

The Medical Literature

Users' Guides to the Medical Literature

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

B. What Are the Results and Will They Help Me in Caring for My Patients?

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CLINICAL SCENARIO

You recall from the first of our 2 articles¹ concerning economic analysis of clinical practice that your chief of medicine has asked you to review relevant economic evidence from the literature and report to the hospital's pharmacy and therapeutics committee, which is trying to decide on formulary guidelines for the use of streptokinase and tissue-type plasminogen activator (t-PA) in the treatment of acute myocardial infarction (AMI). Your literature search identified 2 recent key cost-effectiveness studies: an analysis of economic data collected prospectively as part of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial² of streptokinase vs t-PA by Mark et al,³ and a decision-analytic model by Kalish et al.⁴ In the first article of this

2-part series we showed you how to evaluate the validity of the different economic appraisal study methods. In this article, we will show you how to interpret the results of an economic evaluation and how to examine the applicability of such data to your local practice setting and patients. We will do so by applying the Users' Guides to economic analysis of clinical practice in Table 1 to both studies.

WHAT ARE THE RESULTS?

What Were the Incremental Costs and Outcomes of Each Strategy?

Let us start with the incremental costs. Look in the text and tables for the listings of all the costs considered for each treatment option and remember that costs are the product of the quantity of a resource used and its unit price. These should include the costs incurred to produce the treatment such as the physician's time, nurse's time, materials, and the like—what we might term the *up-front costs*, as well as the *downstream costs*, which refer to resources consumed in the future and are associated with clinical events that are attributable to the therapy. The study by Mark et al³ quantifies resources used by treatment group in 3 periods of time over 1 year: initial hospitalization, discharge to 6 months, and 6 months to 1 year. Both treatment groups were very similar in their use of hospital resources over the year; both experienced a mean length of stay of 8 days, of which 3.5 days were in the intensive care unit. Both groups had the same rate of coronary artery bypass graft

(CABG) surgery (13%) and percutaneous transluminal coronary angioplasty (PTCA) (31%) on initial hospitalization. As summarized in Table 2, the 1-year health care costs, excluding the thrombolytic agent, were \$24 990 per patient treated with t-PA, and \$24 575 per patient treated with streptokinase. As is clear from Table 2, the main cost difference between the 2 groups is the cost of the thrombolytic drugs themselves: \$2750 for t-PA and \$320 for streptokinase. The overall difference in cost between patients treated with t-PA and patients treated with streptokinase is therefore our incremental cost at \$2845 over the first year. This is discounted at 5% per year for a final figure of \$2760. The authors argue that there is no cost difference between the 2 groups after 1 year. These data for incremental costs for t-PA are very similar to those estimated by Kalish et al,⁴ who found a difference of \$2535 in the use of t-PA to treat AMI in preference to streptokinase.

The measure of effectiveness chosen in the study by Mark et al³ is the gain in life expectancy associated with t-PA. The available follow-up experience was to 1 year, with 89.9% surviving in the streptokinase group vs 91.1% in the t-PA group ($P < .001$). To translate these observations into life expectancy gains, the authors project survival curves for another 30 years or more using first a 14-year AMI survivorship database from

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The original list of members (with affiliations) appears in the first article of this series (JAMA. 1993;270:2093-2095). A list of new members appears in the 10th article of the series (JAMA. 1996;275:1435-1439). The following members contributed to this article: Gordon H. Guyatt, MD, MSc (chair); Roman Jaeschke, MD, MSc; Deborah J. Cook, MD, MSc; Hertzell Gerstein, MD, MSc; Stephen Walter, PhD; John Williams, Jr, MD, MHS; and C. David Naylor, MD, MSc, DPhil.

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

Are the results valid?
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?
What were the results?
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?
Will the results help in caring for my patients?
Are the treatment benefits worth the harms and costs?
Could my patients expect similar health outcomes?
Could I expect similar costs?

Duke University and then an assumption that remaining survivorship will follow a statistical distribution known as Gompertz. Having projected 2 survival curves, the authors calculate the area under each curve, which represents the expected value of survival time or life expectancy. For patients receiving t-PA, life expectancy was 15.41 years and 15.27 years for patients receiving streptokinase. As summarized in Table 2, the difference in life expectancy is 0.14 year per patient; or phrased another way, for every 100 patients treated with t-PA in preference to streptokinase, we would expect to gain 14 years of life.

In other situations, quantifying incremental effectiveness may be more difficult. Not all treatments change survival, and those that do not may affect different dimensions of health in many ways. For example, drug treatment of asymptomatic hypertension may result in short-term health reductions from drug adverse effects, in exchange for long-term expected health improvements, such as reduced risk of strokes. Note that in our t-PA example the outcome is not unambiguously restricted to survival benefit because there is a small but statistically significant increased risk of nonfatal hemorrhagic stroke associated with t-PA.² The existence of trade-offs between different aspects of health, or between length of life vs quality of life, means that to arrive at a summary measure of net effectiveness, we must implicitly or explicitly weight the "desirability" of different outcomes relative to each other.

There is a large and growing literature on quantitative approaches for combining multiple health outcomes into a single metric using patient preferences.⁵ Foremost among current practice is the construction of quality-adjusted life-years (QALYs) as a measure that captures the impact of therapies in

Table 2.—Costs, Effects, and Cost-effectiveness Summary for Tissue-type Plasminogen Activator (t-PA) vs Streptokinase From Mark et al³

	Treatment Group		Difference (t-PA—Streptokinase)	Difference Discounted at 5% per Year
	t-PA	Streptokinase		
Costs, in US\$				
Health care costs for 1 y (excluding thrombolytic)*	24 990	24 575	415	...
Thrombolytic drug cost	2750	320	2430	...
Total 1-year cost	27 740	24 895	2845	2709.6 (=ΔC)†
Effects				
Life expectancy, y	15.41	15.27	0.14	0.029 (=ΔE)†
Incremental cost-effectiveness of t-PA	ΔC/ΔE=\$32 678 per life year gained

*Treatment groups assumed to have no cost differences beyond 1 year.
 †These discounted differences were not reported in the article, but have been imputed. ΔC indicates incremental cost, and ΔE, incremental effect. Ratio differs due to rounding error.

the 2 broad domains of survival and quality of life. (QALYs were described in more detail earlier in this series.^{6,7}) For economic appraisal, the added attraction of the QALY is that it provides decision makers with outcomes data that can be compared across diseases and treatments (eg, thrombolytic therapy for AMI vs nonsteroidal anti-inflammatory drugs [NSAIDs] for arthritis) as well as within a given therapy area. However, the QALY approach is not without criticism and some authors have proposed an alternative preference-weighted outcome measure known as *healthy years equivalents*.⁸

Both cost-effectiveness studies attempt to apply utility weights to estimate QALYs; the study by Mark et al³ calculates QALYs as a secondary analysis using preference weights measured in the trial, and the study by Kalish et al⁴ calculates QALYs as the primary outcome using values from the literature. Both studies conclude that, under plausible preference weights for nonfatal outcomes, the overall cost-effectiveness estimates are robust.

In summary, both studies use the efficacy data from the GUSTO trial as their starting point to conclude that t-PA treatment is more costly than streptokinase treatment, but that it provides an increase in survival (quality-adjusted or otherwise). The next calculation in both studies is to determine the incremental cost-effectiveness ratio for t-PA. This is illustrated using the data from the study by Mark et al³ in Table 2. After discounting future costs and effects at 5% per year to reflect time preference (for the rationale, see our first article¹), the difference (t-PA minus streptokinase) in cost per patient over the year (and by extension into the future because they assume no cost differences beyond 1 year) is \$2709.60, which is divided by the difference in life expectancy per patient (0.029) to yield a ratio of \$32 678 per year of life gained. A simple interpretation of this ratio is

that it is the "price" at which we are buying additional years of life by using t-PA in preference to streptokinase; the lower this price, the more attractive is the use of t-PA. The study by Kalish et al⁴ reaches a similar incremental cost-effectiveness ratio (with their adjusted denominator of QALYs and using the 30-day risk reduction GUSTO data) of \$30 300 per QALY. These are the main results of the studies; we will discuss their interpretation later in this article.

Do Incremental Costs and Outcomes Differ Between Subgroups?

In an editorial accompanying the GUSTO economic analysis, Lee⁹ stresses that "cost-effectiveness should focus on strategies, not drugs. The cost-effectiveness of t-PA depends on how the drug is administered and to whom it is given." The first point relates mainly to the fact that the GUSTO trial had a protocol for accelerated administration of t-PA; slower regimens of administration of the same drug had previously shown no clinical advantage.¹⁰ The second point is that because some patients (eg, the elderly) have a greater prior risk of mortality, the t-PA treatment effect will likely yield a higher absolute risk reduction in mortality.²

This second point has important implications for cost-effectiveness as can be seen in Table 3, which presents cost per life-year estimates among 8 subgroups on the basis of infarction site and patient age. Because the baseline risk of mortality in AMI varies by age and infarct site, the mortality benefit from treatment with t-PA also varies, and it is clear from Table 3 that t-PA is more cost-effective in older patients with anterior infarcts. To take the extreme cases, the cost per life-year gained in a person aged 40 years or younger with an inferior infarct is \$203 071, compared with a person aged 75 years or older with an anterior infarct at only \$13 410 per life-year gained.

In reviewing these studies you decide that the variation in yield per dollar ex-

Table 3.—Incremental Cost-effectiveness of Tissue-type Plasminogen Activator vs Streptokinase in Patient Subgroups From the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)*

	Cost (in \$) Per Life-Year Gained by Age Subgroup, y			
	≤40	41-60	61-75	>75
Inferior myocardial infarction	203 071	74 816	27 873	16 246
Anterior myocardial infarction	123 609	49 877	20 601	13 410

*Data from the GUSTO Investigators.² Table adapted from Mark et al.³

pending may have some important implications for your pharmacy and therapeutics committee decision, because they wish to use t-PA only in selected patients.

How Much Does Allowance for Uncertainty Change the Results?

Both t-PA cost-effectiveness studies explore uncertainty using sensitivity analysis, examining the impact on incremental cost-effectiveness of alternative values for uncertain variables. (One-way and multi-way sensitivity analysis was described in detail in the Users' Guides on decision analysis.^{6,7})

A useful starting point for a sensitivity analysis is to examine the impact of variation in the effectiveness measure on the cost-effectiveness estimates. Where effectiveness is based on clinical trial data, the analyst does not have to make an additional judgment about the plausible range over which to vary the data, but can use a conventional measure of precision around a treatment effect such as the 95% confidence interval (CI). Using data from the study by Mark et al,³ we know the t-PA treatment effect was a 1.1% increase in 1-year survivorship with a 95% CI of 0.46% to 1.74%. Applying this variation to the denominator of the incremental cost-effectiveness ratio, Mark et al³ report a range of \$71 039 per life-year gained to \$18 781 around their baseline estimate of \$32 678, with smaller benefit yielding a higher ratio. Both studies conclude that their estimates of cost-effectiveness are most sensitive to uncertainty in the magnitude of mortality benefit. It should be noted, however, that this form of analysis only partially captures the uncertainty in the cost-effectiveness ratio because it assumes the numerator (cost) does not vary. Investigators are currently developing more formal procedures for estimating CIs for cost-effectiveness ratios that permit the numerator and denominator to vary.¹¹

WILL THE RESULTS HELP IN CARING FOR MY PATIENTS?

Having established the results of the 2 economic studies and the precision of the estimates, we now turn to 2 important issues of interpretation. The first issue is how incremental cost-effectiveness ratios can be interpreted to help in

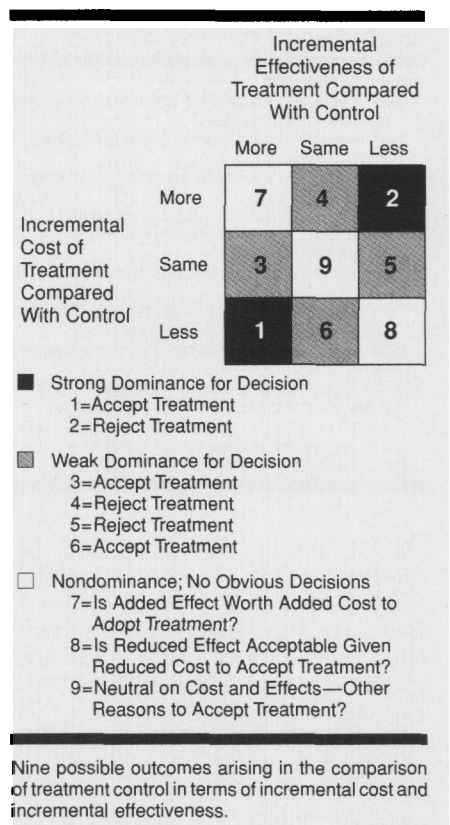
decision making, and the second issue is the extent to which the cost and/or effects from the study can be applied to your practice setting.

Are the Treatment Benefits Worth the Harms and Costs?

In the Figure we present a simple framework for categorizing economic study results when data on incremental costs and effects have been determined. This 3×3 matrix has 9 cells to categorize studies depending on whether the new treatment is more, the same, or less costly than the control and whether it has more, the same, or less effectiveness.

In category 1, the new treatment is both less costly and more effective than the control, so the new treatment is said to be strongly *dominant*. For example, treatment to eradicate *Helicobacter pylori* for duodenal ulcer is strongly dominant over acid suppression with an H₂-receptor antagonist because it is less costly and results in fewer recurrences of ulcer over a 1-year period.¹² Category 2 represents strong dominance to reject a new therapy where the costs are higher and the effectiveness is worse than the control. Then follow 4 cases of so-called weak dominance where one of either costs or effectiveness is equivalent between the 2 therapies: category 3 indicating weak dominance to accept the treatment (equivalent cost but better effectiveness) and category 4 indicating weak dominance to reject the treatment (greater cost with equivalent effectiveness). By analogy, categories 5 and 6 indicate weak dominance to reject and accept, respectively.

All the shaded cells in the Figure indicate comparative cost and effectiveness combinations that provide evidence of strong or weak dominance. To inform decision making, no further analysis, such as calculation of cost-effectiveness ratios, is required for these shaded cells. However, further analysis is needed if results fall into the nondominance unshaded cells of 7, 8, or 9. First, it may arise that the treatment is associated with no statistically significant or clinically important difference in either effectiveness or costs, although it should be noted that the process of implementation and change of programs will generate costs not captured in the analysis.



Nine possible outcomes arising in the comparison of treatment control in terms of incremental cost and incremental effectiveness.

The most common nondominance circumstance is category 7, where the new therapy offers additional effectiveness, but at an increased cost (or its mirror image in category 8). Both t-PA studies in our example fall into category 7. In this circumstance, as undertaken by both our t-PA studies, it is useful to calculate the incremental cost-effectiveness ratios of the new therapy as we discussed above and illustrated in Table 2.

Having estimated the incremental cost-effectiveness of t-PA over streptokinase, and assuming for the moment that these data apply to your practice setting, how do you decide whether approximately \$33 000 is an acceptable price to pay for saving 1 additional year of life? The first important point to note is that this question involves a value judgment and cannot be resolved by the analyst using only the study data. As noted in the conclusion of the GUSTO economic analysis, the study data can inform the decision but cannot make the choice. Some appeal must be made to external criteria to ascertain whether a jurisdiction or society is willing to pay this price for this improvement in outcome.

There are a number of approaches to the interpretation of incremental cost-effectiveness ratios. In an ideal world of complete information we would have data indicating the health outcomes we would be forgoing from other interventions and programs, within and outside

health care, not funded as a consequence of using t-PA. This is what economists refer to as *opportunity cost*. However, data to accomplish this task are very limited and investigators have promulgated a variety of second-best interpretive strategies. One approach assumes that previous decisions to adopt new medical therapies of known cost-effectiveness reveal an underlying set of values with which to judge the acceptability of the current treatment candidate. Our 2 t-PA cost-effectiveness studies both use this interpretive strategy to assess their \$30 000 per life-year estimates: both cite the cost-effectiveness of 2 to 3 other interventions, some non-cardiac, that are currently funded and both conclude that an acceptable cost-effectiveness threshold would be \$50 000 per QALY gained (for Kalish et al⁴) and per life-year gained (for Mark et al³).

Investigators have debated the validity of such interpretive strategies for incremental cost-effectiveness ratios at both theoretical^{13,14} and practical levels.¹⁵ For example, Johannesson and Weinstein¹³ maintain that prioritizing resource allocations among health care programs based on rank orderings of interventions by incremental cost-effectiveness does lead to an efficient allocation of resources, in the sense that we are getting the greatest health yield for the resources expended. However, Birch and Gafni¹⁴ contend that this is only the case where 2 assumptions hold true; programs exhibit *constant returns to scale* and are perfectly *divisible*. What do these 2 terms mean? *Constant returns to scale* implies a linear relationship between costs and outcomes at different levels of production; in many cases this may not hold true because we observe economies of scale, an example being the regionalization of cardiac surgery in 1 center where high volume can produce lower cost per case and often better clinical outcomes. *Divisibility of programs* implies that we can reallocate \$1 or \$1000 to t-PA and purchase benefits at the same rate implied by the cost-effectiveness ratio; this divisibility does not hold because to treat 1 additional patient with t-PA would require a block of resources equal, at least, to the cost of t-PA. While this methodologic debate continues, Drummond et al¹⁵ caution readers about the practical problems of comparisons between cost-effectiveness studies that may have used very different methods, data, and assumptions.

In summary, you should exercise caution when drawing conclusions from incremental cost-effectiveness ratios. The ultimate criterion is one of local opportunity cost: what are the health benefits you will no longer realize if resources are expended on t-PA? The practical

difficulty of applying this criterion is that many existing programs or services currently provided may not have been evaluated and so the opportunity cost of reducing or removing them is unknown or speculative.

Could My Patients Expect Similar Health Outcomes?

After understanding the results, you should now turn to whether they will apply to your own practice setting. There are 2 levels of applicability for economic appraisal to the local setting. The first is the extent to which the evidence from the clinical trial(s) that forms the basis for the estimated treatment effect can be applied to routine clinical practice in any jurisdiction. A distinction is sometimes made between the efficacy of a treatment—as observed in a highly selected and compliant clinical trial population—and its effectiveness in the real world. For economic evidence to be relevant to policy decisions we would prefer evidence to be more related to effectiveness than efficacy. The second aspect is the extent to which the observed effect and cost data are transferable between jurisdictions. Threats to the transferability of cost-effectiveness data include variation in clinical practice patterns and variation in the prices of health care resources.

The applicability of clinical data to populations other than those studied was previously discussed in our Users' Guide on therapy or prevention.¹⁶ To assess whether patients in your setting can expect the same health outcomes, you must examine 2 factors: (1) Are the patients in the study similar to my patients? (2) Is the clinical management of the study patients similar to my local practice? If your patients meet the inclusion and exclusion criteria of the primary article(s) for effectiveness used in the economic evaluation, then there is little difficulty in passing judgment that the patients are indeed similar. In many circumstances your patients may not be a perfect replicate of the study population, and then you should proceed by considering whether there are reasons to suppose your patients will respond differently to treatment than those included in the study. If the analysis is based on patients different from yours, check the subgroup and sensitivity analyses to see if relevant clinical variables were examined to permit extrapolation to your patients. Note that both of our economic studies used effectiveness data from the GUSTO trial,² which was a large, simple trial where the inclusion and exclusion criteria were sufficiently broad and likely to reflect the mix of patients presenting with AMI in many local settings.

Next, determine if the intervention is, or would be, used in the same way in your community. Local deviation from the observed patient management in the trial can have implications for generalizing both costs and outcomes from the study to the local setting. With respect to outcomes the key question is whether practice differs with respect to factors that will influence the magnitude of the treatment effect. First, let us consider whether these data apply to nonstudy hospitals in the United States. Kalish et al⁴ doubt whether the efficacy data from the GUSTO trial are good predictors of effectiveness in routine practice:

It has been questioned whether the results achieved in the GUSTO trial are possible in actual practice, largely due to the small time delay between symptom onset and treatment in this trial.^{11,17} The benefit of tPA in the GUSTO trial was seen primarily among patients treated within four hours of symptom onset,² and the majority of patients who have AMI in the United States are not treated within four hours.¹⁸

Another issue is whether the GUSTO efficacy data are applicable to centers outside the United States. The GUSTO trial enrolled patients from 15 different countries; the majority of these patients (56%) were recruited from the United States. Patients from the United States were managed differently from non-US patients in a number of ways, including greater use of invasive revascularization such as PTCA and CABG, and greater use of nonprotocol medications such as antiarrhythmics and calcium antagonists.¹⁹ Statistical analysis by logistic regression reveals that although mortality reduction with accelerated t-PA vs streptokinase was greater in the United States (1.2% absolute decrease vs 0.7% elsewhere), the test for treatment-by-country interaction against streptokinase was not significant ($P=.30$). In other words, if the truth were that there was no difference between the United States and other countries, differences equal to or greater than 1.2% vs 0.7% would be found in 30% of similar trials. Thus, while the results do not exclude a difference in effect between countries, neither do they provide substantial support for this hypothesis.

Could I Expect Similar Costs?

In considering the transferability of cost (and cost-effectiveness) estimates between jurisdictions, it is useful to remember that the cost of a treatment is the summation of the product of physical resources consumed (eg, drugs, tests) and their unit prices. Cost data may not transfer well between jurisdictions for 2 reasons: (1) clinical practice patterns vary in such a way that resource consumption

associated with the treatment differs from that reported in the study and (2) local prices for resources differ from those used in the study. To address these points a good economic evaluation should report resource use and prices separately so that a reader can ascertain whether practice patterns and prices apply to their jurisdiction. The economic analysis by Mark et al³ gives detailed reporting of resources and prices so the reader can judge whether, for example, the 73% rate of cardiac catheterization, 31% rate of PTCA, and 13% rate of CABG are applicable to their institution.

As previously noted, the GUSTO economic analysis is undertaken only on a sample of the US patients from the multinational trial, and the intensity of resource use was lower in other countries. Such resource use differences reflect a number of factors including availability of resources and financial incentives to health care providers. For example, the length of hospital stay was significantly lower in US hospitals than non-US hospitals (8 vs 10 days; $P < .001$) despite a greater incidence of complications among US patients. This difference likely reflects downward pressure exerted on length of stay in the United States by the prospective payment system to hospitals based on diagnosis related groups.

Variation in the prices of health care resources can threaten the validity of cross-jurisdictional inferences about cost-effectiveness. The problem is not due to variation in overall price levels between countries, but variation in the price of one health care input relative to another

(ie, relative prices). For example, in a cost-effectiveness study of misoprostol as prophylaxis against gastrointestinal events in persons taking NSAIDs for arthritis, Drummond et al²⁰ found that among 4 countries compared, the price of misoprostol was highest in the United States but, surprisingly, the cost-effectiveness analysis was most favorable in the United States, indicating that prophylaxis actually reduced costs. This result is explained largely by different prices for health care resources because the use of misoprostol reduced the risk of surgery, the relative price of which was highest in the United States. The results of the GUSTO economic analysis³ are clearly dependent on the relative prices of t-PA and streptokinase. Furthermore, we know that these relative drug prices vary between countries. For example, if the drug costs were those typical in Europe (approximately \$1000 for 100 mg of t-PA and \$200 for 1.5 million units of streptokinase), the cost-effectiveness ratio would be \$13 943 per year of life saved.

Finally, it should be recognized that countries may differ with respect to the value they place on health benefits vs other commodities. There is no reason why \$50 000 per life-year as an acceptable cost-effectiveness threshold for the United States is applicable to, for example, a less-industrialized country where the opportunity cost of such resources will be much higher. Countries vary in their willingness to pay for health and health care as evidenced by the varying proportions of gross national product they devote to the latter.

RESOLUTION OF THE SCENARIO

Returning to our scenario and referring to the framework in the Figure, both t-PA cost-effectiveness studies indicate that t-PA is not dominant over streptokinase but falls into category 7, implying that a trade-off between increased effectiveness at increased cost needs to be resolved. Since the effectiveness, resource use, and price data are applicable to your hospital, you inform the committee that the analyses you have reviewed can help inform their decision, but they must make the choice and decide what cost-effectiveness threshold is acceptable. You help frame this choice as one of local opportunity cost; by diverting resources to t-PA, what health benefits will be forgone on other treatments or programs no longer being funded? The committee decides that universal use of t-PA in all AMI cases will be very costly and divert resources from other health-producing programs in the hospital (although the benefits of these programs have not been as clearly documented as the new program!). They decide that t-PA should be used selectively based on the cost-effectiveness evidence in Table 3 and adopting the cutpoint of \$50 000 per life-year suggested by Mark et al.³ The committee decides that the preferred clinical strategy in their hospital is streptokinase in patients younger than 60 years with an inferior infarct and patients 40 years or younger with an anterior infarct; all other patients would receive t-PA.

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