Risk in Perspective

The Importance of Modeling in the Economic Evaluation of Medical Technologies

Clinical trials are designed to answer a specific clinical question and not to assess cost-effectiveness, and thus the use of models is often necessary to fill in the gaps when completing a CEA.

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If there were unlimited resources to spend on health, then a reasonable approach for a society would be to implement any medical intervention that has an overall health benefit. Given that resources are limited, it is useful to know how various medical interventions compare with one another in terms of the amount of health benefit provided for each additional dollar spent.

Cost-effectiveness analysis (CEA) is an analytical tool that provides the means for a reasoned approach to the allocation of health-care dollars in light of constrained resources. CEA determines the optimal use of available medical technologies, where "optimal" means maximizing the health of a population for a given budget. Because there exist political, ethical, and legal issues that are relevant to the allocation of health care resources, CEA is offered only as an aid to policy makers and does not "make the decision."

Among the pioneers and practitioners of CEA, it is customary to use analytical structures—or mathematical models—to synthesize data on the costs and benefits of alternative clinical strategies. More recently, economic analyses have become integrated into the framework of clinical trials which previously focused on clinical outcomes alone. One of the controversies surrounding the application of CEA in this context involves the appropriate use of modeling techniques as a supplement to the primary data collection and analysis. Specifically, mathematical models are used to link data from multiple sources, extrapolate costs and health effects beyond the time horizon of a trial, and investigate how cost-effectiveness ratios might change if the values of key parameters in a model are changed.

This issue of **RISK IN PERSPECTIVE** discusses the use of CEA for the evaluation of medical technologies, and highlights the importance of modeling in this context.

The Use of Models in Cost-Effectiveness Analysis

In CEA, mathematical representations are often used to simulate the prognosis of a hypothetical cohort of patients under various treatment scenarios. The utility and properties of these models have previously been demonstrated by decision analysts, systems analysts, and operations researchers. Of particular value to clinicians is the ability of a model to simulate a patient's life experience based on data from multiple sources including clinical trials, meta-analyses, observational databases, and expert opinion. Once the structure of a model is established, data on short- and long-term events (e.g., heart attack, cancer recurrence, or death), health-related quality of life, and costs are used to operationalize the structure. Typical outputs from a model are life expectancy, quality-adjusted life expectancy, and lifetime costs.

Recently, the Food and Drug Administration (FDA) issued draft guidelines on the regulation of commercial claims made about the cost-effectiveness of pharmaceuticals. While the guidelines recognize the value of CEA and embrace the use of randomized controlled trials to assess the cost-effectiveness of a drug, they seem to adopt an unfavorable view of the use of modeling. This stance toward modeling is of concern to practitioners of CEA. Clinical trials are designed to answer a specific clinical question and not to assess cost-effectiveness, and thus the use of models is often necessary to fill in the gaps when completing a CEA.

Importance of Models

Economic analyses are increasingly becoming standard adjuncts to clinical trials. Economic outcomes and health-related, quality-of-life measures are collected during the trial on all or a subset of the trial participants. Although this new source of data is useful in CEA, there are a number of situations where a modeling effort is warranted in the context of a clinical trial.

Clinical trials are often not designed to evaluate the long-term differences between two study groups of patients. For example, trials designed to evaluate therapies for patients who are positive for HIV often use a biological endpoint to measure effectiveness rather than disease per se. An example of a surrogate marker is the CD4 count in a patient's blood rather than mortality. It is widely accepted that a patient's CD4 count is a valid predictor of mortality and thus it is not always necessary to study patients all the way until death. In this

FURTHER READING

M.R. Gold, J.E. Siegel, L.B. Russell, M.C. Weinstein (eds.) "Cost-Effectiveness in Health and Medicine." New York: *Oxford University Press*, 1996.

The Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. *JAMA.* 1996;276:1409–1415.

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type of study, an incremental cost-effectiveness ratio calculated directly from the trial would yield an incremental cost per decrease in CD4 count averted. A ratio presented in these units would only be useful for comparison to other cost-effectiveness studies that utilize the same units. A modeling effort that specifies the known relationships between CD4 count and AIDS incidence, and AIDS and death, is required to convert the trial outcome into a more broadly useful measure of effectiveness such as years of life saved or quality-adjusted life years (QALYs) saved. Use of these measures permits comparisons of cost-effectiveness ratios across diverse medical interventions.

In a CEA, all competing clinical strategies for a particular indication should be evaluated simultaneously. Competing strategies are ordered by increasing cost and increasing benefit, and the incremental cost-effectiveness ratio of a particular strategy is compared to the next less expensive strategy. Hence, the comparison strategy for an intervention is not arbitrary and may not coincide with the choice of comparator in a trial designed simply to measure effectiveness. For example, a clinical trial comparing a statin versus placebo for cholesterol reduction may not be appropriate for an economic analysis because it does not consider dietary therapy or less expensive alternative medications such as niacin. Thus, a model would be necessary to combine data from various sources to compare the cost-effectiveness of all relevant cholesterol-reduction strategies.

The average cost estimated for each arm in a clinical trial can be influenced greatly by high-cost, infrequent events like hospitalizations. A clinical trial may not be powered sufficiently (i.e., have sufficient numbers of patients) to provide stable estimates of the rare-event rates; however, there may exist large databases that provide better estimates for these rates. A model can be used to calculate the overall cost for each arm using the external estimates of rare-event rates, and can also investigate a number of alternative scenarios about the relative frequencies of rare-events between treatment arms and their long-term costs. Without a model, CEA results may be unduly influenced by imbalances in high-cost infrequent events between the two arms that are solely due to chance.

An Example

Insulin-dependent diabetes mellitus (IDDM) is a disease with a number of progressive comorbid conditions. Early complications such as proliferative retinopathy (eye disease) can lead to more devastating conditions such as blindness. The Diabetes Control and Complications Trial (DCCT) was a multicenter randomized controlled clinical trial designed to compare the effects of intensive and conventional therapy in patients who have IDDM. Intensive diabetes therapy was shown to delay the onset and slow the progression of early complications of

IDDM. However, the trial did not continue long enough to demonstrate reductions in the costly, end-stage complications of IDDM such as blindness, end-stage renal disease, and lower extremity amputation. A CEA based solely on the trial data would clearly be biased against the intensive therapy because it would exclude the cost and health consequences associated with these late events.

In order to perform a valid CEA of intensive therapy versus conventional therapy for patients with IDDM, the DCCT Research Group developed a mathematical model to calculate the lifetime benefits and costs of these two arms. Initially, they used the 9 years of observed data from the DCCT to establish a mathematical relationship between treatment and cumulative incidence of each of the early complications. DCCT could not be used directly to assess the risk of progression to end-stage complications and thus data from other large clinical trials and epidemiological studies were used to portray the progressive nature of each complication. A conservative assumption was made that the risk of progression from an early to end-stage complication was the same for both treatment groups. In this example, a modeling effort was necessary to account for the high cost, morbidity, and mortality associated with end-stage complications that were not directly observable in the DCCT.

SUMMARY

Clinical trials can provide important information about cost and health-related quality-of-life measures for new technologies, but there often exist data from other sources that can and should be incorporated into an economic analysis. In addition, the time frame of clinical trials is often too short to obtain adequate estimates of the number of quality-adjusted years of life saved by a treatment. For these reasons, the use of models remain an important and necessary component of CEAs. The Panel on Cost-Effectiveness in Health and Medicine concluded that "modeling to estimate effectiveness is a valid mode of scientific inquiry for cost-effectiveness analyses." The Panel also provided guidance on the proper construction of models and their proper role in a CEA.

USES FOR MODELING IN THE ECONOMIC EVALUATION OF MEDICAL TECHNOLOGY

- To calculate the benefits and costs beyond the time horizon of a clinical trial

- To consider relevant clinical strategies not evaluated directly in a clinical trial

- To incorporate data from a number of different sources

- To evaluate "what if" scenarios for various data parameters and assumptions