Evidence-based medicine (EBM) is designed to improve the quality of clinical decisions and improve patient outcomes. Sackett et al. define EBM as “the conscientious explicit and judicious use of current best evidence in making decisions about the care of individual patients.” EBM was developed to help clinical practitioners make better decisions about the therapies they prescribe, the procedures they perform, and the advice they give to patients. It is not intended to be onerous, but it requires clinicians to frame questions accurately, conduct literature searches to identify the evidence, and then make appropriate interpretations of that evidence.

Sackett et al. begin by stating that EBM is not cookbook medicine. Rather, it is a process of obtaining the best available evidence and merging this with clinical expertise and patient-specific factors and preferences. Secondly, they state that EBM is not a panacea for controlling costs—that it may, in fact, lead to increased costs when these expenditures are for the most effective interventions to maximize the patient’s quality of life. Finally, they state that EBM is not based solely upon randomized trials or meta-analyses. The essence of EBM is to identify the “best” available information relevant to the question at hand. There are many more questions than answers in medicine today. Sackett et al. specify that practitioners of EBM should have good clinical interviewing skills, be self-directed life-long learners, and maintain humility in clinical practice because, without it, physicians “become immune to self-improvement and advances in medicine.”

Why Are Pharmacoeconomic Evaluations Important in the Context of EBM?

Although pharmacoeconomics (PEs) involves processes similar to EBM, it deals with decisions on the population level and not the patient level. The overall goal of PE is to provide the most efficient use of resources, taking into account both the cost and the value derived from using a technology. The factor driving the use of PE is monetary. Resources are scarce and many innovative products are expensive. This is especially true as we move from small molecule medications to therapies based upon proteins and DNA techniques. Biological agents are much more difficult to manufacture because of issues related to potency, stability, and packaging. The person evaluating PE information needs to understand the limitations of PE studies and not expect them to provide the answers to all questions of interest. In this sense, PE contributes information to the decision process, but it does not supplant clinical and safety data.

The basis for PE studies is usually derived from clinical trials conducted as part of the drug-development process. The standards necessary for market approval are often at odds with the data needed by clinical decision makers. Consequently, manufacturers...
must weigh the time and cost of conducting PE studies.

In a PE context, those studies in which patients are randomized to treatment arms, both the patients and observers are blinded, and an active comparator is included are of higher value than similar studies conducted using placebo or no treatment arms. From a technology assessment perspective, nontreatment is not common, and may be unethical. Randomized studies are the gold standard because they control for threats to internal validity. In theory, randomized studies are less likely to be invalid because of systematic bias.

Not as useful are observational studies where treatments are not randomly assigned. These studies are often conducted in a pre-post fashion and may or may not have a control group. Many observational studies suffer from “confounding by indication,” where patients are assigned to a therapy group because of the severity of their illness. A specific medication may be used because the severity of disease warrants its use. In such studies, comparisons between medications, even those in the same class, may not be appropriate because the patient groups are inherently different.

PE analyses can be based upon a variety of study types. The quality of the information used in cost-effectiveness analyses can range from large randomized controlled trials (RCTs) to observational studies. Large trials, such as GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), CLASS (Celecoxib Long-term Arthritis Safety Study), VIGOR (Vioxx Gastrointestinal Outcomes Research), and 4S (Scandinavian Simvastatin Survival Study) present an excellent opportunity to examine the cost-effectiveness of new therapies. These large studies typically involve patient populations that are more reflective of usual clinical practice, and the protocols often require only usual medical care monitoring. In this sense, they tend to reflect “effectiveness” rather than “efficacy.” Because of this, economic evaluations based upon these studies can generally be applied to a broad variety of health care environments.

A step-down from large RCTs are economic studies based upon meta-analysis of smaller clinical trials. These analyses are slightly less desirable because the study sample is frequently more limited. In addition, protocol-induced utilization and monitoring can influence the economic results. Economic studies based on a single RCT are even less desirable. This is true of many economic analyses, especially those performed at the time the product is initially marketed. Because these are based on only a single study, these analyses must be interpreted with caution because the results may not fully reflect the “effectiveness” of a given product when it is prescribed by a variety of health care providers.

At the other end of the spectrum are observational studies, often based upon an analysis of medical and pharmacy claims. These frequently lack measures of clinical effectiveness because the study populations were assembled for administrative, not clinical, reasons. Despite this limitation, these studies can be useful in examining the economics of multiple medications as they are used in everyday clinical practice. Many practitioners of EBM tend to discount the value of observational studies. This is not always advisable, as Smith and Pell demonstrate in discussing the evidence to support the use of parachutes for “gravitational challenge.” These authors conducted a literature search for published RCTs involving the use of parachutes and state, as a challenge to the use of only RCTs for EBM:

Advocates of evidence-based medicine have criticized the adoption of interventions evaluated using only observational data. We think that everyone might benefit if the most radical protagonists of evidence-based medicine organized and participated in a double-blind, randomized, placebo controlled, crossover trial of the parachute.

Decision Making Under Uncertainty

Because members of pharmacy and therapeutics (P&T) committees often make decisions in the absence of perfect data, the question of error arises. In this context, the data needed to make informed decisions are a function of the risk being undertaken. For questions of safety and efficacy, only high-quality studies should be used. However, as one moves from safety to coverage and purchasing decisions, the tolerance of error can increase.

As a further illustration, when a product's safety profile is questionable, a P&T committee may choose to wait until phase IV studies are completed before adding it to the formulary. The consequences of this decision are not only to deny the therapy to some patients who may benefit but also to prevent the occurrence of potentially negative outcomes such as severe morbidity or death. On the other hand, if a decision is made to add a medication to the formulary on the basis of its perceived cost-effectiveness and a subsequent analysis suggests that the medication was not worth the additional cost, the harm induced is often only financial. This is not to belittle the potential financial consequences of decisions but rather to illustrate that all decisions are likely to include a degree of error. In the end, every health plan must determine its own tolerance of uncertainty in adopting new technologies.

Cost-effectiveness analysis (CEA) is the most common economic analysis conducted for pharmaceuticals. It centers around the additional cost and value gained by using a new technology relative to usual medical care, which can be a pharmaceutical, a procedure, or no treatment. Thus, for CEA, the incremental cost-effectiveness ratio (ICER) is most desirable. Many CEAs are piggybacked onto clinical trials where both cost and efficacy or effectiveness are determined within a subset of subjects. Because there is a sample to draw upon for an estimate of the mean cost and efficacy, these studies are referred to as stochastic—“involving or containing a random variable.” An economic analysis based upon an RCT often has a high degree of internal validity due to randomization and binding of patients and observers. Common disadvantages include the lack of an active comparator (many studies are placebo comparative), a relatively short study...
duration, and protocol-induced utilization and monitoring.

An example of stochastic CEA is an analysis of the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial, which evaluated the use of abciximab in coronary revascularization. In this study, data on the use of health care resources were collected on a subset of hospital billing records. The outcome of interest was quality-adjusted life-years. Because both costs and outcomes were based upon an actual trial, the resulting economic analysis was completely stochastic.

Stochastic data are often not available because the economic analysis is being conducted after the completion of pivotal trials or access to the data from clinical studies is not permitted. This often happens in attempts to compare products of different manufacturers. In such cases, economic analyses are often based upon deterministic data—defined as precisely limited or defined data. These analyses typically involve the use of a measure of central tendency, such as a mean or median. Cost data for these types of studies are often limited, relying upon an estimated price based upon typical dose and frequency of administration. By definition, deterministic economic studies fail to capture the inherent variability in medical care. That said, they can often contribute to discussions about the adoption of new technologies.

An example of a deterministic cost-efficacy study is a comparison involving the use of etanercept or infliximab for the treatment of disease-modifying antirheumatic drug-resistant (DMARD) patients with rheumatoid arthritis. This particular analysis was based upon 2 separate clinical trials that evaluated these products. Both studies enrolled patients with similar inclusion/exclusion criteria. The data for medical costs were based upon the U.S. Food and Drug Administration-approved dosing regimens and average wholesale prices (AWP).

The primary outcome was the cost per patient achieving a 50% improvement according to the American College of Rheumatology criteria (ACR50). The analysis suggested that etanercept was more cost-effective than infliximab because of its higher efficacy and lower cost. Etanercept supplies were limited at the time of this particular economic analysis and, as a result, many managed care plans could only use infliximab. Consequently, the economic analysis assumed that infliximab was the current treatment and that etanercept was the new technology.

In comparing etanercept with infliximab in terms of cost-effectiveness, etanercept was a dominant strategy relative to infliximab. The major limitation of this type of analysis is that cost-effectiveness results are based on deterministic data. Threshold analyses to determine where the decision would change from etanercept to infliximab showed, in one case, that the efficacy of infliximab 3 mg/kg every 8 weeks would need to improve from 21% to 44% of patients achieving an ACR50.

Often, economic analysis indicates that a new therapy costs more but is more effective than the therapy it is replacing. In those situations, the adoption of the new therapy depends on the health plan's willingness to pay for the incremental value. Unfortunately, no widely accepted standards for what is “cost-effective” exist—especially when the analysis is conducted with natural or clinical outcome as the denominator.

Figure 1 displays a hypothetical cost-effectiveness threshold for a health plan in terms of accepting or rejecting a new pharmaceutical. Deterministic CEA will generate a single estimate of the ICER, which we will assume falls on the upward sloping line. With a stochastic cost-effectiveness study, the resulting ICERs would have some variation and the shape of the 95th percentile confidence intervals would become an oval (Figure 2). Figure 2 also shows that the shape of the oval is a function of the relationship between cost and effect, with a negative relationship resulting in a larger difference between the upper and lower bounds. Therefore, the decision to adopt a new medical technology can be influenced by the type of cost-effectiveness study.
Health care organizations find themselves in the unenviable position of having to decide what is and is not cost effective. There are 2 approaches that an organization or program may use when determining which technologies to purchase. The first is an absolute budget constraint rule whereby all health care technologies would be ranked and the most cost-effective technologies would be adopted first. This would continue until the entire budget was consumed and is essentially what was implemented in the Oregon Medicaid program. The other approach is to use a relative budget constraint rule where the organization would adopt all technologies whose cost fell below a stated threshold. The problem with a relative budget constraint rule is that an organization could exhaust its entire budget on cost-effective therapies.

**Summary**

EBM is a process that attempts to identify and use the best available evidence, which includes observational as well as randomized prospective studies. Economic studies are usually based on data from clinical trials. These evaluations can assist health care payers in the decision-making process because both cost and effectiveness are considered. More manufacturers are incorporating economic data collection into the clinical trial design, but decision models are still common. New therapies are becoming more complex in terms of administration, effects, and cost. As a result, PE models are likely to become more complex. Finally, there is no standard threshold of what is cost effective, so each organization is likely to have its own threshold of acceptance. Research can provide estimates of what is cost effective but cannot determine whether a given technology represents a good buy for a specific organization. Ultimately, that is a line in the sand that has to be crossed by the purchaser.

**DISCLOSURES**

The author received an honorarium from Amgen, Inc., and Wyeth for participation in the symposium upon which this article is based. He discloses that he is a consultant to Amgen.

**REFERENCES**