Clinical Economics in Clinical Trials: The Measurement of Cost and Outcomes in the Assessment of Clinical Services through Clinical Trials

Kevin A. Schulman, Akira Ohishi,† Jaewon Park,1 Henry A. Glick2 and John M. Eisenberg3

The Clinical Economics Research Unit, Department of Medicine, Georgetown University Medical Center, Washington D.C., 1Department of Internal Medicine, Tokyo Daini National Hospital, Tokyo, Japan, 2Division of General Internal Medicine and the Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA, 3Agency for Health Care Policy and Research, US Department of Health and Human Services, Washington D.C., USA

(Received for publication on August 17, 1998)

Abstract. As the population ages and more expensive high-technology services become available, health care costs continue to spiral upward. Because the financial resources for health care are limited, economic analysis can help to evaluate expenditures and set priorities. Economic analysis of medical technology or medical care evaluates a medical service by comparing its dollar cost with its dollar benefit (cost-benefit), by measuring its dollar cost in relation to its outcomes (cost-effectiveness) as well as in relation to its utility or quality-adjusted outcomes (cost-utility), or simply by tabulating the costs involved (cost-identification). Direct costs are generated as services are provided. In addition, patients' productivity is affected, and these costs can be considered, especially in determining the benefit of a service that decreases morbidity or mortality. Intangible costs are those of pain, suffering, and grief. The point of view, or perspective, of the study determines the costs and benefits that will be measured in the analysis. Sensitivity analysis, which can evaluate the stability of the conclusions to the data used, is an important assessment within economic analysis. Economic analysis of new pharmaceutical therapies is increasingly being incorporated into clinical trials. Although there are some limitations of pharmacoeconomic information in clinical studies of drug safety and efficacy, these trials are often the only opportunity for economic data collection before adoption and reimbursement decisions are made. Validation after the drug has been introduced should complement economic information developed from clinical trials. (Keio J Med 48 (1): 1-11, March 1999)

Key words: clinical economics, pharmacoeconomics, cost-effectiveness analysis, clinical trials

Introduction

As populations age and as the use of expensive high-technology services increases, health care costs have been increasing at rates greater than inflation in most developed countries. For example, with one person in six already older than 65, the challenge of how Japan will support its aging society grows more bedeviling with each passing year.1 Moreover, in Japan, health care costs have recently been increasing every year by at least 1 trillion yen ($8.3 billion),2 although the fund of premiums to support the health care system has been relatively decreasing. As a result, copayments by patients, including aged patients, have been increasing in Japan. A consequence of scarce resources available to fund health care services is that it might not be possible to fund every treatment that might have some benefit. When resources for health care are scarce, allocating

Presented at the 1035th Meeting of The Keio Medical Society in Tokyo, July 23, 1998.
Reprint requests to: Dr. Kevin A. Schulman, Department of Medicine, Georgetown University Medical Center, Washington, D.C. 20007, USA
* Present address: Department of Internal Medicine, Kasumigaura National Hospital, 2-7-14 Shimotakatsu, Tsuchiura, Ibaraki 300-8585, Japan
these resources requires careful decision making. In this setting, information with which to make these decisions becomes critical. Asking questions about effectiveness (health benefits in real practice settings rather than efficacy or health benefit derived under ideal conditions), efficiency (the effectiveness of the treatment in actual clinical practice compared with its cost), and cost is important for this purpose. Economic analysis has been introduced as a means to improve information for decision makers facing these allocation decisions. In order to help meet these information demands, the Japanese government established the Institute for Health Economics and Policy, a non-profit organization, in 1993.

Although the importance of economic analysis for purchasing care or for regulation has been stressed, clinical uses of economic analysis should not be ignored. For patients themselves, the data from economic analysis may be useful in understanding the outcomes and resource use associated with a treatment. Pharmaco-economic studies are often designed to meet the different information needs of health care purchasers, regulatory authorities, clinicians, and patients. In recent years, pharmaceutical companies have been submitting pharmaco-economic data to the government in Japan. With the increased use of economic data in reimbursement discussions worldwide, the methods of economic evaluation have evolved rapidly. Economic evaluation of pharmaceuticals (pharmacoeconomics) has been implemented in phase III clinical trials in order to improve data for setting priorities and determining whether to provide reimbursement for new pharmaceutical products. This effect complements previously established modeling methodologies for economic analysis. Thus, economic analysis is becoming increasingly more informative at a time when use of the data it provides is more critical.

In this paper, the methods of economic analysis will be explained and issues related with incorporation of economic analyses into clinical trials will be introduced.

Methods of Clinical Economic Analysis

In considering economic analysis of medical care, there are three different dimensions of analysis, represented by the three axes of the cube in Fig. 1. Along the horizontal axis there are three different types of economic analysis: cost-identification; cost-effectiveness including its subtype, cost-utility; and cost-benefit. Along the second axis there are four different types of costs and benefits that can be included in economic analysis of medical care: direct medical costs and benefits, direct non-medical costs and benefits, productivity costs and benefits, and intangible costs and benefits. Along the third axis are four points of view, or perspectives, that one may take in assessing the costs and benefits of a new medical therapy: society, patient, payer, or provider. Each of these dimensions will be reviewed in the following sections.

Types of Economic Analysis

If two or more alternatives are compared and if both costs and consequences of alternatives are examined, a full economic analysis is being performed. There are four full economic analyses performed in clinical economics: cost benefit, cost-effectiveness, cost utility, and cost identification analysis.

Cost-benefit analysis: Cost-benefit analysis of medical care compares expenditures in different programs and values all outcomes or health states noticed by the patient in the same economic units, usually monetary units (e.g. yen). Cost benefit analysis is potentially a broad form of economic evaluation which allows policy analysts to compare the economic impact of newly developed health care technology with other investments in health care or with investments in other fields such as education, construction, or the environment. If properly done, benefit-cost analysis can be of great help to agencies participating in the development of health, environmental, and safety regulations. In practice, however, the full implementation of this paradigm is often restricted by measurement difficulties caused by the disadvantages of this method.

The major disadvantage of cost benefit analysis of health care is the requirement that human lives and
outcomes (treatment benefits), including quality of life, be valued in monetary units. Many decision makers in the health sector find this transformation difficult or unethical, not only because they consider life to be priceless and because life cannot easily be valued, but also because each patient values his or her life differently. Thus, cost benefit analysis is used less frequently than cost-effectiveness analysis in the medical literature.

Cost-effectiveness analysis: Cost-effectiveness analysis provides an alternative approach to the dilemma of assessing the monetary value of health outcomes as part of the evaluation of new services or other products. Outcomes might be reported in a single unit of measurement, either a conventional clinical outcome, such as years of life saved, or a measure that combines several outcomes on a common scale. Alternatively, health outcomes can be reported in terms of a change in an intermediate clinical outcome, such as cases with a complete response to treatment or costs per mm Hg reduction in blood pressure. If an analysis employs quality-adjusted survival outcomes, it is called a cost-utility analysis, a form of cost-effectiveness analysis measuring outcomes in terms of their value to patients.

Cost-effectiveness analysis has been used to compare costs and years of life saved for interventions using various outcomes. Life years and quality-adjusted life years are the most widely used outcomes. There are many examples: screening for breast cancer, colorectal cancer, and left main coronary artery disease. These papers have "years of life saved" as an outcome. Quality-adjusted life year was used as an outcome in treatment of chronic myelogenous leukemia, bypass surgery for coronary artery disease, and vaccination against pneumococcal pneumonia (see cost-utility analysis). Sometimes, intermediate outcomes such as percent reduction in blood cholesterol level with drugs were used. The results of a cost-effectiveness analysis can be summarized in a series of cost-effectiveness ratios that show the cost of achieving one unit of health outcome (e.g. the cost per year of life saved) for different kinds of patients and interventions.

The additional or "incremental" cost of an intervention (e.g. the difference in cost between a new therapy and conventional medical care) may be compared with its additional or "incremental" benefit or effectiveness. If the cost of a new therapy and conventional therapy is $CN$ and $CC$, respectively, and if the effectiveness of a new therapy and conventional therapy is $EN$ and $EC$, respectively, the incremental cost-effectiveness is $(CN - CC) / (EN - EC)$ as in Table 1. Incremental analysis is generally preferred to comparisons of the totals because it allows the analyst to focus on the differences between any two treatment modalities rather than between a treatment modality and doing nothing. In assessment using the same measure of health outcome, such as cases of a particular disease prevented, the same comparator, and the same analytic method, one can rank interventions on the basis of their cost-effectiveness ratios (e.g. among $C/E$, $C'/E'$, and $C''/E''$).

Figure 2 shows the possible combinations of incremental cost and incremental effectiveness. Programs that are cost-saving with improved or equivalent treatment outcomes are said to be dominant and should always be adopted. Programs that cost more and are more effective should be adopted if both their cost-effectiveness and incremental cost-effectiveness ratios fall within an acceptable level, and the budget for the program is acceptable. Programs that cost more and have worse clinical outcomes are said to be dominated and should never be adopted. Programs that cost less and have reduced clinical outcomes may be adopted depending upon the magnitude of the cost and outcome changes.

Unlike cost-benefit analysis, the cost-effectiveness approach does not always allow the comparison of programs and activities with widely differing outputs, such as health, education, defense, energy, transportation, and other areas. If the same outcome, such as lives saved, is used, cost-effectiveness can be compared across these sectors (assuming life years are equivalent across treatments being compared; for example, life years for

<table>
<thead>
<tr>
<th>New Therapy</th>
<th>Conventional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>$CN$</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>$EN$</td>
</tr>
<tr>
<td>Cost-effectiveness ratio</td>
<td>$CN/EN$</td>
</tr>
<tr>
<td>Incremental Cost-effectiveness</td>
<td>$(CN - CC) / (EN - EC)$</td>
</tr>
</tbody>
</table>

**Table 1 Incremental Cost-Effectiveness and Cost-Effectiveness Ratio**

<table>
<thead>
<tr>
<th>Improved or Equal Clinical Outcome as a Result of Treatment Strategy</th>
<th>Worse or Equal Clinical Outcome as a Result of Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in Medical Costs as a Result of Treatment Strategy</td>
<td>+</td>
</tr>
<tr>
<td>Increase in Medical Costs as a Result of Treatment Strategy</td>
<td>+/−</td>
</tr>
</tbody>
</table>

**Fig. 2 Results of an economic study.**

Adapted from Schuelman and Yabroff 1996
patients receiving dialysis may not be equivalent to life years for patients not receiving dialysis). However, this model has been applied in most cases for resource allocations only within the health sector, and usually just within a single therapeutic area.

Cost-effectiveness analysis without utility analysis may lead to conclusions unacceptable for some patients. For example, continuous ambulatory peritoneal dialysis (CAPD) for patients with end-stage renal disease is reported to be more cost-effective than hospital hemodialysis. However, CAPD requires a patient to have a permanent catheter placed into the abdominal cavity to allow them to conduct dialysis at home, and patients need to instill and drain fluid into this catheter several times per day. In hospital hemodialysis, patients must go to the hospital a few times a week, but they are not required to do any of the procedures themselves and are released from the machine after three or four hours. There are no studies of patients’ preferences for type of dialysis in Japan. If we assume that the survival from these two procedures is identical, and patients have significant loss of utility for their health state from CAPD, it is possible that an analysis from a patient perspective or a cost-utility analysis may recommend hospital hemodialysis, even if a cost-effectiveness analysis based only on survival recommends CAPD.

Cost-utility analysis: As described above, this analysis is a variant of cost-effectiveness analysis. Cost-utility analysis adds quality of life adjustment to outcomes in cost-effectiveness analysis. Utility refers to the desirability or preference that individuals or societies have for a given outcome. In most cases of utility assessment, the worst imaginable health state is scored at 0.0 and perfect health is scored at 1.0. Utility is shown by a number between 0.0 and 1.0. There are several popular methods for the direct measurement of such preferences, including the visual analog scale, time trade-off method, and standard gamble. Methods that examine patient preferences under conditions of risk or uncertainty are considered true utility assessments (time-trade-off or standard gamble). Methods that examine patient preferences not under these conditions are considered value assessments (visual analog scale). For example, if a patient with hospital hemodialysis thought that 10 years of life with hospital hemodialysis would have the same value as 8 years of healthy life without dialysis (i.e. the patient would be indifferent between the two), the patient would have a utility value of 8/10, or 0.8 for hospital hemodialysis by the time trade-off method. The comparison of costs and utilities is referred to as cost-utility analysis.

Utility analysis is used for the calculation of quality-adjusted survival. Quality-adjusted life years (QALYs) attempt to combine expected survival with expected quality of life in a single metric. If an additional year of healthy life is worth a value of 1 (year), then a year of less healthy life is worth less than 1 (year). For example, if a patient’s life expectancy is 10 years and utility of patients on lifelong hospital hemodialysis is 0.3, the patient would be reported to have a life expectancy of 3 quality-adjusted life years.

Figure 3 depicts quality-adjusted life years gained through an intervention. Quality of life sometimes decreases and recovers, so the quality of life and the resulting QALYs vary over time as a result of a given treatment program. The difference in quality-adjusted life years between two programs, which is shown as an area “QALYs Gained,” represents the incremental outcome of the treatments over time.

Utility is determined using either community preferences of the general public, of health professionals, or of patients experiencing the health states (and their surrogates), according to the purpose of the study. For the reference case, community preferences are often adopted. When an analysis is designed to evaluate alternative interventions for the same condition, or when assessing new interventions, patient preferences can be employed. Utility assessed using patient preferences for a condition is likely to result in higher numeric values than that assessed using community preferences for the same condition. This may be because patients tend to adjust themselves to a diminished health state, or because community preferences may be biased due to incomplete knowledge of the disease or the treatment.

Cost-identification analysis (cost-minimization analysis): If treatment outcomes or benefits are equivalent for the therapies being evaluated, it is appropriate to employ cost-identification analysis, which compares

![Fig. 3 Quality-adjusted life years gained.](source: Torrance and Feeny 1989)
different treatments based on their costs alone. This measurement is expressed in terms of the cost per service provided (e.g. dollars spent per case treated). Cost-identification analysis is also called cost-minimization analysis, because it is used for identification of the lowest cost of different available diagnostic or therapeutic strategies. For example, cost identification analysis can be used to compare the total cost of care using early hospital discharge of patients with osteomyelitis followed by outpatient antibiotic treatment with the total cost of care for conventional inpatient treatment, presuming that treatment outcomes are equivalent.24

Types of Cost

For economists, the most general concept of costs is opportunity cost (sometimes called social cost). Opportunity cost is defined as the cost of a good or service as measured by the alternative uses that are forgone by producing (or consuming) the good or service.25 Because resources are limited, any decision to produce (or consume) more of one good means doing without some other good. When a magnetic resonance image (MRI) is produced, for example, an implicit decision has been made to do without a CT that could have been produced using the labor and raw materials that went into producing the MRI image. Thus, the opportunity cost of one MRI image is equal to that of some number of CT images.

The second dimension of economic analysis of clinical practice illustrated by Fig. 1 is the evaluation of costs of a therapy. Economists consider four different types of costs – direct medical, direct non-medical, productivity, and intangible.

Direct medical costs: The direct medical costs of care usually are associated with monetary transactions and represent costs that are incurred in providing care. The types of direct medical costs usually considered include those of hospitalization, pharmaceutical products, physicians’ fees, the salaries of allied health professionals, laboratory tests, radiological procedures, rehabilitation, durable medical equipment, and long-term care. Since the charge for medical care may not accurately reflect the resources consumed, accounting or statistical techniques may be needed to determine these direct costs.26–30

Direct non-medical costs: Other monetary transactions undertaken as a result of illness or health care to detect, prevent, or treat disease are direct non-medical costs. These are costs which are incurred because of illness or the need to seek medical care, but are not costs involved in purchasing medical services. These expenditures include the cost of transportation to and from the hospital or physician’s office (e.g. 3-times-a-week taxi fees of patients on hemodialysis), the cost of special foods (e.g. low protein rice, low protein flour, or low protein noodles for patients with chronic renal failure), the cost of special clothing needed because of the illness (e.g. tight stockings for varicosities in the lower extremities), the cost of hotel stays for receiving medical treatment at distant medical facilities, the cost of family care or home aides, and the cost of special housing (e.g. the cost of modification of a home to accommodate an ill individual). Recently, patient time costs, which consist of travel and waiting time as well as the time actually receiving treatment, were recommended to be included as a direct non-medical cost.31 However, we incorporate patient time costs into productivity costs (indirect costs), as has usually been the case. Since direct non-medical costs are rarely covered by insurance, they may directly affect a patient’s finances.

Productivity costs: Productivity costs, in contrast to direct costs, are not produced by transactions for goods or services. Instead, they represent the economic cost of loss of livelihood (for example, time lost from work or impaired earning ability), or loss of life (for example, premature death leading to removal from the workforce). These morbidity and mortality costs represent the loss of opportunities to use a valuable resource, that is a human life, in alternative ways. These types of costs may be important from a societal perspective or from the perspective of an employer. A variety of ways of calculating these productivity costs have been developed.32–36

Intangible costs and benefits: Intangible costs are another category of non-transactional costs. Intangible costs are often difficult to measure, like productivity costs. These are costs of pain, suffering, and grief and other nonfinancial outcomes of disease and medical care that are often considered by clinicians and patients in reviewing potential alternative treatments. Examples are cancer-associated pain, stress caused by illness, worry about losing one’s occupation, concern about being a burden to one’s family, worry about the restriction of water intake in hemodialysis patients, grief with losing sight or amputation of a leg, or concern about being restricted to liquid foods in Crohn’s disease. Investigators are developing ways to measure intangible costs, such as willingness to pay analysis in which patients are asked to place monetary values on intangible costs.10 However, these costs are often omitted in clinical economics research. In cost-benefit analysis, intangible costs and benefits should be measured in the same units as direct and productivity costs (usually in terms of currency). In cost-utility analysis,
intangible costs may be incorporated into the outcome by measuring utility values for health states, as in quality-adjusted life years.

**Perspective of Analysis**

The third axis in Fig. 1 shows the perspective of an economic analysis of medical care. Costs, outcomes, and benefits might be calculated differently from different points of view, such as society, the patient, the payer, and/or provider. A study's perspective determines how costs and benefits are measured, and the economic impact of an intervention will be reported differently depending upon the perspective taken.

For example, the cost of hospitalization from the perspective of the patient is the amount paid out-of-pocket, or the portion not covered by insurance and the other costs that might be incurred because of illness or treatment, including time missed from work. The cost of hospitalization from the perspective of the provider, such as a hospital, is the cost of providing the service which includes labor costs, the costs of the buildings in which the services are provided, and other overhead costs. The cost of hospitalization from the perspective of the payer, such as Employees' Health Insurance, National Health Insurance, or health insurance for the elderly in Japan, is the amount of money that the payer pays to the hospital under the coverage plan for the individual who is hospitalized. The cost of hospitalization from the perspective of society as a whole is the total net cost of all of the different components of society, including the patient's lost productivity due to the illness as well as the resources consumed in giving and receiving medical care.10

Because the broad nature of the health care cost problem suggests that the perspective should be equally broad, the preferred perspective in economic analysis for government authorities or decision makers is societal. A societal perspective seeks to determine the net costs of the treatment or intervention to all payers for all persons. Other perspectives can also be important components of an overall economic assessment and may be of greatest interest to other decision makers.

**Economic Evaluation of New Clinical Therapies**

The cost of drugs includes not only their purchase price but also the accompanying costs of preparation, administration, monitoring for and treating side effects, and the economic consequences of successful disease treatment, all of which are influenced by clinical and pharmacologic characteristics of pharmaceuticals. Thus, in addition to differences in efficacy and safety, differences in efficiency are pivotal in distinguishing drugs from each other.37

**Research Methods of Clinical Economics**

There are several methods to evaluate efficiency of clinical therapies, e.g. prospective and retrospective analysis of clinical trials, retrospective analysis of specific patient populations, analysis of administrative data bases that describe the experience of a specific patient population defined by the type of health care payer, and decision-analytic models that predict the effectiveness of therapies using existing clinical data.38 Here, we principally discuss prospective economic analysis of clinical trials.

**Prospective Analysis of Clinical Trials**

Prospective economic studies of clinical trials are designed specifically to measure the costs and benefits of new pharmaceutical therapies. Although generalizability is an issue in early clinical trials, prospective economic evaluation within phase III clinical trials is a must if systematic decision-making is to be performed prior to making a reimbursement decision for a new product.

Prospective study design has been considered to be needed especially for expensive drugs such as recombinant drugs (e.g. recombinant human erythropoietin and interferons), drugs that are likely to be prescribed in high volume (e.g. antihypertensive drugs), or new and innovative drugs that may be more effective than existing therapy (e.g. HMG Co-A reductase inhibitors).39 In fact, over the last few years, the number of prospective economic evaluations of new pharmaceutical products has grown rapidly.40,41,42,43 as these expensive drugs of great importance have been developed despite limited health care resources. Pharmacoeconomic data have become increasingly important for reimbursement decisions by national health programs and private health care organizations in the United States and other developed countries.5 Such economic evaluations aim to compare the costs and benefits associated with a new drug with the current therapy.

Randomized controlled clinical trials are recognized as the best source of data on the efficacy of new interventions and are the preferred approach for evaluating health care technologies. Since clinical trials often precede reimbursement decision-making (phase III clinical trials), they provide an opportunity to collect economic data for reimbursement decision-making.39 In fact, Australia and Denmark have implemented and Canada is considering a set of national guidelines that would mandate the presentation of pharmacoeconomic data at the time of product registration for pharmaceuticals to qualify for reimbursement through the national health insurance systems.42,43 In many European countries, submission of economic data is encouraged, although
not officially required.\textsuperscript{44} Several major organizations that run trials, such as the UK Medical Research Council (MRC) and the European Organization for Research and Treatment of Cancer (EORTC), have a policy of always considering health economics and quality-of-life implications when a new randomized clinical trial is designed. These tendencies have led to an effort to integrate economic evaluation and economic concepts throughout the clinical development process. In Japan, pharmaceutical companies have been submitting post-adoption pharmacoeconomic data to the government in recent years.\textsuperscript{4}

\textit{Economic Studies Alongside Development of New Pharmaceutical Drugs}

Both economic and clinical research have common important factors to consider in clinical trial design.\textsuperscript{45} Good economic evaluation needs planning, pilot studies, and development of models of disease and treatment. Pharmaceutical companies will require greater coordination of these efforts to integrate clinical and economic research into clinical trials as the cost in lost sales or market share for underdeveloped economic assessments becomes more apparent. In addition, companies can consider the use of economic models in their internal planning processes.\textsuperscript{46}

Development of new clinical therapies, especially pharmaceuticals, generally proceeds along four well-defined phases that are referred to as phase I through IV studies. Clinical economics can be integrated throughout this development process.

\textit{Phase I:} Phase I studies, which are performed only after preclinical information obtained in vitro or in animals, evaluate the safety and dosage using a small number of (usually healthy) humans. Phase I studies determine the maximally tolerated dose (MTD), a dose just before unacceptable toxicity is experienced by patients. At this stage, economic analysis should provide a discipline to the business case based on pharmacoeconomic principles, and clearly establish the types of clinical and economic information that should be collected during the clinical development program.

During this planning phase, pharmaceutical companies should develop strategies for economic analysis for the clinical development process. They should consider epidemiologic models of disease, economic models of disease episodes, and broader economic analyses of burden of disease that include direct costs, productivity costs, and intangible costs of disease. Both assessment of the new therapy and marketing planning will be conducted using these data.

\textit{Phase II:} Once the MTD is established in phase I trials, evaluation of biologic effect and adverse events is the purpose of the next series of clinical trials. Thus, phase II trials evaluate the feasibility, treatment effects including side effects, and dosage in a patient population with the disease of interest. Phase II design depends principally on the quality and adequacy of phase I trial data. The results of the phase II studies, in turn, are used to develop pilot data to help design phase III studies. During the phase II studies, variance estimates for costs, quality-of-life, and utilities for patients with a specific clinical syndrome should be assessed for sample size calculations and power determination. Evaluation of economic case report forms and clinical assessment instruments also should be performed for economic analysis at this stage. Economic investigators need to develop and refine models of disease and treatment to guide assessment of potential critical trial parameters.\textsuperscript{45,47} The data collected in phase II studies can be used to determine which data elements are high-cost, high-frequency, or are likely to be affected by treatment. The target audience for phase I and phase II assessment is decision makers within the pharmaceutical company.

\textit{Phase III:} Phase III studies are randomized trials, in which randomization can exclude the possibility of systematic bias, to assess and compare the safety and efficacy of a new therapy either with those of a placebo or those of a therapy that the new treatment will potentially replace. Phase III studies are also pivotal reimbursement and marketing studies. Economics investigators will need to address common study design issues such as required sample size, expected duration of clinical benefit, and external validity of the study population, and ensure that there is no economic bias resulting from the clinical study design.\textsuperscript{46} For example, if a certain laboratory defined endpoint is needed for discharge of patients on a new chemotherapy regimen, the protocol may prolong hospital stays if the new treatment has less of an effect on the end discharge parameter than the existing therapy. This would result in a bias if the laboratory parameter was not correlated to the clinician’s usual discharge criteria.

The time horizon, or the duration of the clinical study, is another critical parameter in the economic assessment of the therapy that clinical investigators do not always consider adequately. This parameter can have a significant effect on the estimation of clinical benefits of therapy for patients.\textsuperscript{18} If a study assesses patients with a chronic disease, such as chronic renal failure, patient resource use may be postponed from the study period to some subsequent period. Low protein diet or angiotensin converting enzyme inhibitors may delay the progression of chronic renal failure without avoiding renal replacement therapy. In this case,
resource consumption for renal replacement therapy may be delayed but not avoided. If the time horizon of a study is too short, there may not be sufficient information to assess whether resource consumption is avoided or delayed.

Trial endpoints in phase III treatment protocols are usually cure, progression or improvement, failure, and other adverse endpoints. Economic analysis usually relies on final endpoints such as survival or quality-adjusted survival. Thus, economic protocols may have a duration that is different from that for the clinical endpoint. Often, economic trials continue to follow patients when they have stopped the active treatment phase of the protocol. This is because patients often become most important from an economic perspective when they progress in their disease from a clinical perspective.

Because the ratio of the difference in the effect size to the variance is usually smaller for economic data than for clinical data, economic studies generally require a larger sample size than do clinical studies. Budget and time constraints often will limit the sample size of phase III studies, and thus limit the statistical power of economic evaluations. Early communication would allow calculation of sample size requirements for the economic portion of the study based on the phase II economic data, or could allow the development of economic evaluation as a primary study endpoint with an appropriate sample size calculation. Sample size calculations may be performed using pilot data from phase II studies, but the limited number of centers in phase II studies may result in misleading estimates of variances for sample size calculation for multinational phase III studies.

In phase III studies, resource-utilization information is often collected within the clinical protocol. In many trials, the costs of these resources will be assessed through a separate data-collection exercise. Quality of life and utility information can be collected periodically in the trial from study patients (patient assessment), or health states of study patients can be collected periodically within the trial to be valued later from a population sample (societal assessment).

Possible audiences for economic data from phase III trials include government, politicians, physicians, the public, patients, and formulary committees (in hospitals or within government organizations, for example). However, seldom can a single study provide appropriate data for all of these groups. Various decision makers will use economic data in order to determine if they will approve the service or product, if they will use it in practice, if they find it valuable as taxpayers, or if they want to use it themselves.

Phase IV: Clinical economics studies in phase IV consist of efficiency trials and post marketing surveillance studies. These studies are conducted after the product is licensed and marketed and collect data that can be used to perform post-marketing validation of data collected in phase III studies and to look for uncommon effects of treatment. Economic evaluation within phase IV studies are important because of the potential for increased generalizability (the results of phase IV studies may be closer to actual results of future patients in a community) and are conducted to validate in a real-world setting the results of clinical economics studies in phase III clinical trials, or to compare a new drug with other conventional drugs or therapies, or to assess the use of the agent in a special population.

In post-marketing settings, economic data can be collected using prospective and retrospective analysis of clinical trials, retrospective analysis of specific patient populations, analysis of administrative databases that describe the experience of a specific patient population defined by the type of health care payer, or decision-analytic models that predict the effectiveness of therapies using existing clinical data.

Generalizability of Clinical Economics Data Collected Alongside a Clinical Efficacy Study

Both clinical investigators and health care purchasers have concerns about the external validity (generalizability) of both clinical and economic data from clinical trials. Since many clinical trials are performed in teaching hospitals using patients mainly of university hospitals and public hospitals, the clinical results and resource consumption may not be generalizable to all primary care practices. Teaching hospitals, in general, consume more resources than non-teaching hospitals, because teaching hospitals must spend time and money for education of medical students and residents and for better patients’ care expected by society. Patients in clinical trials frequently have better survival and better response to therapy than non-trial patients, irrespective of whether they receive the control or the experimental therapy. The closer monitoring of patients in a trial of an antibiotic drug resulted in economic findings different from those that would be observed in normal practice.

There are limitations in economic analysis incorporated into phase III trials. External validity may be limited because the number of patients participating in the trial is relatively small and those patients may lack variability compared to the patients using the product once it has been approved and marketed. Budget issues may restrict sample size and time horizon. Generalizability to the health system of decision-makers may be limited by differences in cultures and health care sys-
Figure 4 depicts the generalizability of clinical economic data, which increases after initial adoption, and as data represent more typical patients and more typical practice uses. This means that more reliable data can often be obtained from phase IV studies that are conducted in community settings, because there are more diverse participants (in terms of factors such as age, morbidity, and compliance). However, these data are available only after decisions have been made about reimbursement for the therapy and the amount of detail available is often less than in phase III. Economic analyses have recently been included in growing number of phase III clinical trials, since these trials are the final opportunity to collect economic data prior to negotiating either drug approval or reimbursement. As a response to this concern, the design of phase III trials is being revisited to try and improve the external validity of these studies. The results of these studies can then be validated by post-marketing economic studies. These data can be used to reassess reimbursement decisions several years after a product has been adopted.

Examples of Economic Analysis Alongside Phase III Clinical Trials

An example of a prospective economic analysis as a secondary endpoint in a phase III clinical trial was reported in the FIRST study,\(^5\) a randomized international multicenter trial which compared a continuous infusion vasodilator, epoprostenol, with the best usual care for patients with severe congestive heart failure. Prospective economic evaluation served as a secondary endpoint for the study. The clinical trial ended prematurely due to increased mortality in the epoprostenol-treated patients. In multicenter (multicountry) clinical trials, economists are concerned about the possibilities that those trials can incorporate only minimal data collection.\(^9\) However, the economic analysis demonstrated the feasibility of incorporating economic evaluations in multinational phase III clinical trials, although the generalizability of the study was limited in that cost data were developed from a single US hospital.

Another example of an economic study alongside a phase III clinical trial is the IL-3 bone-marrow transplantation study, a multicenter (academic medical centers), randomized, controlled clinical trial.\(^5\) The study assessed economic impact of a new cytokine therapy followed by GM-CSF that was being compared to standard therapy, GM-CSF alone as supportive care, in patients receiving autologous bone-marrow transplant (ABMT) for treatment of lymphoma. Economic analysis of this study showed no significant impact of IL-3 on the costs of care for patients undergoing ABMT for a period of up to 13 months after the procedure. Although there is a limitation that the economic study enrolled only 115 of the 206 patients enrolled in the clinical trial, this study demonstrated the feasibility of prospective economic evaluation within phase III trials of new cancer therapies.

Problems to be Solved in the Future

Reimbursement authorities are increasingly aware of the limitation of economic evaluations conducted in phase III clinical trials and are beginning to design periodic reviews to reassess product indication, effectiveness, and price at periods after the original reimbursement negotiation to validate the claims from phase III trials for wider populations and health care settings.\(^4\) For example, unexpected side effects may be observed after clinical trials, e.g. dry cough by angiotensin-converting enzyme inhibitors, making early estimates of the costs and effects unreliable. In addition, pharmaceutical costs may change after a product has been approved and marketed. Since pharmaceutical companies do not publicize actual costs for production of a drug, the price of the drug is determined according to a price of other drugs or procedures of similar effects. But once it is accepted as standard, bulk discounts are expected and price competition will emerge.\(^4\)

The difficulty with generalization may be more severe for quality-of-life assessments than for objective responses such as survival. Differences in quality of life seen in a trial may bear little resemblance to the magnitude of differences when patients are treated routinely.\(^2,5\) One possible reason for this is a phenomenon of 'trial-induced benefits' where clinical trials are accompanied by better nursing support and extra attention paid to patients.\(^4\) Further empirical evidence is needed to assess the magnitude of this issue.
Pharmacoeconomic analysis in phase III clinical trials should be considered to better inform licensure and reimbursement decisions for pharmaceutical therapies. Because economic analyses alongside phase III clinical trials may have limitations in generalizability, validation after the drug has been introduced (phase IV) should complement the clinical trial economic information. To be successfully implemented, physicians, payers, pharmaceutical companies, politicians, and government must first understand the importance of economic analysis and methods of economic analysis, and then must put it into practice. Although there are valid criticisms of clinical economics, no ideal method of rationing medical care exists. Despite the limitations of economic analysis, these methods are valuable tools for improving resource allocation in the health sector. Increasing interest has helped these methods evolve to improve the information available to decision-makers.

References

28. Bridges JM, Jacobs P: Obtaining estimates of marginal cost by DRG. Health Financ Manage 1986; 40–46
42. Laupacis A, Feeny D, Detsky AS, Tugwell PX: How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992; 146: 473–481
46. Schulman KA, Llana T, Yabroff KR: Economic assessment within the clinical development program. Med Care 1996; 34: DS89–DS95