

## CHAPTER 161

# Economic Evaluation of Drug Treatment for Psychiatric Disorders:

## The New Clinical Trial Protocol

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During the 1980s and continuing into the 1990s, health-care cost containment has received increasing attention as health care costs have risen more rapidly than inflation. At the same time, many new drugs have been introduced at such high prices that they have become a target for third-party payer and government efforts for cost containment.

In response to the public outcry over drug prices, many researchers have designed and performed studies to evaluate the costs and outcomes of new drug therapies (e.g., see refs. 15,23,32,38-40) These cost and outcome studies, which we refer to as drug valuation or economic evaluation studies, are important to drug companies, clinicians, patients, and public policymakers. Valuation studies can provide marketing information and enhance pharmaceutical companies' competitive advantage (17). For patients and their physicians, valuation studies can identify whether new therapies justify their potentially greater financial expense. In addition, valuation studies can help

patients assess whether future health benefits justify a reduction in the quality of life caused by a current therapy. For policymakers who must make resource allocation decisions, a valuation study that reflects a more complete picture of societal benefits can help differentiate between therapies with marginal differences in clinical efficacy.

The Food and Drug Administration (FDA) currently requires clinical trials to demonstrate the safety and clinical efficacy of new drugs. Although safety and clinical efficacy data clearly are of primary importance, they provide policymakers with insufficient information about the economic implications of approving a new drug. Pharmaceutical companies have not had the incentive to collect the data required for economic valuation studies, at least for drug approval in the U.S. market. However, in several countries (e.g., Australia), pricing and reimbursement decisions for new drugs are based on economic valuation studies (2,6,12). In the United States, insurance providers are indicating the desire for economic valuation studies of drugs (12), and health-care reform in the United States may bring an increased demand for economic evaluations of clinical trial data. These trends have induced U.S. pharmaceutical companies to include economic measures as an integral component of clinical trial protocols.

Thus far, these new protocols have been primarily introduced for treatment of nonpsychiatric conditions. Published economic studies of psychotherapeutic medications are just beginning to emerge. To understand the role economics plays in the evaluation of new drug treat-

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ments for psychiatric disorders, we reviewed economic evaluations of drug treatment for schizophrenia, major depression, and anxiety disorders. Although psychiatric disorders are prevalent and impose substantial individual and societal costs, we found relatively few published economic evaluations of psychotherapeutic drugs (18,22,26,27,29,31).

This chapter describes the type of economic data that are being collected in trials of drug treatment for psychiatric disorders and discusses the use of these data in economic valuation studies. Possible economic outcomes in clinical trials include changes in patient well-being (defined as the patient's quality of life), work days gained for patients and caregivers, and changes in medical resource use and associated medical care costs. We also describe how these enhanced clinical trials data can be used to develop decision-tree models. These models are useful because they capture the dynamics of disease/treatment patterns over the entire course of the disease, providing a basis for evaluating the effects of alternative therapeutic interventions over a patient's lifetime. Many of the initial parameters required for these models can be estimated using clinical trial outcome data. After the drug has been introduced to the market, however, the initial model parameters may be validated and improved with data from actual clinical practice and post-marketing studies.

This chapter is organized as follows. The section entitled "Cost-Outcome Valuation Methods" briefly reviews economic valuation methods, including cost-effectiveness, benefit-cost, and cost-utility analyses as well as the recently introduced idea of healthy-years equivalent. The section entitled "Outcome Data Collected in Traditional Clinical Trial Protocols" discusses the outcomes collected in traditional clinical trial protocols for depression, schizophrenia, and anxiety disorders and discusses their limitations in economic valuation studies. In the section entitled "Recent Enhancements to Clinical Trial Protocols for Psychiatric Disorders," we highlight recent additions to clinical trial protocols and their use in valuation studies. The section entitled "Using the Results of Clinical Trials" describes how clinical trials data can be used to develop decision-tree models. Finally, the section entitled "Conclusion" summarizes our discussion and reviews our suggestions for using clinical trial data in economic analyses of drug therapy for psychiatric disorders (see Chapters 72, 73, and 160, *this volume*).

## COST-OUTCOME VALUATION METHODS

Cost-outcome analysis aids policymakers in deciding whether the costs of a new drug treatment are justified by the benefits it generates. One method of analyzing the benefits of a new drug therapy is to list the relevant clinical

endpoints and compare the differences in clinical endpoints between an old drug therapy and a new drug therapy. For example, analysts might compare the differences in symptoms and side effects between two alternative drug therapies. If the new drug therapy results in more symptomatic improvement and fewer side effects compared to an older drug, the new drug would be more valuable from a purely clinical viewpoint. However, the clinical viewpoint neglects changes in the patient's overall quality of life and differences in resource use, including differences in the cost of the treatment regimens. An expanded value analysis might compare the differences between an old drug therapy and a new drug therapy in terms of the relevant clinical, quality-of-life, and resource-use endpoints.

For many purposes, comparing all the relevant outcomes may be sufficient to demonstrate that one drug is more valuable than another. For example, if a new drug has better clinical outcomes, uses fewer resources (including expenditures for the drug itself), and is associated with a better quality of life than an older drug, the new drug is more valuable and should be used in place of the older drug. More often, a new drug may improve clinical outcomes and the quality of life, but cost more than a competing drug. In these cases, researchers must perform "cost-outcome" studies to account for changes in both costs and outcomes attributable to drug therapy, and to provide a rational basis for assessing whether a drug's extra expense justifies the improvements in clinical and quality-of-life outcomes. Three cost-outcome valuation methods can be applied to drug valuation studies: cost-effectiveness analysis, benefit-cost analysis, and cost-utility analysis.

Economists often employ an alternative method of valuing drugs: individuals' willingness to pay for a drug rather than go without it. Although this willingness-to-pay definition is considerably more encompassing than cost-outcome analyses, and it captures economists' fundamental definition of value, willingness to pay must be measured by a preference elicitation method such as questionnaire-based models or revealed preference method (14). Because these elicitation methods are still relatively new, they are not yet widely accepted by the medical community (14). Consequently, in this chapter we will focus on cost-outcome methods for measuring the value of drugs.

*Cost-effectiveness analysis* compares the differences in cost and outcome across alternative therapies. The outcome generally refers to a clinical outcome and is measured in its natural units. The results are usually expressed as the incremental cost (relative to an alternative treatment) per unit of incremental outcome change, yielding ratios such as cost per averted sick day or cost per life-year(s) gained.

To perform a cost-effectiveness analysis, a researcher

should have one unambiguous objective of the intervention yielding a single outcome measure of effectiveness (4). If there are many outcomes of interest, cost-effectiveness measures are often computed for each of the alternative outcomes (4); but if the therapy under study is not clearly superior for all possible outcomes, decisionmakers are left in a quandary as to the desirability of the therapy. Under these circumstances, a *benefit-cost analysis* may be performed. By translating all the costs and benefits (including the health-outcome and quality-of-life improvements, days of work loss averted, days of caregiver time saved, hospital and physician days avoided) into dollars, benefit-cost analysis allows researchers to assess directly whether the benefits of treatment justify the treatment costs.

Benefit-cost analysis potentially provides the broadest estimate of the total value to society attributable to a drug therapy. In practice, however, measuring and quantifying all the costs and benefits of a drug therapy—especially the dollar value of quality-of-life changes—is extremely difficult and often controversial. For example, some analysts have raised concerns about assigning dollar values to improvements in labor market productivity (5). Furthermore, analysts are often uncomfortable assigning dollar values to changes in people's well-being (10).

Because of these concerns, many analysts turn to *cost-utility analysis*. Cost-utility analysis is similar to cost-effectiveness analysis in that it compares the incremental cost and outcome attributable to a particular therapy, but cost-utility analysis also accounts for changes in the quality of health caused by drug treatment (4). Thus, cost-utility analysis incorporates changes in the *quality of life* resulting from the clinical effect in addition to changes in the *length* of life. In cost-utility analysis, the entire array of health improvements is converted to a single common unit, most commonly quality-adjusted life-years (QALYs) gained, which makes comparing alternative treatments easier. Recently, researchers have developed an alternative to QALYs—health-years-equivalent (HYE)—that reflects the number of years in good health that is equivalent to a longer lifetime in poor health (3,13). Gafni et al. (13) claim that HYE are more consistent with economists' utility maximization paradigm, but others are not persuaded that HYE are better than QALYs (3).

Recently, researchers have designed models to simulate the effect of therapeutic interventions on outcomes such as incidence, mortality, and resource use. The transition patterns between severity levels are estimated using state-transition or decision-tree models that capture the dynamics of treatment patterns over the entire course of the disorder. For example, Weinstein et al. (41) used a state-transition model to simulate future trends in incidence, prevalence, mortality, and resource cost under alternative assumptions about preventive and therapeutic interventions for coronary heart disease (CHD). Their model

allows for simulation of the initial outcomes attributable to the CHD event, as well as subsequent events (such as recurrence) in persons suffering from CHD.

Given that psychiatric disorders tend to be chronic and recurring, we recommend using state-transition or decision-tree models in economic analyses of psychotherapeutic drugs. These models allow researchers to consider economic outcomes in a dynamic context over the lifetime of the individual. These models incorporate (a) the potential resource savings from reducing the intensity and length of acute episodes and (b) the gains from preventing future acute episodes.

In the section entitled "Using the Results of Clinical Trials" we present an example of a decision-tree model applied to the acute and maintenance phases of major depression.

### OUTCOME DATA COLLECTED IN TRADITIONAL CLINICAL TRIAL PROTOCOLS

Although hundreds of clinical trials have been conducted to determine the efficacy of medications for major depression, schizophrenia, and anxiety disorders, there are very few published economic valuation studies of these drugs. A review of the literature on health-care cost-benefit and cost-effective analyses between 1979 and 1990 found only nine published studies on psychiatric medications, compared to close to 200 studies on medications for nonpsychiatric diseases (9).

The small number of economic evaluations of psychotherapeutic drugs may be attributable to the difficulty in measuring psychological states with reliability and validity. Disease states and concomitant economic outcomes may be easier to measure for nonpsychiatric illness than for psychiatric disorders. Another problem is that, until recently, clinical trials have not collected the data needed by economists to conduct valuation studies. Traditionally, clinical trials for pharmacotherapy of depression, schizophrenia, and anxiety disorders focused on safety and clinical efficacy. For acute treatment, efficacy was determined by general or disease-specified psychometric measures indicating the presence, frequency, and intensity of symptoms, behaviors, or feelings (30). Common clinical outcome measures of general psychopathology include the Brief Psychiatric Rating Scale, Hopkins Symptom Checklist, Global Assessment Scale, and Clinical Global Impressions scale. Disease-specific scales, such as the Hamilton Rating Scales for Depression and Anxiety and the Schedule for Affective Disorders and Schizophrenia, are more popular among clinical researchers (7).

Similarly, trials of maintenance drugs have not collected the specific economic outcomes required for valuation studies. Maintenance therapies generally have mea-

sured outcomes such as relapse rates, time between episodes (survival time), number and severity of subsequent episodes after treatment, and duration and severity of symptoms.

Social functioning (e.g., Social Adjustment Scale) and quality-of-life scales have been more widely used in recent years. Quality-of-life instruments are available to measure emotional and social functioning, well-being, disability, and overall health status attributable to diseases and their treatments (16,19). These instruments usually include questions about (a) physical, social, and role functioning, (b) bodily pain, and (c) overall well-being. Although these measures provide more meaningful information about the drug's effect on functioning and well-being, they still do not provide the direct quantifiable utility-based, quality-of-life measure that economists prefer (described in the following section), nor are they substitutes for direct, quantifiable measures of productivity and resource use that are necessary for economic valuation studies. Apart from using an expert elicitation process to link scores on these scales to utility-based, quality-of-life measures, resources used, or productivity levels, there is no direct way to determine a drug's economic value based on these scales.

Thus, until recently, clinical trials for pharmacotherapy of psychiatric disorders have not provided the data economists need to conduct drug valuation studies. Because of these data limitations, most published economic studies of the costs of psychiatric disorders have relied on secondary data for their estimates (e.g., see refs. 1 and 33). Very few have been able to determine the economic value of alleviating a psychotic episode or preventing recurrence.

### RECENT ENHANCEMENTS TO CLINICAL TRIAL PROTOCOLS FOR PSYCHIATRIC DISORDERS

Recently, researchers have started to collect economic outcomes as part of their clinical trial protocols, especially for expensive drugs with improved efficacy relative to alternative treatments. For example, clozapine, a new treatment for neuroleptic-resistant schizophrenia, has instigated several cost-effectiveness studies in the past several years (18,24,26,31).

Many clinical trial protocols are now collecting the following economic outcomes for psychotherapeutic drugs:

1. Mortality
2. Resource-use measures
  - a. Hospital admissions and days
  - b. Housing costs (nursing home or group home)
  - c. Visits to health professionals
  - d. Other outpatient costs (e.g., case management, day care)

- e. Lab procedures
- f. Drugs prescribed
- g. Other costs related to illness (e.g., transportation, legal fees)
- h. Unit costs of resource use measures
3. Labor market and household productivity measures
  - a. Working time
  - b. Paid and nonpaid caregiver time
  - c. Patient's time (including transportation time) associated with treatment
4. Quality-of-life measures

Conducting a resource-use analysis for treating psychiatric disorders entails collecting data during the clinical trial on inpatient and outpatient resource use. Health-care resource costs can be estimated separately from the clinical trial using standard charge schedules and cost-to-charge ratios. Examples of economic outcome studies that have collected data on hospitalization costs and physician charges for psychiatric disorders include Meltzer et al. (26), Revicki et al. (31), and Kamlet et al. (20).

Other important endpoints that should be collected in clinical trials are labor market and household productivity effects. These measures include the days of work the patient gained, the level of function of those days gained, and the paid and nonpaid caregiver time avoided as a result of treatment. Examples of questions that might be added to assess these effects include: "Since we saw you last, how many days of work did you miss because of panic attacks?"; and "Since we saw you last, how many days did a nonpaid caregiver miss work to take care of you while you felt depressed?"

A dollar value of lost work time can be calculated by multiplying the foregone days of work attributable to the disorder by a wage measure. However, this method has some limitations. First, if the patient is not employed, no wage measure exists. Thus, an estimated wage would have to be developed for those patients who are too ill to work, are unemployed, are retired, or who work as homemakers. Second, patients may be reluctant to provide income information during the clinical trial. Finally, this method of valuing productivity changes, known as the *human capital approach*, is controversial. Grabowski and Hansen (14) suggest that such a procedure "measures health and quality of life as though they are a unit of production, not something of intrinsic value." As a result, the human capital approach to valuing the productivity gains of a new depression drug treatment gives more weight to high-wage earners than to low-wage earners.

Many clinical trial protocols for new medications (including those mandated in Australia) do not currently collect productivity measures. However, in spite of the limitations, we believe that valuing productivity gains or losses is important and we recommend routinely including productivity questions in clinical trial protocols.

Because psychiatric disorders can have pervasive effects on individuals' lives, changes in patients' quality of life are also important endpoints being measured during many clinical trials (25,42). Most economists prefer to measure quality-of-life changes as the difference in the patient's utility between perfect health and alternative impaired health states (4,36,37). Several techniques exist to elicit individuals' utility of alternative health states. One technique, category scaling, asks a person to place several alternative health states in the appropriate place on a line bounded by zero (death) and one (perfect health). Other quality-of-life valuation techniques include the standard gamble and time trade-off methods (4). Using the standard gamble method, people are asked to choose between a certain less-than-perfect health outcome and an outcome of either perfect health with probability  $1 - p$  or death with probability  $p$ . The probability of death at which the person is indifferent between the choices is equal to the utility of the certain less-than-perfect outcome (4). A typical standard gamble question might be: "Imagine that there is a new, free medication available which will either completely cure your mental illness or kill you. Suppose that 50% of the people who take the new medication are cured of the disease, and 50% die. Would you risk taking the new medication?" If the individual answered "yes," the probability of dying would be successively increased until the individual answered "no." Similarly, if the individual initially answered "no," the probability of death would be successively reduced until their answer changed to "yes." In either case, the probability at which the answer to the question changes represents the utility of being mentally ill (34). In the time trade-off method a person is asked to give the length of time in perfect health that is equivalent to a full lifetime in selected, less-than-perfect health states (37). These methods may be limited, however, because people do not give necessarily give consistent or sensible answers to these elicitation methods (34).

Another method of determining value is the willingness-to-pay method, which quantifies the utility of alternative health states in dollar values. This method determines the amounts of money people are willing to pay for various possible health states (34). For example, an investigator might ask the patient (35): "Consider all the effects of your anxiety on your life. How much would you currently be willing to pay each week, realistically, to get rid of your anxiety and all the problems it brings?" As above, this method is potentially limited because respondents may not be able to give consistent or rational personal judgments on their willingness to pay (34). Furthermore, willingness-to-pay estimates are controversial because the magnitude of the estimates is likely affected by the income level of the respondents, such that higher-income respondents may have a greater willingness to

pay for good health (and hence a greater value of good health) than would lower-income respondents.

We recognize that methods of valuing economic outcomes, particularly productivity and utility-based quality-of-life changes, have limitations and are currently controversial. Although none of these techniques or scales has been widely used or accepted as standard, conceptual work to advance their use in clinical trials for mentally ill persons is underway. The development of common definitions and standards of measurement will allow researchers to accumulate comparable data across studies and across populations (21). In turn, these data will help economists improve their economic valuation studies of drug treatment.

### USING THE RESULTS OF CLINICAL TRIALS

Clinical trials data can be used in conjunction with other data sources to develop decision-tree models that highlight clinical decision points, alternative treatment choices, and the resulting possible outcomes. Using these models, researchers can illustrate the temporal and logical sequence of the disease/treatment dynamics, combine the results of acute and maintenance clinical trials, and control for natural recovery that may occur apart from drug treatment.

We suggest that clinicians develop decision trees concurrently with clinical trial protocols to help guide choices of outcome measures and to ensure that the trials collect data on the appropriate economic endpoints. Well-designed clinical trial protocols can estimate the transition probabilities between alternative disease states that are needed for decision-tree models.

Figures 1 and 2 illustrate treatment choices, disease/treatment dynamics, and outcomes using a simplified example of a decision-tree model. Our focus in these figures is on modeling the treatment of major depression, but this is meant to be illustrative of modeling psychiatric disorders more generally. The basic structure of this decision-tree model would be essentially the same for anxiety disorders or schizophrenia.

Figure 1 represents the disorder/treatment dynamics for an acute depressive episode, while Figure 2 represents a phase in which the patient is stable and under maintenance therapy. We make several simplifying assumptions in this model: (a) Depression occurs at four basic severity levels (i.e., mild, moderate, severe without psychotic symptoms, and severe with psychotic symptoms); (b) the patient is only affected by unipolar depression; (c) four treatment choices (i.e., drugs only, psychotherapy only, drugs and psychotherapy combined, and electroconvulsive therapy) are available; and (d) treatment-switching decisions are made only at 8 weeks and 6 months after initial treatment.

As illustrated in Fig. 1, the patient enters treatment in

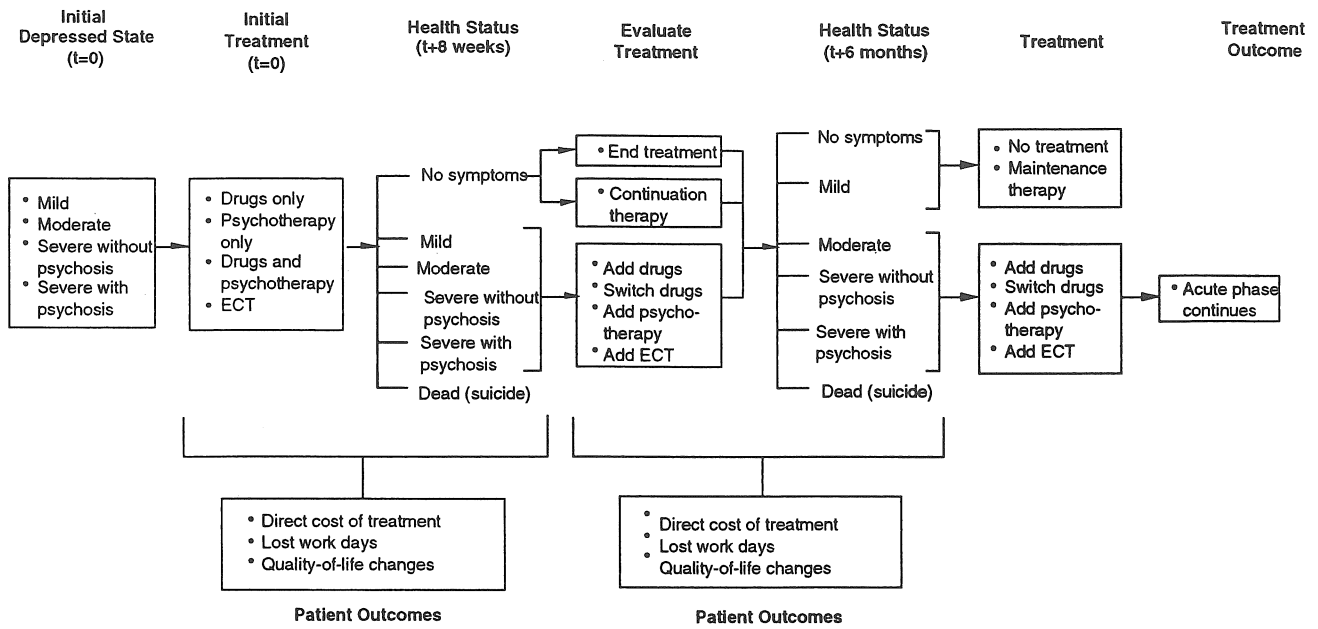


FIG. 1. A decision-tree model for evaluating the acute phase of treatment for depression.

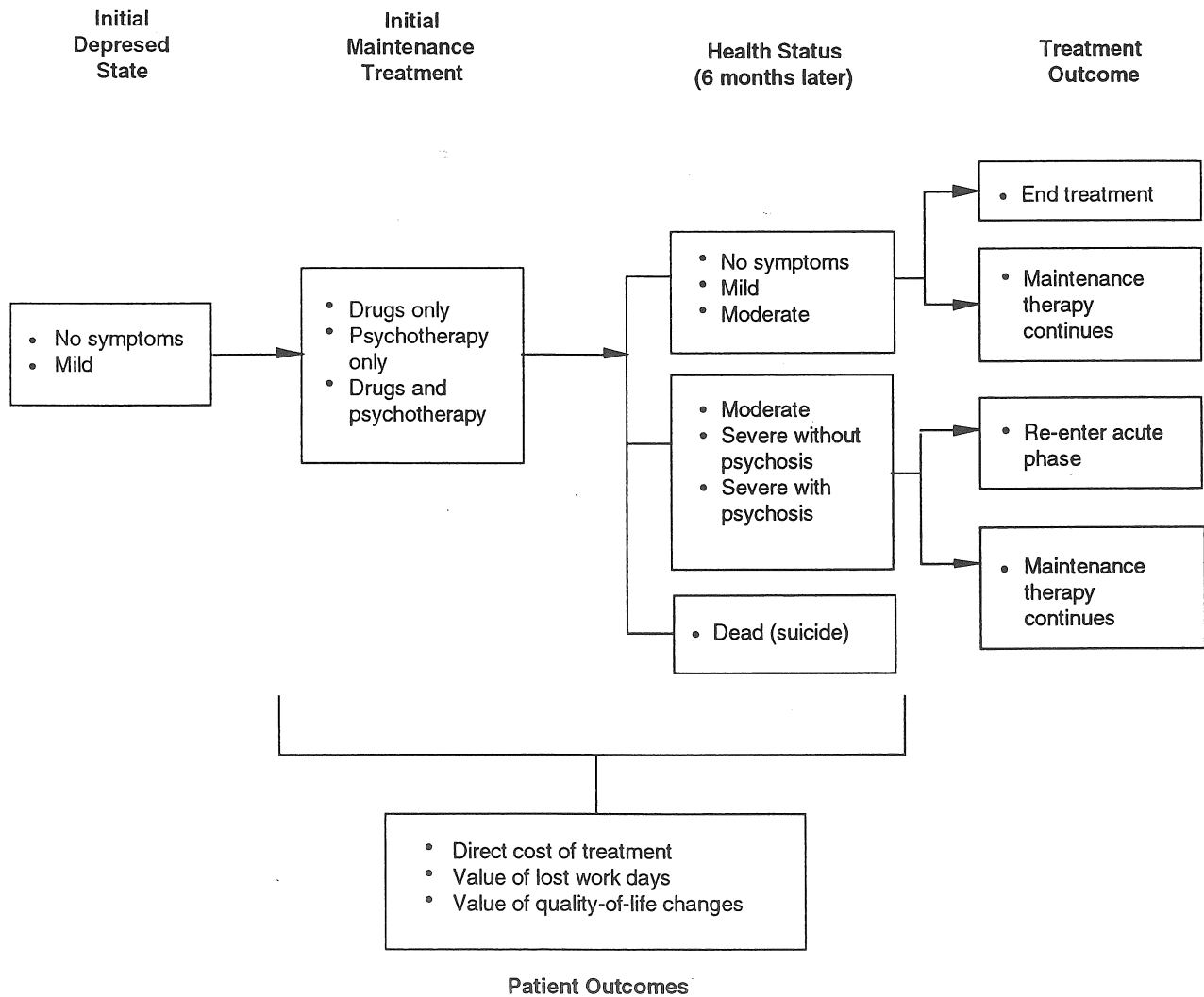


FIG. 2. A decision-tree model for evaluating the maintenance phase of treatment of depression.

one of the four possible severity levels. Based on the patient's initial severity level, the physician selects a treatment. After the initial treatment visit, the patient is reexamined periodically; in subsequent visits, the patient's health status will have improved, worsened, or remained the same. Alternative treatments may affect the length of time spent in each severity level and, hence, the functional loss of the patient. Each severity level is associated with health-care resource use, days of lost work or reduced productivity, and quality-of-life-changes that can be measured at various time intervals.

Depending on the success of the acute treatment and the patient's history of depression, several treatment paths may be taken at the 8-week and 6-month time points. Those patients who are asymptomatic after 8 weeks or 6 months and have no previous history of depression may end treatment at either point. Those patients who still have mild depression or worse at the 8-week or 6-month time points are still in the acute phase; their treatment will be evaluated and possibly changed. Asymptomatic or mildly depressed patients with a history of three or more prior depressive episodes may be treated with continuation therapy to avoid relapse at the 8-week point, or these patients may enter maintenance therapy to avoid recurrence at the 6-month point. Most patients with a history of recurrent depressive episodes will likely proceed to maintenance therapy.

Figure 2 summarizes the disorder/treatment dynamics for the maintenance phase of depression treatment. Patients enter maintenance therapy with either mild residual symptoms or no symptoms. After the initial maintenance treatment visit, the patient periodically visits the physician, who assesses the efficacy of the treatment. At the 6-month assessment point, the patient's mental status will have either improved, worsened, or stayed the same.

This example of depression/treatment dynamics illustrates the connection between changes in disease stages, resource use, and quality-of-life endpoints. Measuring the movements between severity levels provides estimates of transition probabilities for decision-tree models. These estimates can then be used in conjunction with estimates of resource use to simulate the costs and benefits of new drugs in the context of the complete drug/treatment dynamics.

Kamlet et al. (20) recently operationalized this type of decision model in their cost-utility analysis of maintenance therapy for recurrent depression. They drew on results from the Pittsburgh Recurrent Depression Project (11), in which the clinical effectiveness of alternative treatments in delaying recurrence of depression was evaluated. Although the trial lasted only 3 years, Kamlet et al. developed a lifetime model of acute episodes followed by stable periods under maintenance treatment. To implement their cost-utility model, they required estimates of the following variables: time until recurrence, time spent

in a depressive episode, probability of suicide, quality of life during a depressed episode and during maintenance treatment, and direct costs per episode of acute and maintenance treatment. Because their clinical trial data were limited to the maintenance phase, the analysis had to base the other parameter values on secondary data supplemented with assumptions or consensus of expert opinion.

Although decision-tree models are useful tool for economic evaluation of new drugs, analysts must use caution when attempting to generalize the results of clinical trials beyond the trial setting. First, the results of individual clinical trials—which often evaluate short-term effects and are directed at the acute phase of a disorder—may provide a misleading picture of the entire disorder/treatment dynamics of that drug. This is especially likely to be a problem for drugs used for treating either (a) diseases with a prolonged duration or (b) chronic diseases that recur over a person's lifetime (as with many psychiatric disorders). Another limitation of clinical trials data is that patients in a clinical trial may not be representative of the diseased population. Because trials are typically conducted in tertiary care settings, patients participating in the trial are a highly selected subset of all those who have the disorder being studied. Furthermore, the clinical trial takes place in an idealized setting, where patient compliance with dosage is monitored more closely than with typical patients in an actual clinical setting. Thus, the drug's efficacy is likely to be overestimated when applied to patients outside the clinical trial setting. Finally, clinical trials usually compare the new drug to placebo rather than to an existing drug or the suggested medical therapy, leaving policymakers with little information about comparative outcomes (12,28).

Because of these limitations, we suggest performing a sensitivity analysis of model parameters and validating parameter estimates from clinical trials against other data. Sensitivity analysis involves substituting a range of estimates for the probabilities and resource-use estimates to see whether they alter the model's conclusions. Eisenberg et al. (8) suggest comparing clinical trial data with data from other trials, expert opinion, and information from large databases such as Medicare claims files. Finally, researchers can validate decision-tree models with data from actual clinical practice or from post-marketing economics studies. For example, randomized trials may be developed with the primary purpose of estimating differential resource use across alternative drugs. As more information becomes available, researchers will be able to build better models of the mental disease/treatment dynamics.

## CONCLUSION

Improved economic valuation studies will help patients, physicians, pharmaceutical companies, and policy-

makers decide whether new therapies justify their additional expense. Given the advent of expensive new drugs and limited health-care resources, comprehensive economic evaluation studies based on clinical trials data are critical to sound decisionmaking.

In the past, clinical trials have not provided adequate data for economic analysis of psychotherapeutic drugs. However, researchers are increasingly recognizing the importance of incorporating economic outcomes into clinical trial protocols. Trials are now collecting data on the resource use, lost labor market productivity, and quality of life that are needed for sound economic analysis.

These enhanced data can be used to develop decision-tree models to guide a comparison of the costs and outcomes of alternative drug therapies. Decision-tree models can be developed that incorporate the results of separate acute and maintenance trials into a single model. These models can be validated and improved with data from other trials, expert opinion, post-marketing studies, and large databases such as Medicare claims files. As clinical trial protocols continue evolving to collect more economic information, researchers will be able to build more sophisticated economic models that evaluate the merits of new psychotherapeutic drugs in the context of the mental disorder/treatment dynamics.

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