Learning Objectives

1. Describe the concept of value in the health care system.
2. Differentiate between the concepts of outcomes research, pharmacoeconomics, and patient-reported outcomes assessment.
3. Classify outcomes using the Economic, Clinical, and Humanistic Outcomes (ECHO) model.
4. Categorize costs by classification and perspective.
5. Describe the mechanisms for valuation of productivity costs.
6. Determine the role of the different types of economic study designs.
7. Describe the role of discounting and sensitivity analysis in pharmacoeconomic analyses.
8. Assess the differences between the pharmacoeconomic analysis types.
9. Describe the differences between the three common methods of determining utilities.
10. Determine the components and calculate quality-adjusted life years.
11. Describe the use of patient-reported outcomes to place valuation on health-related quality of life.
12. Distinguish the components of a patient-reported outcomes instrument.
13. Appraise the types of reliability and validity required for a patient-reported outcomes instrument.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter

1. Which of the following is the best example of an intermediary (surrogate) outcome?
   A. Blood pressure (in mm Hg).
   B. Death.
   C. Pain.
   D. Satisfaction on a Likert scale.

2. The local health system, consisting of the hospital and three physician practices, is conducting a cost-benefit analysis from the provider perspective on opening a dialysis center in a town where the nearest center is currently 75 miles away. Which of the following is an opportunity cost to the health system?
   A. Opening a new cancer center.
   B. Equipment for the dialysis center.
   C. Decreased transportation costs.
   D. Work hours gained.

3. The human capital approach is often used to determine indirect costs. For which of the following pharmacoeconomic studies would the human capital approach be most appropriate?
   A. Premenstrual depression in high school students.
   B. Shift-induced insomnia in middle-aged male oil workers.
   C. Stress in nongovernment organization volunteers in disaster areas.
   D. Congestive heart failure readmissions in Medicare recipients.

4. You are conducting a patient-reported outcomes study on relapsing-remitting multiple sclerosis. You want to use an instrument to monitor patient response to the drug therapy. Which of the following would be the best reason to select a disease-specific instrument?
   A. Extensive history in research of this type.
   B. Responsive to small changes.
   C. Identifies impact of rare adverse effects.
   D. Ability to compare results with those of patients with rheumatoid arthritis.

5. You are attempting to measure the construct validity of the propensity for drug abuse by comparing youth in drug rehabilitation with youth who abstain from recreational drugs. What is this type of validity?
   A. Content.
   B. External.
   C. Face.
   D. Known-groups.
6. A new drug, WalkAgain, is extremely effective for returning the ability to walk in patients with multiple sclerosis to normal. However, it is very toxic, and death rates are high. What is the utility of MS in wheelchair for 15 years, as determined by “fully informed members of the public” without MS.
   A. 0.16.
   B. 0.42.
   C. 0.58.
   D. 1.0.

7. The SF-12v2 consists of 12 questions that cover the same eight domains found in the SF-36. Each domain receives a score from 0 to 100. Considering the standard components of instruments, which of the following components is represented by a print-out listing the eight domain scores for an individual?
   A. Items.
   B. Scales.
   C. Profile.
   D. Battery.

8. Over a 4-year period, patients with hepatitis B treated with HepSlow would have an average of 2.5 years of usual chronic hepatitis B symptoms (utility 0.68), 0.5 years of decompensated cirrhosis (utility of 0.35), 0.75 years of liver transplant (1st year, utility of 0.57), then die. ImprovedHepBCare yields 2.75 years of chronic hepatitis B symptoms, 0.25 years of decompensated cirrhosis, and 1 year of liver transplant (first year). How many quality-adjusted life years (QALYs) are gained from the use of ImprovedHepBCare?
   A. 0.225 QALYs.
   B. 0.250 QALYs.
   C. 2.30 QALYs.
   D. 2.53 QALYs.

9. The hospital is conducting a pharmacoeconomic study of patients who have had myocardial infarctions from the provider perspective. Which of the following would be the best input to determine value in this study?
   A. Cost analysis of the entire stay.
   B. Microcosting of pharmacy services.
   C. Aggregation of hospital day costs.
   D. Satisfaction surveys.

10. Your colleagues are designing a randomized controlled trial of a new drug for psoriasis compared with the current standard drug therapy. You decide to conduct a piggyback economic study in association with their study. Which of the following aspects will be of greatest concern?
    A. Collecting data on costs.
    B. Generalizability of the results.
    C. Internal validity.
    D. Missing data.

11. You are conducting a retrospective pharmacoeconomic study using claims data from the past year. You want to determine the robustness of the cost-benefit analysis and have calculated the confidence intervals for components with the most impact on the analysis. Which of the following would be the strongest test for robustness?
    A. Conducting a Bayesian analysis.
    B. Identifying the discount factor.
    C. Using an analysis of the extremes.
    D. Identifying the states of the disease.

12. An employer wants to evaluate the effects of a new pain clinic on employee presenteeism. You decide to use the SF-36v2 as part of the study protocol. Changes in which of the following domains would be of most interest to the employer?
    A. Role limitations due to physical problems.
    B. General health.
    C. Role limitations due to emotional problems.
    D. General mental health.
13. A national group is conducting a study on the change in the cost of illness for a major disease after the first biological specialty drug had been on the market for 1 year. Based on the usual cost-of-illness study, which of the following types of outcome study would be most applicable to the data?
   A. General outcomes research study.
   B. Cost-benefit analysis.
   C. Cost-utility analysis.
   D. Cost-effectiveness with patient-reported outcomes.
ECONOMIC AND PATIENT-REPORTED OUTCOMES ASSESSMENT

I. INTRODUCTION

A. Background of the Problem

The problem is the cost of health, or in easier-to-measure terms, the cost of health care. In 2002, the Institute of Medicine stated, “The [United States] health care system as currently structured does not, as a whole, make the best use of its resources.” National health expenditures for 2013 were $2.9 trillion, an increase of 3.6% from 2012. The health care share of gross domestic product (GDP) was 17.4% in 2013 (remaining essentially the same since 2009). Real GDP is the output of goods and services produced by labor and property located in the United States, with all dollars adjusted to the same point of time. Most policy-makers in the United States believe that this is too large; it is also much larger as a percentage of GDP than in any other country. Outcomes research and pharmacoeconomics, with its special interest to pharmacists, are methods to evaluate whether interventions are potential solutions to this problem.

The Centers for Medicare and Medicaid Services has specific definitions for what is included in their calculations of health expenditures. Prescription drugs (outpatient only) were responsible for $271 billion (1.6% of GDP or 9.3% of health care expenditures). This does not include over-the-counter drugs (which have their own category), dietary supplements, or inpatient drugs. Pharmacoeconomics can be an important tool in determining whether these expenditures are the best use of health care dollars.

Case Study Part 1: Quantifying the Problem

In 2010, diabetes affected 25.8 million people in the United States (8.3% of the population), where 18.8 million people were diagnosed and 7.0 million were undiagnosed. About 1.9 million people aged 20 years or older were newly diagnosed with diabetes in 2010. During 2002–2005, 15,600 youth were newly diagnosed with type 1 diabetes and 3,600 youth were newly diagnosed with type 2 diabetes annually. Diabetes was the seventh leading cause of death, based on 71,382 U.S. death certificates in 2007 in which diabetes was the underlying cause of death. Diabetes was a contributing cause of death in an additional 160,022 death certificates. State an economic problem from this information.

B. Content of the Chapter: The purpose of this chapter is to provide an overview of the techniques of pharmacoeconomics and patient-reported outcomes (PRO) assessment. The information will allow the pharmacotherapy specialist to evaluate studies using these concepts or to select a PRO instrument. Because of the complexity of the techniques, additional resources will be needed for complete comprehension. Hundreds of studies using these techniques exist; the reader is referred to the literature for specific examples. This chapter presents methods to evaluate the value of health care, with emphasis on evaluation of pharmaceuticals and pharmacy services. Concepts such as outcomes, costs, perspective, and the effects of time and assumptions are included.

Pharmacoeconomics and outcomes research are really about the population, using statistical probability for achieving benefit. To paraphrase an old saying, “If you have the outcomes and costs for one patient, you have seen one patient.” Therefore, determining the benefit requires large sample sizes.

1. Definition of Outcomes Research and Pharmacoeconomics: Outcomes research is “research on measures of changes in patient outcomes (such as patient health status and satisfaction resulting from specific medical and health interventions),”

   One of the many independent subcategories of outcomes research is pharmacoeconomics, “the field of study that evaluates the behavior or welfare of individuals, firms, and markets relevant to the use of pharmaceutical products, services, and programs.” Kozma et al. described pharmacoeconomics as the systematic framework for decision-making based on the evaluation of pharmaceutical alternatives.
2. Value: Much of the recent health care reform is oriented to a value-based system. Value is defined by Porter (referencing himself and Teisberg in a recent commentary) as “health outcomes per dollar spent.” The commentary goes on to emphasize that outcomes are those that are important to the customer, and the costs are total costs for the full cycle of the patient’s care, not the cost of specific services (such as pharmaceuticals). When done well, pharmacoeconomic analyses provide data on comparative value of pharmacy-associated products and services. The results provide input into decisions attempting to balance the need for access and quality with the constraints of finite resources.

3. Evaluation of Interventions: Four types of evaluation for interventions must be done for value to be determined. These evaluations are efficacy, effectiveness, efficiency, and ethics. Optimum health care resource decisions need information from all four of these evaluations.
   a. **Efficacy** is the degree to which an intervention works. Efficacy is determined by results achieved in carefully designed and well controlled studies. This internal validity provides good cause and effect information. The highest levels of evidence are efficacy studies.
   b. **Effectiveness** is the degree to which the intervention can work in practice. Outcomes research is interested in effectiveness or the results achieved in the real world. When using observational studies which provide external validity, only an association can be identified.
   c. **Efficiency** is an assessment of whether the intervention is worth its price. Efficiency is the measurement of the resource utilization function of value. Pharmacoeconomics provides efficiency evaluations.
   d. **Ethics** is an assessment of whether the intervention should be used regardless of the cost; this is the human worth.

Equity is an underlying component of ethics and is an assessment of whether the intervention represents a fair allocation of resources. PRO analysis can provide some insight into ethics decisions.

Pharmacoeconomic analyses are based on two components: outcomes and costs. Health-related outcomes are the result of the resources input into the system (costs). Patient-reported outcomes (PROs) are a specific category being used with increasing frequency; this topic will be covered in a separate section below.

II. OUTCOMES

A. Definition: Outcomes (also known as consequences or benefits) are the ultimate result of a pharmacy intervention or service; this may be a desirable result or a reduction in an undesirable result. When looking back to the problem being addressed, the outcome is the measurement of the results of the solution being implemented (the intervention or interventions). The outcomes of interest are those directly related to health status or economic indicators of status. Health-related outcomes are often the objects of assessment in health care evaluations. Donabedian, in the 1966 article “Evaluating the Quality of Medical Care,” presented the concept of outcomes; his outcomes are the same outcomes presented here even though this chapter is interested only in economic efficiency, an area he specifically excluded. Important to pharmacoeconomic analyses is the end point, or how the outcome is being measured.

B. ECHO Model: In 1993, Kozma et al. presented a model that has become the classic in categorizing the measurements of health care while preserving the overlapping relationships. The Economic, Clinical, and Humanistic Outcomes (ECHO) model creates a visualization of the relevant outcomes for the intervention. This visualization shows the multidimensional nature of health and health care outcomes. It maintains the concept that outcomes are the results of disease or treatment.
   1. Clinical outcomes are changes in biomedical and physical events.
   2. Economic outcomes are changes in the utilization of resources.
3. Humanistic outcomes are changes in patient status or quality of life. The model portrays an optimal balance of the types of outcomes that establish ultimate value. Outcomes are stated in directional terms (usually as the desired change).

![Diagram](image)

**Figure 1.** Components of clinical decision making.

![Diagram](image)

**Figure 2.** Relationship of outcomes in ECHO model.
A1C = Hemoglobin A1C; ED = emergency department; ESRD = end-stage renal disease; HRQoL = health-related quality of life; ICU = intensive care unit.

C. Types of Outcomes: Some outcomes can be quantified and accurately determined (death, myocardial infarction) but are often rare or take a long period of time to manifest. Other outcomes are more difficult to measure.
   1. To decrease sample size or research time or to clarify a concept, a surrogate may be used.
   2. Surrogates may be intermediary in the continuum to the quantifiable outcome or final end point. An example of an intermediary would be a decrease in lumen diameter as a surrogate for myocardial infarction.
3. Surrogates that are not intermediary but are established as clinical indicators (such as laboratory values or physical transformations) are also used; for example, blood pressure readings are not intermediary but have a positive association with myocardial infarction or stroke.

4. Side effects and satisfaction may serve as surrogates for humanistic outcomes; adverse effects may be a surrogate for quality of life, and satisfaction may be a surrogate for quality. A choice usually must be made on the clinical outcome to be used in a pharmacoeconomic analysis where economic and humanistic outcomes may have a specific outcome or may be combined into a more general category in some types of analyses.

**Case Study Part 2: Identifying Outcomes**

Diabetes mellitus has numerous outcomes. The ECHO model can be used to identify these outcomes. Identify as many outcomes in each category as possible. Include some direct and some surrogate outcomes for each. Remember, outcomes are directional.

**III. COSTS**

A. Definition of Costs and Opportunity Cost: Costs are the resources used (resource consumption). Pharmacoeconomic analyses are being used because resources are finite, and if a resource is used, say for health care, it cannot be used for any other purpose. This is known as the opportunity cost, where, even more specifically, the resource cannot be used for its next best use. As the percentage of GDP for health care expenditures increases, the amount left for other important uses decreases (e.g., for food or durable goods in the form of cars or houses). Evaluation of alternatives, pharmacy-related in pharmacoeconomics, can identify the alternative with the most efficient use of resources or the use that provides the highest value.

B. Pareto Principle: In accordance with the Pareto principle (80–20 rule), approximately 80% (80.3%) of health care expenditures in the United States in 2010 were incurred by 20% of the population. The 20% created opportunity costs that are borne by the other 80% of the population. Therefore, the high-utilization segment (the 20%) of the population, or a subgroup within it, is the usual target for enhanced programs or therapeutics. Because the 80–20 rule usually plays out in most settings where a pharmacoeconomic study will be conducted, the resources used (or the monetary valuation of the resources used) are skewed, and appropriate consideration should be given when selecting the statistical test.

C. Presentation of Costs

1. The difference between a cost and an economic outcome may be hard to distinguish, and occasionally, as in cost-benefit analysis, putting a name on the component may not be necessary. Costs may have valuation assigned in two different ways:
   a. Microcosting: Each item is priced separately (e.g., the drug, syringe, catheter, time to prepare, time to administer). Microcosts are time intensive to collect or can have a broad range of variation, so many providers, such as hospitals, use a technique to estimate these costs, called a cost-to-charge ratio.
   b. Aggregated: An average cost for the sum of the individual items is combined into a cost for a unit of resource (e.g., an intensive care unit hour). Aggregation can be a simple average or can entail complex processes.
2. Cost-to-charge ratio: The charge is the price of the resource unit (the billed amount); cost is what is paid for the components (the amount expended). Because actual costs may be time consuming to collect, hospitals often use an estimate known as the cost-to-charge ratio, the total accounting cost for the hospital divided by the total billing amount. This ratio is then used for each department by multiplying it by that department’s total billing amount.

3. Another method of costing is to use national or regional estimates of costs. This method is most often used for estimating the cost of lost work time, but it can be used for many costs. The accuracy of any of these methods depends on how well they were done. The generalizability increases with the larger databases, but an individual organization may not be able to apply the results as their costs.

4. Costs include fixed costs and variable costs.
   a. Fixed costs are costs that exist whether or not patients are present; these include the costs of major equipment or buildings.
   b. Variable costs (are those that differ depending on the needs of the patient, such as amount of drug received or amount of time spent by a pharmacist calculating doses).
   c. Differences of opinion exist on whether salaries are fixed or variable costs, because the opportunity to use the worker for the next best task often does not occur (health care workers usually do not have chargeable and nonchargeable time), but some argue that if efficiencies occur, the number of hours worked will decrease. Ideally, the methods presented for a particular study are transparent on how salaries are categorized. Unless the use of different settings is the intervention, fixed costs are often not included in any of the types of costs.

5. Costs are always reported in a monetary unit (for this chapter, the U.S. dollar is used as the unit). Several countries require results of pharmacoeconomic analyses before drugs or health care technology can be approved in their countries. Thus, because so many pharmacoeconomic studies are conducted in other countries, the monetary unit may need to be converted to dollars for comparison.

D. Types of Costs: Regardless of the method of obtaining cost valuation, costs for pharmacoeconomic analyses include cost of the treatment, cost of adverse effects, and costs of failure. Although other methods of categorizing costs exist, the standard is to divide costs into direct, indirect, and intangible categories.

1. Direct: Direct costs are divided into two categories: direct medical and direct nonmedical.
   a. Direct medical costs
      i. Direct medical costs are the only aspects included in government health care expenditure data (which is the only aspect included in the GDP as health care).
      ii. The components of these costs include the drugs (being compared or used to treat adverse effects or failure), devices for administration, devices for monitoring, laboratory values for monitoring, clinic visits, hospital days, ICU hours, surgery and recovery room minutes, labor costs (with benefits) if not included in the previous categories, and relevant other resources.
      iii. Expenditures for benefits from health insurance are included under the specific cost (e.g., prescription drugs or hospital days); any difference between the total premium collected and the expenditure for benefits is included under a category called net insurance cost in U.S. health care expenditure data (this would be a direct cost to society).
   b. Direct nonmedical costs
      i. Direct nonmedical costs are those that would not be expended in the absence of the disease but are not considered medical purchases.
      ii. These include transportation, child care, special diets (not including medical supplements), modification of the home, lodging, and away meals.
2. Indirect
   a. Indirect costs in pharmacoeconomic analyses include only the costs of lost productivity caused by morbidity and mortality.
   b. The longest-studied indirect cost is lost work days (hours), which is called absenteeism. The cost of absenteeism may be directly measurable if sick leave is paid or a replacement is used or can be estimated by the cost of not getting the work completed.
   c. A more difficult indirect cost to measure, but one with increasing research reports, is presenteeism, the cost of lost productivity of being at work but not producing at the expected level.
   d. Productivity can be measured by several end points including lost work days (hours, minutes) to employers, lost wages to individuals (including caregivers), and lost taxes to society.
   e. Valuing the indirect cost of being a child, retired person, or unpaid worker (homemaker, volunteer) is difficult. Wage disparities within a country and between countries affect the ability to establish generalizable valuation of indirect costs. Three methods attempt to establish this valuation.
      i. Human capital approach: The human capital approach measures the cost of lost productivity. This is also known as the forgone earnings approach. If actual wages are not known, this approach uses a sample of individuals and creates a comparable earnings estimate for that group (by age and sex). These estimates are adjusted for probable life span when valuing mortality (and the remaining years are discounted). These estimates can be obtained from sources such as the Census Bureau and the Bureau of Labor Statistics. One assumption that may or may not be accurate is that the cohort’s earnings will increase each year because of increased expertise. The very young, women, minorities, and older adults are undervalued. The pure approach does not adjust for lost earnings for unpaid work such as homemaking, child care, or volunteer work. Proxy prices (the cost to pay someone to do the work) or shadow prices (a valuation that estimates the opportunity costs of wages they would have made if employed) are used to place a valuation on this unpaid work.
      ii. Frictional cost: Another method related to human capital is frictional cost, which is the cost to replace the worker. Acute illness is not captured, nor is the loss of leisure time (for the alternate worker taking on overtime). The frictional method is a conservative estimate of indirect costs. A variation is the Washington Panel Approach, which separates the friction costs from productivity costs, with only the latter included in quality of life assessment.
      iii. Willingness to pay: Willingness to pay (WTP) is often used method to measure the benefit of an intervention by providing the maximum amount that people are willing to pay for it (or to prevent an adverse outcome such as lost productivity). The contingent valuation methods include a question or series of questions about payment based on a carefully phrased question. The question can be a simple “Would you pay X amount?,” choosing a card (from a continuum of prices) that indicates how much you would pay, or a bidding game that goes up or down depending on the answer to a price. Each of these has its advantages and problems. The first price or range of prices can bias the results; adjustments are made for variations in incomes. Although some question the technique, WTP is conducted on large sample sizes and has been found to be reliable, valid, and generalizable (for most English-speaking countries, if conducted in an English-speaking country).

3. Intangible costs: The third category of costs is intangible. These are the aspects of loss of health that are related to the personal costs such as effects of pain or decreased social and role functioning. Placing a valuation on these is very difficult, and therefore they are often not included in pharmacoeconomic analyses. Techniques that can be used are WTP or incorporating the costs into the quality of life evaluations.
IV. PERSPECTIVE

A. Viewpoint: One of the basic concepts in pharmacoeconomic analysis is that of perspective (viewpoint), and the valuation of those costs will be used in the analysis. Most discussions of perspective have four categories: society, payer, provider, and patient (Figure 3).

B. Society: The societal perspective is considered to be the preferred viewpoint for most pharmacoeconomic analyses. This perspective is the combination of all other perspectives and, in its pure form, includes all types of costs. This makes it very difficult to conduct. For example, for the cost of a drug, should acquisition, production, or some other cost be used? Often, a proxy price is used (one older method was the average wholesale price); multiple problems exist with this type of costing, but the costs can then be the same across evaluations. The societal costs should be based on opportunity cost: prevention of lost work time, the next best use for the money used to make drugs, leisure time, and other examples. At times, government can serve as the proxy for the societal perspective if it is making policy based on the good for the public. If the government is serving as the source of health insurance, then the perspective is that of payer.

C. Payer: The payer perspective is most concerned with direct medical costs and direct nonmedical costs, which would be their administrative costs. The cost is the negotiated reimbursement to the provider minus patient contributions (copayments, coinsurance, and deductibles). Depending on the purpose of the evaluation, indirect costs (preventing loss of productivity) and intangible costs (satisfaction) can be important in the payer perspective. A health maintenance organization selling its product to an employer group would act from the payer perspective, whereas identifying what interventions and services to provide would be done from a provider perspective.

D. Provider: The provider perspective is interested only in direct medical costs. The scope of the evaluation is based on the breadth of the provider’s services. A comprehensive health maintenance organization needs to look at costs from both inpatient and outpatient services, including the pharmaceuticals in all areas. A patient-centered medical home may look only at the cost of clinic visits for the services provided (physicians, nurses and nurse practitioners, case management, vaccines, sutures, and numerous other items). A hospital would examine only costs relative to their services. Cost-to-charge ratios are often used because of the difficulty in microcosting.

E. Patient: The patient perspective is concerned about all categories of costs. These costs are only the out-of-pocket costs and the valuation of the intangible costs. Insurance premiums (just patient cost) must be divided into the categories of direct medical costs if benefits are received and direct nonmedical for the difference between the premium and the paid benefits; of course, the patient does not care which category. (A negative cost cannot exist; the patient may then perceive a value from the insurance plan.)

Figure 3. Perspectives.
Case Study Part 3: Determining Costs
In Part 1, the costs of diabetes mellitus were presented. Those costs are aggregated and described from a societal perspective. In the table below, identify one cost for each category for each of the perspectives.

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<th>Societal</th>
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V. COMPONENTS OF PHARMACOECONOMIC ANALYSES

A. Alternatives: Pharmacoeconomic studies are studies of alternatives. Ideally, all logical alternatives are evaluated in a study, but usually this evaluation is limited to one or two options being compared with the intervention being considered. The alternatives may include the current interventions, usual care, and no treatment (which is different from placebo, which is an intervention [treatment] without activity).

B. Valuation of Costs and Outcomes: Costs and economic outcomes for each alternative must be identified, measured in units, and assigned a “worth,” called valuation in this chapter. Clinical and humanistic outcomes are left in the unit of measure. Then, sources of data must be identified. Sources can be actual patient records, billing departments, claims data, national registries and compilations of data (e.g., the Bureau of Labor Statistics), literature, or patient reports (diaries and survey instruments). The strength of these sources varies, as does the generalizability.

C. Types of Economic Studies: Because this chapter is not intended to be an overview of study design but rather a presentation of the concepts of pharmacoeconomic techniques, the types of economic studies will be very briefly presented. The reader is referred to the literature for additional information.

1. Randomized controlled trials and piggyback studies: The theory of evidence-based medicine uses a hierarchy where the randomized controlled trial is considered strong evidence because of the internal validity. However, a randomized controlled trial usually does not have a primary outcome that is economic. Often, an economic study will run concurrently, or economic data will be collected while the study is being conducted (called a piggyback study). The problem with economic costs and outcomes generated from a randomized controlled trial, either directly or as a piggyback study, is that the study creates an artificial “world” because of the controls and inclusion and exclusion criteria; therefore, costs exist, or are controlled, based on the protocol.

2. Randomized naturalistic and cohort studies: In an effort to obtain more generalizability, randomized naturalistic studies with economic outcomes may be conducted. The study is originally randomized, but then becomes observational rather than following a protocol. The patients and health care professionals make decisions as they normally would, including switching or discontinuing the interventions. Cohort studies are similar but without the randomization; the lack of randomization can make the study groups very different because the decision to use the intervention of interest may be reserved for specific patients (sicker, wealthier). These prospective studies are stronger than retrospective studies because the costs and outcomes are determined a priori, and the collection of data can be targeted at these data elements.
3. Retrospective studies: Retrospective cohort and case-control economic studies use historical information that was collected not for use in a study but for other reasons, such as health care documentation and reimbursement. Both types have all the biases of retrospective studies, including missing and incorrect data. Studies that use claims data as the source find that clinical outcomes are usually not available in these databases. Patient records have missing data because of incomplete documentation.

4. Modeling: A frequently used study design in pharmacoconomics is modeling, which uses information from multiple sources including clinical studies, epidemiologic studies, databases (including census, claims), and electronic medical records to create an electronic roadmap of the disease being studied. The model is based on the probability of events occurring. The most commonly used techniques are decision trees, Markov modeling, and Bayesian modeling. Although simple models can be done by hand or in simple spreadsheet programs, the more complex models require specialized software.

   a. Decision analysis: Decision tree analysis is a visual roadmap to the range of outcomes from the comparison of interventions. The decision tree is a simplification of the major components leading to the outcome. Decision trees create a linear progression to the outcome. For many decisions, this simplistic model can give reasonable results for making a decision.

   Decision trees can model multiple alternatives at the same time, but the complexity increases for each additional alternative above two. The tree branches out from the base (the choice of intervention or choice node). Each of the alternatives has identical branches (with each branch being identified by a chance node); however, the probabilities for each chance node may differ between alternatives.

   Basic requirements for the decision tree (as in the more complex Markov and Bayesian models) are that uncertainty exists and that the probabilities are nominal data that total 1.0 at each chance node. Organization of the events in the decision tree can keep the number of branches to a minimum but is not a requirement because the outcomes remain the same. Figure 4 is an example decision tree showing path probabilities. Costs of each branch can be added and a total cost for each intervention calculated.

   ![Figure 4. Example of a decision tree.](image_url)
i. Markov model: The Markov model is used when the analysis must consider the complexity of the disease. The differences between this model and the decision tree include the inclusion of the concept of time and the potential for reverting to an earlier state. The disease is divided into mutually exclusive transient states that sequentially lead to a terminal (absorbing) outcome (usually death).

(a) Transient states have probabilities of remaining in the state or transitioning to another state (either forward or backward); the terminal state cannot be escaped; states can be skipped.

(b) The total probability of entering, leaving, and staying in a state equals 1.0. Each state may have multiple probabilities that are different from those at other stages. The model is run over time using a cycle that has a specific time limit. For example, the full model may be 5 years with cycles of 6 months (for a total of ten cycles). Figure 5 is a schematic of Markov states.

Figure 5. Markov model states.

ii. Bayesian models: Similar to Markov models, Bayesian models use existing data to predict the probability of outcomes in the future. The major difference is that Bayesian models can do this even when important data elements are missing or inconclusive.

iii. Monte Carlo technique: The results from the models are produced by using a hypothetical healthy group of subjects (cohort) and running a sample of the cohort through the model. Probabilities are close to true outcomes if samples are run an infinite number of times. Therefore, a Monte Carlo technique is used to simulate the infinite number of times; this technique samples from the hypothetical population and runs the model several thousand times. The outcomes are presented as a confidence interval. Two basic sampling techniques are used.

(a) Bootstrapping samples from the population by random selection. A sample size is selected (e.g., 1000 subjects) and run through the model. Two bootstrapping techniques can be used: “with replacement,” where an individual may be included in multiple samples, or “without replacement,” where the individuals in each sample are unique.

(b) Jackknifing samples from the population by randomly deleting samples, without replacement, from the original population. The model is run until the population is depleted.

iv. Discrete event simulation: A newer, more naturalistic model may be used more in the future. This discrete event simulation does not mandate mutually exclusive events (or states) or fixed time cycles.

b. Indirect treatment comparison or network meta-analysis may be incorporated into any of these models.
D. Sensitivity Analysis: Unless all data are from actual patients, costs and probabilities of outcomes are estimates, and a concept called sensitivity analysis is used to test the strength of those estimates. If the valuations are changed and the decision remains the same, the analysis is considered robust. If the decision changes with the change in valuation, the estimates must be reevaluated for feasibility. Many types of sensitivity analysis exist.

1. One-way (univariate): One-way (univariate) sensitivity analysis varies one estimate at a time while all others are held constant. A graph, often called a tornado diagram, is created, with the spread of valuations for each estimate being presented, and the estimate showing the most effect is represented at the top.

2. Scenario: Scenario (multivariate) analysis varies two or more estimates at the same time (creating scenarios).

3. Threshold analysis: Threshold analysis changes one or more estimates until the decision changes.

4. Analysis of extremes: Analysis of extremes (worst-case/best case) identifies the most optimistic or pessimistic estimates for the scenarios. This analysis often uses the ends of the confidence intervals for each estimate.

5. Probabilistic: Probabilistic sensitivity analysis draws randomly from the distribution of the estimate, running the model multiple times.

E. Discounting: When the costs and benefits occur over a time period that exceeds 1 year, economic theory states that discounting must be done. This concept is based on the preference of society (and individuals) for paying later and receiving benefits now. Controversies exist about the choice of discount factor and whether the costs and benefits should be discounted at the same rate.

West presents the four basic assumptions for discounting and argues that because currency is just used to make the units of resource alike, whether the result is a cost or benefit is immaterial. He states that economic theory is understood as not being accountancy; it is measuring opportunity cost, resources are in natural units, and preference is given to the present over the future. Time span is important and should include the horizon during which most or all of the health care costs occur. This makes valuing prevention more difficult if the costs being prevented (benefits) are too far in the future.

A discount rate indicates how much less a good will be worth in a year’s time than it is today; over many years, the value of the good is reduced by that rate each year, and the sum of those discounts becomes the valuation of the present year. Selection of the societal rate should be based on very large sample sizes of individual rates (preferences) adjusted for socioeconomic levels. Often the discount rate is chosen based on previous studies or some element including rate of return on investments and inflation. In other words, the selection is arbitrary even when sensitivity analysis is included.

Figure 6 is the discount factor. The years start with year 0 (a valuation raised to the power of zero is 1, or the full valuation). Therefore, for example, a 5-year time line would have years 0, 1, 2, 3, and 4.

\[
\frac{1}{(1+r)^t}
\]

where

- \( r \) is the rate of discount in year \( t \)

Figure 6. Discount factor.
VI. PHARMACOECONOMIC EVALUATIONS

Pharmacoeconomic evaluations (or analysis techniques) must be a comparison of alternatives with at least one intervention involving a pharmacy product or service. The input data are the costs and the output is the outcomes. Some evaluations either do not measure or do not compare outcomes.

A. Partial Evaluations
   1. Cost analysis: If outcomes are not the output of the analysis, then the evaluation is considered a partial analysis. Usually this would result in a list of costs and is considered a cost analysis. Cost consequence analyses often are a list of costs and of consequences without direct comparisons; however, some researchers consider cost consequence analyses a version of cost-benefit analyses.
   2. Cost-of-illness: Cost-of-illness (COI) analyses are intended to assess the burden of illness or a specific illness on society. Whether COI studies are full or partial analyses is debatable because COI studies do not separate out alternatives, nor are outcomes evaluated (although costs of outcomes are included). These analyses often provide a framework for full evaluations such as cost-benefit and cost-effectiveness analyses. Cost-of-illness studies do not measure the effectiveness or efficiency of resource utilization, and the numerous methods used to generate them make comparisons very difficult.

   The total COI in the United States in a particular year (not including intangible costs) is the total of the health care expenditures (direct medical costs) plus lost productivity (morbidity and mortality; indirect costs) for that year. Most COI studies are assessing a specific disease state or subcategory of that state. Some disease states, such as alcoholism, may also include costs of incarceration and costs of injury to others. These types of studies are very difficult to conduct because identifying which costs are directly associated with the disease or which disease to associate costs is complex.

B. Full Evaluations: If outcomes are measured and compared, full evaluations are conducted. One of four types of analyses can be done depending on the end point (measurement) of the outcome. These evaluations are cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost minimization analysis (CMA).
   1. Cost-benefit analysis
      a. Cost-benefit analysis measures both costs and benefits in monetary units. This allows comparisons of alternatives across different health interventions or programs and between health and other social projects. Benefits are often costs averted, so care must be taken not to double count one as the other.
      b. The decision to choose an alternative over comparators is that a net gain (benefits exceed costs) to society is achieved. Depending on resources, allocations can select the results that are net positive or the result with the highest net benefit (excess of benefits over costs). Cost and benefits of external exigencies must be included. For example, a positive external exigency from a smoking cessation program for a large employer may be the decrease in second-hand smoking in the community, and a negative exigency would be a change in income from tobacco taxes.
      c. Valuation of costs and benefits use the human capital or the WTP approaches. Discounting and sensitivity analysis are applied as needed. The results can be presented as benefit/cost ratio, but the net benefit also needs to be presented because the ratio does not give the magnitude of the benefits or costs (for example, a 5:1 ratio may be $5 benefit for $1 invested or $500,000 benefit for $100,000 invested).
d. Cost-benefit example with discounting and one-way sensitivity analysis: You gross $250,000 per year from your specialty clinics. You are offered a new diabetes program that costs $30,000 and $1,000 per year thereafter. In return, most clinics increase their gross by 7% (not compounded for simplicity). The program has a life of 5 years. The program requires several hours a week of documentation (done after hours; you do not get paid extra). Do you purchase the program? What if the gain is only 4%?

Answer:

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<th>Year 2</th>
<th>Year 3</th>
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Sum of each year

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Sum of each year
Case Study Part 4: Cost-Benefit Analysis

A group of employers in a large rural area (RuralCare) has created a self-insurance program. A population of 100,000 adults is enrolled. In the United States, the percentage of adults younger than 65 with diabetes is 8%, with 23.8% having microalbuminuria, 14.1% having Stage 3 chronic kidney disease, and 1.1% having Stage 4 disease. Your standard of care for diabetes is average for the region, but the company is concerned about the kidney disease. A new therapy, SlowDown, has been approved for use in diabetes-associated Stage 3 and Stage 4 chronic kidney disease as an addition to standard of care (therefore, both groups have the same costs of treatment and adverse effects for the standard of care, so these are not included in the analysis). SlowDown has been shown in clinical trials to decrease the progression to end-stage renal disease (Stage 5) by 50%. The main SlowDown adverse effect is stroke, which occurs in 0.5% more patients than standard of care. SlowDown costs $2000/year. Patients receiving standard of care have a 10% chance of moving from microalbuminuria to Stage 3 within 3 years. Stage 3 has a probability of moving to Stage 5 of 4% within 2 years, and Stage 4 has a probability of moving to Stage 5 of 15% in 2 years. The cost of microalbuminuria is $450/year, Stage 3 and 4 cost $4000/year, and Stage 5 costs $79,000. Stroke costs $82,000 the first year, and $29,000 thereafter; stroke usually occurs in the first year of therapy. The average salary is $25 per hour. Employees with microalbuminuria are unable to work for 30 additional hours per year. Employees with Stage 3 and 4 chronic kidney disease miss an additional 110 hours, and patients with Stage 5 miss 1600 hours. A stroke averages 1200 hours lost the first year and 500 hours/year thereafter. Direct nonmedical and intangible costs were not considered. For ease of calculation, assume the progression is sudden at the third year. The analysis is just for the cohort starting this year, again for ease of calculation. A discount factor of 5% is used.

1. Which perspective is to be considered for this CBA?
2. What is the net benefit amount?
3. Should SlowDown be used to prevent end-stage renal function in this insurance program, based on the first 3 years? Why?

C. Cost-Effectiveness Analysis

1. Description: Cost-effectiveness compares the relevant costs and outcomes (benefits or consequences) of two competing therapies, with costs presented in monetary units and the outcomes in their natural units (units of effectiveness). The cost-effectiveness ratio is expressed as cost per case cured, cost per life year saved, or similar ratios. The decision is to choose the lowest cost per unit of effectiveness. The advantage of this method is that value (health outcome per dollar spent) can be directly presented. The disadvantage is that only alternatives with the same outcome can be compared. When a single unit of resource outcome is used, an appropriate “sample size” might be the number needed to treat or the number needed to harm (depending on what the outcome is measuring), in that gain of one benefit or prevention of one harm for the comparator would be the basis of the sample size selection.

2. Presentation: Cost-effectiveness can be presented as five situations, always considering the new intervention. If the cost is lower and the effectiveness greater, the decision is always to choose the new intervention; this is said to be dominate. If the cost is greater and the effectiveness less, then the decision is never to choose the new intervention; this is said to be dominated. The intervention is said to be cost-effective if the new intervention is less expensive and at least as effective, more expensive but with additional benefit worth the additional cost, or less expensive and less effective, but the extra benefit is not worth the extra cost. Figure 7 is the cost-effectiveness plane.
3. **Threshold**: Another difference, in addition to the units of outcome, between cost-benefit and cost-effectiveness is that with cost-benefit, any positive net benefit is selected. With cost-effectiveness, a “worth” or minimum value has to be established, and the cost-effectiveness ratio has to be equal to or less than the threshold amount, which is analogous to WTP from the payer’s perspective. This amount depends on the outcome being measured. Standard amounts exist for cost-utility (discussed below), but often the value of something like a cure is equal to the cost of treating the failure. Thresholds may have bias against preventive interventions and for high-cost drugs that target a small population (orphan drugs).

4. **Average cost-effectiveness ratio**: The average cost-effectiveness ratio is the total costs of one alternative divided by the effectiveness for those costs; this is independent of other alternatives. The different alternatives can be evaluated by looking at the cost per unit of effectiveness.

\[
A = \frac{\$265,000}{12 \text{ hospitalizations avoided}} = \$22,083.33/\text{hospitalization avoided}
\]

\[
B = \frac{\$375,000}{15 \text{ hospitalizations avoided}} = \$25,000/\text{hospitalization avoided}
\]

**Figure 8.** Average cost-effectiveness ratios.
5. Incremental cost-effectiveness ratio: The incremental cost-effectiveness ratio (ICER) is the difference between the intervention and comparison costs to the difference in units of outcome (analogous to a net cost-effectiveness); this is the result that has the most meaning because it provides the cost per one additional unit of outcome. The incremental cost-effectiveness ratio can then be plotted on the cost-effectiveness plain. As with any analysis using estimates, the result is a point in the possible true result. Sensitivity analysis is used to fill in the graph. In a robust analysis, the possible results will lie within the “adopt” or “do not adopt” areas 95% of the time (when the 95% confidence intervals are being used).

\[
\frac{\$375,000 - \$265,000}{15 - 12 \text{ hospitalizations avoided}} = \frac{\$110,000}{\text{3 hospitalizations avoided}}
\]

\[
\frac{\$110,000}{\text{3 hospitalizations avoided}} = \$36,666.67 \text{ per hospitalization avoided}
\]

Figure 9. Incremental cost-effectiveness ratio.

a. Choices between numerous alternatives can be made by listing the ICERs from the lowest to the highest (such a list is called a league table when each ICER is mutually independent), then drawing a line at the threshold value. Using an opportunity cost approach, an alternative must be removed in order to pay for the new intervention when it is considered cost-effective; in reality, this is very difficult to implement.

b. ICERs compared with incremental cost-benefits. The difference between ICERs and incremental cost-benefit ratios (ICBRs) is that the WTP for ICBRs is from the societal or patient perspective. Some believe that this is the only true valuation for outcomes, and ICER should not be used. This method incorporates the threshold into the calculation.

6. Marginal: Incremental marginal cost-effectiveness compares an intervention with itself (e.g., two doses of the drug or two sequential laboratory tests). A threshold is still needed to determine the cost-effectiveness.

7. Value of information: Another variant in health care economics is the value of information. This technique determines a value for perfect information (that is, no uncertainty exists for any parameter). If the cost to conduct more research is less than this calculated value, then a study should be conducted.

Case Study Part 5: Cost-Effectiveness Analysis

A group of employers in a large rural area (RuralCare) has created a self-insurance program. Because the data indicated that SlowDown was more effective but more expensive than the standard of care, RuralCare wanted to know whether it was cost-effective for their program. All the data are the same as for cost-benefit. The standard of care has been found to reduce the number of patients transitioning to Stage 5 by 10% (or approximately 6 people at 3 years).

1. What is the average cost-effectiveness ratio for each treatment?
2. What is the incremental cost-effectiveness ratio?
3. Should SlowDown be used to prevent end-stage renal function in this insurance program, based on the first 3 years? Why?
D. Cost Utility Analysis: The previous types of full evaluations have not incorporated any function for quality of life. Even WTP for the standard CBA is usually based on a clinical or economic outcome. A subcategory of cost-effectiveness that does incorporate a measure of quality of life is the CUA. The unit of outcome for CUA is the quality-adjusted life year (QALY) gained.

1. Use of CUA: The complete CUA is the most expensive economic analysis technique because of the time required from both researchers and subjects to collect the utilities. It should be used only when quality of life is the outcome of interest or is one of the outcomes of interest. The benefit over CEA is that the common outcome allows comparisons of very different interventions. Although human capital is biased against the very young and old, the QALY has been criticized because it does not adjust for age (a 30-year-old life is valued the same as an 85-year-old). Other outcomes that have been substituted for QALYs include healthy-year equivalents, well-years, quality-adjusted time without symptoms or toxicity (Q-twist), function years, value-adjusted years, and quality-adjusted life expectancy. However, the QALY is the most accepted.

2. QALY: The QALY is a function of quality multiplied by quantity of life, which are independent. The life-year is simply the change in survival (the measure of mortality). Quality is more difficult to measure. For pharmacoconomics and PROs, only quality of life related to the domain of health (HRQoL) is considered.

3. Utilities: Health is the construct (surrogate) for being able to participate in life at the level desired; other non–health-related aspects of quality of life are not considered here. Several dimensions can be measured individually with PRO instruments. These can be summed to give a more complete picture, but this result is not considered to reflect the preference for the level of HRQoL being measured. If desirability is measured under conditions of uncertainty, the result is called a “utile” and provides the relative utility of the health state. Utiles can only be assigned to final end points (intermediate end points cannot be used). Utility has a value similar to money in that it has diminishing returns (marginal utility), where the more you have the less each unit of gain is valued, but no one has true perfect health where the gain would be zero. This can make changing very good health to even better health very expensive, and it is often difficult to measure the effects of the change (ceiling effect). Although very poor health can be moved to better health for less expenditure, a floor effect can exist where measuring the difference between extremely poor health and very poor health is difficult.

4. Utility determination: Three direct methods of determining utilities are commonly used.

a. Standard gamble: The standard gamble is often considered the only true measure of utility because it includes uncertainty, whereas the time trade-off and rating scales are often considered measures of preference. The results of these techniques range from 0 for death to 1 for full health. Health states worse than death are not measured with the standard versions of these techniques. Detailed scenarios must be used to give the rater enough information to make a decision. The results of the three methods differ, with standard gamble usually providing the highest utility and ranking scale the lowest. The sample population involved in the ranking will also produce different results, with patients scoring the highest utility and health care providers the lowest; the public and caregivers are in between.

The standard gamble uses the economic assumption that people with poorer health would accept a greater probability of dying for a chance at full health. The rater’s choice is between a sure (100%) probability of having a very specific health state, often for a set number of years, or the chance at full health linked with a probability of immediate death (the gamble). A probability \( p \) of full health is presented (with death being \( 1 - p \)). This probability is varied until the rater is indifferent to the risk of sudden death and the certain health state. The \( p \) at this state is the utility (Figure 10).
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Figure 10. Standard gamble.

b. Time trade-off.
Time trade-off assumes that people with a loss of health would be willing to give up part of their life span to live in perfect health. The rater is given two certain states: the scenario with the poorer health and full health. The person is told he or she will live a specific number of years \( t \) in that state of poor health or can give up some of those years and live the rest in full health \( (x) \). The utility is \( x/t \) years (Figure 11).

Figure 11. Time trade-off.

c. Ranking scale: The ranking scale (usually a visual analog scale similar to the 100-millimeter pain scale, where the distance between each millimeter mark is equal) has been used, but because it does not give a choice between two alternatives, has been considered an indirect technique similar to PROs rather than a utility generator. The rater places a mark at the point where he or she believes the scenario belongs relative to several other scenarios, with the top being “full health” and the bottom being “death.”
5. Calculating QALYs: Once the utilities are determined, the QALY can be calculated. QALYs were developed for long-term or chronic diseases, so acute diseases are often undervalued because of the life-year (quantity) component. Any difference in QALYs must be reviewed to see whether the quality, quantity, or both changed. The stages of a disease and the amount of time in the stage must be calculated separately then summed to get the total QALY for the full time period.

6. Threshold: The threshold for a QALY gained is still arbitrary. The threshold should be the maximum ICER of cost/QALY gained that is acceptable to the society (the cut-off point, or threshold, for the decision). Although frequently cited as the source of the value, the evidence for an association with the cost of dialysis in the 1970s is weak. The value can be based on society’s WTP for 1 year of full health or, alternatively, on the GDP per capita (or some recommend two to three times the per capita value). In the United States, the threshold is often $50,000 (slightly below the GDP per capita of approximately $53,000/person). Recently, an ICER of $100,000/QALY gained has been used in more publications (either alone or as a second threshold value to the $50,000).

7. CUA calculation examples. Use the following fabricated utilities to solve the examples.

**Utilities**

- Perfect Health = 1.0
- Dialysis center for 1 month = 0.85
- Ambulatory dialysis for 8 years = 0.65
- Kidney transplant = 0.58
- Dialysis center for 8 years = 0.56
- Ambulatory dialysis for life = 0.40
- Dialysis center for life = 0.32
- Death = 0.0

a. Questions (QALY = utility × time in state)
   i. Patient gets a kidney transplant and lives for 15 years.
   ii. Patient did not get the transplant, so he or she must choose between dialysis at a center for 8 years then death or ambulatory dialysis for 12 years (life) then death.
   iii. Patient develops acute renal failure and has dialysis at a center for 1 month.

b. Answers
   i. 15 years × 0.58 quality = 8.7 QALYs
   ii. Total of 12 years
      - Option 1 = 8 years × 0.56 + 4 years × 0.0 = 4.48 QALYs
      - Option 2 = 12 years × 0.4 = 4.8 QALYs
      - Option 2 – Option 1 = 0.32 QALYs
   c. 1/12 years (1 month) × 0.85 utility = 0.07 QALY
      This is an example of an acute situation where the benefits may be undervalued. For example, a new treatment may change the outcome by only 0.005 QALY; the cost/QALY often greatly exceeds the threshold.
Case Study Part 6: Cost-Utility Analysis

RuralCare has found that SlowDown is not cost-effective within the 3-year time frame, but they are concerned about the quality of life of their employees. They conduct a cost-utility analysis where the costs do not change. For simplicity, all people with Stage 5 will have ambulatory dialysis for 8 years (remaining life span). Should SlowDown be implemented?

E. Cost Minimization Analysis: Cost minimization can be conducted in the very uncommon situation where the outcomes (effectiveness and adverse effects) are essentially equal for equivalent doses. Equivalence is determined by determination of the clinically significant differences; if this difference is not achieved, then cost minimization can be used. The valuation in cost minimization would be in dollars with no outcomes presented. Costs that are included in cost minimization analyses include the cost of the drug as well as costs of administration, labor, and monitoring via microcosting.

VII. PATIENT-REPORTED OUTCOMES

“We're all human, aren't we? Every human life is worth the same, and worth saving.”


Outcomes research is used for a variety of purposes in addition to economic studies. This section presents basic information about how outcomes can be measured when a direct measurement is not available. The intent of this chapter is to describe assessment techniques. The techniques are often used for measurement of health status, HRQoL, quality of or satisfaction with care, and some aspects of productivity. According to theory, only the individual has this information. These outcomes are the humanistic outcomes in Kozma’s model and can be used in cost-effectiveness analysis.

A growing area of emphasis is HRQoL research using PROs, even though the techniques have been around for several decades. One of the drivers to this growth is the opportunity to conduct comparative clinical effectiveness research through funding from the Social Security Act; this funding is administered through a nonprofit organization known as the Patient Center Outcomes Research Institute or PCORI. Central to comparative clinical effectiveness research is the emphasis on the evaluation of PROs.

A. Definition: The Food and Drug Administration defines a PRO as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.” Technically, reports from proxies, such as caregivers, are not true PROs; studies that allow a proxy response have a limitation that the results may not be truly reflective. The reporting of PROs is done using questionnaires (also called instruments, surveys, tools, measures, or tests). These instruments evaluate patients’ ability to function in various areas of their lives and reflect their experiences with their disease and their care. The questionnaires can contain one question or many; the Medical Outcomes Study: Measures of Quality of Life Core Survey (MOS), used in a 1989 landmark study, consisted of 116 items. Over time, many of the longer instruments have had shorter versions developed, not a simple task because the new versions have to show that they measure the appropriate aspects measured by the longer versions. The MOS survey has several short form versions. PRO instruments are used in research and in clinical practice; the same instruments may or may not be applicable in both settings.

The reader will gain an appreciation for the complexity of designing surveys in general and PRO instruments in particular. The information will help readers evaluate literature and select a previously developed survey for a new project.
B. Domains: HRQoL instruments are broadly based on the health belief model that ultimately implies that everyone wants to live as long as possible with normal function (free of pain and physical, social, and psychological dysfunction) without adverse health or economic effects from treatment. These instruments attempt to measure how far an individual is from an ideal level of HRQoL, which is thus a measure of impact of disease, disorder, treatment, or the combination. Central to these instruments is the concept of health status domains. The main domains are general health, physical, social, and psychological. A domain is defined as a “realm of influence” or “sphere of activity, concern or function,” and they need to be mutually exclusive. Because domains influence each other, this exclusivity is often difficult to maintain. Different theories have differing total numbers of domains; some call them dimensions, and others consider dimensions as subgroups within the domains. For example, the MOS 36-Item Short-Form Health Survey, revised (SF-36v2), measures physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and general mental health.

C. Requirements for Instruments: Instruments must cover the entire range of health from death or extremely poor health to full health and ability, similar to utilities. They also must be sensitive enough to detect important changes but not so sensitive that the change is a normal variation (similar in concept to clinical significance). Care must be taken to avoid, as much as possible, response bias such as socially acceptable answers (avoidance of reporting behaviors that are not considered acceptable), acquiescence (agreement with any item regardless of the question; this can be detected by incorporating a few negatively worded questions), and regression to the mean (when the same instrument is completed frequently enough, all answers will eventually be toward the middle of the options).

D. Work and Social Functioning: The role function is central to the concept of health status. The ability to work is not only a personal value but also a societal value. The inability to function is also costly in that it not only affects the individual but can also affect the role of others (caregivers). Social functioning can affect entire families and communities.

E. Satisfaction: The PROs measure not only the ability to function but also satisfaction with the level of ability. Some instruments, such as the frequently used Hospital Consumer Assessment of Healthcare Providers and Systems surveys, or HCAHPS, measure satisfaction with a process (can be considered the intervention, with satisfaction the outcome). This is important as part of the value equation.

F. Psychometrics: The science of quantifying the attributes of these instruments is psychometrics.
      a. Items: The basic unit of an instrument is an item; this has a stem (the question) followed by response options. The creation of items is designed to measure a concept within the domain or dimension. Only one concept at a time is measured with an item, and multiple items may be used for each concept.
      b. Scales, indices, profiles: The items are measured with a scale; this can be nominal, ordinal, interval, or ratio. If the domain has subcategories of dimensions, the results may be summed to produce an overall score. Multiple domain scores can be summed to create an index or can be left disaggregated (a list of domain scores) to create a profile. Often, individual instruments will not provide a full understanding, so a series of instruments (a battery) will be used.
   2. Respondent burden: The usefulness of instruments decreases as the amount of effort required to complete the form or forms increases. This concept of respondent burden should be considered at all times and for all groups when selecting instruments, but the older adult should be given particular attention. For example, the standard gamble has a very high respondent burden. Respondent burden is also a major factor in the development of the short forms of the MOS.
G. Reliability, Validity, Responsiveness: Instruments to measure HRQoL must be reliable, valid, and responsive to any changes. Validity measures what is intended to be measured, and reliability produces the same result every time if no change has occurred. Reliability can exist even if validity does not (measuring the wrong thing), but not the reverse. Responsiveness is the ability to identify important (as determined by the researcher) change over time (longitudinal), even if the important difference is small.

1. Reliability: Reliability can be tested over time (longitudinal or test-retest reliability) to determine whether the instrument results are the same if no change occurred or shifted in the correct direction if a change occurred. This is normally done by using the same instrument. This is measured by the intraclass correlation coefficient, which determines the amount of true difference and the extent of random error. One of the areas of survey research that is problematic is the determination of how much time between administrations of the same survey is enough.

Cross-sectional reliability must also be tested. This is done in one of two ways, either using equivalent items or instruments to determine the agreement between the instrument being tested and the reliable comparator. The items can be incorporated into the new instrument (internal consistency) or given as a separate instrument (alternate forms). Tests of inter-rater reliability are used. The comparator must, in fact, be previously determined as being equivalent or the instruments are being tested for equivalency, not reliability. Respondent burden needs to be considered as does the order of questions.

2. Validity: For an instrument to be determined valid, it has to be tested in large sample sizes for several components of validity. Even a validated instrument for one group has to be revalidated for another group. This must also be done if the method of administration is changed (e.g., from pen-and-paper to computer-assisted). Whether an instrument can be used for different levels of literacy, physical or mental limitations, language or cultural diversity, and maturation is determined by the groups in the validation studies. Assurance that the item is measuring what it is supposed to measure, not a cofactor, such as age or concomitant non–health-related factor, is needed. In addition to the individual items being validated, the entire survey must meet the same qualifications.

   a. Face validity: The simplest type of validity is face validity, or the appearance of validity obtained by examining the questions.

   b. Content validity: Content validity is the presence of items measuring all the important aspects of the domain or dimension being assessed.

   c. Construct validity: Constructs for humanistic outcomes (e.g., HRQoL) use the survey items in a manner similar to surrogates for clinical outcomes. Construct validity attempts to measure how well an entire instrument or series of items produces results consistent with the theory of what should happen; ideally the instrument will produce results similar to those of other tools attempting to measure the same construct (convergent validity) while not producing results consistent with tools measuring other domains or dimensions (divergent or discriminant validity).

   d. Criterion validity: Criterion validity compares the outcome of the item with another way of measuring the same construct that has been validated and is, preferably, the gold standard for that measurement (this is difficult because various definitions for HRQoL exist).

   e. Known-groups validity: Discriminant validity often uses known groups, those with the disease and those without or different age groups, to measure whether the instrument can make this discrimination. Factorial validity is determined using factor analysis, a statistical technique to assess convergent and divergent validity.

H. Purpose: Instruments have three main purposes, which are similar for populations or individuals. The first is discrimination, or the ability to identify differences between subjects. The second is prediction, or the ability to determine probable subject outcome at some point in the future. The third is monitoring, or the ability to measure change within a subject if change occurs.
I. Types of Instruments: HRQoL instruments can be classified into one of two categories: generic or disease specific.

1. Generic instruments: Generic instruments measure general health (or health status as a whole). Generic instruments have several advantages, including being applicable to broad segments of the population and able to compare across diseases, summarize a range of domains and subdimensions, and detect unanticipated effects (e.g., the effect of infrequent but bothersome side effects). They have some important disadvantages: They cannot detect smaller changes, they may not be relevant to a specific population, they usually have a higher respondent burden than disease-specific instruments, and the results may be difficult to interpret because respondents with similar scores may have differences in responses within domains.

Some commonly used generic instruments include the SF-36v2 and its variations (12-Item Short-Form Health Survey [SF-12v2,] and the adaptation that uses 10 or 7 items to create an assessment of the six health dimensions [SF-6D], which can be used for economic and utility assessment), the various versions of the Health Utility Index (HUI I, Mark2, Mark3), the EuroQol (EQ-5D), and the Quality of Well-Being Scale (QWB). Appendix A models the links between the SF-36v2 and SF-12v2 questions and the domains.

2. Disease-specific: Disease-specific instruments are more responsive to smaller changes and are relevant to specific populations. The disadvantages are that the results cannot be compared across populations, unanticipated effects are unlikely to be detected, and fewer research data are available (to strengthen knowledge about reliability and validity).

3. Ceiling and floor effects: Survey instruments (or series of item) have limitations in the ability to discriminate at the top of the scale (ceiling) and at the bottom (floor). A point occurs when the difference between really good health and excellent health or the difference between really poor and extremely poor health cannot be detected. Well-established instruments present the value above which differences in responses may be random error (ceiling) or below which random error may be a large factor (floor). This is similar in concept to beta error in statistics. Disease-specific instruments are often better able to detect differences at the ends of the scale.

J. Determining which instrument or battery of instruments to use can be difficult. An excellent site that can help in making the decision and provides information on how to access to more than 800 different instruments is PROQOLID (www.proqolid.org).
Case Study Part 7: Evaluation of General Health Status Instrument

As part of your medication therapy and pain management services for RuralCare, you have your patients complete the SF-12v2. The reports provide scores in a profile for populations and individuals based on a large 2009 survey of the general U.S. population. The results of the 12-question SF-12v2 have been found to closely match those of the longer SF-36v2. The norms have been converted from a score to a T-score, with a mean of 50 and a standard deviation of 10%, for all eight domains and both the physical and mental health summary components. Each one-unit change in T-score is 0.1 standard deviation. For individuals, the normal range is 45–55. Changes of 5 units of T-score are considered clinically significant. See Appendix A.1 for an example of a profile, including only the physical and mental health component scores, with interpretation.

Mr. Smith is a 35-year old worker who originally was referred to your clinic in December 2010 [it is now December 20, 2011] for pain management. He completed an initial SF-12v2 at that first visit last year. In addition to the latest results of the SF-12v2, he completed the instrument on March 15 and June 18 of this year. He had surgery on June 5. You are reviewing his physical and mental health component scores and the pain impact scores. Use Appendix A.2.

- Compared with the average score for men of a similar age, how does Mr. Smith’s physical health compare?
- What about his mental health?
- What is the impact of pain on his life?
- How severe is his pain?
- How does his physical health compare with his initial profile of 12 months ago
- What about his mental health?
- Over the year, did he have any significant changes?
- How does his physical and mental health compare with his June scores? Explain his June scores.

VIII. CONCLUSION

Value is an important concept in health care, especially as it relates to being able to provide, and receive reimbursement for, services and interventions. The decisions about what services or interventions to provide can be assisted by the use of outcomes research, pharmacoeconomics, and patient-related outcomes evaluation. The pharmacist must be familiar with the different types of analyses in order to interpret the literature or assist in the decision-making process.
REFERENCES


ADDITIONAL READING


1. **Part 1:** In 2010, diabetes affected 25.8 million people in the United States (8.3% of the population), where 18.8 million people were diagnosed and 7.0 million were undiagnosed. About 1.9 million people aged 20 years or older were newly diagnosed with diabetes in 2010. During 2002–2005, 15,600 youth were newly diagnosed with type 1 diabetes and 3,600 youth were newly diagnosed with type 2 diabetes annually. Diabetes was the seventh leading cause of death, based on 71,382 U.S. death certificates in 2007 in which diabetes was the underlying cause of death. Diabetes was a contributing cause of death in an additional 160,022 death certificates (CDC). Part 1 of the case establishes that diabetes is very common. The problem is implicit because of the familiar knowledge of the effects of diabetes on health status and resources. The information can be divided into morbidity (presence of illness) and mortality (death). Prevalence is the number of people affected at a point in time; the individuals include those who recently acquired diabetes and those with end-stage disease. The incidence is new cases within a time period (usually 1 year); the spectrum of disease is usually much narrower. A multitude of interventions have been or will be developed in attempts to solve the problem. The health care system needs to have a way to evaluate the value of these interventions.

2. **Part 2:** Diabetes mellitus has numerous outcomes. The ECHO model can be used to identify these outcomes. Identify as many outcomes in each category as possible. Include some direct and some surrogate outcomes for each. Remember, outcomes are directional. Examples of clinical outcomes include decreased fasting plasma glucose, hemoglobin A1C, albuminuria, foot infections (or cure of infection), end-stage kidney disease, retinopathy, neuropathy, and life-years. Examples of economic outcomes include decreased total dollars, emergency room visits, hospitalizations, ICU hours, and clinic visits. Increased use of glucometer strips and pharmaceutical expenses would be a surrogate for adherence, which is a humanistic outcome. Examples of humanistic outcomes include increased quality of life, satisfaction with care, adherence, and ability to care for self. Decreased pain (which can also be clinical) and loss of work (which is also an economic outcome) are other examples. Many others could be provided. The interrelationship is presented in the examples above.

3. **Part 3** of the case study required completing the table.

4. **Part 4:** See Appendix B for the answers to Parts 4–6. The perspective is the payer, who is also the employer, so indirect costs are important. The net benefit is about a negative $7 million. RuralCare would not add SlowDown based on the first 3 years of data. Because the costs for end-stage continue and the human suffering continues, inclusion of intangible costs or other method of valuation may change the decision.

5. **Part 5:** The perspective still is the payer plus employer; however, the ICER is more than the cost of a case of end-stage renal disease. Therefore, the new therapy would not be selected if only 3 years are considered.

6. **Part 6:** Eight years of ambulatory dialysis is 5.2 QALYs. The incremental cost-utility of SlowDown is $57,851; using the $50,000 threshold, the drug is still not cost-effective.

7. **Part 7:** Mr. Smith’s physical health is 5 units of T-score lower than the average range for men of his age. This is considered substantially lower. His mental health is 3 units lower and is considered lower than average. He has had changes over the year of 5 units or more in pain impact (increased on March 15), physical health (decreased on June 18), and mental health (increased on June 18). He has a pain impact 3 units worse than the average range, indicating that it has negative impact on his life. His pain would be considered moderate. Both his physical and mental health and his pain impact are basically unchanged from 12 months earlier. The June 2011 scores may indicate the physical effects of surgery with the hopeful outlook. His physical health has increased and the mental health has decreased 4 units; this change may be related to the small decrease in pain impact.
In Part 1, the costs of diabetes mellitus were presented. Those costs are aggregated and described from a societal perspective. In the table below, identify one cost for each category from each of the perspectives.

<table>
<thead>
<tr>
<th></th>
<th>Societal</th>
<th>Payer</th>
<th>Provider</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct medical</td>
<td>Hospital day (all costs plus net insurance)</td>
<td>Hospital day (payment to provider less patient contribution)</td>
<td>Hospital day (cost to provide care)</td>
<td>Hospital day (contribution only)</td>
</tr>
<tr>
<td>Direct nonmedical</td>
<td>Transportation to clinic</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Transportation to clinic</td>
</tr>
<tr>
<td>Indirect</td>
<td>Lost productivity</td>
<td>Lost productivity (to show benefit of services)</td>
<td>Not applicable</td>
<td>Lost productivity (including leisure)</td>
</tr>
<tr>
<td>Intangible</td>
<td>Social functioning</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Social functioning</td>
</tr>
</tbody>
</table>

The perspective determines what costs are important and how they are measured; some types of costs are not relevant or are of minor importance for some perspectives.
ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: A**
   An intermediary (surrogate) outcome is a change that has been identified as preceding a direct outcome; blood pressure increases have been identified as an indicator of the direct outcomes of stroke, myocardial infarction, and others. Death is a direct outcome (Answer B is incorrect). Pain is a symptom that can be considered a direct outcome in some cases but is not directly linked to another directed outcome (Answer C is incorrect). Satisfaction is a construct and is similar to pain as an outcome (Answer D is incorrect).

2. **Answer: A**
   Opportunity costs are the ability to use resources for the next best use. Equipment for the dialysis center is part of the actual cost, whereas decreasing transportation costs is a reduction in direct nonmedical costs and work hours gained is an economic outcome (Answers B, C, and D are incorrect). The new cancer center is a foregone outcome (Answer A is correct).

3. **Answer: B**
   The human capital approach uses average wages for age and gender as the basis. Because middle-aged men are considered the highest wage earners, the approach gives a high valuation for this group. Children, women, non-wage-earning workers, and older adults are usually not working or are paid less than men, so the approach is less useful for valuation of their productivity (Answers A, C, D are incorrect).

4. **Answer: B**
   You want to monitor changes over time in relapsing-remitting multiple sclerosis, and these changes are often small. Disease-specific instruments have less research history than generic instruments because of the limited numbers with a disease (Answer A is incorrect). Generic instruments can identify unanticipated effects, but disease-specific instruments cannot (Answer C is incorrect). In most cases, a disease-specific instrument has not been validated for other disease states; therefore, different groups cannot be compared (Answer D is incorrect).

5. **Answer: D**
   Construct validity consists of convergent and divergent measures. The divergent measure includes discriminate validity, which is tested using known groups. Content and face validity look at the questions and the coverage of domains (Answers A and C are incorrect). External validity is the generalizability of the results, which may or may not be a function of construct validity (Answer B is incorrect).

6. **Answer: B**
   The utility is the value of the healthy outcome at the point of indifference between remaining in a wheelchair for 15 years then dying or dying immediately. The other answers can be selected from the decision tree (or calculated by subtracting for the healthy probability from 1 minus the probability of death); Answers A, C and D are incorrect.

7. **Answer: C**
   The SF-12v2 printout listing these eight scores is a profile. The questions are items (Answer A is incorrect). The numbers are scales (Answer B is incorrect). A battery is the use of multiple instruments (Answer D is incorrect).

8. **Answer: A**
   The number of years for each state is multiplied by the utility, then added together. The equation is QALY = Σ(Utility * Time in state)_{new drug} minus Σ(Utility * Time in state)_{current drug}. To get the additional benefit from ImprovedHepBCare, the QALYs for HepSlow are subtracted from those of the new drug. Answers B, C, and D do not include all of the process and therefore are incorrect.

9. **Answer: A**
   The value of an intervention is based on all costs being included, not just one component (Answer A is correct, Answers B and C are incorrect). Although satisfaction is one component of value, it too is incomplete (Answer D is incorrect).
10. **Answer: B**  
The costs (utilization of resources) in randomized controlled trials are tightly controlled by the protocol, so they are easily collected and little data is missed (Answers A and D are incorrect). Randomized controlled trials have high internal validity (Answer C is incorrect). The problem is that because of the controlled protocol, the costs are artificial and would not be easily generalizable (Answer B is correct).

11. **Answer: C**  
Robustness is a function of sensitivity analysis. Because confidence intervals are available, analysis of the extremes can be easily done (Answer C is correct). Data are not missing, so Bayesian analysis is not needed (Answer A is incorrect). The data come from a claims database, so identifying which costs go with which states of a disease would not be possible (Answer D is incorrect). The time frame is only 1 year, so discounting is not needed (Answer B is incorrect).

12. **Answer: A**  
Presenteeism is a role limitation. Pain is considered a physical problem, although it can be exacerbated by emotional problems (Answer A is correct, Answer C is incorrect). Changes in general health and general mental health are important but are not as directly related to presenteeism (Answers B and D are incorrect).

13. **Answer: B**  
Cost-of-illness analyses normally include direct medical costs and indirect costs. Health-related quality of life and utilities cannot be determined from these data points (Answers C and D are incorrect). Because the study is looking at a comparison of treatment with and without the new drug, a pharmacoeconomic analysis rather than a general outcomes study is the best approach (Answer A is incorrect). Because the data are most easily collected as dollars of cost and outcome, a cost-benefit analysis can be done (Answer B is correct).
APPENDIX A: Short form health survey measurement model. With permission from Optum. For permission to reproduce the survey and/or any associated intellectual property (e.g., trademarks, scoring algorithms, interpretation guidelines, and normative data) for any purpose must obtain a license at https://www.optum.com/life-sciences/develop-evidence/patient-reported-outcomes.html or call Optum 800-572-9394
**RESULTS**

**Survey Date:** August 28, 2011  
**Mode:** eForm  
**Age:** 28  
**Gender:** Female  
**Timepoint/Visit:** 6 Months  
**Conditions:** None

**PHYSICAL HEALTH SUMMARY**

Average score for similar age and gender: 52.71

Compared to a person of the similar age and gender, your physical health summary score is about average.

**MENTAL HEALTH SUMMARY**

Average score for similar age and gender: 47.22

Compared to a person of the similar age and gender, your mental health summary score is very much above average.

**HISTORY**

The following history scores track physical health and mental health progression over time. This section will display up to the last 7 survey results.

**PHYSICAL HEALTH SCORE HISTORY**

**MENTAL HEALTH SCORE HISTORY**

**PROGRESS**

<table>
<thead>
<tr>
<th>Date</th>
<th>Physical Health</th>
<th>Mental Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current: 08/28/2011</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>Previous: 05/13/2011</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>Change (current/previous):</td>
<td>Better</td>
<td>Better</td>
</tr>
</tbody>
</table>

Your physical and mental health summary scores changed significantly compared to the last time the survey was taken. Be sure to mention this to your doctor.

**INTERPRETATION**

Based on your answers about health in the past 4 weeks, our research shows that

**Compared to the general population...**

**Physically, your...**
- pain is much less
- functioning is better than most
- performance of work, home or school activities is the same or better

**Emotionally...**
- bothered less than most
- performance of work, home and school activities is limited more

**Overall, your...**
- rating of your health is a little worse
- participation in social activities is less limited
- energy level is much higher

*Note: This survey is not a diagnostic tool. It is intended to supplement clinical decision making. Visit us at www.amihealthy.com for more information. This report uses normative data from the QualityMetric 1998 General Population Sample*

APPENDIX A.1: Sample SF-12v2 Member Report. With permission from Optum. For permission to reproduce the survey and/or any associated intellectual property (e.g., trademarks, scoring algorithms, interpretation guidelines, and normative data) for any purpose must obtain a license at https://www.optum.com/life-sciences/develop-evidence/patient-reported-outcomes.html or call Optum 800-572-9394
APPENDIX A.2: Sample SF-12v2 Provider Report. Modified for Case Study Part 7 With permission from Optum. For permission to reproduce the survey and/or any associated intellectual property (e.g., trademarks, scoring algorithms, interpretation guidelines, and normative data) for any purpose must obtain a license at https://www.optum.com/life-sciences/develop-evidence/patient-reported-outcomes.html or call Optum  800-572-9394
SF-12v2® Health Survey with PIQ-6™
Provider Report

Report for Jim Smith

December 13, 2011

RESULTS
Survey Date: December 13, 2011
Mode: eForm
Age: 35
Gender: Male
Timepoint/Visit: 12 Months

PAIN IMPACT

This individual reported [ ] , taking into account the margin of error.

PAIN SEVERITY

This individual’s Pain Severity is [ ] taking into account the margin of error.

HISTORY

The following history scores track pain impact and pain severity progression over time. This section will display up to the last 7 survey results.

PAIN IMPACT SCORE HISTORY

PAIN SEVERITY SCORE HISTORY

Note: This survey is not a diagnostic tool. It is intended to supplement clinical decision making. Visit us at www.amihealthy.com for more information. This report uses normative data from the QualityMetric 2005 General Population Sample for the PIQ-6

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## APPENDIX B

### COST-Benefit Analysis

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Cost/Unit</th>
<th>Numbers Standard</th>
<th>Standard Year 0</th>
<th>Standard Year 1</th>
<th>Standard Year 2</th>
<th>Numbers SlowDown</th>
<th>Units SlowDown</th>
<th>SlowDown Year 0</th>
<th>SlowDown Year 1</th>
<th>SlowDown Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population with Diabetes</td>
<td></td>
<td>8,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population with Microalbuminuria</td>
<td></td>
<td>1904</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population with Stage 3</td>
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<td>1,128</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Population with Stage 4</td>
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<td>88</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Population with Stage 5</td>
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<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</table>

### Direct Medical

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Cost/Unit</th>
<th>Numbers Standard</th>
<th>Standard Year 0</th>
<th>Standard Year 1</th>
<th>Standard Year 2</th>
<th>Numbers SlowDown</th>
<th>Units SlowDown</th>
<th>SlowDown Year 0</th>
<th>SlowDown Year 1</th>
<th>SlowDown Year 2</th>
</tr>
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<tbody>
<tr>
<td>SlowDown</td>
<td>$2,000</td>
<td>0</td>
<td>$0</td>
<td>$0</td>
<td>$1,216</td>
<td>$2,432,000</td>
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<td>$2,432,000</td>
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<tr>
<td>Stroke First year</td>
<td>$82,000</td>
<td>0</td>
<td>$0</td>
<td>$0</td>
<td>6</td>
<td>$402,000</td>
<td>$174,000</td>
<td>$253,000</td>
<td>$253,000</td>
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<tr>
<td>Microalbuminuria</td>
<td>$450</td>
<td>1904</td>
<td>$856,800</td>
<td>$856,800</td>
<td>$771,120</td>
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<tr>
<td>Stage 3</td>
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<td>1128</td>
<td>$4,512,000</td>
<td>$4,512,000</td>
<td>$5,092,000</td>
<td>$4,512,000</td>
<td>$4,512,000</td>
<td>$5,092,000</td>
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<tr>
<td>Stage 4</td>
<td>$4,000</td>
<td>88</td>
<td>$352,000</td>
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<td>$300,000</td>
<td>$352,000</td>
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<td>$328,000</td>
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<tr>
<td>Stage 5</td>
<td>$79,000</td>
<td>56 Year 2</td>
<td>$0</td>
<td>$0</td>
<td>$4,582,000</td>
<td>$2,9 Year 2</td>
<td>$2,9 Year 2</td>
<td>$2,9 Year 2</td>
<td>$2,9 Year 2</td>
<td>$2,9 Year 2</td>
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<tr>
<td>Total Direct</td>
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<td>$10,745,120</td>
<td>$8,644,800</td>
<td>$8,326,800</td>
<td>$11,167,120</td>
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### Indirect

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Cost/Unit</th>
<th>Numbers Standard</th>
<th>Standard Year 0</th>
<th>Standard Year 1</th>
<th>Standard Year 2</th>
<th>Numbers SlowDown</th>
<th>Units SlowDown</th>
<th>SlowDown Year 0</th>
<th>SlowDown Year 1</th>
<th>SlowDown Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>$25</td>
<td>1904</td>
<td>$1,428,000</td>
<td>$1,428,000</td>
<td>$1,285,500</td>
<td>194</td>
<td>30</td>
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<tr>
<td>Stage 3 and 4</td>
<td>$25</td>
<td>1216</td>
<td>$3,344,000</td>
<td>$3,344,000</td>
<td>$3,707,000</td>
<td>1216</td>
<td>110</td>
<td>$3,344,000</td>
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<tr>
<td>Stroke First year</td>
<td>$25</td>
<td>0</td>
<td>$0</td>
<td>$0</td>
<td>40</td>
<td>1200</td>
<td>1200</td>
<td>$1,200,000</td>
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<tr>
<td>Stage 5</td>
<td>$25</td>
<td>1600</td>
<td>$0</td>
<td>$0</td>
<td>$2,320,000</td>
<td>29</td>
<td>1,600</td>
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<tr>
<td>Total Indirect</td>
<td></td>
<td>$4,772,000</td>
<td>$4,772,000</td>
<td>$7,312,500</td>
<td>$5,999,000</td>
<td>$5,299,000</td>
<td>$6,652,500</td>
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</table>

Total Cost for Each Therapy

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<tr>
<th>Cost Category</th>
<th>Cost/Unit</th>
<th>Numbers Standard</th>
<th>Standard Year 0</th>
<th>Standard Year 1</th>
<th>Standard Year 2</th>
<th>Numbers SlowDown</th>
<th>Units SlowDown</th>
<th>SlowDown Year 0</th>
<th>SlowDown Year 1</th>
<th>SlowDown Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SlowDown</td>
<td>$10,492,800</td>
<td>$10,492,800</td>
<td>$18,057,620</td>
<td>$14,643,800</td>
<td>$13,529,800</td>
<td>$17,819,620</td>
<td>$17,819,620</td>
<td>$17,819,620</td>
<td>$17,819,620</td>
<td>$17,819,620</td>
</tr>
<tr>
<td>Stroke First year</td>
<td>$1,050</td>
<td>1.05</td>
<td>$1,050</td>
<td>1.05</td>
<td>1.05</td>
<td>1.05</td>
<td>1.05</td>
<td>1.05</td>
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</tr>
<tr>
<td>Total discounted Cost</td>
<td>$10,492,800</td>
<td>$9,993,143</td>
<td>$16,378,794</td>
<td>$14,643,800</td>
<td>$12,976,952</td>
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<td>$16,162,921</td>
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</tr>
</tbody>
</table>

Net Benefit ($6.918,936.51)

### Summary

- **Average Cost-Effectiveness**: $36,864,737
- **Average Cost-Utility**: $6,144,123/ESRD prevented
- **Net Benefit**

### Incremental Cost-Effectiveness

- **Incremental cost-effectiveness ratio**
  - $4,378,367 - $3,636,847 / 37,029 = 29
- **Net Present Value**
  - $36,864,737

### Incremental Cost-Utility

- **NPV of one case of ESRD**
  - $279,725
- **Incremental Cost-Utility**
  - $8 year *0.65 = 5.20ALYs

### APPENDIX B: Answers to Case Study Parts 4-6

- **NPV of one case of ESRD**: $279,725
- **Incremental Cost-Utility**: $57,851

- **Average Cost-Effectiveness**: $36,864,737/ESRD prevented
- **Average Cost-Effectiveness**: $6,144,123/ESRD prevented
- **Net Benefit**: $36,864,737