

Introduction to Pharmacoeconomics

CHAPTER

1

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Health expenditures in the United States have been increasing as a percentage of the nation's gross domestic product (GDP).¹ Although the proportion of GDP spent on total health care has climbed steadily, the percentage spent on outpatient prescriptions has remained relatively constant over the past 30 years. Even though private health insurance and government programs cover a growing portion of drug expenditures, a sizable amount of drug costs is still paid directly by consumers. The cost of pharmaceuticals and pharmacy services have, therefore, become an important issue to patients, third-party payers, and governments alike. Today, and in the future, it is necessary to scientifically value the costs and consequences of drug therapy.

The basic value of drug therapy to prescribers and patients in the United States is evidenced by the increased therapeutic use of prescriptions. Community pharmacists dispense approximately three billion prescriptions annually.³ The number of prescriptions dispensed per person per year in the United States has increased dramatically over the past 50 years. The nation's hospitals provide billions of dollars worth of drugs and drug

products to hospitalized patients.⁴ Drugs available over the counter also serve an important role in the country's health care. Sales of nonprescription drugs have increased from \$700 million in the 1950s to well into the billions of dollars.⁵ These figures may be indicative of the value and perceived benefit that society attributes to medications. Most economists would acknowledge that a crude, lower-bound estimate of the value and benefits of drugs to consumers is the amount they spend on these products.

Pharmaceuticals and other therapeutic interventions have contributed to the important progress being made in the health status of the United States population. Corresponding to the introduction of new drug entities during the past several decades, the mortality rates for a number of diseases have declined substantially.⁶ Drugs account for only a small proportion of the expenditures in hospital budgets, but drug therapy plays a crucial role in the efficient treatment of hospitalized patients. An average hospitalized patient receives six to eight different drugs on a typical day. Effective drug therapy helps to partially explain why the mean length of stay in hospitals has decreased over the years.⁴

Despite the general evidence supporting the use of pharmaceuticals, few data exist regarding the actual costs and benefits attributed to specific drug therapies. A primary reason is the lack of defined methodologies to evaluate medical interventions. Perhaps the current focus on reducing expenditures of pharmaceuticals and pharmacy services to save costs to the total health-care system is inappropriate. One purpose of this book is to present economic and humanistic measurement methodologies that may be used not only to evaluate the outcomes of drug therapy, but also put them in perspective with other related healthcare expenditures.

Outcomes

The term "outcomes" is increasingly being used to describe the results and value of healthcare intervention. However, depending on perspective, the outcomes of health care are multidimensional. The clinician has traditionally been most concerned with clinical outcomes of treatments. More recently, healthcare payers and administrators have focused on the resource use or economic outcome of healthcare decisions. Patients, on the other

hand, are becoming increasingly knowledgeable and involved in decisions regarding their own health care and are seeking more information regarding the humanistic outcomes of therapy. Patients want to know how their quality of life will be affected or how satisfied other patients with their condition have been with various treatments.

As the healthcare marketplace is rapidly changing, there is a danger that the change will be driven primarily by the desire to contain cost. Clearly, cost-containment is an important objective. However, successful healthcare management as measured by the objectives of patients, physicians, and other healthcare providers, as well as by societal expectations, requires that the quality of care also be maintained. Outcomes measurement must take into account economic considerations while recognizing that acceptable clinical and humanistic outcomes are also important objectives. The true value of healthcare interventions, programs, and policy can be assessed only if all three dimensions of outcomes are measured and considered.

Definition of Pharmacoeconomics Research

Economics is about trade-offs and choices between wants, needs, and the scarcity of resources to fulfill these wants. When considering economics, most people think of the trade-offs between goods and services and money; however, the trade-off might also be expressed in humanistic terms. We are, therefore, careful to include both resource use and humanistic evaluations of drug therapy within pharmacoeconomic assessment.

Pharmacoeconomics has been defined as “the description and analysis of the costs of drug therapy to health care systems and society.”⁷ Pharmacoeconomic research identifies, measures, and compares the costs (ie, resources consumed) and consequences (ie, clinical, economic, humanistic) of pharmaceutical products and services. Within this framework are included the research methods related to cost-minimization, cost-effectiveness, cost–benefit, cost-of-illness, cost-utility, cost-consequences, and decision analysis, as well as quality-of-life and other humanistic assessments. In essence, pharmacoeconomic analysis uses tools for examining the impact (desirable, undesirable) of alternative drug therapies and other medical interventions.

Questions that pharmacoeconomics may help to address are as follows: What drugs should be included on the hospital formulary? What is the best drug for a particular patient? What is the best drug for a pharmaceutical manufacturer to develop? Which drug delivery system is the best for the hospital? How do two clinical pharmacy services compare? Which drugs should be included in a Medicaid formulary? What is the cost per quality-adjusted year of life extended by a drug? Will patient quality of life be improved by a particular drug therapy decision? What is the best drug for this particular disease? What are the patient outcomes of various treatment modalities?

In essence, pharmacoeconomic analysis uses important tools for examining the outcomes or impact of drug therapy and related healthcare interventions.

Historical Perspective

The emerging discipline of pharmacoeconomics has become a health science discipline by the pharmaceutical industry, academic pharmaceutical scientists, and pharmacy practitioners worldwide. As stated previously, it is generally defined as the description and analysis of the costs and consequences of pharmaceuticals and pharmaceutical services and their impact on individuals, healthcare systems, and society. The research methods used by scientists in this discipline (eg, cost-effectiveness, cost-utility, quality-of-life evaluations) are drawn from many areas: economics, epidemiology, medicine, pharmacy, and the social sciences. We believe that pharmacoeconomic analysis will have a significant impact on the delivery and financing of health care throughout the world. Furthermore, we believe that pharmacoeconomics may influence health care and the practice of pharmacy at a magnitude equivalent to the impact of clinical pharmacy and pharmacokinetics.

During the early 1960s, pharmacy began evolving as a clinical discipline within the healthcare system. It was during this time that the pharmaceutical science disciplines such as pharmaceuticals, clinical pharmacy, drug information, and pharmacokinetics became a critical and integral part of pharmacy education and science. In the 1970s, pharmacoeconomics developed

its roots. In 1978, McGhan, Rowland, and Bootman, from the University of Minnesota, introduced the concepts of cost–benefit and cost-effectiveness analyses.⁸ Bootman et al.⁹ also published an early pharmacy research article in 1979 in which cost–benefit analysis was used to evaluate the outcomes of individualizing aminoglycoside dosages in severely burned patients with gram-negative septicemia using sophisticated pharmacokinetic protocols. The actual term “pharmacoeconomics” did not appear in the literature until 1986 when the first of a two-part presentation by Townsend¹⁰ was published describing the need to develop research activities in this evolving discipline. To date, many of the efforts in this discipline have been directed toward the refinement of the research methods and their application to evaluating pharmaceutical services and specific drug therapies.

Pharmacoeconomics continues to evolve similarly to another relatively new pharmaceutical science: pharmacokinetics. Pharmacokinetics surfaced in the 1950s in United States colleges of pharmacy and, in the 1970s, became an integral part of the pharmacy curriculum. Many of the theoretical models for pharmacokinetics are based on the physicochemical principles developed by physicists, chemists, and engineers. As a parallel, pharmacoeconomics has borrowed from the basic economic and social sciences for most of its theoretical models. McGhan, Rowland, and Bootman introduced course material related to pharmacoeconomics into the undergraduate and graduate pharmacy curricula as early as 1976 at the University of Minnesota. However, the educational content was emphasized at the graduate level—not at the undergraduate professional program levels. We are beginning to see much of this material incorporated at the PharmD education level alongside the discipline of pharmacotherapy.

Furthermore, upon examining the evolutionary path of pharmacokinetics, it is clear that its application in the clinical setting was a driving force that ensured its place in the professional pharmacy curriculum. We believe that pharmacoeconomics will obtain the same level of recognition when its application in the clinical setting is more complete. In other words, when pharmacy practitioners begin to apply the results of pharmacoeconomic research to therapeutic decision-making, thus positively influencing patient outcomes, the discipline will become an in-

creasingly critical component of the pharmacy curriculum. Likewise, the successful implementation of “pharmaceutical care” will come about only with sufficient pharmacoeconomic research that adequately documents the degree to which the benefits of such care outweigh the costs associated with those services. In fact, the profession of pharmacy is unlikely to succeed in its role of providing pharmaceutical care without this critical body of knowledge. Pharmacists must become the key players in ensuring that drug therapy and related pharmacy services are not only safe and effective, but also provide real value in both economic and humanistic terms.

Overview of Pharmacoeconomic Methodologies

The purpose of this section is to acquaint the reader with the basic methodologic approaches regarding the economic evaluation of drug therapy. By definition, *pharmacoeconomic evaluations* include any study designed to assess the costs (ie, resources consumed) and consequences (clinical, humanistic) of alternative therapies. This includes such methodologies as cost–benefit, cost-utility, and cost-effectiveness (Table 1). Each of these methodologies is discussed in more depth in later chapters. Review articles that discuss the application of these techniques to healthcare evaluations also may assist readers in becoming more aware of the role of these tools.⁸⁻³⁰ The evaluation mechanisms delineated were often helpful in demonstrating the cost impact of innovative treatments, therefore granting them greater acceptance by healthcare providers, administrators, and the public.

Table 1. Pharmacoeconomic Methodologies

Methodology	Cost	
	Measurement Unit	Outcome Unit
Cost–benefit	dollars	dollars
Cost-effectiveness	dollars	natural units (life-years gained, mg/dL blood glucose, mm Hg blood pressure)
Cost-minimization	dollars	assume to be equivalent in comparative groups
Cost-utility	dollars	quality-adjusted life-year or other utilities

COST-MINIMIZATION ANALYSIS

When two or more interventions are evaluated and demonstrated or assumed to be equivalent in terms of a given outcome or consequence, costs associated with each intervention may be evaluated and compared. This typical cost analysis is referred to as *cost-minimization analysis*. An example of this type of investigation regarding drug therapy may be the evaluation of two generically equivalent drugs in which the outcome has been proven to be equal, although the acquisition and administration costs may be significantly different.

COST-BENEFIT ANALYSIS

Cost-benefit analysis is a basic tool that can be used to improve the decision-making process in allocation of funds to healthcare programs. Although the general concept of cost-benefit analysis is not overly complicated, many technical considerations require a degree of explanation and interpretation to understand how it can be or has been applied.

Cost-benefit analysis consists of identifying all of the benefits that accrue from the program or intervention and converting them into dollars in the year in which they will occur. This stream of benefit dollars is then discounted to its equivalent present value at the selected interest rate. On the other side of the equation, all program costs are identified and allocated through a specific year and, again, the costs are discounted to their present value. Then, if all relevant factors remain constant, the program with the largest present value of benefits less costs is best in terms of its economic value.

Ideally, all benefits and costs resulting from the program should be included. This presents considerable difficulty, especially on the benefits side of the equation, as many benefits are either difficult to measure, difficult to convert to dollars, or both. For example, the benefits of improved patient quality of life, patient satisfaction with the healthcare system, and working conditions for the physician are not only difficult to measure, but are extremely difficult to assign a dollar value to. This problem has been addressed by many researchers in health economics, but has not been completely resolved. Generally, the analyst or researcher will convert as many benefits as possible into mone-

tary units. The remaining variables are labeled as “intangible benefits” and left to decision-makers to include in their final deliberations. Cost-benefit analysis often has been used when comparing the value of dissimilar programs where the outcomes are in different units (eg, cost-benefit of having a neonatal care program vs a cardiac rehabilitation program).

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis is a technique designed to assist a decision-maker in identifying a preferred choice among possible alternatives. Generally, cost-effectiveness is defined as a series of analytical and mathematical procedures that aid in the selection of a course of action from various alternative approaches. Cost-effectiveness analysis has been applied to health matters where the program’s inputs can be readily measured in dollars, but the program’s outputs are more appropriately stated in terms of health improvement created (eg, life-years extended, clinical cures).

An important point to be considered in both cost-benefit and cost-effectiveness analysis is that a program/treatment providing a high benefit (effectiveness)-to-cost ratio in terms of value to society may not be valued in the same way by all members of society. For example, drug therapy that reduced the number of patient-days in an acute care institution may be positive from a third-party payer’s point of view, but not necessarily from the view of the institution’s administrator who operated under a fixed level of revenue and depended on a fixed number of patient-days to meet expenses. What is viewed as cost-beneficial for society as a whole may be viewed differently by plan sponsors, administrators, health providers, governmental agencies, or even individual patients. One must consider whose interests are to be taken into account when using these analyses.

COST-UTILITY ANALYSIS

In examining Table 1, one can better appreciate the subtle differences between the techniques discussed to this point. *Cost-utility analysis* is an economic tool in which the intervention consequence is measured in terms of quantity and quality of life. It is much the same as cost-effectiveness analysis, with the

added dimension of a particular point of view, most often that of the patient. Quite often the results of cost-utility analysis are expressed in the intervention cost per quality-adjusted life-year gained or changes in quality-of-life measurement for a given intervention cost. Although cost-utility analysis has been used somewhat successfully to aid in decisions regarding healthcare programs (eg, surgery vs chemotherapy), instruments that are reliable and sensitive enough to detect changes with drug treatments (eg, one antihypertensive agent vs another) are still needed.

COST-OF-ILLNESS EVALUATION

Cost-of-illness studies are important to pharmacoeconomic evaluations of new therapies. By evaluating the humanistic impact of disease and the resources used in treating a condition prior to discovery of a new intervention, the pharmacoeconomist can effectively establish a baseline for comparison. Although the value and methodologies of cost-of-illness studies have been debated, they remain prevalent in the pharmacoeconomic literature.^{28,29} As with all pharmacoeconomic evaluation, when conducting or evaluating the cost-of-illness, it is important to carefully consider the design and intent of the study. There is value in having baseline information, but absolute conclusions regarding the value of an intervention versus an alternative can be made only after direct comparison.

COST-CONSEQUENCE ANALYSIS

A *cost-consequence analysis* has been defined as one “in which costs and effects are calculated but not aggregated into quality-adjusted life-years or cost-effectiveness ratios.”³¹ Simply, this type of analysis comprises a listing of all relevant costs and outcomes of drug therapy or healthcare intervention including direct medical costs, direct nonmedical costs, indirect costs, clinical outcomes, utility impacts, and quality-of-life impacts. Cost-consequence analysis provides the most comprehensive presentation of information describing the value of an intervention and has the advantage of being more readily understandable and more likely to be applied by healthcare decision-makers.³² In this application, weighting of different costs and benefits is left to each decision-maker. Although this should lead to improvements in

decision-maker welfare from an economic perspective, a possible drawback for disaggregated presentation of health outcomes is that decisions made at the individual decision-maker's level might not be made in the patient's or society's best interests. Another potential weakness of cost-consequence analysis is that all of the data are not always of comparable quality. Cost-consequence analyses in the literature often include a variety of data from clinical trials and other sources, since no single source is adequate to provide the breadth of information required.³³⁻³⁷ Imputation and extrapolation are often necessary. Despite these considerations, cost-consequence analysis remains a useful approach to presenting relevant information for a wide range of healthcare concerns.

Pharmacoeconomics and Drug Development

The pharmaceutical industry spends billions of dollars annually for development of new drugs. As a percentage of pharmaceutical sales, these research and development (R & D) costs are certainly higher than those found in other industries.² The large number of compounds that must be evaluated to bring one drug to market contributes to the high R & D costs of drug development. This percentage is also higher than that found in other industries. It has been estimated that it takes \$802 million and 14 years to bring a new drug to the market.² The process by which a drug is evaluated and developed for the marketplace is illustrated in Figure 1.

Because pharmacoeconomic data are becoming increasingly important to practitioners making drug formulary decisions, it is important to have these data as soon as possible after Food and Drug Administration approval. To do this, discussion and planning for pharmacoeconomic evaluation should begin during the early stages of drug development. A major question arises as to the ideal time to conduct pharmacoeconomic studies and the best process by which to do so. Pharmacoeconomic studies may be planned and conducted at the clinical development and Phase IV stages of postmarketing research. Basic research and development activities may be partially guided by preliminary pharmacoeconomic analyses. Therefore, studies may need to be

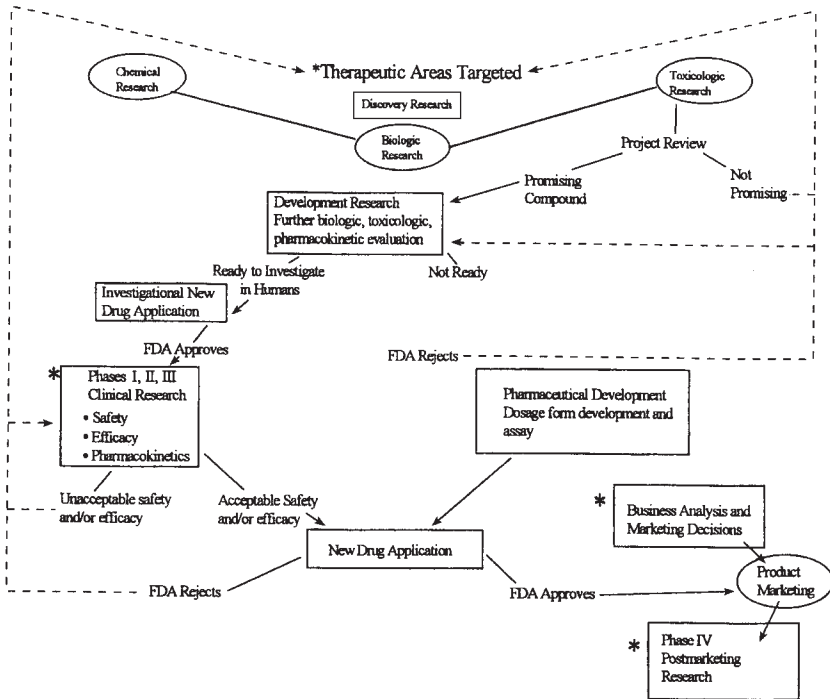


Figure 1. Research and development stages of a new drug. FDA = Food and Drug Administration. * = Pharmacoeconomic evaluations may be designed or conducted at these levels.

conducted at several stages of pharmaceutical research. The following is a summary of the research activity for each phase.

PHASE I TRIALS

The objective of the initial clinical trials, or Phase I, is to determine the toxicity profile of the drug in humans. The first Phase I trials usually consist of administration of single, conservative doses to a small number of healthy volunteers. The effects of increasing the size and number of daily doses are evaluated until toxic effects surface or the likely therapeutic dosage is substantially exceeded. It is during this stage that cost-of-illness studies should be accomplished to aid in deciding whether to further develop the drug and gather background data for future pharmacoeconomic evaluations. Cost-of-illness data may also aid in the development of preliminary models to assess the clinical benefits that must be achieved in order to have a marketable product.

PHASE II TRIALS

In Phase II trials, the drug is administered to a limited number of patients with the target disease. Patients without complicating, coexisting medical conditions are preferred for these trials. This reduces the number of variables that could confound analysis of the drug's activity and permits the potential therapeutic benefit of the new drug to be more clearly demonstrated.

Even in carefully selected patients, however, demonstrating the efficacy of a new drug is not easy or certain. To provide unequivocal evidence of the drug's therapeutic benefit, it is necessary to compare its effectiveness with that of standard medically accepted treatments or, where ethically appropriate, with a placebo. These comparisons also are used to establish the optimal dosage range for therapeutic activity of the new drug. During this phase, cost-of-illness studies can begin or continue, as can preliminary development of quality-of-life and resource utilization instruments. Models can be refined as more information is available about the clinical aspects of the drug.

PHASE III TRIALS

In Phase III trials, larger numbers of patients are given the new drug in the established dosage range and in the final dosage form. This larger sample size refines the knowledge gained during Phase II and helps identify patients who might have rare reactions to the drug. Patient selection is still closely supervised in Phase III, although some patients with coexisting medical problems are intentionally included to allow assessment of complication in the drug's use.

Discussion, planning, and implementation of pharmacoeconomic studies during this level of research are important. The prospective clinical study that has incorporated a pharmacoeconomic evaluation during the final stages of efficacy evaluation is close to the ideal situation. Critics of these studies claim that pharmacoeconomic evaluations will hinder the new drug application (NDA) process. Advocates of pharmacoeconomic evaluation correctly note that, unless a new drug treatment has no alternatives and is truly a breakthrough, the value of using it must be scientifically studied.

PHASE IV TRIALS

During the postmarketing phase, or Phase IV, retrospective and prospective pharmacoeconomic studies can be designed and conducted to gather data in support of the use of the drug. Postmarketing pharmacoeconomic studies are extremely important in that they allow evaluation of the costs and consequences of drug therapy without the altered interventions that occur in strictly controlled clinical trials. During tightly controlled clinical trials, pharmacoeconomics can only put value on efficacy; this only approximates the “real world.” Once a product is on the market, cost-effectiveness can be determined. NOTE: *Efficacy* studies answer “can it work?” *Effectiveness* studies evaluate “does it work?”

As previously indicated, clinical trials are used to evaluate the efficacy and safety of therapies. The relationships between pharmacoeconomic evaluations and clinical trials are threefold.

1. The pharmacoeconomic evaluation may be a secondary objective of a trial designed primarily to study safety and efficacy.
2. The pharmacoeconomic evaluation may be the principal purpose of a clinical trial.
3. A pharmacoeconomic evaluation may be done retrospectively using clinical data obtained in previous trials.

Once a drug is marketed, either retrospective or additional prospective pharmacoeconomic studies may be designed and conducted.

Epidemiologic studies are frequently used to evaluate the effectiveness and safety of drugs. Epidemiologic data with regard to the disease and treatment under investigation can yield highly important information for economic evaluation of a specific drug therapy. Understanding the natural progression of the disease comorbidities and treatment enables estimation of the variables that may have pharmacoeconomic implications with regard to cost of illness and quality of life.

Epidemiology’s role in pharmacoeconomic evaluations and considerations for conducting pharmacoeconomic research within clinical trials are the subject of Chapters 9 and 11, respectively.

Pharmacoeconomic Guidelines

Researchers and evaluators continue to develop and refine guidelines for pharmacoeconomic analysis. The uses and subject of the proposed guidelines are as follows:

1. Methodologic guidelines would guide researchers to appropriately design, conduct, analyze, and report economic and humanistic evaluations.
2. Reimbursement and pricing guidelines would outline the content, presentation, and evaluation of pharmacoeconomic data to determine or justify the price or reimbursement of a pharmaceutical product.
3. Approval guidelines would set the standards acceptable to a particular government to obtain approval to market a new product.
4. Promotional guidelines would set the criteria for the use of pharmacoeconomic data in support of pharmaceutical promotion to prescribers and consumers.

Although the intent of the call for guidelines is understandable, at present, the science of pharmacoeconomic research is still developing. It would not be desirable to implement guidelines that would limit the development of knowledge in this area. Suffice it to say that the substance of any guidelines involving research must be well grounded in appropriate methodology and sound scientific principles.

Challenges of Pharmacoeconomic Research

In the future, we will be routinely challenged to do pharmacoeconomic research, although merely performing the research will not solve all of the problems all of the time. To be useful, appropriate pharmacoeconomic evaluations must be tailored to the specific problem and decision at hand. Our challenge, therefore, begins with looking beyond the obvious and easy solutions.

Cost-minimization analysis is useful when comparing interventions with identical clinical and humanistic outcomes, but this can be the exception rather than the rule for many clinical applications outside of true generic substitution. Cost-benefit analysis would, at first glance, be the answer to more complex problems in that it would allow for evaluation of various interventions with multiple and dissimilar outcomes. Here, too, one must be careful to note the pitfalls and challenges associated with converting all of the benefits to monetary terms. (How do you place a monetary value on reduced blood pressure, insulin control, or improvement in quality of life?)

Allowing consequences to remain in natural and measurable terms means that cost-effectiveness analysis can be appropriate for many problems and help with many decisions when the outcomes of the interventions are measured in the same terms. But what about the patient and how the various treatments affect daily living and quality of life? Should decisions be made strictly on providing the best clinical outcome for the dollars spent? If so, perhaps cost-utility analysis, which takes into account patient preference and quality of life, should be the gold standard of pharmacoeconomic research. Alas, here too are the problems of measuring quality of life and preference in a changing world.

Present and future controversies surrounding pharmacoeconomic research also include arguments for methodologies of valuations and discounting. What is the most appropriate perspective to take when valuing costs and consequences: the patient, the third-party payer, or perhaps society? What of ethics? Will we be able to justify our decisions solely on the numbers obtained through scientific research?

One of the biggest challenges for pharmacoeconomic research lies in the education of those who are going to be evaluating the data derived from this research. Although the end users of pharmacoeconomic research data would like to have simple, clear-cut answers to their questions regarding the allocation of resources and the healthcare benefits derived from them, in actuality, the answers are quite complex. Pharmacoeconomics remains an art as well as a science. Even though the science may be perfectly clear, applying that science must be done artfully using professional judgment. Just as it is impossible to develop an algorithm for the treatment of a disease that is appropriate for all patients, it would be impossible to develop one for making pharmacoeconomic decisions. In the end, the user of pharmacoeconomic research data must be able to evaluate the scientific appropriateness and robustness of the research and make a decision regarding its usefulness in a particular situation. To do this, evaluators will need to understand the basic principles of pharmacoeconomic research.

The challenges of pharmacoeconomic research are inexhaustible; many are addressed within the chapters of this book. The real challenge, however, is not identifying the tools of phar-

macroeconomic research, but rather discovering how and when to use them.

Summary

The overall costs of medical and pharmaceutical care continue to rise. The added value to society, individual healthcare institutions, and patients as weighed against cost has not been well established. The problem has become increasingly difficult to address because of the lack of understanding of methodologies for evaluation of new and existing drug therapy. The remaining chapters of this text provide in-depth information on specific methodologies often used in pharmacoeconomic investigations.

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