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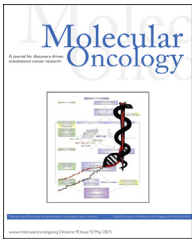

Review

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

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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

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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.