

AN EXAMPLE OF USING COMPUTER SIMULATION TO PREDICT PHARMACEUTICAL COSTS AND OUTCOMES

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ABSTRACT

This paper summarizes the major forms of socioeconomic analysis, the examination of comparative costs and outcomes for new medical interventions. Socioeconomic analysis can be performed in prospective or retrospective studies as well as in computer simulations. The steps involved in developing a computer model to estimate the costs and outcomes of medical interventions are discussed, as well as the limitation of this technique. We conclude by presenting a recent example of socioeconomic analysis using computer simulation, a model examining a new asthma medication in comparison to current standard asthma therapy.

1 INTRODUCTION

In the present era of health care reform and limitation on health care spending, new medical drugs and devices need to show more than efficacy in fighting disease or preserving health. New medical technologies need to show clinical effectiveness relative to the amount of health care resources (dollars) they consume. To examine issues related to cost and clinical outcomes, medical industries, professional organizations, and governments are increasingly turning to socioeconomic analysis. Socioeconomic analysis is a technique to quantify the gain in benefit of a medical therapy in relation to the increase in cost. While socioeconomic data may be collected in prospective clinical trials, manufacturers in the health care industry are increasingly performing socioeconomic analysis through computer simulation.

This paper will discuss basic concepts and methods

in socioeconomic analysis, focusing on the use of simulation for estimating the costs and benefits of new medical drugs or devices. We will also discuss a project we have recently completed, using a Markov model to estimate the costs and outcomes associated with alternative therapies for asthma.

2 BASIS OF SOCIOECONOMIC EVALUATION

Socioeconomic evaluation of a health care intervention involves determining the costs and outcomes associated with the intervention as compared to alternative therapies or treatments. The basic form for evaluating the incremental impact of an intervention is:

$$\frac{\text{COST}_A - \text{COST}_B}{\text{OUTCOME}_A - \text{OUTCOME}_B}$$

where COST_A represents the costs associated with the therapy under study, COST_B represents the costs of a comparative therapy, and OUTCOME_A and OUTCOME_B represents the outcomes of the study and comparative therapies, respectively. It is important to note that socioeconomic analysis involves comparison of marginal or incremental differences; the resulting ratio is the change in cost for the given change in benefit.

Socioeconomic evaluations fall into three broad categories: cost-effectiveness, cost-benefit, and cost-utility (Detsky and Naglie 1990; Drummond et al. 1990; Freund and Dittus 1992). All three of these evaluation techniques utilize costs in a similar fashion, but regard outcomes differently. Costs can be broken into two categories: direct costs and indirect costs. Direct costs

include the cost of providing and administering medical treatments and medications, laboratory tests and diagnostic procedures, and side effects related to the treatment. Indirect costs refer to intangibles, such as pain and suffering, loss of productivity, and ultimately loss of life (Luce and Elixhauser 1990). While indirect costs are more difficult to capture and quantify than direct costs, they are also highly relevant in health care-related economic evaluations.

While similar cost estimates may be used for the three types of socioeconomic evaluation, the outcomes of these evaluations differ significantly. Cost-effectiveness analysis examines the costs of a new medication relative to changes in appropriate "natural or physical units" (Drummond et al. 1990). These units often take on values such as "years of life saved" or "disease-free months". Cost-benefit analysis differs from cost-effectiveness analysis in that cost-benefit analysis expresses all outcomes in monetary equivalents. In cost-benefit analysis, a ratio is determined comparing the costs associated with a new medication to the economic benefits (i.e., health care savings due to decreased morbidity and mortality) resulting from the medication's use.

Cost-utility analysis may be considered a variant of cost-effectiveness analysis (Freund and Dittus, 1992). Here, the outcomes are adjusted by health utility values, weights that describe the relative desirability or quality of one health state versus a different health state (Drummond et al. 1990). The quality-adjusting weights range from 1, describing perfect health, to 0, representing death. Using these weights, outcomes are expressed as quality-adjusted life years, or QALYs. Cost-utility analysis allows for greater assessment of the relative effects of a medical therapy on "intangible" factors, such as pain, functional status, and activity limitations.

3 PERFORMANCE OF SOCIOECONOMIC ANALYSIS

There are three principle methods for carrying out socioeconomic analysis of new medical technologies: retrospective studies, prospective clinical trials, and modeling. Retrospective studies examine costs and outcomes of patients who have received the comparative therapies. This can be done through patient interviews, review of medical charts, or use of computerized databases. Retrospective studies have the advantage of being based on currently existing data; the intervention has already taken place, and all that a researcher needs to do is tally the results. However, this is also the main limitation of retrospective studies. Sufficient numbers of patients must have had the

comparative therapies to allow for sufficient statistical power in determining results. Biases caused by different types of patients receiving the two therapies, different institutions where the therapies were administered, etc., must be addressed. Further, the available records, be they medical charts or computer databases, are almost always geared towards assessing the medical treatment of the patient. Such data are often not easily usable in determining the costs associated with a given therapy.

Prospective clinical trials have been considered the "gold standard" for showing efficacy of medical therapies. They may also be the gold standard for determining the costs and relative benefits of therapies for socioeconomic analysis. Patients in prospective clinical trials are randomized to treatment groups, thereby controlling potential biases. Instruments can be developed for inclusion in clinical trials to accurately record costs (including indirect costs) and outcomes (including impacts on quality of life). However, clinical trials are conducted over months to years at a significant level of expense. While simplified clinical trials (known as prospective economic trials) can be conducted to gather cost and outcome information without the rigorous protocols needed to assess treatment efficacy, these may also require significant investments of time and money. In certain instances, the delays and expenses of conducting prospective studies are not acceptable.

Modeling of costs and outcomes associated with new medical therapies has many advantages. Models can be developed quickly at reasonably low cost. Sample size calculations are unnecessary, as no real patients are involved. Whatever data are currently available can be used, with unknown parameters being appropriately estimated (see below). Modifications can be made in models at any stage, to reflect newly acquired data or changes in the desired treatment plan. Sensitivity analysis can easily be performed, examining the impact on overall costs and outcomes by altering model parameters or assumptions. This allows for the identification of items which are key in influencing therapeutic results; in future prospective studies, special efforts can be made to focus on these key areas.

Models do have certain limitations. Many officials in the government and health care industry are unfamiliar with models, and are less likely to accept their findings than those of even a poorly-performed retrospective or prospective study. The main limitation of models is the source of data. While model parameters may be based on published literature and unpublished reports, expert opinion is often used to fill in gaps in the available data. Use of expert opinion may bias the results of simulations; we discuss below (in Section 5) a

technique to improve the reliability and validity of model parameters obtained using expert opinion.

4 DEVELOPMENT OF SOCIOECONOMIC MODELS

Development of a computer simulation for performing socioeconomic analysis of medical technologies involves several steps:

4.1 Development of Model Pathways

Alternative therapies for a selected clinical condition are identified and described. All possible outcomes and complications resulting from these therapies are then delineated as a clinical decision tree. Figure 1 shows a generic model of such a tree comparing medical and surgical therapies.

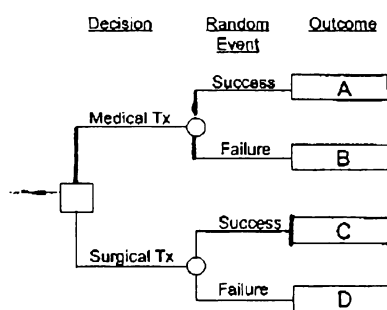


Figure 1: Generic Decision Tree

4.2 Selection of Outcome Measures

Appropriate outcomes for the comparative therapies are selected. As described above, these outcomes can be natural units (cases avoided, life-years saved), dollars (medical costs avoided), or health-related quality of life values (QALYs). The choice of outcomes depends on the disease under study, comparative therapies, available data, and desired goal of analysis.

4.3 Assignment of Costs

The costs associated with comparative therapies, including procedures, medications, hospitalizations, and physician consultation are determined.

4.4 Determination of Model Parameters

Model parameters reflect the likelihood of experiencing the above costs or outcomes in the specified clinical pathways. Health status parameters may also be included to produce quality of life estimates.

5 SOURCES OF MODEL DATA

The pathways, parameters, and costs used in socioeconomic simulations are derived from a number of sources. Data from the published medical literature are used whenever possible. Computerized databases are also used to estimate model parameters, costs, and outcomes. However, in examining new medical therapies, there may be little or no published literature or database information, particularly on long-term outcomes and costs. Therefore, much of the development of simulations is based on clinical judgement. Judgement on appropriate comparative treatments, probabilities of adverse events, and alternative therapeutic outcomes is collected from one or more clinicians with expertise in the field being modeled.

Unfortunately, judgements from clinical experts are often biased, and may lead to erroneous model projections. To prevent this, we use a modified Delphi approach in collecting expert opinion values for socioeconomic models. A panel of expert in the relevant disease area (usually three to five health professionals) is selected by identifying authors of recent publications and obtaining referrals from known experts. These individuals supply values to be used in the model based on their clinical experience and judgement during a semi-structured interview process. Summary information is sent to all panel members, for their comments, criticisms, and potential modifications. All information is then re-assembled and sent to external reviewers, additional experts in the field who were not part of the initial expert panel. Comments from the external reviewers are then returned to the panel members for their consideration. This iterative process reduces potential bias in opinion-based model parameters, improving estimates from models.

6 SENSITIVITY ANALYSIS

Sensitivity analysis is performed in order to improve the estimates from medical simulations. This involves alteration of key model parameters to examine the impact of these parameters on model outcomes and costs. Special attention in sensitivity analysis is paid to parameters with high degrees of uncertainty, such as values determined through expert opinion.

7 TYPES OF SIMULATIONS USED IN MEDICAL SOCIOECONOMIC ANALYSIS

Many clinical models are based on linear statistical expectation models, involving a single pass through a set of treatment pathways. These pathways may be as simple or complex as required to fully model a set of therapies and produce realistic estimates of costs and outcomes. In going through the treatment pathways, outcomes and costs are accumulated and totaled at each terminal node (the end of each treatment pathway branch). Comparative costs and outcomes are then used for socioeconomic analysis.

Linear simulations may require multiple levels of branching to encompass treatment alternative and associated health states. Model probabilities and costs may also depend on factors that change over time, such as the age of a patient. If two branches occur during each year of a simulation, over one billion branches would be needed for a linear model covering 30 years. Markov processes can be used to simplify such models. Markov models specify a number of health states, and allow transitions over time between the health states (Pauker and Kassirer, 1987). Specific clinical events, costs, and outcomes measures (e.g., QALYs) occur with each state. These values are summed over the course of the model, representing the entire treatment pathway of a patient and the impact of each health state he or she passed through. Cumulative costs and outcomes for each patient are determined for a specified time period or until all simulated patients have died.

8 EXAMPLE: SOCIOECONOMIC ANALYSIS OF ASTHMA TREATMENTS

We have recently completed a Markov model to examine alternative therapies for asthma. This model was written in SMLTREE, a decision analysis language developed by Dr. Jim Hollenburg. The Markov processes of SMLTREE are not true Markov process, in that probabilities may change over time. In our model, patients with mild to moderate asthma are randomized to two treatments: standard therapy with inhaled steroids or a new asthma drug. With consultation from a clinical expert in asthma, we initially developed the treatment pathways (decision trees) describing the treatment alternatives and ensuing sequelae. An overview of the model is shown in Figure 2.

Once in each arm, patients enter Markov health states for two week cycles. In each cycle, patients may

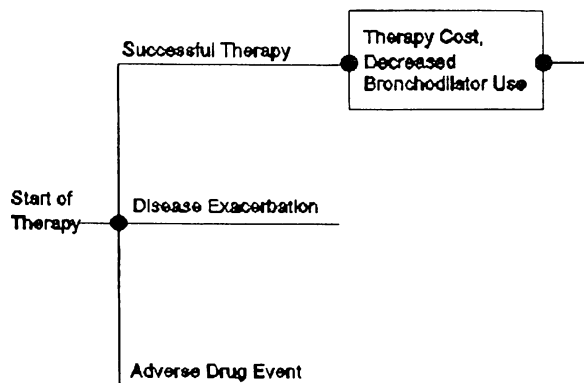


Figure 2: Overview of Asthma Model

remain in their treatment state without incident. Alternatively, patients may transition to alternative health states involving exacerbations (worsenings) of their disease symptoms or develop adverse drug events (ADEs) associated with the specified therapy. An overview of these model pathways are shown in Figure 3.

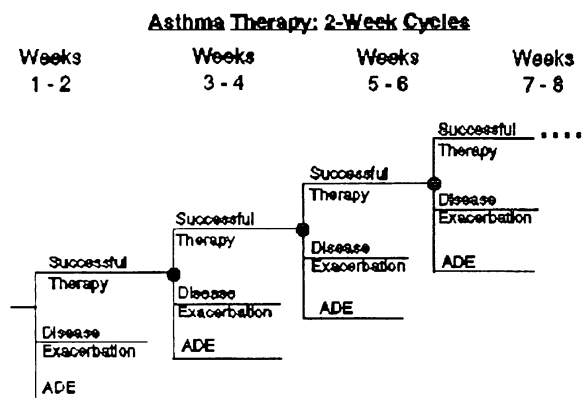


Figure 3: Markov Cycles of Asthma Model

We next specified potential model outcomes. As mild to moderate asthma has little impact on mortality, outcomes involving premature mortality (e.g., deaths postponed or years of life saved) were not appropriate. The main emphasis in therapy for mild to moderate asthma patients is to avoid disease exacerbations; we therefore used exacerbations avoided as an outcome. Also, as new therapies may have significantly fewer adverse events than older therapies, we also used adverse events avoided as an outcome. However, neither of these outcomes takes into account the full impact of asthma on patients' quality of life. To more adequately assess the impact of alternative therapies on asthma, we performed a supplementary study to

develop health utility scores for asthma health states. Using these scores, we assessed the impact of alternative therapies using Q-TWiST (Quality-adjusted Time Without Symptoms or Toxicities), a variant on QALYs. Q-TWiST allows us to quality-adjust each day for an asthmatic patient, quantifying the impact of disease exacerbations and adverse events with weights between 0 and 1. We therefore used symptom-free days as the primary outcome measures.

The final steps in developing this simulation involved selection of costs and model parameters. Patients experiencing exacerbations or ADEs will incur additional therapies and associated costs. Following exacerbations or adverse events, patients may return to their original treatment state or transition to an alternative treatment state, again accumulating associated costs (see Figure 4 and 5).

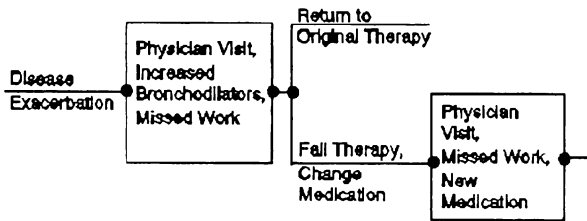


Figure 4: Treatment Pathway Following Disease Exacerbation

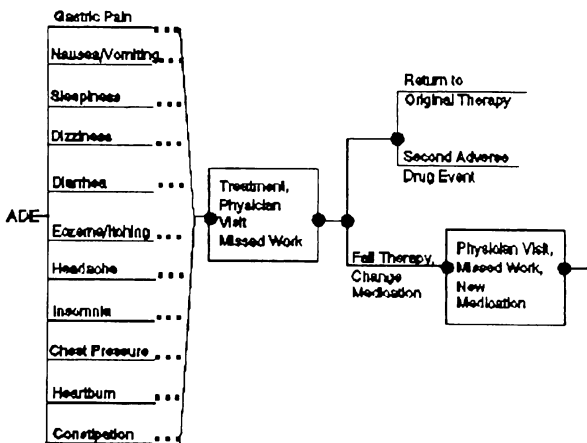


Figure 5: Treatment Pathway Following ADEs

Other factors, such as the impact of differences in patient compliance between inhaled medications (standard therapy) and oral medications (new therapy) are also included in the model.

9 CONCLUSION

This has been a brief introduction to the use of simulation in socioeconomic analysis of new medical technologies. This is a relatively new field. However, the use of these models is greatly expanding and will continue to grow with the increasing pressure to conserve limited health care resources. It may be necessary to develop standards for modeling in this field, to insure accurate and unbiased estimations. Use of rigorous techniques in developing these models will lead to improved acceptance of model results as well as increased reliance on their outcomes.

REFERENCES

Detsky, A. S., and I. G. Naglie. 1990. A clinician's guide to cost-effectiveness analysis. *Annals of Internal Medicine* 113:147-154.

Drummond, M. F., G. L. Stoddart, and G. W. Torrance. 1990. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press.

Freund, D.A., and R. S. Dittus. 1992. Principles of pharmacoeconomic analysis of drug therapy. *PharmacoEconomics* 1:20-32.

Luce B.R., and A. Elixhauser. 1990. Estimating costs in the economics evaluation of medical technologies. *International Journal of Technology Assessment in Health Care* 6:57-75.

Pauker S. G., and J. P. Kassirer. 1987. Medical progress: Decision analysis. *New England Journal of Medicine* 316:250-258.

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