8. Discussion

Statistical methods may compensate to some extent for the inability of clinical studies that are intended to gain market authorization also to provide the data required for HTA. But some shortcomings, such as a comparison with an irrelevant alternative, cannot be mitigated using statistical methods. This problem may lessen with the expanding practice of soliciting advice from both HTA and regulatory agencies during the development process (Elvidge, 2013).

Progression-free survival is increasingly questioned both as an outcome measure and from a regulatory perspective. However, it will remain an important endpoint. Its usefulness in estimations of cost-effectiveness can be increased if decisions are made before a study begins about how to measure progression-free survival and establish a link to overall survival and quality of life, the two measures used to calculate gains in QALYs. Reducing the use of cross-overs in clinical trails also can improve the value of progression-free survival as an outcome measure.

Indirect comparisons play an important role in assessing cost-effectiveness. An EUnetHTA assessment of the relative effectiveness of pazopanib based on a review of studies found no evidence of difference in the effectiveness of targeted therapies for mRCC (EUnetHTA WP5, 2012). This was supported by the results of a direct comparison between pazopanib and sunitinib in a clinical trial (Casper et al., 2013).

9. Conclusions

The value for patients of new cancer therapies is based on access to the treatment and optimal use. Realising potential value depends on successful completion of a series of steps, from the initial economic evaluations based on clinical trial data, to the reimbursement decisions based on the evaluations and the implementation of these decisions in clinical practice.

Considerable resources have been devoted to the study of cost-effectiveness of new cancer drugs as a basis for decisions about payment and use. Such resources could be used much more effectively if industry and HTA agencies were to collaborate at an early stage in the development process. This could

increase both the quality and the credibility of studies, making them more useful in guiding decisions about reimbursement. A number of initiatives now are underway to facilitate such collaboration (Berntgen et al., 2014).

The methodology for cost-effectiveness studies, which continues to evolve, can be improved further. Most important from a general methodological point of view is accounting for all sources of benefit. Although debate continues about whether the QALY includes all relevant elements of value, stakeholders generally accept that estimates of cost per QALY are relevant to decisions about coverage. Since improvement in survival is the objective for the cancer patient, it is important that cost per life-year gained also is calculated and presented in parallel with the cost per QALY. Results of calculations of gains in QALYs may differ significantly depending on whether these are based on the patient's or the general public's perception of the value of various health states.

A major problem arises for HTA when clinical trial data do not provide clear evidence on outcome, for example when surrogate endpoints or cross-over designs are used. Statistical methods for extrapolation may help overcome this problem to some extent, but avoiding the problem is possible only if clinical studies are specifically designed to take HTA requirements into account. The traditional clinical trial approach of using progression-free survival and cross-overs has serious shortcomings, producing data that cannot be used to determine outcomes and, so, cost-effectiveness. A new standard is needed; both regulatory and HTA authorities should be involved in its development.

Indirect comparisons are often necessary for assessing cost-effectiveness because it is not feasible to undertake clinical trials for all alternatives potentially relevant in clinical practice. A limitation of all indirect comparisons, however, is that they still are based on clinical trial data. The potential for observational studies in clinical practice to answer questions about alternative treatments should be determined as soon as possible. Such studies should be initiated directly after marketing authorization and combined with data collection for assessment of relative efficacy and risk-benefit.

A closer link between studies, decisions about coverage, and the allocation of resources for new drugs also is needed. The data needed to study actual implementation of reimbursement decisions are scarce; available evidence indicates a gap between decisions and implementation, which produces inefficiency in the use of new drugs and, thus, lost value. Linking economic incentives in schemes such as such as pay-for-performance is one option for closing this gap.

Economic evaluations and coverage decisions are based on less than perfect data and the impact of both on actual outcomes in clinical practice is uncertain. Collecting data on actual use and outcomes in clinical practice, then, is important. Since outcomes depend on a number of factors, individual patient data are essential. Analyses based on such data also may help inform decisions in clinical practice that are not, and often cannot, be guided by clinical trial data—for example, the cost and outcome of the use of drugs in particular combination and/or sequence. These data must include not only drug therapies, but also all relevant diagnostic and therapeutic interventions that are important for optimizing and enhancing the value of new drugs in clinical practice.

REFERENCES

Berntgen, Michael, Gourvil, Anne, Pavlovic, Mira, Goettsch, Wim, Eichler, Hans-Georg, Kristensen, Finn Børlum, 2014. Improving the contribution of regulatory assessment reports to health technology assessments—a collaboration between the European medicines agency and the European network for health technology assessment. Value Health 17 (5), 634–641.

Bonsel, G.J., Rutten, F.F., Uyl-de Groot, C.A., 1993. Economic evaluation alongside cancer trials: methodological and practical aspects. Eur. J. Cancer 29A (Suppl. 7), S10–S14.

Booth, C.M., Eisenhauer, E.A., 2012. Progression-free survival: meaningful or simply measurable? J. Clin. Oncol. 30 (10), 1030–1033.

Casper, J., Schumann-Binarsch, S., Kohne, C.H., 2013. Pazopanib versus sunitinib in renal cancer. N. Engl. J. Med. 369 (20), 1969.

Davies, Andrew, Briggs, Andrew, Schneider, Dphil John, Levy, Adrian, Ebeid, Omar, Wagner, Samuel, Kotapati, Srividya, Ramsey, Scott, February 2012. The ends justify the mean: outcome measures for estimating the value of new cancer therapies. Health Outcomes Res. Med. 3 (1), e25–e36.

Djalalov, Sandjar, Beca, Jaclyn, Hoch, Jeffrey S., Krahn, Murray, Tsao, Ming-Sound, Cutz, Jean-Claude, Leighl, Natasha B., 24 February, 2014. Cost-effectiveness of EML4-ALK fusion testing and first-line crizotinib treatment for patients with advanced ALK-positive non-small-cell lung cancer. JCO.

Drummond, M.F., Davies, L., 1991. Economic analysis alongside clinical trials. Revisiting the methodological issues. Int. J. Technol. Assess. Health Care 7 (4), 561–573.

Ekman, M.C.C., Ramsberg, J., Jonsson, L., Sandin, R., Jonsson, B., Drummond, M., Weinstein, M.C., 2010. PCN162 extrapolation in trial-based cost-effectiveness modeling: in search of a standard. Value Health 13 (7), A282.

Elvidge, S., 2013. EMA's parallel advice workshop bridges regulatory and reimbursement divide. Nat. Rev. Drug Discov. 13 (1), 8.

EUnetHTA WP5, 31 December 2012. Relative effectiveness of pharmaceuticals. Pilot Assessment Using the Draft HTA Core Model for Rapid Relative Effectiveness Assessment. Version 4. Final version. http://www.eunethta.eu/outputs/wp5-ja1-pilot-pazopanib-reportappendix.

Glick, H.A., Doshi, J.A., Sonnad, S.S., Polsky, D., 2007. Economic Evaluation in Clinical Trials. Oxford University Press, New York.

Hotte, S.J., Bjarnason, G.A., 2011. Progression-free survival as a clinical trial endpoint in advanced renal cell carcinoma. Curr. Oncol. 18 (Suppl. 2), S11–S19.

Ishak, K.J., Proskorovsky, I., Korytowsky, B., Sandin, R., Faivre, S., Valle, J., 2014 Jun. Methods for adjusting for bias due to crossover in oncology trials. Pharmacoeconomics 32 (6), 533–546.

Jönsson, L.S.R., Ekman, M., Ramsberg, J., Charbonneau, C., Huang, X., Jönsson, B., Weinstein, M.C., Drummond, M., 2014. Analyzing overall survival in randomized controlled trials with cross-over and implications for economic evaluation. Value Health, 707–713.

Latimer, N.R., 2013 Aug. Survival analysis for economic evaluations alongside clinical trials–extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med. Decis. Making 33 (6), 743–754.

Latimer, N.R., Abrams, K.R., Lambert, P.C., Crowther, M.J., Wailoo, A.J., Morden, J.P., Akehurst, R.L., Campbell, M.J., 2014 Apr. Adjusting survival time estimates to account for treatment switching in randomized controlled trials–an economic evaluation context: methods, limitations, and recommendations. Med. Decis. Making 34 (3), 387–402.

Lauer, M.S., D'Agostino Sr., R.B., 2013 Oct 24. The randomized registry trial—the next disruptive technology in clinical research? N. Engl. J. Med. 369 (17), 1579–1581.

Lee, S., Earle, C., Weeks, J.C., 2000. Outcomes research in oncology: history, conceptual framework, and trends in the literature. J. Natl. Cancer Inst. 92, 195–204.

Luce, B., Drummond, M., Dubois, R.W., Neumann, P.J., Jönsson, B., Siebert, U., et al., 2012. Principles for planning and conducting comparative effectiveness research. J. Comp. Effectiveness Res. 1, 431–440.

Neumann, P.J., Cohen, J.T., Weinstein, M.C., 2014. Updating cost-effectiveness – the curious resilience of the $50,000-per-QALY threshold. N. Engl. J. Med. 371 (9), 796–797.

Ramsey, Scott D., Moinpour, Carol M., Lovato, Laura C., Crowley, John J., Grevstad, Patra, Presant, Cary A., Rivkin, Saul E., Kelly, Karen, Gandara, David R., February 20, 2002. Economic analysis of vinorelbine plus cisplatin versus paclitaxel plus carboplatin for advanced non-small-cell lung cancer. J. Natl. Cancer Inst. 94 (4).

Ramsey, Scott, Willke, Richard, Briggs, Andrew, Brown, Ruth, Buxton, Martin, Chawla, Anita, Cook, John, Glick, Henry, Liljas, Bengt, Petitti, Diana, Reed, Shelby, 2005. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA task force report. Value Health 5, 521–533.

Shih, Ya-Chen Tina, Mullins Daniel, C., Drummond, Michael, 2014. The role of economic evaluation in meeting IOM's recommendations on delivering high-quality cancer care. Value Health 17, 497–500.