

Design and Analysis Issues for Economic Analysis Alongside Clinical Trials

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Introduction: Clinical trials can offer a valuable and efficient opportunity to collect the health resource use and outcomes data for economic evaluation. However, economic and clinical studies differ fundamentally in the question they seek to answer.

Objective: The design and analysis of trial-based cost-effectiveness studies require special consideration, which are reviewed in this article.

Summary: Traditional randomized controlled trials, using an experimental design with a controlled protocol, are designed to measure safety and efficacy for product registration. Cost-effectiveness analysis seeks to measure effectiveness in the context of routine clinical practice, and requires collection of health care resources to allow estimation of cost over an equal timeframe for each treatment alternative. In assessing suitability of a trial for economic data collection, the comparator treatment and other protocol factors need to reflect current clinical practice and the trial follow-up must be sufficiently long to capture important costs and effects. The broadest available population and a measure of effectiveness reflecting important benefits for patients are preferred for economic analyses. Special analytical issues include dealing with missing and censored cost data, assessing uncertainty of the incremental cost-effectiveness ratio, and accounting for the underlying heterogeneity in patient subgroups. Careful consideration also needs to be given to data from multinational studies since practice patterns can differ across countries.

Conclusion: Although clinical trials can be an efficient opportunity to collect data for economic evaluation, careful consideration of the suitability of the study design, and appropriate analytical methods must be applied to obtain rigorous results.

Key Words: economic evaluation, clinical trial, cost-effectiveness, study design and analysis

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In the current health care climate, healthcare systems, reimbursement authorities, and care providers need evidence demonstrating economic value, in addition to clinical outcomes and safety, to make decisions about alternative medical interventions.^{1–3} Recent policy initiatives highlight payer's interest in "real-world" effectiveness data demonstrating benefit in routine practice settings for coverage and reimbursement decisions to support efficient use of limited resources.^{4,5} As a result, there has been increased attention on appropriate study designs that will provide valid and reliable information on the actual effectiveness of an intervention in routine clinical practice^{6,7} and support economic evaluation.

Although there are a variety of alternative approaches, including decision analytic modeling and retrospective database analysis, to conducting an economic evaluation, prospective, and randomized studies are recognized as the most scientifically valid evidence for cost-effectiveness.⁸ The randomized and blinded experimental design of a clinical trial reduces bias and clinical trials can offer a valuable and efficient opportunity to collect the health resource use and outcomes data for economic evaluation. However, since the primary purpose of clinical trials is typically to measure clinical outcomes under controlled experimental conditions, not all trials are suitable for incorporating economic analysis. Several design issues must, therefore, be considered to ensure that the trial will provide appropriate data for a high quality economic study. Furthermore, special considerations for analysis of these economic data from clinical trials must subsequently be addressed.

The objective of this article is to review specific design and analysis issues that researchers need to consider in planning and evaluating cost-effectiveness of medical interventions in the context of trial-based studies. First, we discuss the fundamental difference between the clinical question and the economic evaluation question. Then, we consider the resulting implications for the design and analysis of cost-effectiveness studies in the context of a clinical trial.

DIFFERENCES IN THE CLINICAL AND ECONOMIC QUESTION

Economic and clinical studies differ fundamentally in the questions they seek to answer (Table 1). Traditional randomized controlled trials (RCTs), using an experimental design with a protocol controlled to evaluate safety and efficacy, are designed for product registration and considered the gold standard for efficacy. However, RCTs do not gen-

TABLE 1. The Clinical Question Versus the Health Economic Question

Feature	Clinical Trial	Economic Evaluation
Audience	Licensing regulatory authorities and clinicians	Purchasers and payors of health care
Objective	Demonstrate safety and efficacy	Value for money—lowest cost per unit benefit
Outcome measure	Efficacy “Does it work?”	Effectiveness and efficiency “Does it work in the real world?” consider quality of life
Comparison	Choose which treatment is better?	Estimate incremental cost-effectiveness
Timeframe	Driven by clinical events intermediate clinical outcome	Long enough to measure “downstream” consequences typically longer than clinical trial

erally measure effectiveness, and rarely collect health care resource use required for cost-effectiveness analysis. In contrast, an economic evaluation seeks to estimate efficiency based on effectiveness and cost, evaluating how the medical intervention performs against existing alternatives under routine clinical practice, and considering outcomes of importance to the patient.^{4,6,9–12}

Furthermore, the audience for clinical trials and economic studies differ. Clinical trials aim to identify which treatment is better for regulatory licensing and informing clinical decisions about treatment choice. Economic evaluation studies aim to inform decisions of health care policy makers and payors, estimating “value for money” measured as additional benefit per additional unit of cost—the incremental cost-effectiveness ratio (ICER).

As a result of these differences between clinical and economic questions, the relevant timeframe differs between clinical and economic studies. The clinical trial is driven by the occurrence of clinical events—once the event of interest occurs, there is generally no further follow-up. However, the economic time horizon includes downstream consequences of events, and is frequently longer than for clinical trials. For example, in a clinical trial of statins in cardiovascular disease, the primary trial end point may be myocardial infarction, and once this occurs, there is no further follow-up. In economic analysis, once myocardial infarction occurs, it is critical to

collect related data on health outcomes and resource use to observe treatment differences.

To estimate downstream differences in costs and effects, sufficient detail about clinical events and associated health care resource use must be collected. Some of these data would be collected in the context of the clinical trial, and others would not. For example, to capture changes in health-related quality of life, measurement is required frequently enough to reflect maximum and minimum values over the course of disease. To capture health care resource use associated with medication treatment, sufficient detail including the exact type of drug and treatment regimen, with dose and frequency must be recorded.

ALTERNATIVE APPROACHES TO ECONOMIC EVALUATION

There are multiple approaches to obtaining data for economic evaluation (Table 2), with a tradeoff between internal versus external validity. Observational studies comparing patient cohorts using retrospective data from administrative datasets or prospective observational trials without randomization of treatments have relatively low internal validity. Statistical adjustments such as propensity scores and econometric modeling techniques are typically applied to these data in an effort to achieve “post hoc” comparability of treatment groups.^{13–15} Observational data, although extremely useful for documenting practice patterns and estimating burden of illness, are not always considered optimal for economic evaluation because of potential bias introduced by lack of randomization.^{16,17}

Alternatively, data for economic evaluation can be collected alongside clinical trials, allowing an economic evaluation to be “piggybacked” onto a clinical trial with the primary purpose of estimating efficacy and safety. Evaluating incremental effectiveness and cost in the same population as efficacy can provide consistent information for consideration by treatment and payor decision-makers. Pragmatic trials evaluate effectiveness compared with standard care in “real-world” patient populations and practice settings, and although internal validity may be lower than a standard RCT, they are more suitable for collection of health economic data.^{10–12,18,19} These trial designs differ primarily in the degree of protocolization (Table 2).

TABLE 2. Comparative Overview of Prospective Approaches to Economic Data Collection

Feature	Observational Study	Pragmatic Economic Trial	Piggyback on Clinical Trial
Context	Database analysis or cohort study	Comparative real-world RCT	Comparative clinical RCT
Design	Prospective or retrospective non-interventional	Prospective interventional	Prospective interventional
Validity	Low internal, high external	Medium internal, high external	High internal, low external
Research question	Disease history, practice patterns, burden of illness	Test hypothesis of effectiveness	Test hypothesis of efficacy
Population and comparator	Cohort(s) defined by patients with a specific disease or receiving a specific treatment	“Usual care” control group in broad patient population and routine practice settings	Placebo control group with highly selected patients and standardized, intense follow-up
Suitable for economics?	Not usually	Highly	Moderately

A further consideration is the type of intervention being evaluated. The majority of cost-effectiveness analyses to date are of drug interventions, but increasingly, evaluations of medical devices and diagnostic tests are being undertaken.^{2,20,21} Evaluations of devices and tests can present additional challenges for economic evaluation because these trial designs do not always include a relevant comparator or follow patients long enough to capture important health care events. Similarly, evaluations of behavioral interventions present some unique challenges for economists. Behavioral change is a time-dependent cognitive process, and including partial behavioral change requires additional information to link partial to fully successful behavioral change, which may not be observable within the context of the trial.²²

Regardless of the study design, if important costs occur beyond the trial, modeling may be needed to project data beyond the trial timeframe, and a need may remain for modeling costs of screening and diagnosis or real-world treatment and compliance to address policy-relevant economic questions.^{18,23}

DESIGN CONSIDERATIONS IN IMPLEMENTING A TRIAL-BASED HEALTH ECONOMIC STUDY

Since economic outcomes are often not the primary end point of interest, the investigator needs to balance the tradeoff between internal validity and external validity, and consider carefully whether the clinical trial is suitable for economic data collection.^{10,11,18,19}

Selection of Comparator Treatment

The comparator treatment of interest in economic evaluation is typically “usual care” or “standard of care” or the most commonly used treatment, enabling incremental assessment of outcomes and costs of the new treatment compared with current practice for the calculation of the ICER. For example, in a study of controlled-release treatment for osteoarthritis pain, the comparator was the most commonly prescribed pain treatment in the relevant market.²⁴ A trial with a placebo comparator can be appropriate for economic evaluation if a new treatment is added on to current treatment, or there are no currently used treatments. For example, an RCT of donepezil versus placebo for patients with moderate to severe Alzheimer disease that included collection of health resources in the community as well as medical care, was used as the basis for an economic evaluation of costs and clinical consequences associated with adding donepezil to usual supportive care for these patients.²⁵

Selection of Effectiveness Measure

In selecting an appropriate treatment effectiveness measure, the “gold standard” outcome that is definitive must be considered versus the outcome measures typically applied in routine practice. Although the investigator seeks to minimize measurement biases introduced by a measure other than the gold standard, there is also a risk of bias from using a gold standard that is not common practice. A classic example of this is diagnosis of deep vein thrombosis using the gold standard of venography.¹⁸ Venography is painful, requires an injection, and is more expensive than routine diagnosis based

on clinical signs and symptoms. Venography also diagnoses more cases than would be routinely identified in clinical practice. For the purposes of measuring effectiveness for economic evaluation, the appropriate outcome measure for diagnosing deep vein thrombosis would be routine diagnosis based on clinical signs and symptoms.

Another related issue is the use of intermediate biomedical markers rather than final health outcomes because of the prohibitively large sample sizes required to test for differences in final outcomes. For example, initial trials of drugs for osteoporosis often examine changes in bone mineral density rather than fracture outcomes.^{26,27} However, for economic evaluation to inform resource allocation, the outcome needs to be translated into the impact on final health outcomes, such as mortality and morbidity, to enable an estimate of cost-effectiveness ratio using a metric that can be compared across disease areas and interventions.

Selection of Study Population

To capture effectiveness in routine practice, the study population should include a broad, representative sample of patients treated in routine practice. Recruitment of highly selected patients for RCTs may compromise data relevance for measuring effectiveness in economic evaluation. The impact of selective recruitment was observed in studies of coxibs, whereby the RCTs were mostly designed to assess upper gastrointestinal effects, and largely excluded patients with cardiovascular disease, whereas observational studies and analyses of administrative databases showed that 40% of patients in practice had a history of cardiovascular disease.^{28–30}

Time Horizon

For economic evaluation, the ideal time horizon is a lifetime so that all downstream consequences of the medical intervention can be captured. In contrast, trial follow-up often terminates when the clinical event of interest has occurred. If the clinical event is death, then the time horizon for the economic and clinical perspectives is the same. The investigator needs to assess whether sufficient data are available to conduct an analysis within the study timeframe or to model subsequent clinical events and associated resource use beyond the timeframe of the clinical trial. For example, in a trial-based evaluation of topical growth factor for nonhealing neuropathic diabetic foot ulcers, the healing over 20 weeks in both treatment groups was extended to a 1-year time horizon to capture the downstream clinical and cost consequences of differences in the healing rate.³¹

Sample Size

Given the large variability of cost data, a trial powered on the basis of economic hypotheses would require a sample size larger than that required for the primary clinical outcome. However, the clinical question commonly predominates the policy question in selecting sample size for trials with primary outcomes of efficacy and safety. In the absence of sufficient power to test economic hypotheses, there have been substantive methodological advances in examining sampling uncertainty for ICERs.^{32–34}

Protocol Driven Care

It is important to exclude protocol-driven components of care such as study assessments not typical in routine practice.³⁵ For example, visits and procedures mandated by strict RCT protocols often reflect a more intense level of monitoring and so resource consumption than standard practice. This more frequent monitoring may also lead to identification of additional health problems that may not have been discovered otherwise and therefore increased health resource use. Although it is possible to adjust the estimates post hoc after accounting for protocol-driven care based on adjudication of the patient records, this is difficult to do in practice.

ANALYTICAL CONSIDERATIONS IN IMPLEMENTING A TRIAL-BASED HEALTH ECONOMIC STUDY

The basic steps in any economic evaluation include: (1) quantify clinical outcomes, (2) quantify health care resource use, (3) value health care resource use to estimate health care costs, (4) calculate incremental outcomes and incremental costs (the difference in means between treatment groups) and the ICER, (5) evaluate uncertainty around the ICER.

An economic evaluation, even when conducted using clinical and resource use data collected within a clinical trial, requires a separate analysis plan to that of the clinical trial. Additional analytical issues are addressed for differential censoring of cost data and the need to estimate variability jointly for both outcome and cost data within the cost-effectiveness ratio. It is possible that the clinical findings from a trial are not statistically significant, but examining the joint density of cost and effect differences when the differences in outcomes are small is even more relevant to quantify uncertainty around the ICER. For example, the economic analysis of the atrial fibrillation follow-up investigation of rhythm management trial demonstrated that rhythm control is not cost-effective compared with rate control (rhythm control was dominated by rate control) despite the finding of a nonsignificant trend toward reduced survival in patients with atrial fibrillation who attempt rhythm control compared with rate control.³⁶

Measuring Cost

The goal in a cost-effectiveness analysis is to estimate long-run marginal costs. There are several approaches for estimating these disease-related costs. In some cases, costs and health resource use can be obtained directly from access to administrative medical billing records of trial patients. Patient self-report onto study case report forms can be used for costs known only to the patient such as out-of-pocket payments for health products. A frequently used method is the collection of health resource use for all patients within the trial, and then application at the time of analysis of standard/typical unit prices from a source outside of the trial. This method has the advantage to reduce the variability in cost due to variation in unit prices that are not meaningful to the treatment comparison, and also minimizes the problems caused when billing information is available for only some centers or patients.^{19,37}

Dealing With Skewed, Missing, and Censored Cost Data

Cost is a summary measure over the fixed evaluation timeframe. Health resource use, and consequently cost data, can be missing due to: premature study withdrawal; loss to follow-up; or variable follow-up due to either patients terminating at the clinical event end point or fixed termination of the trial with varied enrolment. Including only complete cases is not usually possible or appropriate since there may be few complete cases with full follow-up and these may not be representative of the entire population of interest.^{38,39} Imputation may be required to “fill in” missing assessments or visits, and extend estimated cost from the patients study participation to the fixed equal timeframe. Choice of imputation method will depend on underlying assumptions regarding missing cost and the importance of retaining variability in the final cost estimate.⁴⁰ Possible methods including linear extrapolation beyond the observed time, substituting the mean value for similar patients, regression approaches, and multiple imputation. Oostenbrink et al⁴¹ have reported that results of these methods can vary substantially.

Cost data generally violate the assumption of independent censoring because patients accrue costs at different rates. For long follow-up periods, advanced methods such as the Kaplan Meyer sample average to partition the study duration into multiple time intervals have been shown to provide consistent estimators of average costs that are asymptotically normal under the assumption that censoring occurred at the boundaries of the defined time intervals.^{42–47}

The ICER is calculated based on the mean costs and outcomes for each treatment group. Even though it is well known that cost data can be skewed, with many low costs and a few very high costs so that the arithmetic mean is greater than the median or “typical” value for most patients, it is still the arithmetic mean that is the most appropriate and robust measure of expected costs and is the measure that should be used in cost-effectiveness.^{48,49} Transparent and clear reporting of the rate of patient study withdrawal and methods of imputing data or adjusting for censoring data is recommended.

Assessing Uncertainty of the ICER

Assessment of uncertainty includes sampling and parameter uncertainty. Sampling variability, most commonly reported as a confidence interval, depends on variation in both the numerator (incremental cost) and the denominator (incremental effectiveness) of the ICER, and is not a straightforward calculation.^{50,51} A method that has become common is use of bootstrapped resamples with replacement to provide ICERs for hypothetical repeats of the study under the assumption that the study sample is a valid representation of the underlying population of interest. The ICERs are plotted on the cost-effectiveness plane as a “cloud” of points representing uncertainty,^{52,53} and cost-effectiveness acceptability curves are used, to show the probability that the new intervention should be considered cost-effective at a range of willingness-to-pay values.^{34,54,55}

Parameters such as unit costs and the discount rate should be assessed for uncertainty using sensitivity analysis

to determine robustness of the ICER. One-way sensitivity and multiway sensitivity analysis, varying multiple parameters simultaneously, are commonly applied.⁵⁶

Cost-Effectiveness Estimate for Patient Subgroups

Although the overall analysis estimates cost effectiveness for the patient population represented in the trial, there is an underlying heterogeneity in the cost-effectiveness whereby some subgroups of patients may receive greater clinical benefit from the new therapy, and this can also mean there is greater savings of health care related to better clinical outcomes. Therefore, the cost-effectiveness can vary between different subgroups, and it can be important to identify groups of maximum clinical benefit and cost-effectiveness to maximize the chance of reimbursement. Within a trial-based economic evaluation, patient subgroup analyses may be considered to address this, although this can be limited by available sample size. This type of analysis can be conducted using regression approaches to maximize the efficiency of estimates.^{32,57,58}

Analytical Issues Related to Multinational Studies

Increasingly clinical trials are conducted on a multinational basis, and economic evaluations for a specific country using clinical and health resource data collected within a multinational clinical trial have certain challenges.⁵⁹ Such studies are designed to estimate clinical effectiveness by pooling all patients regardless of the country in which they are treated. However, disease-related costs are relevant to a specific perspective (audience or payor) usually specific to country. They require country-specific unit prices and are expressed in a particular country's currency.

Furthermore, resource use for patients who do not respond to initial therapy, treatment of adverse events, and supportive care or associated productivity time loss may differ between countries based on differences in physician practice, culture, structure of the health care system, and available resources.⁶⁰ Therefore, the total disease-related cost for the country of interest has to be calculated for each patient in the study based on their reported health resource use and unit prices for the specific country for which economic evaluation is being conducted. Barbieri et al⁶¹ in a review of published multicountry economic evaluations found cost-effectiveness results for pharmaceuticals to vary from country to country in Western Europe.

A commonly used approach to address generalizability of resource use across countries for a particular multinational study-based analysis is to first test whether the effect of treatment choice on intensity of resource use differs across countries.⁶⁰ If this test is nonsignificant as was found in a multinational study conducted across Europe comparing antibiotic regimens for hospitalized patients with community-acquired pneumonia,⁶² then it is assumed that the resource use of all patients can be used with unit prices applied for the country of interest. If the effect of treatment on the intensity of resource use is found to be different across countries, or if more country-specific cost estimates are required, the cost/

TABLE 3. Design and Analytical Considerations in Trial-Based Economic Evaluations

Issue	Description
Choice of comparison therapy	Compare new intervention against most widely used current therapy or standard of care
Selection of effectiveness measure	Is the gold standard for the trial efficacy outcome used in routine practice? More appropriate measure for effectiveness in secondary trial end points?
Study population	Can the study population be considered reasonably representative of the population who will receive the treatment in routine care
Length of follow-up	Are key clinical and cost impacts captured within the follow-up timeframe?
Sample size	Estimation of uncertainty is the focus rather than hypothesis testing since there is greater heterogeneity in resource use and costs than clinical end points
Protocol driven care	Economic evaluation seeks to exclude outcomes and costs that result from the trial protocol
Dealing with skewed, missing, and censored cost data	Imputation is used to provide aggregate cost estimate over the fixed timeframe for all patients. The mean for each group is used to estimate incremental difference in cost between treatments
Assessing uncertainty of the incremental cost-effectiveness ratio	Sampling uncertainty estimated using bootstrapping. One-way and multi-way sensitivity analyses to address parameter uncertainty
Cost-effectiveness estimate for patient subgroups	Cost-effectiveness estimates for patient subgroups may be of interest to decision-maker audiences
Analytic issues related to multinational studies	Practice patterns and health care resource use may vary considerably by country in the context of multinational trials

resource use can be adjusted to the country of interest using a regression-based analysis.⁶³ These models can be extended to include characteristics of the sites and countries if these are known.^{64,65}

CONCLUSIONS

Clinical trials can provide an efficient opportunity to collect data for economic evaluation, taking advantage of the rigorous experimental design and the data collection infrastructure. Nonetheless, the suitability of the study design for economic evaluation must be considered carefully because of the differences between clinical studies and economic studies in the questions that they seek to answer. In situations where study comparators and other treatment reflect routine clinical practice, and study follow-up captures important costs and effects, clinical trials, even those conducted multinationally, can provide a valuable and efficient opportunity to collect data for economic evaluation. In conducting a trial-based economic evaluation, it is important to involve a broad patient population, measure effectiveness reflecting important

benefits for patients, and to apply appropriate analytical methods to obtain relevant results.

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