

## The Medical Literature

# Users' Guides to the Medical Literature

## XIII. How to Use an Article on Economic Analysis of Clinical Practice

### A. Are the Results of the Study Valid?

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#### CLINICAL SCENARIO

You are a general internist on the staff of a large community hospital. Your chief of medicine knows of your interest in evidence-based medicine, and she asks you to help her solve a problem. The hospital's pharmacy and therapeutics committee has been trying to decide on formulary guidelines for the use of streptokinase or tissue-type plasminogen activator (t-PA) in the treatment of acute myocardial infarction (AMI). Members of the committee have been arguing for weeks about the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial<sup>1</sup> and whether the added expense of t-PA is worth it. The committee has reached an impasse and has asked the chief of medicine for some outside help to reach a good decision. Knowing that the hospital faces pressure to keep costs down, the chief wants good information about this question to bring to the next committee meeting later this week. She asks you to help her find out if a formal economic analysis that compares thrombolytic agents for AMI has been done and then help her present it to the committee.

#### The Search

From your office computer you enter the hospital library's CD-ROM MEDLINE system via the hospital's information network. In the current MEDLINE file, you cross the terms "myocardial infarction" (11 099 citations), "thrombolytic therapy" (3350 citations), and "cost-benefit analysis" (4232 citations). This yields a set of only 11. Reviewing these on screen, you find 3 articles directly relevant to your question. One is an economic analysis done as part of the GUSTO study,<sup>2</sup> and another is an economic analysis using data from the GUSTO trial in a decision model.<sup>3</sup> Your searching program includes a "Local Messages" field, and this field reports that both of these studies are available in your hospital's library. Your search also turns up another analysis based on modeling,<sup>4</sup> but the "Local Messages" note indicates that this journal is not available in your library. You request a copy via interlibrary loan, but realize it will probably arrive long after the committee's meeting later this week. You thus turn to the first 2 articles, hoping to find some evidence you can use to help the committee.

but should also consider whether these benefits will be worth the health care resources consumed. Resources used to provide health care are vast, but not limitless. This is particularly the case in managed care settings where, in essence, a fixed sum is available to provide care for enrollees. Thus, more and more, clinicians will have to convince colleagues and health policymakers that the benefits of their interventions justify the costs.

To inform these decisions, clinicians can use economic analyses of clinical practices. Economic analysis is a set of formal, quantitative methods used to compare alternative strategies with respect to their resource use and their expected outcomes.<sup>5,6</sup> Economic evaluations seek to inform resource allocation decisions, not make them. Economic analyses have been attracting more attention in recent years and could potentially inform decisions at different levels in the health care system, such as managing major institutions like hospitals and in determining regional or national policy.<sup>7-9</sup>

Randomized trials generate data about relative treatment efficacy, but sometimes investigators may also collect data about cost. As with other integrative studies such as decision analyses<sup>10</sup> and practice guidelines,<sup>11</sup> economic analyses may use estimates of cost and effectiveness from summaries of several studies of therapy, diagnosis, and prognosis. Either way, the main distinction between economic analyses and other studies is the explicit measurement and valuation of resource consumption or cost. The integration of cost data often involves placing values on the health outcomes so that they can be related to the costs of alternative treatment strategies.

#### INTRODUCTION

In the course of their work, clinicians make many decisions about the care of individual patients. Clinicians are also asked to participate in decisions for large groups of patients, whether to set clinical policy for an institution ("Should streptokinase or t-PA be recommended routinely for patients with an AMI who present to our hospital?"), or to set health policy at a more macro level ("Which thrombolytic agents should our national or local health authority choose to purchase and provide for our citizens who suffer AMI?"). When making decisions for such patient groups, clinicians need to not only weigh the benefits and risks,

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In helping you understand economic analyses, we will introduce you to how these analyses are conducted and review some of their strengths and weaknesses. This is not, however, an article on how to perform economic analysis; should you wish to do so, you should look elsewhere.<sup>12-14</sup> Since you may frequently encounter economic analyses that are based on decision models, you may also find it useful to review the earlier articles in the series on clinical decision analysis<sup>10</sup> when reading such studies.

## THE FRAMEWORK FOR THE USERS' GUIDES

We will approach articles on economic analysis of clinical strategies with the same 3 organizing questions introduced in earlier articles in this series:

### Are the Results Valid?

This question addresses whether an economic analysis truly determines which of the clinical strategies would provide the most benefit for the available resources. Just as with other types of studies, the validity of an economic analysis is primarily determined by the strength of the methods used.

### What Were the Results?

If the answer to the first question was yes, and the economic analysis likely yields an unbiased assessment of the costs and outcomes of the clinical strategies under study, then the results are worth examining further. The guides under this second question consider the size of the expected benefits and costs from adopting the most efficient strategy and the level of uncertainty in the results.

### Will the Results Help in Caring for My Patients?

If the economic analysis yields valid and important results, you can then examine how to apply these results in your own clinical setting.

Table 1 summarizes the specific questions you can ask in addressing these 3 areas. We will explore the guides by applying them to the articles we found in our search. This article will deal with the validity guides, while the next in the series will address the results and applicability.

## ARE THE RESULTS VALID?

### Did the Analysis Provide a Full Economic Comparison of Health Care Strategies?

Economic analyses compare 2 or more treatments, programs, or strategies. If 2 strategies are analyzed but only costs

are compared, this comparison would inform only the resource-use half of the decision and is termed a *cost analysis*. Comparing 2 or more strategies only by their efficacy (such as in a randomized trial) informs only the outcomes portion of the decision. A full economic comparison requires that both the costs and outcomes be analyzed for each of the strategies being compared. To help you understand the structure of the comparison further, some additional questions will be useful.

**Was a Broad Enough Viewpoint Adopted?**—Costs and outcomes can be evaluated from a number of viewpoints: the patient, the hospital, the third-party payer (eg, health maintenance organization), or society at large. Each viewpoint may be relevant depending on the question being asked, but broader viewpoints are most relevant to those concerned about the overall allocation of health care resources.<sup>9</sup> That is, an evaluation adopting, for example, the viewpoint of the hospital will be useful in estimating the budgetary impact of alternative therapies for that institution. However, economic evaluation is usually directed at informing policy from a broader societal perspective.

For example, in an evaluation of an early discharge program, it is not sufficient to report only hospital costs, since patients discharged early may consume substantial resources in the community. These costs may not be borne by the hospital, but are likely to impact on a third-party payer or the patient in some way or another. This was a limitation of the study by Topol et al,<sup>15</sup> which assessed the feasibility and cost savings of hospital discharge 3 days after AMI, considering only hospital and professional charges. We have no knowledge of other community services consumed and whether these differed between early discharge and conventional discharge patients.

One of the main reasons for considering narrower viewpoints in conducting an economic analysis is to assess the impact of change on the main budget holders, since budgets or payments may need to be adjusted before a new therapy can be adopted. This is particularly true in countries like the United States, where resource-allocating decisions are made in a decentralized way by a range of actors rather than a health ministry. Weisbrod et al<sup>16</sup> pointed out that while a community-oriented mental illness program was worthwhile from the perspective of society as a whole, it would be more costly to the organization responsible for providing the care. Even within the same institution, narrow budgetary viewpoints can prevail. In our example

Table 1.—Users' Guides for Economic Analysis of Clinical Practice

<b>Are the results valid?</b>
Did the analysis provide a full economic comparison of health care strategies?
Were the costs and outcomes properly measured and valued?
Was appropriate allowance made for uncertainties in the analysis?
Are estimates of costs and outcomes related to the baseline risk in the treatment population?
<b>What were the results?</b>
What were the incremental costs and outcomes of each strategy?
Do incremental costs and outcomes differ between subgroups?
How much does allowance for uncertainty change the results?
<b>Will the results help in caring for my patients?</b>
Are the treatment benefits worth the harms and costs?
Could my patients expect similar health outcomes?
Could I expect similar costs?

comparing streptokinase with t-PA, it would be wrong just to focus on the relative costs of the drugs, which fall on the pharmacy budget, if there are also impacts on the use of other hospital resources.

The patient's perspective may also merit specific consideration if costs (eg, in travel) reduce access to care. Also, some patients may not be able to participate in community care programs if these impose major costs in terms of informal nursing support in the home. In some countries, most notably the United States, patients may also be responsible for a sizable proportion of their health care bills. Many economic analysts do not track all of these costs, owing to the time and effort required. However, the patient's perspective is partially integrated into the analysis by measuring the outcomes of therapy, such as impact on quality of life.

The way in which the articles by Mark et al<sup>2</sup> and Kalish et al<sup>3</sup> handle these and other key methodological issues is presented in Table 2. Mark et al<sup>2</sup> point out the importance of considering a broad, societal viewpoint, whereas Kalish et al<sup>3</sup> do not discuss the issue. In practice, both analyses concentrate on the identification and quantification of direct medical care costs, both inside and outside the hospital. The reasons for exclusion of other cost items, such as patients' costs, are not explicitly discussed, but may relate to the practical problems of data collection.

The breadth of outcomes considered varies according to the type of economic analysis. In cost-effectiveness analyses the health outcomes are not valued, but reported in physical units such as *life years gained* or *cases successfully treated*. In a variant of cost-effectiveness analysis, sometimes called *cost-utility analysis*, outcomes of different types are weighted to produce a composite

Table 2.—Key Methodological Features of the 2 Studies

Feature	Mark et al <sup>2</sup>	Kalish et al <sup>3</sup>
Overall study design	Cost-effectiveness and cost-utility analysis concurrent with clinical trial	Cost-utility analysis using a decision-analytic model
Viewpoint for analysis	Societal	Not stated
Alternatives compared	t-PA or streptokinase for patients with acute myocardial infarction	t-PA or streptokinase for patients with acute myocardial infarction
Benefit measure(s)	Life-years saved and quality-adjusted life-years saved	Quality-adjusted life-years saved
Source(s) of effectiveness data	GUSTO trial (1-y survival) and Duke Cardiovascular Disease Database (long-term survival)	GUSTO trial (1-y survival) and Worcester Heart Attack Study (long-term survival)
Source(s) of quality of life (utility) weights	Sample of 2600 US patients enrolled in the GUSTO trial	GISSI-2 trial
Estimates of resource use	23 105 US patients enrolled in the GUSTO trial (for initial hospitalization); sample of 2600 US patients (for resource use up to 1 y)	Brigham and Women's Hospital and the literature
Source(s) of cost data	Duke cost accounting system and Medicare DRG rates	Brigham and Women's Hospital and the literature
Discounting	5% per year	5% per year
Sensitivity analysis	Varied estimates of survival and cost; also varied discount rate and considered importance of disabling strokes	Varied estimates of survival cost and stroke rate; also varied discount rate

\*t-PA indicates tissue-type plasminogen activator; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; GISSI-2, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; and DRG, diagnosis related group.

index, such as the quality-adjusted life year (QALY)<sup>12</sup> or healthy years equivalent.<sup>17</sup> Quality adjustment involves placing a lower value on time spent with impaired physical and emotional function than time spent in full health. On a scale where 0 represents death and 1 represents full health, the greater the impairment, the lower the value of a particular health state. These approaches are particularly useful when alternative treatments produce outcomes of different types, or when increased survival is bought at the expense of reduced quality of life.

Finally, in cost-benefit analyses, the health consequences are valued by asking health care consumers what they would be willing to pay for health services that achieve combinations of outcomes of particular types. This has an advantage in that it would be possible to assess directly whether the intervention is worthwhile to society, as all costs and outcomes would be valued in the same units (usually dollars). However, this approach may introduce a bias toward interventions for the rich, if their willingness to pay were higher than that of the poor. Nevertheless, it is worth remembering that most of the methods of economic evaluation ultimately lead toward some type of social valuation, such as how much we are willing to pay to gain an extra year of life or an extra QALY. Also, the QALY approach introduces another kind of bias in favor of those individuals with potentially more years to live in a good health state.

In the study by Mark et al,<sup>2</sup> the primary analysis was cost-effectiveness analysis, using the outcome *years of life saved*. The outcome in QALYs was considered in a secondary analysis. In the study by Kalish et al<sup>3</sup> the primary analysis used QALYs. In both cases the value of states of health were obtained by the time trade-off approach; that is, by asking patients how many years in their current state of health they would be willing to give up to live their remaining years in excellent health. Mark et al<sup>2</sup> obtained these values from patients in the GUSTO trial 1 year after treatment. Kalish et al<sup>3</sup> obtained them from a subset of patients in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial.

Another type of consequence is the impact that therapy may have on the patient's ability to work and hence her or his contribution to the nation's production. These impacts are known as *indirect costs and benefits* in much of the health economics literature, but this terminology is falling from favor as it is at odds with the accounting use of the term *indirect costs*, to mean overhead. The issue of inclusion or exclusion of productivity changes is a frequent topic of debate. On one hand, these represent resource-use changes just like those occurring in the health care system. On the other hand, production may not actually be lost if a worker is absent for a short period. Also, for longer periods of absence, a previously unemployed worker may be employed. Furthermore,

inclusion of productivity changes biases evaluations in favor of programs for those individuals who are employed full-time. Therefore, you should be skeptical about any economic analysis that includes productivity changes without clearly presenting the implications.

Neither of the thrombolytic studies discussed here considered productivity changes. The inclusion would be unlikely to substantially influence the comparison between streptokinase and t-PA, and may not be appropriate. However, the exclusion of lost productivity could constitute another argument for thrombolysis over a treatment strategy of no thrombolysis.

**Were All the Relevant Clinical Strategies Compared?**—The second assessment of the breadth of an economic evaluation relates to the range of alternative strategies examined. A frequently omitted strategy is that of maintaining the status quo. Another mistake is to view alternatives as being all or nothing. In medicine it is not often a question of whether one should adopt a particular test or apply a particular therapy, but how much of it should be applied. Thus, the interesting and more clinically relevant questions often relate to whether a given procedure should be applied selectively or routinely, whether a treatment should be given to low-risk patients as well as to high-risk patients, or whether the dose of a drug should be intensified.

One difficulty faced by economic analysts is that the comparisons they would like to make are to some extent limited by the availability of clinical data. A particular concern is the fact that clinical trials of many new medicines make a comparison with placebo rather than another active therapy. This means that, often, economic analyses cannot be based on either a particular clinical trial or an overview of several trials. Rather, they become integrative studies that, of necessity, employ a number of assumptions. Therefore, users of economic analyses need to check on the methods of the studies generating the clinical data for the economic analysis and whether such studies are really comparable. They may be concerned if the clinical data used in an economic evaluation came from studies that enrolled patients of different baseline risk, or measured clinical outcomes in a slightly different way.

Both the articles by Mark et al<sup>2</sup> and Kalish et al<sup>3</sup> examine only the strategies compared in the GUSTO trial. This is reasonable because previous randomized trials had shown that thrombolysis was both effective and cost-effective when compared with no treatment, so the issue of a do-nothing strategy does not

arise. However, the question of which patients should be treated with a particular therapy is likely to be important (we return to this point later).

### **Were the Costs and Outcomes Properly Measured and Valued?**

**Was Clinical Effectiveness Established?**—To be valid, economic evaluations require evidence on the effectiveness of the alternatives being compared. The standards for assessment of effectiveness correspond to those discussed in earlier guides in the series. Although evidence based on experiments, such as that obtained from randomized trials, is considered the best evidence for answering questions of therapy, economic evaluations are more valid if effectiveness data reflect normal clinical practice as closely as possible. Some economic evaluations are now being undertaken concurrently with randomized trials. Others are being based on systematic overviews of a number of trials. For example, Mugford et al<sup>18</sup> used data from a systematic overview of 58 controlled trials to estimate the cost-effectiveness of giving prophylactic antibiotics routinely to reduce the incidence of wound infection after cesarean delivery.

The decision about whether to base an economic evaluation on results of a single trial, an overview of a number of trials, or a broader synthesis (in a modeling study) of trial and other evidence is not straightforward. In principle, all 3 approaches can be used. The considerations that guide the choice of approach in a given situation are as follows.

An evaluation based on prospective economic data collection alongside a single methodologically rigorous trial has high internal validity. However, the results may not be widely generalizable (that is, they may have low external validity) if the setting for the trial was atypical, the protocol highly prescriptive, or compliance higher than one would expect in routine clinical practice. An evaluation based on an overview of a number of trials is likely to be more precise, as the pooled estimate of effectiveness will have a narrower confidence interval (CI), and is likely to be more widely generalizable because of a wider range of patients, practice settings, and ways of administering the intervention in several trials.

Sometimes data from trials require adjustment when used in an economic analysis. In their economic evaluation of misoprostol, a drug for prophylaxis against gastric ulcer in patients receiving long-term nonsteroidal anti-inflammatory drugs (NSAIDs), Hillman and Bloom<sup>19</sup> used clinical data from a trial undertaken by Graham et al.<sup>20</sup> This evalua-

tion compared misoprostol (400 µg and 800 µg daily) with placebo in a double-blind randomized controlled trial of 3 months' duration. An important issue for economic analysis was that ulcers prevented by misoprostol may generate savings in health care expenditure, which could balance the cost of adding the drug. However, it was not possible to use the rates of ulcer observed in the trial for the economic analysis without adjustment. First, lesions were discovered by endoscopy, which was performed monthly. Many of these ulcers would not have come to the notice of the patient or her physician in regular practice. Second, the compliance rate observed in the trial was higher than that typically observed in patients taking NSAIDs. Therefore, Hillman and Bloom adjusted the observed ulcer rates to reflect the fact that 40% of endoscopically determined lesions remain silent. They also adjusted for lower compliance by using the ulcer rates in the evaluable cohort and assuming that only 60% of this efficacy would be achieved in practice.

Sometimes the length of follow-up in the clinical trial may be too short for the purposes of economic evaluation, as this tends to use long-term end points such as survival. The problem of length of follow-up is equally relevant for both costs and benefits. In some cases an increase in length of follow-up in a clinical trial by a number of months may make a lot of sense. For example, although it is common in trials of thrombolytic therapy to record 30-day mortality, most major trials, such as the GUSTO study, incorporate 1-year follow-up.

In other fields, such as lowering cholesterol levels, data on final outcomes such as all-cause mortality may take years to obtain. Here modeling studies have been undertaken, making projections of long-term outcomes from short-term trial data relating to intermediate end points, such as percentage reduction in cholesterol. Therefore, the problem of short-term follow-up is compounded by the use of an intermediate end point. The wisdom of this approach depends on the validity of the hypothesis linking intermediate and final outcomes. In at least 1 case, projections based on short-term evidence turned out to be wrong. Schulman et al<sup>21</sup> concluded that early use of zidovudine therapy in asymptomatic individuals with human immunodeficiency virus infection was cost-effective based on projections of disease progression from a clinical trial with 1-year follow-up. However, a subsequent study with 3-year follow-up showed that the advantages of therapy in the first year were eroded in subsequent years.<sup>22</sup> The authors also called into question the

uncritical use of CD4 cell counts as a surrogate end point for assessment of benefit from long-term antiviral therapy.

Where long-term evidence is lacking, economists are in a quandary, particularly where the treatment concerned is already in use. Do they say nothing at all, or undertake a modeling study that may help the decision maker understand the likely range of cost-effectiveness outcomes? The same problem confronts the user of economic evaluation results. Should a decision be postponed until definitive data are available, or should an interim policy be formulated, pending further results?

Of the 2 thrombolysis studies discussed here, the one by Mark et al<sup>2</sup> was undertaken concurrently with the clinical trial, whereas that by Kalish et al<sup>3</sup> is a modeling study using the GUSTO trial results as its main source of clinical evidence. Therefore, the cost-effectiveness results are likely to be more similar than in a situation, for example, where the modeling study draws on clinical data from a number of different sources.

The main methodological difference between the 2 studies is that the resource consumption (eg, days in hospital, number of outpatient visits) in the study by Mark et al<sup>2</sup> are those actually observed during the trial. By contrast, the estimates in the study by Kalish et al<sup>3</sup> are drawn from other sources, although the probabilities of resource-consuming events (eg, coronary artery bypass surgery) are taken from the GUSTO trial.

Finally, it should be noted that by using observational databases, both articles extrapolated survival data beyond the 1 year observed in the trial. This reaffirms the point that, even when good quality clinical data are available, modeling is often necessary to conduct an economic evaluation.

**Were Costs Measured Accurately?**—While the viewpoint determines the relevant range of costs and outcomes to be included in an economic evaluation, there are many issues relating to their measurement and evaluation. First, it is useful to report the physical quantities of resources consumed or released by the treatments separately from their prices or unit costs. Not only does this allow us to scrutinize the method of assigning monetary values to resources, it also helps us to interpret the results of a study from one setting to another, as prices are known to vary by location.

Second, there are different approaches to valuing costs or cost savings. One approach is to use published charges. However, charges may differ from real costs, depending on the sophistication of accounting systems and the relative

bargaining power of health care institutions and third-party payers.<sup>23</sup> Where there is a systematic deviation between costs and charges, the analyst may adjust the latter by a *cost-to-charge ratio*. However, very little is currently known about how charges differ from costs, so simple adjustments may not suffice. From the third-party payer's perspective, charges will bear some relation to the amounts actually paid, although in some settings payments vary by payer. From a societal perspective we would like the real costs, since these reflect what society is forgoing, in benefits elsewhere, to provide a given treatment.

For example, Cohen et al<sup>24</sup> compared costs and charges for conventional angioplasty, directional coronary atherectomy, intracoronary stenting, and bypass surgery. Previous studies had suggested that total hospital charges for directional coronary atherectomy or intracoronary stenting are significantly higher than those for conventional angioplasty. However, when costs were examined, by adjusting itemized patient accounts by department-specific cost-to-charge ratios, it was found that the in-hospital costs of angioplasty and directional coronary atherectomy were similar. Also, although the cost of coronary stenting was approximately \$2500 higher than that of conventional angioplasty, the magnitude of this difference was smaller than the \$6300 increment previously suggested on the basis of analysis of hospital charges. The implication is that we may be deterred from using coronary atherectomy or stenting because of the high cost, whereas this may be an artifact of hospital accounting systems or bargaining power, rather than a reflection of the real value to society of the resources consumed by those procedures.

Mark et al<sup>2</sup> use costs from the Duke Transition One cost-accounting system, Medicare diagnosis related group (DRG) reimbursement rates, and Medicare physicians' fees in their estimations. Since the costs of the thrombolytic agents are an important component of the analysis, drug costs are calculated in 2 ways: from the *Drug Topics Red Book* average of 1993 wholesale prices,<sup>25</sup> and from the average costs of the drugs in 16 randomly selected GUSTO hospitals. The impact on cost-effectiveness of the different estimation methods is examined. Kalish et al<sup>3</sup> used medication costs and Medicare DRG reimbursement rates for 1 hospital. They took costs of treating serious hemorrhage and the costs of managing coronary artery disease and stroke from the literature.

**Were Data on Costs and Outcomes Appropriately Integrated?**—When making comparisons between alternatives in terms of cost per life year gained or cost per QALY gained, it is important to compute the incremental cost-effectiveness ratio of one therapy over another. This is because the most relevant information for the decision maker relates to the extra benefit that would be gained compared with any extra cost. Of course, if one therapy is dominated by another, having both higher benefits and lower costs, then the incremental comparison is not needed. In this case both articles calculate the incremental cost per life year or QALY gained from the use of t-PA, compared with streptokinase.

One important point to note about incremental analysis is that the incremental cost-effectiveness ratio of a given intervention is critically dependent on the comparison made. The most relevant comparison is current care, which could include doing nothing where this is ethically defensible. In the example discussed here, most would argue that streptokinase is the appropriate comparison and that doing nothing is not really an option. Where there are multiple interventions, each of which could be delivered at different scales or intensities, the ranking of options becomes quite complex.<sup>26</sup>

A final issue in the measurement and valuation of costs and consequences relates to the adjustment for differences in their timing. It is normally assumed that we prefer benefits sooner and prefer to postpone costs because of uncertainty about the future and because resources, if invested, usually yield a positive return. The accepted way of allowing for this in economic evaluations is to discount costs and benefits occurring in the future to present values.<sup>12</sup> The effect of this is to assign a lower weight in the analysis to costs and benefits occurring in the future. An annual discount rate of 5% is common in the published literature, although this choice is not necessarily theoretically or empirically justified. There are also debates about whether health outcomes should be discounted at the same rate as costs.<sup>27,28</sup>

In both studies considered here, the authors discount costs and benefits occurring in the future at a rate of 5% per year. Mark et al<sup>2</sup> also report results for discount rates of 0% and 10%, whereas Kalish et al<sup>3</sup> report results for rates of 1% and 10%.

#### **Was Appropriate Allowance Made for Uncertainties in the Analysis?**

Uncertainty in economic evaluation can arise either from lack of precision in

estimation or from methodological controversy. The conventional way of allowing for uncertainty in economic analyses is to undertake a sensitivity analysis (discussed in an earlier guide<sup>10</sup>) where the estimates for key variables are altered to assess what impact they have on study results.

In addition, conducting economic evaluations concurrently with clinical trials provides the opportunity to apply conventional tests of statistical significance to the resource quantities or costs.<sup>29</sup> Also, where measurements from a clinical trial inform us of the distribution of cost variables, it is possible to set the range of estimates for sensitivity analysis in relation to the statistical properties of the distribution (eg, 2 SDs from the mean). This raises a number of important issues, such as the size of the "economically important difference" when comparing the cost or cost-effectiveness of 2 alternatives, and the appropriateness of, and methods for, statistical tests on cost-effectiveness ratios.

Both articles report extensive sensitivity analyses, many of which relate to different methodological choices (eg, source of cost estimates) rather than to observed variability in the data. Mark et al<sup>2</sup> use the 95% CI for the increase in 1-year survival to explore the possible range in cost per life year saved. They also perform statistical tests for differences in cost but not for differences in cost-effectiveness ratios.

Because economic evaluation methods are in their infancy compared with those for randomized trials, investigators still debate many issues.<sup>30</sup> We've already mentioned one major issue: the appropriateness of alternative methods for valuing outcomes. Other issues relate to the appropriateness of considering some types of outcome (such as the costs of lost production if individuals are away from work because of illness) or the choice of discount rate. Some methodological uncertainties can be taken into account by sensitivity analysis (eg, if the choice of discount rate does not affect the choice of strategy in a given situation, then this particular controversy, though important, may not be critical to the decision).

The other way in which methodological uncertainties can be accommodated is in the reporting and discussion of results. Economists are often criticized for failing to reach a firm conclusion, but if the result is truly equivocal, that information will be important for the decision maker. It is important to remember that economic evaluation is no more than an aid to decision making, since there are often many difficult value judgments in reaching a decision.

## Are Estimates of Costs and Outcomes Related to the Baseline Risk in the Treatment Population?

Finally, we must recognize that in clinical practice the costs and outcomes of treatment are likely to be related to the baseline risk in the treatment population. For example, the cost-effectiveness of drug therapy for elevated cholesterol level, compared with no treatment, will depend on age, sex, pre-treatment cholesterol level, and other risk factors; the greater the patients'

risk, the lower the cost per unit of benefit.<sup>31</sup>

Division of patients into risk categories is common in clinical practice. In a study of the cost-effectiveness of  $\beta$ -blockers after AMI, Goldman et al<sup>32</sup> found that the cost per life year gained was \$2400 for those patients at high risk, compared with \$13 000 for those at low risk. The differences in the cost-effectiveness ratios were driven primarily by the patient's ability to benefit from therapy, rather than treatment cost.

Both articles investigate the impact of patient age on cost-effectiveness, as older patients have a higher mortality risk and fewer years of life left to live. In addition, Mark et al<sup>2</sup> investigate the impact of infarction location on the cost-effectiveness estimates.

In this article we have outlined some of the threats to validity in economic evaluations. In the next article on economic analysis, we will show you how to determine the results and how to use them in your practice.

### References

1. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329:673-682.
2. Mark DB, Hlatky MA, Califf RM, et al. Cost-effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med.* 1995;332:1418-1424.
3. Kalish SC, Gurwitz JH, Krumholz HM, Avorn J. Cost-effectiveness of model of thrombolytic therapy for acute myocardial infarction. *J Gen Intern Med.* 1995;10:321-330.
4. Goel V, Naylor CD. Potential cost-effectiveness of intravenous tissue plasminogen activator versus streptokinase for acute myocardial infarction. *Can J Cardiol.* 1992;8:31-38.
5. Eisenberg JM. Clinical economics: a guide to the economic analysis of clinical practices. *JAMA.* 1989;262:2879-2886.
6. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med.* 1990;113:147-154.
7. Elixhauser A, Luce BR, Taylor WR, Reblando J. Health care CBA/CEA: an update on the growth and composition of the literature. *Med Care.* 1993;31(suppl):JS1-JS11, JS18-JS149.
8. Backhouse ME, Backhouse RJ, Edey SA. Economic evaluation bibliography. *Health Econ.* 1992;1(suppl):1-236.
9. Russell LB, Gold MR, Seigel JE, Daniels N, Weinstein MC, for the Panel on Cost-Effectiveness in Health and Medicine. The role of cost-effectiveness analysis in health and medicine. *JAMA.* 1996;276:1172-1177.
10. Richardson WS, Detsky AS, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature. VII: how to use a clinical decision analysis. A: are the results of the study valid? *JAMA.* 1995;273:1292-1295.
11. Wilson MC, Hayward RSA, Tunis SR, Bass EB, Guyatt G, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, VIII: how to use clinical practice guidelines. B: what are the recommendations and will they help you in caring for your patient? *JAMA.* 1995;274:1630-1632.
12. Drummond MF, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes.* Oxford, England: Oxford University Press; 1987.
13. Luce BR, Elixhauser A. *Standards for Socio-economic Evaluation of Health Care Products and Services.* Berlin, Germany: Springer Verlag; 1990.
14. Kamlet MS. *A Framework for Cost-Utility Analysis of Government Health Care Programs: Report to the Office of Disease Prevention and Health Promotion.* Washington, DC: Public Health Service, US Dept of Health and Human Services in cooperation with the Foundation of Health Services Research; 1990.
15. Topol EJ, Burek K, O'Neill WW, et al. A randomized controlled trial of hospital discharge three days after myocardial infarction in the era of reperfusion. *N Engl J Med.* 1988;318:1083-1088.
16. Weisbrod BA, Test MA, Stein LI. Alternative to mental hospital treatment, II: economic benefit-cost analysis. *Arch Gen Psychiatry.* 1980;37:400-405.
17. Mehrez A, Gafni A. Quality-adjusted life years, utility theory, and healthy-years equivalents. *Med Decis Making.* 1989;9:142-149.
18. Mugford M, Kingford J, Chalmers I. Reducing the incidence of infection after caesarian section: implications of prophylaxis with antibiotics for hospital resources. *BMJ.* 1989;299:1003-1006.
19. Hillman AL, Bloom BS. Economic effects of prophylactic use of misoprostol to prevent gastric ulcer in patients taking nonsteroidal anti-inflammatory drugs. *Arch Intern Med.* 1989;149:2061-2065.
20. Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with the synthetic prostaglandin misoprostol: a multicentre, double-blind, placebo-controlled trial. *Lancet.* 1988;2:1277-1280.
21. Schulman KA, Lynn LA, Glick HA, Eisenberg JM. Cost-effectiveness of low dose zidovudine therapy for asymptomatic patients with human immunodeficiency virus (HIV) infection. *Ann Intern Med.* 1991;114:798-802.
22. Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet.* 1994;343:871-881.
23. Finkler SA. The distinction between cost and charges. *Ann Intern Med.* 1982;96:102-109.
24. Cohen DJ, Breall JA, Kalon KLH, et al. Economics of elective coronary revascularization: comparison of costs and charges for conventional angioplasty, directional atherectomy, stenting and bypass surgery. *J Am Coll Cardiol.* 1993;22:1052-1059.
25. Sifton DW. *1993 Red Book: Pharmacy's Fundamental Reference.* Montvale, NJ: Medical Economics Data; 1993.
26. Karlsson G, Johannesson M. The decision rules of cost-effectiveness analysis. *Pharmaco Econ.* 1996;9:113-120.
27. Parsonage M, Neuberger H. Discounting and health benefits. *Health Econ.* 1992;1:71-76.
28. Cairns J. Discounting and health benefits: another perspective. *Health Econ.* 1992;1:76-79.
29. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic economic appraisals. *Med Care.* 1994;32:150-163.
30. Udvarhelyi IS, Colditz GA, Rai A, Epstein MA. Cost-effectiveness and cost-benefit analysis in the medical literature: are the methods being used correctly? *Ann Intern Med.* 1992;116:233-244.
31. Epstein MA. Cost-effectiveness of antihyperlipidemic therapy in the prevention of coronary heart disease: the case of cholestyramine. *JAMA.* 1987;258:2381-2387.
32. Goldman L, Sia STB, Cook EF, Rutherford JD, Weinstein MC. Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. *N Engl J Med.* 1988;319:152-157.