Clinical-Economic Trials

Background Paper 5

SUMMARY

One consequence of the desire for better information about the economic implications of medical technologies and practices has been the growing practice of collecting and analyzing economic data in clinical trials. This type of research entails incorporating economic measures into the prospective data collection activities of a clinical trial conducted to determine the safety and efficacy of a technology. Both the economic and clinical data from the trial are then analyzed to provide information about the treatment's cost-effectiveness. Clinical-economic trials-trials that include both clinical and economic components-can be initiated either early in a treatment's development (e.g., before its approval by the Food and Drug Administration) or after the treatment has been used in routine clinical practice.

The number of clinical-economic trials is still very small but is growing rapidly. Many of the methodological and practical issues that arise in these trials also arise in traditional clinical trials and in other methods of obtaining cost-effectiveness data. These include, for example, the importance of the economic perspective selected by the researcher and the great variations in methodological techniques that can affect the comparability of cost-effectiveness results. In addition, however clinical-economic trials raise some new issues, such as how to deal statistically with economic data that is more skewed or requires larger sample sizes for statistical significance than the clinical data from the same trial. Also, economic data from a clinical trial may reflect cost- efficacy (15) rather than cost-e festiveness in the real world, just as clinical trials may reflect clinical efficacy (under highly controlled and ideal circumstances) rather than clini-

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cal effectiveness. The data from a study that has strict criteria for selecting patients and is performed at the best academic medical centers may contrast greatly with the data from a trial that is conducted in several community hospitals that are representative of the average U.S. hospital.

Nonetheless, clinical-economic trials offer the opportunity to examine the potential cost- effectiveness of a technology before it becomes irrevocably established in everyday practice, and they can provide sponsors with useful information. The demand for early information on the costs and effectiveness of new technologies is driven by health care policymakers who hope to improve medical care without increasing its costs; by providers who want to remain competitive in a cost-conscious environment; by insurers who must make decisions about coverage and reimbursement; and by manufacturers who adapt their research and marketing strategies in response to these concerns. In view of these demands, clinical-economic trials are likely to become increasingly common. The usefulness and validity of clinical-economic trials can be improved through the futher development of clinical-economic methodology and the establishment of some consensus standards for methods and dissemination of study results.

The cost of health care in the United States has risen rapidly in the past decade. The proportion of the gross national product (GNP) spent on health care rose from 9.1 percent in 1980 to 14 percent in 1992 (69). As a nation, we now spend more than $800 billion annually on health care, which is more per capita than is spent in any other country.

Concern over the rising costs and the deficiencies in our health care system has led to a widespread desire to increase the availability and quality of care while containing or reducing the costs. Policies have been implemented to contain costs and to promote a more rational allocation of resources for health care services. The federal government has established a per-case prospective payment system (Public Law 98-21) to control the cost of hospital care for Medicare patients and a resource-based relative value scale (56) to control the costs of physicians' services. State Medicaid programs have also imposed severe constraints on payments for medical services. Managed care has become an important alternative for employers who are struggling to keep costs down and was incorporated into the Clinton Administration's proposals for health care reform.

Expensive and new medical technologies and practices (e.g., magnetic resonance imaging (63) and recombinant erythropoietin (52)) have received considerable attention as one factor that has contributed to the increase in health care costs (23,45). When used widely, they may not only raise costs directly but also indirectly, by increasing the use of other services (34). Attempting to control the costs of new and expensive technologies, the federal government has implemented policies such as requiring drug manufacturers to of--fer discounts to state Medicaid programs (75). Also, although no formal mechanism exists, Medicare officials have suggested that they may establish cost-effectiveness as a criterion for coverage (42), as is done in Australia and other countries (29). The importance of economic evaluation was recently reconfined in Congress's mandate to the Agency for Health Care Policy and Research (AHCPR) when it was reauthorized in 1992 (Public Law 102-410).

Still, many technologies continue to make their way into routine medical practice without being accompanied by economic information to promote cost-effective use. In part, this reflects the fact that economic information based on experiment and observation has not been widely available to those who determine the use of health care technology. The analyses that have been performed have primarily used data on efficacy derived from clinical trials, but have resorted to the use of economic data that are not derived empirically and that are sometimes derived outside of the context of the clinical use of the technology (60). Most of these economic evaluations of technologies have been performed using decision

modeling, claims data analysis, and other secondary data analytic techniques.

To date, relatively few economic analyses have been based on the economic data collected in clinical trials. In part, this reflects concerns about how adequately the economic consequences of treatment can be appraised at the same time that clinical benefits are evaluated. Nonetheless, integrating the collection and analysis of economic data in clinical trials is a growing practice with several potential benefits:

- Clinical trials, particularly randomized trials, provide a scientifically rigorous method of assessing the clinical benefits (e.g., efficacy and safety) of new technologies (38).
- Clinical trials conducted for the FDA-approval process provide opportunities to collect economic data at the time when they may be most needed for planning and guiding the appropriate use of a treatment by health care providers.
- In contrast to clinical trials, studies using secondary data often incorporate data from disparate and sometimes incompatible sources, which makes the results difficult to interpret or apply. Thus, relevant economic data collected early and rigorously could be especially useful when coupled with strong experimental designs.

Role in Evaluating Health Technologies

Clinical-economic trials provide helpful data for organizations and individuals who must decide how to develop, pay for, or use medical technologies. The decisionmakers include insurers, providers, manufacturers, and panels that formulate national clinical practice guidelines.

Each type of decisionmaker evaluates the economic aspects of a particular technology from a different perspective, which affects what kinds of economic data are collected and how they are analyzed and interpreted. An insurer may want information about the technology's effect on claims for health services in order to promote the appropriate use of the technology and to adjust premiums; a provider may be concerned about how the technology would affect the cost of providing care; a manufacturer may use economic data to facilitate the development and application of new technology, the availability of health insurance coverage, and the strategies for marketing; a national guideline panel may use economic data to arrive at recommendations that meet the public interest in conserving national resources. The consumer's perspective influences the decision about which data to collect in a clinical-economic trial and about how to analyze and interpret the data.

Insurers

Private insurance companies are concerned about how expensive medical technologies will affect their ability to set competitive insurance premiums and about whether new technologies will result in unexpected payments that exceed the revenue from premiums. Early and better information about the cost-effectiveness of treatments is thus increasingly valuable to private insurers who are attempting to predict and control their costs. The need will be even greater if managed care organizations such as health maintenance organizations (HMOS) continue to spread.

In the future, it is even possible that denials of payments for particular health care services might be defended on the ground that the benefits are small in relation to the costs or that other services could result in equal benefits at lower costs. Data on cost-effectiveness would be crucial in such a debate.

Public health insurance programs, such as Medicaid and Medicare, are under pressure to control the rising costs that have resulted from increased enrollment and the expansion of federally mandated benefits. Like their private counterparts, public insurers are concerned about the costs arising from the widespread use of expensive technology. Data on the economic consequences of such technology are needed for informed decisions about coverage and payment policies. Rules requiring public insurers to provide or withhold coverage based on cost-effectiveness (e.g., the proposed addition of cost-effectiveness to the current "reasonable and necessary" criteria for Medicare coverage of medical services [54 FR 4302]) must be based on credible econom-

ic and clinical data and must be promulgated in a timely fashion.

Published economic analyses of treatments received by the Medicare population (e.g., references 51, 64) suggest that the medical community is increasingly aware of the importance of evaluating the cost implications of expensive new technology from the perspective of third-party payers. Many of these studies, however, are published after the technologies and policies for paying for them have become implemented in routine clinical practice—when both practice styles and payment policies are much more difficult to alter than they would have been in the initial stages of the technology's dissemination. For example, if early clinical trials revealed that using recombinant erythropoietin to treat the anemia caused by chronic kidney disease could reduce the costs of hospitalization and transfusion-related illnesses in dialysis patients, the Medicare program—as the principal payer for the care provided to patients with end-stage renal disease—might be willing to pay more for the use of the drug. Thus, early information about the economic effects of treatments under study in clinical trials could promote the spread of cost-effective technology.

Providers

An important result of the pressure for cost containment has been the establishment of the Medicare prospective payment system, under which providers receive predetermined payments for Medicare beneficiaries' hospital stays (Public Law 98-21). Many state Medicaid programs have also adopted per-case prospective payment systems. This payment method may sometimes discourage hospitals from using expensive new technology because the increased cost it entails does not bring commensurate revenue in the short term (3,70). Consequently, hospital administrators want to know whether purchasing and using new technology would not only improve patients' health but also pay for itself. Assessing the economic implications prior to purchasing a new technology has become more common as changes in reimbursement levels have increased the pressure for limiting costs.

Hospitals' pharmacy and therapeutics committees, which are responsible for determining which drugs are placed on the hospitals' formularies, frequently rely on economic analyses in making their decisions. For example, such committees determine whether patients with acute myocardial infarction will usually be given recombinant tissue plasminogen activator or streptokinase, whether low-osmolality or high-osmolality contrast agents will be used in radiologic-imaging examinations (such as computed tomography and cardiac catheterizations), and whether the expensive new anti-emetic drug odansetron will be used instead of traditional anti-emetic drugs.

Manufacturers

Because new medical treatments may be less likely to be used if they are too costly, manufacturers are increasingly concerned about producing technology that is not only safe and efficacious but also cost-effective. In Australia, for instance, pharmaceutical manufacturers must submit evidence that products are cost-effective before they can be included on the government's list of reimbursed products (12). As more countries adopt such requirements in the future, manufacturers will want to be able to use data from clinical-economic trials that address the issues of different international markets. The growing market pressures have led a growing number of manufacturers to evaluate the cost implications of new technologies at earlier stages of development in order to:

avoid making substantial investments in products that are unlikely to be covered by insurance or accepted by providers,
- ensure that data on the economic implications of the technologies are available for marketing purposes, and

facilitate the establishment of prices that will provide adequate returns on the manufacturers' investments, while maintaining the technologies' economic viability.

In some cases, manufacturers might also use economic information to help make other internal decisions as well. For example, a pharmaceutical manufacturer developing a drug with possible applications for a number of different diseases might find economic data valuable for deciding which of the possible indications for the drug it should seek Food and Drug Administration (FDA) approval for.

Guideline Panels

Expert panels convened by federal agencies (and other organizations) routinely develop clinical practice guidelines based on information about the safety and effectiveness of medical technologies. The use of information about the costs and cost-effectiveness of technologies by such panels is less common but not unknown, and it may increase.

Since 1977, for instance, the National Institutes of Health (NIH) has convened conferences to develop statements of consensus about important management issues in medical care. Although the primary purpose of these statements is to comment on the efficacy and safety of treatments, 16 of these statements have used the word cost- effec*tiveness,* and three conferences have addressed the question of cost-effectiveness (19). Cost issues were discussed at 53 of the 93 consensus development conferences held between 1977 and 1992 (19).

One of the functions of AHCPR, which was established in 1989, is to develop clinical practice guidelines (Public Law 101-239). Although the original mandate emphasized the reduction of variations in medical practice and outcomes as a goal, rather than cost containment, legislation reauthorizing the agency in 1992 directed it to incorporate cost-effectiveness information into its technology assessments, where feasible, and to consider health care costs when developing practice guidelines (Public Law 102-410).

A recent AHCPR guideline on cataract management in adults contains a section on the cost of care, but the panel that developed the guideline found no published data regarding the cost of preoperative, intraoperative, or postoperative care (72). Some panels clearly desire the economic data that could be generated from clinical trials, and the demand for such information may increase in the future.

Current Applications

A variety of medical technologies—such as pharmaceuticals, devices, procedures, and other services—have been assessed in economic components of observational or experimental clinical trials. The fact that these trials have addressed diverse populations (e.g., children and elderly people or inpatients and outpatients) and various illnesses suggests that economic analysis is broadly applicable in clinical studies. The diversity reflects the needs of those who use economic data (often the sponsors) and the capacity and interests of the different types of organizations that actually conduct the evaluations (box 5-1).

Several recent clinical-economic trials sponsored by industry and conducted at academic institutions have assessed both the financial and medical effects of new pharmaceuticals:

In a recent study sponsored jointly by Schering-Plough and Sandoz, for instance, researchers at the Memorial Sloan-Kettering Cancer Center examined the costs and benefits of granulocyte microphage colony stimulating factor (GM-CSF) as an adjuvant therapy in relapsed Hodgkins disease (28).

- A study sponsored by Hoechst-Roussel Pharmaceuticals, Inc., and conducted at the University of Southern California School of Medicine, was designed to ascertain the costs and medical outcomes of treating spontaneous bacterial peritonitis with short courses of antibiotics as compared with long courses of antibiotics (59).
- Researchers at the Johns Hopkins Medical Institutions evaluated the relative cost-effectiveness of low-osmolality and high-osmolality radiographic contrast media in patients undergoing cardiac angiography (50) in a study sponsored by Sanofi Winthrop, a manufacturer of radiographic contrast media.

BOX 5-1: Who Performs Economic Analyses in Clinical Trials?

Those who use economic analyses sometimes sponsor and perform their own clinical-economic trials, as do manufacturers and other sponsors. Academic and government researchers also perform the analyses in clinical-economic trials funded by outside sponsors.

Manufacturers. Manufacturers face tremendous incentives to prospectively evaluate the economic implications of new technologies in order to ensure that economic data are available at the time the products are launched. The trials may be initiated by any of several departments with the firms, including the clinical research and marketing departments, Because most manufacturers currently lack the extensive expertise necessary for conducting such studies, academic institutions or other private entities are usually given grants or contracts to conduct them, but many manufacturers are recruiting experts (e.g., doctoral- or master's-level health economists) to improve their in-house capabilities.

Academia. The economic analysis of medical technology has evolved into a discipline in some universities in response both to concern for health policy and financing and to demands from industry (27,51 ,55,62). Many of the analytic techniques applied in economic analyses, whether performed in the context of clinical trials or not, have been developed by academicians, which makes universities a source of expertise. The demand for economic information has led to an initial collaboration between academia and health care providers, especially within academic medical centers. Inasmuch as academic medical centers are often the loci for clinical trials of the efficacy and safety of emerging technologies, economic evaluations in conjunction with these trials are natural extensions.

Private consulting firms. Other private sector organizations, such as consulting firms and think tanks, are often called upon to perform economic analyses of medical technologies. The funding for this work has come, in large part, from manufacturing firms. A firm conducting a clinical trial-either internally or through a grant or contract with an academic organization or health care provider—might turn to consulting firms with expertise in health policy and economics. These firms might be asked to identify the reimbursement and marketing issues associated with a new product and then to collaborate with the investigators who are designing the clinical trial to collect economic information that will be useful for launching the product.

Government. The government is an important sponsor for biomedical research in general, but aside from a few studies funded by the Agency for Health Care Policy and Research, government sponsorship of economic analysis in clinical trials has been limited. Some institutes of the National Institutes of Health have occasionally permitted the collection and analysis of economic data within their clinical trials, although the funding for the economic components has come from elsewhere (such as foundations and AHCPR). The potential exists for more such trials, inasmuch as the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Institute on Aging occasionally consult with extramural scientists on economic issues and implications and also have intramural scientists (including economists) engaged in economic studies other than clinical trials. These scientists often perform post-hoc analyses of data using economic modeling. Although the Health Care Financing Administration and other public payers are becoming important consumers of economic information from clinical trials, there IS little evidence that they are conducting or sponsoring such studies.

SOURCE: Neil R Powe and Robert I Griffiths, 1995.

Other types of manufacturers have also provided funding, technical support, and equipment to researchers collecting economic data in clinical trials, for example:

- Support Systems International, which makes air-fluidized beds, provided equipment, consultations, and technical services to researchers who compared the cost-effectiveness of home air-fluidized therapy with that of conventional home therapy for pressure sores (65).
- Burron Medical, Inc. sponsored a study comparing the time and cost of filling syringes with automated versus manual methods (l).
- Researchers at the Nuffield Department of Obstetrics and Gynecology at Oxford received a loan of equipment to compare the costs and outcomes of videopelviscopy with those of laparotomy for treating ectopic pregnancies (4).

Several economic studies have also been performed by health care providers to justify their own costs or to improve efficiency:

- A study conducted by the First Hill Orthopedic Clinic in Seattle, for example, demonstrated that despite requiring relatively long hospital stays, total hip arthroplasty for patients older than 80 was a cost-effective alternative to placing the patients in nursing homes (5).
- A Department of Veterans Affairs (VA) study demonstrated that the costs of VA-hospital-based home care for the terminally ill were comparable to those of community home care or hospice care, and that patients and caregivers expressed the greatest levels of satisfaction with hospital-based home care.
- A cost-effectiveness study comparing erythromycin with mupirocin as treatments for impetigo in children, conducted by researchers in the Department of Pediatrics at the Johns Hopkins Medical Institutions, evaluated not only the costs of the medical treatments but also the nonmedical costs incurred by the families as a result of the illness (58).

Public agencies and private philanthropic organizations have also played important roles in conducting or sponsoring clinical trials with economic components.

- The World Health Organization, for example, was one of the sponsors of a study in which the use of biobrane was compared with the use of l-percent silver sulfidiazine in the outpatient management of partial-thickness bums (22).
- The National Center for Health Services Research[1] sponsored several clinical studies with economic components. The studies investigated the costs and benefits of cyclosporine relative to prednisone and azathioprine in improving the results of renal transplantation (61).

These assessments reflect the diversity of approaches to economic analysis of medical technology such as study design (e.g., perspective of the analysis and types of costs considered). The scope of these trials demonstrates that providers, payers, and patients are concerned with economic issues in all types of health technology applications. Despite the variety of health technologies studied, however, a recent study indicates that few clinical trials (0.2 percent) include economic analyses (2) and that no relationship has been established between the methodology for economic analysis and the quality of the research. Therefore, clinical-economic analyses have so far produced few sound data to which health care policy makers can turn for guidance.

METHODOLOGICAL CONSIDERATIONS

Conducting clinical-economic trials to assess the cost-effectiveness of emerging technologies entails a number of methodological considerations that can challenge researchers and affect the usefulness of the information generated by the trials.

[1] NCHSR was eliminated with the establishment of the Agency for Health Care Policy and Research In 1989.

| Analytic Framework

Traditional Clinical vs. Clinical-Economic Trials

Because a clinical-economic trial is a particular type of clinical trial, many of the methodological and practical issues that arise in traditional clinical trials also pertain to clinical-economic trials. The nonrandom allocation of treatments to groups of patients can bias both economic and clinical findings, because important characteristics of the patients in the experimental and control groups may differ. Also, clinical trials, particularly those conducted in the early stages of a technology's development, require designs that may diverge from normal clinical practice. The early clinical trials of the drug recombinant human erythropoietin (18), for example, included only a small number of relatively healthy dialysis patients (those without systemic illnesses) and were performed in institutions where patients were likely to receive superior care. Although the early trials yielded very encouraging results, a subsequent study of more than 50,000 patients suggested that the efficacy demonstrated in the early trials might not be as high for the general population of dialysis patients, in part because of differences in the patient populations, the physicians' practices, the regulatory influences, and the quality of care (53).

What distinguishes clinical-economic trials from traditional clinical trials is the incorporation of resource usage and costs as outcome measures and their subsequent availability for further analysis. These economic measures and the rationale for collecting them pose distinct issues for researchers. Hypotheses to be tested in a clinical-economic trial include a technology's effects on both the patients' health and the costs of treatment. The clinical trial's protocol and setting may place their own special constraints on the collection of relevant data about costs.

Economic data can be collected prospectively in longitudinal studies ranging from observational studies to experimental studies (e.g., randomized controlled trials). Although the traditional definition of clinical trials excludes studies with historical control groups, some of the considerations that apply to clinical-economic studies probably extend to studies without control groups or to studies with historical controls. The purpose of collecting economic data in observational studies in which no direct comparisons are made between technologies is usually to identify or enumerate the costs of applying specific technologies or the costs associated with specific illnesses. An economic comparative trial, whether experimental or observational, compares the costs or cost-effectiveness of two or more alternative strategies for managing a condition or disease. These distinctions affect the types of conclusions researchers can draw about comparative efficiency and outcomes, because comparative studies yield information on relative outcomes.

Clinical-economic trials may also be viewed in the same way as other economic analyses. Such trials are most commonly performed as part of cost-effectiveness analyses, which assess the comparative costs and effectiveness of alternative technologies (see box 5-2). Within this framework, the trials can be thought of as providing a way to incorporate economic measures into prospective clinical studies. The economic measures include: 1) resources consumed as a result of the application of medical technologies, and 2) the costs of those resources from different perspectives.

Types of Resource Consumption and Costs

Any resources consumed in providing health care, or as a result of illness, cannot be used for other purposes. Resources are typically valued by economists in terms of the next best alternative uses, known as the *opportunity costs.* Because the opportunity costs are reflected in the price one is willing to pay for using resources, the resources are usually valued in dollars, but economists may also speak of the value of the resources in terms of utility. Dollars and utilities are simply different ways of valuing the resources that are consumed.

It is important to distinguish between accounting and economic costs (20). *Accounting costs are* the monetary outlays associated with the con-

BOX 5-2: Types of Economic Analyses

The demand for evaluating the costs and benefits of medical technology has led to three basic types of comparative health economic analyses: cost-identification, cost-benefit, and cost-effectiveness (10,15,73), Each method requires economic data that may be collected during a clinical trial.

Cost-identification analysis enumerates all the costs of applying a technology to a specified population under a particular set of conditions (such as inpatient care). The analysis is usually performed in conjunction with a longitudinal and observational clinical study that does not compare the benefits of one technology with those of alternative technologies. Researchers examine the natural history, in an economic sense, of the group of patients in the study. The resources expended by the providers and the patients for the technology and all associated interventions are measured, and the overall costs are calculated. Analysts can also enumerate the contributions of different types of resources (labor, supplies, and capital), as well as the contributions of particular subgroups of patients, to the overall costs. Researchers can determine, for example, whether labor costs are greater than capital costs or whether the costs of therapy are similar for young and old patients, male and female patients, black and white patients, or high- and low-risk patients. Cost-identification studies are also performed to obtain pilot data for use in planning experimental trials or comparative studies (54). Cost-identification data can also be integrated with other clinical data (from outside the trial) using modeling or simulation approaches to compare technologies.

Cost-benefit analysis enumerates and compares both the costs of applying the technology and the net savings resulting from its therapeutic benefits. One strength of this type of analysis is that it provides a rule for deciding whether to adopt or reject a technology from a strictly economic perspective. Health care providers may want to know not only that a particular drug prevents a certain number of heart attacks per year at a specific cost, but also that the drug saves money for the provider or the insurer. If the sum of the benefits is greater than the sum of the costs of using the technology, the net benefit is positive and the technology should be adopted. One limitation of this approach, however, is that the therapeutic benefits must be expressed in monetary terms. Placing dollar values on decreased mortality or morbidity is highly controversial, and existing techniques may systematically undervalue or overvalue the lives of individuals in certain groups (such as very young, elderly, or impoverished people).

Cost-effectiveness analysis also entails the explicit valuation of the costs and therapeutic benefits of applying medical technology and compares net costs to net benefits. In contrast to cost-benefit analysis, however, cost-effectiveness analysis expresses therapeutic benefits in such reduced-mortality or -morbidity measures as years-of-life-saved or quality-ad justed-years-of-life-saved, The strength of this approach is that it obviates the need to assign dollar values to life-years saved or to reduced morbidity. At the same time, however, it produces no explicit decision rule for adopting or rejecting the technology. Whether a technology whose cost-effectiveness ratio is $100,000 per life-year saved is adopted depends on whether the decisionmaker considers a year of life to be worth at least $100,000.

Cost-identification analyses may be most appropriately incorporated into observational trials, while cost-benefit and cost-effectiveness analyses may be more appropriately incorporated into experimental trials whose objectives include either comparing the costs and benefits of alternative technologies or comparing the costs and benefits of a technology with those that would occur without intervention.

SOURCE Neil R. Powe and Robert I. Griffiths, 1995

sumption of resources, whereas *economic costs* include not only the monetary outlays but also the opportunity costs. For example, the accounting cost of an illness includes only the cost of the treatment, while the economic cost includes both the cost of the treatment and the loss of earnings that results from the patient's morbidity or mortality. A distinction can also be drawn between fixed costs and variable costs (67). *Variable costs* change (at least in the short term) in accordance with the extent to which health services are provided, whereas fixed *costs are* independent of the quantity of health services provided. Variable costs typically include labor and supplies, while fixed costs often include equipment. Economic analysts also distinguish average costs from marginal or incremental costs. *Average costs* include both the fixed costs and the variable costs apportioned across all units of a particular resource, whereas *marginal costs are* the additional variable costs of providing additional services.

The total value of resources consumed for health care can be categorized as direct medical costs, direct nonmedical costs, and indirect economic costs (15,73).

- *Direct medical costs* result from the consumption of medical resources in applying a technology to produce health care services. For instance, magnetic resonance imaging entails the use of capital equipment (the imaging machine), staff time to operate the equipment, and professional time to interpret the results. Medical complications arising from the use of some technologies may also result in the consumption of additional resources, which are counted as direct medical costs of applying the technology.
- *Direct nonmedical costs are* associated with the application of a technology but do not result from the consumption of medical resources. Such costs may include expenditures for travel or parking, food, lodging, or child care in conjunction with medical treatment (43). For several types of chronic debilitating illnesses, the direct nonmedical costs can be substantial.
- *Indirect economic costs* result from the excess morbidity or mortality associated with the application of a technology or with its side effects. Excess mortality or morbidity frequently entails an individual's loss of the opportunity to produce valued resources, goods, or services. Often referred to as the loss of human capital, such costs include lost wages resulting from decreased life expectancy or earning ability reductions resulting from disability.

The *cost savings* associated with a technology are measured in terms of the expenditures that are obviated by the technology's therapeutic benefits. If the application of one technology eliminates the need for an inferior alternative or for related technologies, the medical-resource costs of applying the inferior technology may be counted among the savings of the superior technology. If the technology's therapeutic benefits decrease the use of medical resources, the costs of the unused resources are additional savings. If the application of a technology eliminates the need for a second technology that is associated with side effects, the medical resource costs of treating those side effects may be counted among the savings associated with the first technology. In radiologic procedures, for example, fewer adverse reactions result from the use of low-osmolality contrast media than from the use of conventional high-osmolality contrast media, which means that the cost of managing complications may be lower with the former than with the latter.

Similar principles apply to valuing the indirect cost savings associated with applying one technology in lieu of another. The increased earnings associated with incremental gains in life expectancy or reduced morbidity may be counted among the savings. For instance, if applying a technology increases a patient's life expectancy by two years, during which the individual is expected to earn $60,000, the indirect savings would be $60,000.

Depending on the purpose of a clinical-economic trial, the availability of data, or the availability of resources for conducting the study, researchers may assess a limited range of resources or costs. The resulting picture of the technology's economic implications may therefore be incom-

plete, and decisionmakers who try to use the data may not understand what has been included in the analysis.

| Selection of an Economic Perspective

An important initial step in any clinical trial is to determine the perspective of the analysis. Analyses can be performed from the point of view of society, of the health care provider (clinic, hospital, or physician), of the payer (Medicare, a private insurance company, or an HMO), or of the patient. The exact methods of collecting economic data and the types of economic data collected may vary for different perspectives.

Choosing a perspective is critical in the design of a clinical-economic trial, because the perspective dictates what resources will be examined, what types of cost data will be collected, how the analysis will be structured, and ultimately what kinds of conclusions and recommendations will emerge. A common problem with economic analyses is the failure to establish or clarify the analytic perspective (24). This failure can result in the collection and synthesis of economic data that are not pertinent to some decisionmakers. For example, using data on a provider's billed charges to estimate the costs of some resources (from the payer's perspective) and using a provider's own cost data to estimate the costs of other resources (from the provider's perspective) yields a hybrid result that represents the view of neither the payer nor the provider.

In addition, there is a common misconception that only one correct perspective exists for measuring costs. Some analysts believe that the societal perspective is best because it addresses the public good. Although the societal perspective may be favored for national allocative decisions and may address the public interest, it does not always address the needs of specific decisionmakers, such as third-party payers, employers who pay for care through health premiums or self-insurance, providers who must decide whether a technology is worth using, or patients who face out-of-pocket costs. The correct perspective is the one that will yield information of relevance to the decisionmaker, whoever that might be.

Another misconception is that the conclusions drawn from a clinical-economic trial will be the same from all perspectives. In fact, however, conclusions can vary substantially. For example, one cost-benefit analysis performed in a clinical-economic trial of the use of low- versus high-osmolality contrast media in cardiac catheterizations suggests that the higher material cost of using low-osmolality contrast media is partially offset by the reduction in the costs of managing adverse reactions, but that the offset is lower from the hospitals' perspective than from society's perspective and that it may not be realized by third-party payers (50).

| Resource Measurement Methods

In addition to clinical information (such as risk factors and outcomes), two types of data are required for a clinical-economic trial: the medical and nonmedical resources that are consumed and the costs of those resources (from the chosen perspective). Quantitative measures of patient preferences for clinical benefits *(patient utilities)* provide another important measure of economic outcomes, but the appropriateness of performing utility measurements on persons enrolled in clinical trials is still the subject of debate. A clinical trial may not always be the appropriate setting for eliciting patients' preferences for outcomes or treatment, inasmuch as the process of the trial may itself influence patients' responses.

Of the several ways to collect data on the resources consumed in the context of a clinical trial, some are better suited than others to particular purposes. Which approach is most useful depends on the characteristics of the technology, the patient population, the clinical setting, and the perspective of the analysis.

Reviewing Charts

The medical records of the patients enrolled in a trial can be reviewed to abstract data about a variety of resources (8,25), including admissions to

the hospital, the use of laboratory or imaging tests, other ancillary services (e.g., electrocardiograms, foley catheters and respiratory or physical therapy), any consultations by specialists, and the days spent in a special care unit (e.g., an intensive-care unit or a laminar-air-flow room). Regardless of whether the review is performed to document outpatient or inpatient services, the medical records must be complete, and those persons reviewing charts must be trained in medical record abstraction to avoid problems such as overcounting resources because of imprecise documentation. (For example, if the time of day is recorded inaccurately, abstracters may have difficulty determining whether separate documentation refers to the same test.)

Chart reviews can be problematic where therecordkeeping is below standard or where the records are kept in different places. Problems also arise when test results are not recorded in the medical record until weeks after the tests have been performed and the orders do not document the submission of samples for testing (e.g., when a physician sends blood for thyroid-function tests directly to the laboratory without entering the information in the order sheet). Abstracters face other difficulties if they must use records at more that one place (e.g.. in a multicenter study) and the organization of the records varies from site to site. An assessment of the interrater and intrarater reliability of the record abstracts is important for any study that uses data from charts.

One limitation of medical records is that they generally do not provide data on direct non-medical resources or on the resources used to estimate indirect costs. The records may also fail to document such direct medical costs as nonprescription drugs taken at patients' homes.

Examining Patients' Bills

Patients' bills are often the source of documentation on the use of medical resources (61,65). In some cases, bills can back up poor recordkeeping, but they only capture the resources that are charged to the patient or to a third-party payer. Many of the resources that are consumed never appear on patients' bills, either because the providers do not receive additional reimbursement for the resources or because the provider sometimes neglects to bill for reimbursable services. At the same time, some of the resources that appear on patients' bills may never have been used for those patients. The extent to which these errors occur may vary from one institution to the next.

Using patients' bills to ascertain the consumption of medical resources maybe most appropriate for assessing costs from the perspective of a third-party payer, because the bills reflect the resources for which the payer will be asked to pay. Patients' bills may not be so useful for identifying costs from the provider's viewpoint, inasmuch as some of the resources consumed may not appear on the bills. Another limitation is that bills from institutional providers do not document the provision of physicians' care, which is usually billed separately. In addition, physicians' bills maybe generated from multiple sources, which makes it difficult to collect data on all the care provided by physicians.

Interviewlng Providers or Patients

Another technique for obtaining data on resources is to ask providers about the services they performed or ordered for patients, or to ask patients about the services they received (65). Although interviews are straightforward when used to identify a few obvious and highly visible resources, they can be complex if they include many economic aspects of treatment, such as complications of treatment, disability, and work loss. Detailed interview protocols with branching logic may have to be developed. In addition, providers who participated in only a limited aspect of the patients' care may have no information about the broader and longer-term consequences of the treatment.

In such circumstances, questionnaires regarding the consumption of medical resources should be administered soon after the services have been provided in order to avoid problems with recall. In addition, patients' questionnaires should be simplified to capture only general categories of re-

source consumption, because most patients cannot provide detailed information either because they were too sick to comprehend their physicians' explanations or because they were never informed in a detailed way (e.g., they knew that they had blood tests or x-rays, but not whether they had complete blood counts or magnetic resonance imaging).

Interviews with patients are particularly useful when patients are served by several health care providers or have multiple sources of payment that are not captured by a single data collection system. To minimize difficulties with recall, patients can also keep diaries or logs of the health care resources they use. Finally, interviews may be the only way to identify the use of resources that comprise direct nonmedical costs or indirect economic costs (such as days lost from work).

Conducting Time-and-Motion Studies

In some studies, researchers must measure the process of producing health services on a more detailed chronological basis (e.g., minute-by-minute) and note all of the labor and nonlabor resources that are expended (17,26,47). To measure the effect of a device for patient-controlled analgesia versus nurse-delivered analgesia for patients who have had recent surgery, for instance, researchers might examine how many minutes nurses use for each strategy to relieve postoperative pain. Typically, in a time-and-motion study, the nurses would be directly observed and the tasks timed with a stopwatch (1).

Although time-and-motion studies yield very accurate results, they are expensive to perform, because they require intensive observation by the researchers. Another concern is that those being observed may alter their behavior in response to the observation.

Cost Assignment Methods

Once the researchers have measured the resources that are consumed by participants in a clinical-economic trial, they must assign the appropriate costs to those resources. It is widely recognized that the actual costs of providing health care services are likely to differ substantially from the charges that providers submit to patients or third-party payers (20). Charges often reflect what the market will bear, rather than the true cost of the resources consumed in providing health care services. Therefore, charges are often set arbitrarily and may vary substantially among facilities whose costs for producing health services are similar. Furthermore, submitted charges are not always fully paid. The amount paid can vary by payer, delivery system (e.g., negotiated discounts by a managed care insurer), and geography (e.g., state-mandated inpatient rate-setting in Maryland). These factors demand that researchers do more than simply collect information about what charges were submitted.

In estimating the total costs associated with a medical technology or clinical management strategy, researchers often take one or both of two approaches.

1. They may build up the costs from the level of the individual resources (such as a dose of penicillin or an hour of a nurse's time), an approach often referred to as *microcosting*.
2. *They* may assign costs to resources at an aggregated (bundled) level of resources (such as a hospitalization or a clinic visit). Under this approach, investigators often use cost-to-charge ratios specific to the institutions or cost centers to estimate the actual costs from the charges.

One practical concern is the availability of systems that can yield data on the various types of costs incurred by institutions or providers. Although the systems of some hospitals and clinical practices are sophisticated (40), those of others are archaic. This may limit researchers' ability to perform studies in some settings or limit the type of data that can be collected (e.g., charges versus costs), which may explain why so many studies have reported on charges rather than costs (5,22,28,46,48,49,65,74).

Microcosting

A very time-consuming process of collecting cost data, microcosting usually requires investigators

to work with the staff of a hospital or clinic to identify the expenses for various resource inputs, such as capital, labor, and supplies (17,32,33,54). In an institution where purchasing and hiring decisions are decentralized, this process may entail contact and discussions with a large number of organizational units (e.g., the pharmacy, nursing, cardiology, laboratory medicine, physical therapy, and professional-fee billing departments).

Some institutions or departments may have sophisticated methods of evaluating the true costs of producing services. For example, the pharmacy may have developed standards for valuing the pharmacists' time, the ancillary supplies, the material used in acquiring a dose of antibiotic from the supplier and getting it to the bedside and into the patient. A detailed and well-documented, centralized cost accounting system can help a great deal. Researchers sometimes turn to published estimates of costs—using, for example, the *Drug Topics Redbook* to arrive at the cost of materials for pharmaceuticals. Although the publication provides useful approximations, in that it lists wholesale costs, the discounts often given to health care institutions by suppliers are not reflected. To assess the use of outpatient resources, researchers might conduct a local survey of providers and calculate the average cost (or charge) for a service (58).

Additional methodological issues in microcosting concern the allocation of overhead costs (also referred to as indirect accounting costs). Average costs include overhead, but analysts may differ on the extent to which certain categories of overhead—such as departmental overhead (e.g., the department manager's salary) and hospital-wide overhead (e.g., the chief executive officer's salary) should be included (39,54). Different approaches to the inclusion of various types of overhead may yield vastly different results. Standardization is lacking.

Assigning the Costs of Aggregated *Resources*

Whether assigning costs on an aggregate level is appropriate depends on the study's perspective and the availability of data. For instance, aggregation at the hospital discharge level may be appropriate in assigning Medicare's cost for a hospital admission using payments based on diagnosis-related groups (DRGs). Cost-to-charge ratios provide a convenient way to estimate the actual costs for medical services from the charges to payers. A ratio of .80 would imply that the true cost of a service is 80 percent of its charge.

Although cost-to-charge ratios are commonly used to estimate the cost of hospital services (8), there is some debate about how the methods are used. Many researchers have used the ratios from Medicare cost reports, which are widely available, but some investigators advocate the use of department-specific ratios, while others believe that the less complex institutional level ratios are adequate. The distinction is that department ratios purport to value like services the same (e.g., the cost-to-charge ratio for a chest x-ray is the same as that for a knee x-ray, but differs from the ratio for a blood glucose test), whereas institutional level ratios value all services the same (e.g., the ratio is the same for a CT scan and an antibiotic). Thus, institutional-level cost-to-charge ratios may not account for the fact that expensive devices or drugs often have lower ratios than other resources. In addition to obtaining ratios from Medicare cost reports, researchers have used ratios that were generated for purposes other than cost reporting to the Medicare program and that relied less on the grouping of dissimilar services.

Assigning the Costs of Professional Services

Data on the costs of professional services can also be obtained in different ways. The actual costs of physicians' services are difficult to obtain. The new resource-based relative value scale (implemented by Medicare as a basis for physician payment) (35) may be helpful in this regard. It is possible to estimate the actual costs by using the average reimbursements for a geographic area (e.g., by looking at payments by Medicare intermediaries) or from fee schedules maintained by third-party payers.

At the institutional level, it may be possible to identify the actual fees reimbursed by different third-party payers or an average for various payers over a specified period. Some studies have calculated average reimbursements from billed amounts by using a ratio of collected-to-billed charges (40). In examining physicians' costs, knowledge of physicians' billing practices (such as bundling of services) and coding is important.

Assigning Indirect Economic Costs

Researchers estimating indirect economic costs may find it difficult to obtain information about incomes and benefits directly from patients. Alternative sources used by investigators include standard industry profiles merged with primary data (such as the numbers of days lost from work and the nature of patients' occupations).

VALIDITY AND RELIABILITY

The validity of conducting economic analysis during a clinical trial reflects the degree to which the data used for estimation reflect the actual resources or costs of providing services. Its reliability reflects the degree to which investigators would obtain the same results if the study were repeated on the same population of patients and providers. Because of the relative newness of economic data collection in clinical trials of medical treatments, the literature contains few methodologic studies that compare approaches for obtaining economic data. Furthermore, because costs—unlike some clinical variables-change over time, both reliability and validity can be difficult to assess.

Several of the detailed methodological issues and choices described above can potentially affect the validity and reliability of data based on clinical-economic trials. In addition, there are other issues that relate to the basic characteristics of economic data collected during the course of a clinical trial of a technology's efficacy. Some of these broader issues are described below.

| Statistical Distributions of Costs

One particularly problematic issue in measuring and analyzing the use of medical resources is the way in which resource utilization and costs are distributed. The distributions typically are skewed, either with a few persons using a few services (or not using any services) or with a few persons using large amounts of resources. Unfortunately, excluding the patients who use considerable resources may be undesirable because they are important to decisionmakers.

In view of the large variance in costs, large numbers of study participants are usually needed for adequate statistical power. A potential pitfall of incorporating an economic component into a clinical trial is that the sample size needed to test economic hypotheses may exceed that needed to test clinical hypotheses, because of differences in the clinical and economic variables. Several biostatistical techniques, such as transformations of data to achieve normality (e.g., through logarithmic calculations) or the use of hierarchical models (14), are useful both in sample-size calculations and in the analysis of highly skewed data. Some researchers have suggested that in fact costs in trials often need not, and should not, be measured to the same level of statistical precision as health effects in clinical trials (13a,47a).

The problem of disparate sample sizes can be exacerbated by interim findings on the efficacy side of the trial. Clinical trials often have rules for terminating trials when clinically and statistically significant differences in clinical outcomes are observed. For instance, a trial might be stopped when the new treatment is shown to be efficacious at a predefine level of statistical significance after only half the anticipated trial participants have been enrolled. Although stopping a trial because of the clinical results may conserve resources or satisfy ethical considerations, the early termination of a clinical-economic trial could prevent researchers from drawing conclusions about cost-effectiveness if the sample patients had not

reached the level needed for examining important economic outcomes.

| The Influence of Clinical Protocols on the Use of Resources

Another important consideration in estimating the use of resources in clinical trials is the extent to which clinical protocols might influence the use and costs of resources. For example, early studies of a new technology often include the performance of laboratory or radiologic tests to monitor patients for serious or unknown side effects. This monitoring is often driven by the clinical research protocol, which can be influenced by the need for data to assist in the FDA approval process. The monitoring can significantly alter the validity of an economic analysis, however, because the resources consumed in the monitoring process do not always become a necessary component of routine clinical practice. This is true for both the treatment group and the control group in a randomized trial.

In the Women's Health Study conducted by NIH to assess hormonal therapy, for instance, women undergo frequent office followups, electrocardiograms, endometrial biopsies, and mammograms to monitor the safety of hormonal therapy. The exclusion of these resources from the data collection or from the accounting of costs is often proposed as a way to solve the problem, but the monitoring can have more profound effects when abnormal tests lead to further testing or treatment.

Studies that examine the use of aggregated resources without examining the components and their relationship to clinical events are more likely to encounter this flaw than studies that take care to attribute the use of resources to clinical events (51). One solution in a multicenter study might be to modify the clinical protocol at some of the institutions and examine how the resource consumption varies depending on whether a center uses the standard or modified protocol. Although excluding some costs may seem reasonable, however, recommendations for dosing and safety monitoring of complications after FDA approval are often based on the protocol established in the clinical trials. Therefore, investigators collecting and analyzing economic data may wish to perform sensitivity analyses-that is, to perform their analyses more than one way, based on the inclusion or exclusion of certain categories of resources.

I Standardization in Multicenter Trials

Increasingly, large clinical trials are conducted at multiple sites. Multicenter studies raise important issues of standardization, and the best centers for collecting clinical data are not always the best centers for collecting economic data. Although investigators may easily develop standardized criteria for the collection and determination of clinical events (e.g., electrocardiographic and cardiac enzyme evidence for acute myocardial infarction), the standardization of costs is difficult because of differences in accounting systems across sites. Some centers may have sophisticated methods of ascertaining their costs or specific billing information, for instance, while other centers do not. Researchers may also find it difficult to standardize the measurement of costs for different types of providers (e.g., HMOs versus fee-for-service practices, hospital outpatient departments versus physicians' offices, or VA hospitals versus private hospitals) and for different geographic areas (e.g., states with inpatient rate regulation versus states with market competition, or Canadian facilities versus U.S. facilities).

| The Effect of Masking on the Use of Resources

Because it minimizes bias related to treatment, the double-blind trial—in which both patients and physicians are unaware of who is receiving which treatment alternative-is considered an important component of the evaluation of the efficacy and safety of a therapy. In assessing the economic implications of a treatment in normal practice, however, an equally important consideration is the fact that awareness of the treatment can influence providers to use resources in a different fashion.

Suppose, for instance, that radiologists in clinical practice were more likely to initiate aggressive and expensive treatments for contrast-induced

complications if they knew that the patients had received high-osmolality rather than low-osmolality contrast media. In a masked clinical trial, the radiologists might show less restraint in their use of medical resources to manage complications, because they could not be certain which contrast media had been used. Uncertainty as to treatment (as well as more intensive observation) in the clinical trial might influence radiologists to provide more treatment than they would in normal practice. As a result, the masking might increase the costs.

The Timing of Clinical and Economic Outcomes

The economic consequences of treatment choices may extend far beyond the time horizon of a clinical trial. For example, thrombolytic therapy (e.g., recombinant tissue plasminogen activator) administered for an acute myocardial infarction can cause a stroke, a clinical endpoint, and the patient could require long-term nursing care, the cost of which could extend for many years. If the clinical protocol stipulated that followup on a patient would end in the event of a stroke, the full economic consequences would not be obtained.

Clinical benefits and costs may accrue at different times in the course of an illness, and clinical benefits or costs may accrue at different times for each treatment strategy being compared in a clinical-economic trial. An analysis of the benefits and costs accruing at different times must take this into account by adjusting the observed costs for the time value of money. Benefits and costs that accrue now are worth more than they would be if they accrued in the future. The procedure for adjusting for the time value of the resources or costs is referred to as *discounting,* in which benefits and costs incurred in the future are valued in current dollars (73).

Discounting is unnecessary if the time covered by the analysis is short (e.g., less than one year). When discounting is necessary, the rate at which to discount is often controversial because the choice can greatly influence the conclusion about a technology's cost-effectiveness. Different consumers of economic data (including those only affected in the future) might advocate different rates. Therefore, analyses might examine the sensitivity of conclusions drawn from clinical-economic trials to the rate of discounting.

Generalizability

The external validity (i.e., generalizability) of the economic data collected in clinical-economic trials is of great concern. Studies are often performed at individual institutions that are part of, or affiliated with, academic medical centers, where two possible problems influence generalizability.

First, the medical practice may not be similar to that in many other institutions. For example, physicians at teaching institutions may order more tests and consume more resources as a result of their teaching or research activities, which may result in an overestimation or underestimation of costs. More discretionary testing raises cost estimates, although more careful testing may prevent complications of treatment and, therefore, result in the trading of an upfront outlay for a potential reduction in the long-run use of resources. Institutions that adopt technologies early may have the most experience in their application. This experience could lead physicians to select patients more ideally suited for treatment or to be better at identifying or managing side effects. This might translate not only into better outcomes than are realized in general medical practice (51) but also into the more efficient use of resources.

Second, in addition to differences in physicians' practices, the costs of resources vary across institutions of different sizes (economies of scale or scope), location (geographic variation in resource inputs), and organizational characteristics (for-profit versus not-for-profit institutions). Manufacturers that perform economic studies in different countries must be aware of the variability in medical practices, medical costs, and the medical infrastructures required to support use of new technologies.

Other factors to consider are that, for the purposes of clinical trials, investigators may be able

to obtain related medical services (such as monitoring tests) at discounted prices or costs. The discounts may not reflect the true economic cost in everyday practice.

It is worth noting that cost-effectiveness analyses based on synthetic or modeled analyses that use the best data available from various published and unpublished sources, including opinions (55), are not immune from the problem of limited generalizability. They, too, may be limited because they project how resources would be used under optimal circumstances. The effects of the assumptions that are made in using such data and the validity of the estimates of the cost-effectiveness or cost-benefit that are generated are often unknown.

FUTURE PROSPECTS

I Research Needs

The analysis of economic data in clinical trials is afield still in its infancy. In view of how many entities are interested in performing studies and what kinds of techniques can be used in the process, there is a need for studies that compare the results generated by different methodologies and techniques. Few studies have addressed the reliability and validity of cost assignment methods by comparing different methods of obtaining, calculating, or modeling costs (32). Such studies are badly needed in order to improve our understanding of how alternative methods affect the results of economic analyses in clinical trials.

Such studies would compare alternative methods of collecting both resource-utilization data and cost data (including modeling) for the same technologies. The studies would also explore the degree to which summary measures, such as cost-benefit or cost-effectiveness ratios, are affected by the data collection methods. This could be done by analyzing the benefits (or effectiveness) and costs that were measured within the same trial using different techniques.

The extent to which the characteristics of a technology dictate the best approach to collecting data on resources and costs is unclear. The approaches required by diagnostic technologies may differ from those required by therapeutic technologies. Inpatient and outpatient treatments may also require different approaches to resource measurement and the assignment of costs. The best approach for one ailment (such as cardiovascular disease) may differ from that for another (such as arthritis), and chronic diseases that have longer durations may require different approaches from those required by acute diseases.

Another gap in the literature is the lack of studies examining the relative gain from careful attention to the precision of assessments. This is important because the costs of collecting data usually rise with more detailed assessments. We also need to understand how much generalizability increases when economic data are collected from more than one institution, inasmuch as it costs more to collect data from multiple sources. Future studies could assess whether methodological shortcuts are possible and yield valid results.

It is not clear that the private sector, particularly industry, can or will support the necessary methodological development or the particular applications to research in this field. Although it may be able to support a specific evaluation related to a particular need, the private sector has little incentive to take on the tasks of developing methods or examining the economic issues from more than one perspective.

No government agency has currently embraced the responsibility for supporting the development of methods for collecting economic data in clinical trials and for integrating them into clinical trials. In part, this reflects the fact that specific funding has been limited or that it competes with other programmatic areas. AHCPR has a mandate for examining the cost of health care services, and NIH has the authority and are supporting large-scale clinical trials of new therapies, but neither agency has undertaken primary responsibility for research that intersects these areas.

| Standardization

The quality of economic analyses is of considerable concern as the methodology evolves (30) with no established guidelines on appropriate

techniques and no consistency in technique across studies. If information about cost-effectiveness is to be useful as a criterion for decisions such as whether a drug is to be included in a hospital formulary, or whether a procedure should be covered by insurance, some standards for the types of data and the methods of obtaining them must be developed (41). Questions to be addressed include whether more than one perspective should be considered in economic analyses, what types of costs should be considered, and (in order to make allocative decisions) what constitutes the appropriate patient or provider population for an economic study?

Because there are few standards for the proper conduct of clinical-economic studies, studies are susceptible to accusations of bias, particularly if the study results favor the sponsor product or interests. Much of the concern relates to the fact that invalid or unreliable approaches (such as the incomplete enumeration of resources or costs) may be used selectively to obtain particular desired results. Some of this concern could be alleviated with greater methodological standardization.

There may also be pressures to refrain from publishing results that are unfavorable to the sponsors' interests. The degree of publication bias—the tendency for over-representation in the published literature of studies with statistically significant results, or studies whose results favor currently accepted theories—in the cost-effectiveness field generally is unknown, but some observers believe that studies are less likely to be published if they fail to show that a medical treatment saves money or is significantly cost-effective. Publication bias limits the number of studies and results that can be compared by decisionmakers, and it may lead users to draw incorrect conclusions about a technology's overall cost-effectiveness. In addition, it may lead researchers to take methodologically inferior approaches that are more likely to yield positive results.

Conversely, where results favor the sponsor, they sometimes may be disseminated (e.g., used in marketing efforts) without having been adequately peer-reviewed. Both of these factors make it difficult for decisionmakers to trust cost-effectiveness findings. To address these problems, some researchers have advocated the development of rules of conduct for the dissemination as well as the performance of clinical-economic research (30).

| Cost-Effectiveness of Clinical-Economic Trials

Not all clinical trials are good candidates for economic data collection and analysis. Adding an economic component to a clinical trial adds to the cost of the trial (see box 5-3). In view of the considerable expense of clinical-economic analyses and the limitations in generalizing from them, the collection and analysis of economic data in clinical trials may not always be the best way to reach conclusions regarding anew technology cost-effectiveness.

Nonetheless, economic information is badly needed by patients, providers, and payers alike as the nation grapples with the question of how to provide good care at the lowest cost. The clinical-economic trial generates explicit information about which alternative treatment options are the most cost-effective, and it can provide this information early in the life of a new technology, before its use becomes widespread.

Equivalence trials may be particularly appropriate contexts in which to conduct clinical-economic studies. In contrast to a difference clinical trial, which attempts to demonstrate a difference between two therapies, an equivalence trial is an attempt to discover whether one treatment strategy is equivalent to another, perhaps more expensive, strategy. The combined BARIE/SEQOL study, described in box 5-3, is an example of an equivalence trial in that investigators are seeking to establish whether angioplasty—an alternative with potentially lower initial costs—is clinically and economically equivalent to coronary artery bypass surgery.

| Conclusions

The demand for early information on the costs and effectiveness of new technologies is driven by health care policy makers who hope to improve

BOX 5-3: Resources Required for Collecting Economic Data

Economic evaluations within clinical trials add to the cost of the clinical trials, although the additional (or incremental) costs of collecting economic data are less than they are for studies designed strictly to answer economic questions. A clinical trial funded by the National Institutes of Health illustrates this point. The Bypass and Angioplasty Revascularization Investigation (BARIE) is a $35-million, 1,800-patient, 14-center clinical trial that is randomizing patients to receive either angioplasty or coronary artery bypass surgery for symptomatic multivessel coronary artery disease. The trial's major endpoints are death and other morbid cardiovascular events. The study began in 1988, and researchers finished recruiting patients in 1991; The five-year followup will be analyzed in 1996. An evaluation of the economics and the patients' quality of life (SEQOL) (31) was added to the study and funded by the Robert Wood Johnson Foundation at $4.25 million, which was roughly 12 percent of the cost of the clinical trial.

There are five major determinants of the costs of an economic evaluation in a clinical trial:

1. The number of additional research personnel needed for collecting and analyzing data. Few investigators with backgrounds in clinical medicine or epidemiology have also had formal training in such disciplines as health economics, accounting, or health care finance, but the research staff must include personnel with the training to design and help carry out the economic component of the trial.
2. The number of study participants and the duration of patient followup necessary for observing the care. As is true for any clinical study, a clinical-economic evaluation's cost usually varies positively with the length of the observation period and the number of patients studied.
3. The type and comprehensiveness of the economic data elements collected (such as the number of perspectives chosen and the types of costs included). If investigators want greater detail about the use of resources (e.g., ambulatory as well as inpatient services), the costs of data collection rise when the efforts of the current clinical research is fully expended.
4. The extent to which the use of resources can be measured from automated databases rather than by hand. Comprehensive data systems are extremely efficient, which makes the per-patient cost of collecting economic data decrease as the number of patients rises. Most systems, however, are insufficient for the valid identification of resources and costs (e.g., they may include only data on charges or average costs rather than data on marginal costs). This means that the investigators may have to abstract data on resources from patients' records, patients' bills, or surveys of patients; and to collect data on costs from cost (or expense) reports or from manufacturers' invoices.
5. The extent to which modeling and data collection outside the trials are necessary to answer economic or cost-effectiveness hypotheses. Often, the amount of data needed to perform a cost-effectiveness or other economic analysis cannot be generated solely from the patients who are enrolled in a trial. For example, if the researchers need data on patients' preferences for each of the possible outcomes associated with a technology, some of the data may need to be obtained from patients who are not participating in the trial.[1] The substantial modeling of data from the clinical trials to simulate or project economic implications for a collection of providers, a region, or the nation can be a labor-intensive task that is possible only after the results from the primary data collection are available.

[1]The preferences of trial participants may differ from those of patients who were not eligible for the trial. Patients' preferences could also be affected by the trial participation itself.

SOURCE: Neil R. Powe and Robert 1Griffiths, 1995.

medical care without increasing its costs; by providers who want to remain competitive in a cost-conscious environment; by insurers who must make decisions about coverage and reimbursement; and by manufacturers who adapt their research and marketing strategies in response to these concerns. In view of these demands, clinical-economic trials are likely to become increasingly common.

There are tradeoffs between the limitations inherent in clinical-economic trials and the need to anal yze a treatment cost-effectiveness before the technology becomes widely (and perhaps irreversibly) adopted by the medical community. This suggests that there is not one optimal time in the life cycle of a technology to perform a clinical-economic trial, but that researchers and users must understand the limitations in the data (that is, the conditions under which data are generated) and be willing to adjust the estimates in accordance with new medical knowledge or practice patterns.

Despite the demand for sound economic information about medical technologies, the field may not develop in tandem with the needs of policymakers. The need for more methodological research and standardization in particular are potential barriers to the development and wider use of economic evaluation methods in clinical trials.

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