Pharmacoeconomics: integrating economic evaluation into clinical trials

A. Haycox, M. Drummond¹ & T. Walley

Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool and ¹Centre for Health Economics, University of York, UK

Introduction

Increasingly clinical trials are required to generate economic as well as clinical information to meet the needs of health service decision makers [1]. Such economic evaluations aim to compare the costs and benefits associated with a new drug with the current gold standard therapy. Clinical pharmacologists are increasingly being asked to participate in such combined trials and therefore need to develop a broad knowledge of health economics (discussed in the first two articles in this series) [2, 3] as well as understanding the specific issues involved in linking economic and clinical studies. The aim of this paper is to assist clinical pharmacologists to assess the implications of incorporating economic evaluation into the design, implementation and interpretation of clinical trials.

Health economists employ a wide range of information sources including clinical trials, epidemiological studies, economic modelling and expert opinion. The most valuable source of information that can be used to underpin health economic evaluations is reliable and robust systematic reviews or meta analyses of the clinical evidence available in each therapeutic area. In reality however the choice of data source is frequently pragmatic and opportunistic. Unfortunately such an *ad hoc* approach fails to take full advantage of the disciplined scientific methods that have contributed so much to clinical research. In addition such an approach ignores the fact that decisions made in accordance with poor data may be no better than decisions made on the basis of no data [4]. The utilization of a high quality and scientific methodology in pharmacoeconomic studies enables readers to interpret studies in the knowledge that the experimental design utilised was basically sound [5]. The double-blind placebo controlled randomized clinical trial (RCT) provides such a 'gold standard' for controlling the range of confounding variables that may otherwise disguise differences in therapeutic effects. Readers can be reasonably confident that RCTs effectively isolate the variable of interest, namely differences in drug efficacy. Pharmacoeconomic studies must develop a methodological structure that inspires a similar level of confidence in readers.

How should economic analysis be built into clinical trials?

Economic analysis should play a crucial role at each stage of drug development. However, as drug development proceeds, the target audience for such analyses will change. During Phase I and Phase II trials, economic analyses will be predominantly aimed at informing decision makers within the pharmaceutical company whether to continue with drug development or to abandon it. The company must establish

not only that the drug provides clinical benefits but also that such benefits can be obtained at a price which makes further development of the drug worthwhile. Once a drug has entered Phase III however, the target audience becomes the external decision makers who are required to manage the introduction and uptake of the new drug. It is upon this stage of the evaluation process that this paper concentrates.

Pharmacoeconomic evaluations must generate information of practical value to decision makers both in content and timing. Buxton's 'Law of Technological Evaluation' [6] develops the axiom that it is always too early to assess a new technology, until suddenly it becomes too late. Often the full effects of a drug—clinical or economic—cannot be assessed until the drug has been on the market for some time. The optimal timing of economic evaluation therefore requires a balance to be struck between the availability of definitive data and the need for such information to be generated before widespread adoption of a drug. Different decision makers require information at different times and in different forms. To meet such varying requirements it is important that economic evaluation is an iterative process rather than simply a 'one-off', and that any evaluation must be continuously reconsidered as new evidence arises [7].

Given that the information needs of the health services have altered so fundamentally, the crucial question is not whether but rather how economic analyses can best be integrated into clinical trials and what drugs should be evaluated in this manner. Such information is essential not only to restrict the introduction of drugs of limited value, but also to facilitate the introduction of drugs that benefit both the patient and the health service in general. Clinical trials provide the best source of early clinical information but such evaluations are incomplete, since the costs and benefits identified in a clinical trial may bear little relationship to those seen in broader clinical practice. Pharmacoeconomic analyses aim to identify the effectiveness of drug therapy in mainstream use.

Which trials should include an economic evaluation?

A well designed RCT will provide information concerning the safety and the efficacy of a new drug in a strictly controlled setting and population. However the cost of obtaining this benefit, the impact upon quality of life and the extent to which such efficacy can be translated into real-world effectiveness remain unknown. It would be neither appropriate nor feasible for an economic evaluation to be integrated into all Stage III trials of a new drug as this would spread available health economic expertise and resources too thinly and the information generated would probably not be worth the vast investment [8]. To warrant economic appraisal, the drug should be of economic importance; e.g. drugs that are either of high unit cost or likely to be prescribed in high volume, or where a major difference exists between the cost-effectiveness of the new

Correspondence: Professor T. Walley, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

drug and existing therapy. Economic evaluation will also be important where there is a significant difference in the benefits (such as quality of life) arising from a new therapy which is unlikely to be captured by standard clinical measures. In each case a careful preliminary assessment is required of the justification for undertaking an economic evaluation and only where two alternatives appear to exhibit significantly different costs and benefits should economic evaluation be considered.

The trial itself must be sufficiently well designed to be able to give a clear, unbiased and unambiguous answer to the clinical question it poses—otherwise the time and effort of both the clinical and economic evaluation will be wasted. The trial must also be a reasonable representation of current clinical practice, or at least allow a reasonable extrapolation to current practice. Patients in trials are more carefully selected than in everyday practice which may alter the benefits of a therapy and trials often involve increased monitoring of the patients and increased clinic visits which would not occur in routine use of the drug. Consideration should be given to whether such protocol driven resource use should be excluded from the costs in an economic evaluation. Many trials are of short duration compared with the expected duration of treatment in the real world, and the economic evaluation must assess the extent to which a short trial reflects the long term costs and benefits of the drugs. Finally the comparator is of great importance; is the comparator a drug which would be commonly and reasonably used to treat a particular condition? Placebo controlled trials are generally of limited value to economic evaluation unless there currently exists no therapy available for a given indication.

It is important to assess the logistic implications of integrating an economic evaluation into a clinical trial. Trials are already very complex, especially large multi-centre or multinational studies, and economic evaluations inevitably place further pressures on both researchers and patients. Pharmacoeconomic studies add to the range of outcomes that need to be measured in clinical studies. It requires information to be generated on factors such as resource use and quality of life in addition to the clinical endpoints. Multinational studies are a particular problem since although the clinical data may be pooled, the same is not necessarily true of the economic data which will vary in accordance with a range of issues, including the structure of the local health service, local prices, and local medical practice. Table 1 examines a number of issues that must be addressed in assessing the feasibility and value of integrating economic analysis into any given clinical trial.

What type of evaluation should be performed within the trial?

Pharmacoeconomic evaluations can be integrated into clinical trials in three main ways. Firstly, a clinical trial can be established with the primary purpose of informing the pharmacoeconomic evaluation. Secondly, the pharmacoeconomic evaluation may represent a secondary objective within a clinical trial whose primary aim is to assess safety and efficacy. Thirdly, the pharmacoeconomic evaluation can retrospectively analyse data generated by clinical trials and

Table 1 Assessing whether an economic analysis should be conducted alongside a given trial.

- Is the trial well designed and capable of giving unbiased and unambiguous answers to the clinical questions?
- Are the two (or more) interventions of greatly different cost or likely to be widely applied?
- Are there critical aspects of economic benefit not being explored by the trial (e.g. trade-offs between efficacy and side-effects)?
- Is the current practice (which may be 'doing nothing') one of the alternatives being compared?
- Is the trial being conducted in a typical setting and will the results be generalisable?
- Will addition of economic data collection seriously overburden investigators or patients?

Source: Department of Health [1].

use other data collection and modelling techniques to rectify any data deficiencies. The sensitive generation of economic information within a prospective trial typified by the first two approaches provides an objectivity that may not necessarily be replicated in the third approach.

Whichever approach is used the choice of the appropriate methodology to be employed in analysing any new drug is crucial. The range of methodologies available was discussed in detail in the first paper of this series and in general the choice should be based upon the nature of the likely effect of the new drug. If the trial is of two drugs with identical effects then it is only necessary to measure costs. If the clinical effects of the two drugs are similar in nature (e.g. lives saved) but different quantitatively, then it becomes necessary to measure cost per clinical outcome, i.e. a cost effectiveness study. Increasingly, the outcomes of new drugs are beginning to differ in nature as well as extent from those of older drugs, and it becomes necessary to capture this by creating a common denominator such as a measure of quality of life; this then leads us to conduct a cost utility study. If there is only limited evidence on which to base the choice of economic methodology, it may be wise to use a broadly focused methodology (i.e. cost utility) rather than to run the risk of omitting an important component of the drug's impact.

How should data on costs and benefits be collected within the trial?

The data to be collected for an economic evaluation depend on the nature of the trial, the perspective from which the evaluation is undertaken and the changes in resource use arising from the new drug. Identifying such changes requires close collaboration between economists and clinicians as they involve measurements in the hospital, the community care sector, the family and broader public agencies such as social welfare. Such data must be collected for each patient in the trial where there is great variability between individual patients. However, if the consumption of resources by all patients is similar (for example, a fixed number and type of diagnostic tests or outpatient visits), then such common use of resources need only be collected once and an aggregated cost allocated to all patients.

The perspective from which the study is evaluating the

costs and benefits must be specified: is it to consider the perspective of the health service (in which case only healthcare costs are considered such as drug costs and NHS staff time), or does it take a broader societal perspective (in which case indirect costs such as the patient's time, and loss of earnings are included). The amount of direct and indirect resources consumed must be recorded (e.g. number of outpatient visits or blood tests) and appropriate prices applied later. Such prices could be local (which makes a study more relevant to one area) or an average cost across a range of sites (which makes the study more generalisable). In cases where a restricted perspective is used (the drug budget, the hospital, the health service) the nature of such a restriction should be specified and its impact (in terms of a discussion of costs and benefits outside this perspective) discussed.

The 'normal' cost of treating patients in mainstream practice may be disguised by protocol driven costs in a trial and hence difficult to determine accurately. In such cases it may become necessary to resort to the use of an expert panel to identify common resource use; for instance, what proportion of patients with dyspepsia will ultimately have a gastroscopy? In cases where such expert opinion is employed the expert panel must be representative of a range of clinical opinions [9]. The evidence provided by an expert panel is obviously not as strong as directly observed evidence but, in certain circumstances, it may be the only evidence that can be obtained.

The benefits arising from treatment may be captured in a number of ways and at a number of levels. Direct benefits might include avoidance of an operation with its associated costs, while indirect benefits might include the ability to return to work. Outcomes may relate to improved quality of life, measured either by disease specific scales or by general measures such as the short form 36 (SF36) [10] which analyses the patients' perception of their health over a range of aspects of mental and physical well being. An important aspect of outcome will be how the patient values any change in potential outcome; e.g. how would you balance the higher success rate associated with drug A with an additional risk of adverse reactions? The answer will obviously depend on the extent of the benefit and the risks and the patient's perceptions of their importance. Such expressions of patient preferences can be used to interpret the quality of life data—and to place a valuation upon the changes that arise. Patient preferences and patient valuations represent one essential source of quality of life measurement [11].

Outcome data should be collected directly from individual patients within the trial, wherever this is feasible. This can be done through conducting interviews, filling in quality of life questionnaires or assessing patient preferences. Such an approach is likely to be outside the range of measures normally included in a clinical trial. In certain cases ethical consideration or time and resource constraints may make it difficult to collect data on each patient in the trial. It may be necessary to run a parallel exercise to collect data either from patients outside the trial or from historical practice. This will be less expensive but researchers will have to justify the extrapolation of the results to the patient group in the clinical study.

How should economic data generated by the trial be analysed?

The appropriate sample size from economic analyses differs from that in clinical trials. Clinical trials are designed around power calculations that estimate the expected number of patients required to prove that an anticipated variation actually does exist. In contrast pharmacoeconomic analyses are based on point estimates of changes in resource use and clinical benefits. This does not deny variability but rather allows for such variability in the analysis and interpretation of results through the use of sensitivity analysis. A range of sensitivity analyses should be used for testing the robustness of the conclusions arising from a pharmacoeconomic study. For clinical outcomes, the sensitivity analysis might be based on 95% confidence intervals of the outcome. Similarly, the crucial assumptions underlying the results should be varied and the data re-analysed to assess the extent to which such variations alter the outcome of the economic evaluation. The crucial factors are first that a sensitivity analysis is performed in appropriate cases and second that the assumptions and methodology underlying the analysis are transparent and therefore open to criticism. Results reported in pharmacoeconomic analyses that have not been subjected to comprehensive and transparent sensitivity analyses should be treated with extreme caution [12].

When economic analysis is incorporated into an existing efficacy study, it is not normal to alter the sample size to accommodate the economic analysis, but as in the clinical trial, the greater the number of patients evaluated the more useful the results are likely to be. Equally however it is important to recognise that the greater the number of patients included in an economic evaluation the more expensive the trial. In economic evaluations attached to clinical trials, it will be likely that only a proportion of patients in the trial will be analysed. Again a compromise is required between the value of the information generated and the cost incurred in obtaining such information.

One important factor to be considered in analysing economic data is the optimum method of dealing with the differential timing of costs and benefits. In general the sooner that benefits occur and the later that costs occur then the greater will be the overall value of the therapeutic intervention. The UK Treasury currently recommend a 6% discount rate for use in such calculations.

Economic evaluation normally analyses incremental changes, i.e. not just the total costs arising from any intervention, but the additional costs required to achieve any extra benefits over and above what is already provided. For any intervention it is possible to calculate an overall cost effectiveness ratio, and an incremental cost effectiveness ratio, which analyses the additional cost for each extra unit of benefit.

Ensuring the credibility and value of economic information generated in trials

To be useful, economic evaluations must be credible, timely and relevant to the needs of decision makers. The relevance of a study is crucially dependent on how far the results can be generalised outside the trial to common medical practice:

this must be carefully assessed prior to undertaking any economic evaluation alongside a clinical trial. The credibility of pharmacoeconomic studies attached to clinical trials depends not only upon the quality of the work, but also upon other factors such as who undertook the work and the source of funding. Most economic evaluations of new drugs are funded by the pharmaceutical industry which inevitably almost, casts some shadows on the results regardless of how independently the analysis was undertaken. Clinical pharmacologists are used to working with pharmaceutical companies in clinical trials and the standards set in such studies mean that they are content to lend their personal reputations to the credibility of the results. Unfortunately the methodological standards underlying economic evaluations are not as well developed or refined. Economic evaluations are frequently undertaken by the marketing division rather than the research division and there are likely to be major cultural differences between the two [13]. In such circumstances clinical pharmacologists must ensure that they are not investing their reputations in supporting a simple piece of marketing. The scientific validity and independence of economic evaluations can only be ensured by adopting the disciplined statistical methods and approach that underpin clinical research.

Conclusion

To be accepted by clinicians, health economics must ensure that its approach and scientific integrity is beyond reproach. This is best achieved by ensuring the use of sound research methods with transparency and objectivity in all methods, analyses and interpretation. The explicit and scientific integration of economic evaluation into clinical trials will facilitate rational decisions by ensuring decision makers have access to knowledge of the costs and benefits of a new drug. The integration of economic analysis however must not compromise the vital objective of clinical trials to ensure the safety and efficacy of new drugs. The joint objective of combined clinical and economic evaluation must be to generate data that enables decision makers to improve the health of the population served. The collaborative assessment of the costs and benefits within clinical trials will enable the

health services to optimise its use of scarce pharmaceutical resources and in this manner economic evaluation should be perceived as enhancing rather than threatening clinical freedom.

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