

Application of Cost-Effectiveness Analysis to Multiple Products: A Practical Guide

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The appropriate interpretation of cost-effectiveness results and its use in treatment decision making have been debated vigorously. In this report we have summarized the decision rules described in the health economics literature to determine which intervention should be chosen from among multiple treatment options for a given disease, using a graphic framework. The implications of different means of expressing budget constraints on treatment choice are examined.

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Cost-effectiveness ratios are commonly used to compare alternate public programs and health interventions.¹ However, the appropriate use of cost-effectiveness analysis to determine which intervention should be chosen from a set of alternatives remains a subject of considerable debate.²⁻⁸ Hence, decision makers are often confused by how to interpret results of cost effectiveness analysis, and how to use them in making decisions. For instance, what does the statement "Drug A is more cost effective than drug B" imply? Should the decision maker always choose the option with the lowest cost-effectiveness ratio? How does the budget constraint affect the decision-making process?

One decision rule that has been proposed for determining whether an intervention is "cost effective" is to determine whether the incremental cost-effectiveness ratio (ICER) falls below a threshold acceptance value,⁹ such as \$50,000 per quality-adjusted life-year (QALY) gained. This decision rule is appropriate when comparing 2 interventions for a given condition. However, when multiple interventions are available to treat a given condition, the appropriate method of evaluation is not well understood outside of the health economics community, even though the decision rule for such cases has been described in several publications.^{3,4} Note that even if only 2 interventions are being evaluated, the simple decision rule given above cannot be applied if

providing no treatment is an option, because in effect there are 3 interventions (including no treatment) being evaluated.

Often, multiple products are compared based on cost per event avoided (or cost per QALY gained) in comparison with a common baseline (such as no treatment), and it is concluded that the product with the lowest cost per event avoided is the most "cost-effective" product. The cost per event avoided compared with the common baseline is often referred to as the average cost-effectiveness ratio. We describe below why this decision rule of choosing the intervention with the lowest average cost-effectiveness ratio is incorrect and inconsistent with the objective of maximizing societal welfare.

Our main objective was to review and summarize for decision makers without significant health economic expertise the information that has been presented in the health economics literature on how to interpret and use cost-effectiveness results when multiple products are available to treat a given condition. We used a simple graphic framework, similar to the one used by Drummond, Stoddart, and Torrance,¹⁰ to present the decision rules. We believe that such a framework will allow decision makers to gain a more intuitive understanding of the decision rules and the implication of different budget constraint assumptions on allocation decisions.

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A Hypothetical Debate

Assume a baseline intervention and 6 other interventions (A–F) are available to treat a given condition. The effectiveness and cost of each intervention is shown in the **Table**. Consider the following hypothetical debate between 2 decision makers, D1 and D2.

- D1: Intervention B has the lowest average cost-effectiveness ratio. Clearly, from a health economic perspective, B is the product of choice.
- D2: I disagree. Intervention F delivers 0.075 QALYs more than B. That is 7.5 QALYs gained for every 100 patients treated. From a patient perspective, I would advocate the use of F, the most effective agent.
- D1: Let me illustrate why, from a societal perspective, B should be the product of choice. Suppose I have \$100,000 in my budget to treat this condition. Using this budget, I can treat 100 patients with B, providing a QALY gain of 10 to my patient population. If I use F, I can treat only 25 patients, which provides a QALY gain of only 4.375. So, at a societal level, using intervention B results in more QALYs than using intervention F.
- D2: Rather than starting with a fixed budget, let us start with the assumption that you treat about 100 patients every year. Then my recommendation would be to increase your budget for this condition to \$400,000 and treat your

patients with F. This would result in a gain of 17.5 QALYs rather than 10 QALYs. You might find that intervention F is a better use of that extra \$300,000 than other current expenditures for that money.

The above debate and the one described by Eddy¹¹ illustrate some of the challenges that decision makers face in appropriately interpreting and utilizing cost-effectiveness analysis in decision making. D1 advocates using the average cost-effectiveness ratio and argues for adopting the therapy with the lowest cost-effectiveness ratio compared with baseline, whereas D2 argues for adopting the most effective therapy. Even though both D1 and D2 make good arguments to support their respective positions, neither follows the appropriate decision rule for determining which intervention to choose from among multiple alternatives.

What Decision Criterion Should Be Used to Choose Interventions?

To determine which intervention should be chosen from among multiple alternatives, we need to first define the criterion by which this decision will be made. If society had access to unlimited resources, the decision maker would choose the intervention with the greatest effectiveness, regardless of cost. However, all health systems have limited budgets and their decision makers are forced to trade off the costs and benefits of health interven-

tions. In generating decision rules for choosing an intervention, we will consider 2 types of budget constraints—the *implicit budget constraint* and the *explicit budget constraint*.

In the implicit budget constraint, the fact that resources are limited is expressed by means of a maximum amount (*V*) that the health system is willing to pay for a unit gain in effectiveness (say QALYs). The amount *V* reflects the fact that every dollar that can be used to purchase a new drug has potential alternate uses.

Table. Examples of Effectiveness and Cost Associated with 6 Hypothetical Interventions (A–F) to Treat a Given Condition

Drug/ Intervention	Cost per Person	QALYs per Person	Average Cost-Effectiveness Ratio (Compared With Baseline)	Incremental Cost-Effectiveness Ratio (After Eliminating Dominated Interventions)
Baseline	\$0	0.000		
A	\$2000	0.075	\$26,667	—
B	\$1000	0.100	\$10,000	\$10,000
C	\$2000	0.125	\$16,000	—
D	\$2250	0.150	\$15,000	\$25,000
E	\$3000	0.160	\$18,750	—
F	\$4000	0.175	\$22,857	\$70,000

QALYs = quality-adjusted life-years.

Thus, V reflects the “opportunity cost,” or what the decision maker has to give up in diverting this dollar to purchase the new drug. Under this budget constraint, any intervention that increases the QALY of the population, compared with the next best intervention, at a cost of less than V per QALY would be adopted, whereas an intervention that does so at a cost of more than V per QALY would not be adopted. The task of the decision maker is to choose the most effective intervention, as long as the incremental cost per QALY gain of this intervention compared with the next best alternative is less than V . One consequence of using the implicit budget constraint in an economic model is that the allocation decision can lead to an increase in expenditure for the given disease population as new and more expensive drugs become available.¹²

In contrast to the implicit budget constraint, the explicit budget constraint allocates a specific fixed dollar amount for treating the given disease in the chosen patient population. In this case, the objective of the decision maker is to choose the interventions that maximize health benefits without exceeding the given healthcare budget. The disadvantage of the explicit budget constraint methodology is that it will not inform the policy maker when to increase or decrease the fixed budget to maintain parity with alternate uses of that money. Under the explicit budget constraint scenario the decision makers may risk sacrificing significant health gains, which can be achieved at reasonable incremental costs, if they do not adjust the budget to keep pace with changes in healthcare technology.

The implicit budget constraint is more commonly used in economic analysis because of the problems involved in specifying an explicit budget constraint and formulating the decision problem in such a framework.^{3,13} For instance, to truly solve an explicit budget problem at a societal level, it is necessary to identify all possible expenditure options for that budget, including defense, public works, education, and other factors. However, because both the implicit and explicit budget constraints could have relevance to the decision maker, we present decision rules for both types of constraints.

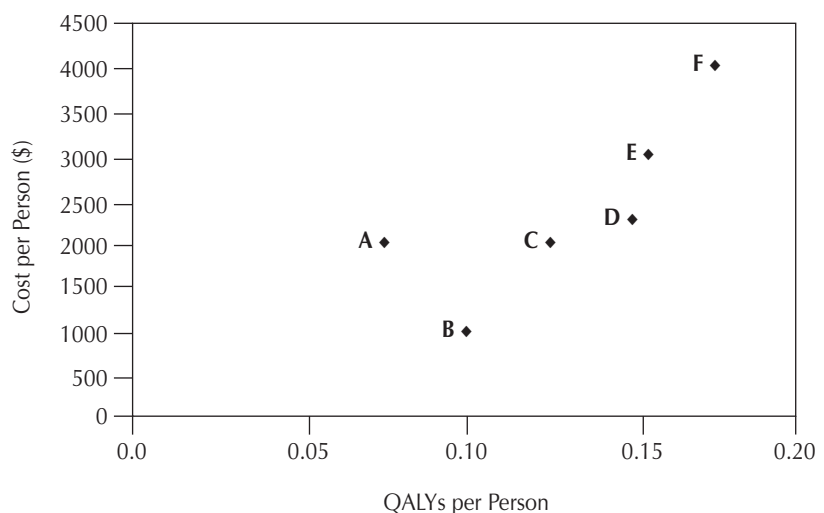
A Graphic Framework

The interventions under consideration in this report are medical intervention(s) for treating a single disease in a homogeneous population of patients. The choices are mutually exclusive in that each patient can receive at most 1 intervention. However, different patients may receive different interventions. The costs are expressed in dollars, and effectiveness is expressed in QALYs. The decision rules presented here are also applicable when cost-effectiveness results are presented in other units, such as cost per event avoided. Later, we will examine potential problems that may arise when data on QALYs are not available.

We use a graphic framework to present simple decision rules for choosing an intervention from among multiple options. Graphs have been widely used to represent the cost and effectiveness of interventions in health economics literature.^{14,15} The advantage of the graphic methodology is that it provides the decision maker with a comprehensive picture of the relative costs and effectiveness of the different interventions. A graph also provides the decision maker with a sense of how changes in the budget constraint affect resource allocation.

We use the graph in **Figure 1** as the framework for developing the decision algorithms. It shows the per-person cost and effectiveness of the set of drugs in the Table, with QALYs on the horizontal axis and cost on the vertical axis. On this graph, the slope of the line joining any intervention to the origin is the

Figure 1. Cost and QALYs for Interventions in Table



QALYs = quality-adjusted life-years; A-F = six hypothetical interventions to treat a given condition.

average cost-effectiveness ratio of that intervention. The slope of the line joining any 2 interventions X and Y is the $ICER_{X,Y}$ of the more effective intervention (Y) compared with the less effective intervention (X). The slope indicates how much more an individual would have to pay for Y compared with X for every QALY gained.

As the first step in choosing an intervention from among multiple alternatives, we generate a curve often referred to as the *efficient frontier*. To do this, we exclude all interventions that lie directly above the line segment joining any 2 other interventions (including baseline). The efficient frontier is formed by joining the remaining interventions using line segments, in order of increasing effectiveness (or cost). In **Figure 2**, the dark line joining the origin and interventions B, D, and F is the efficient frontier for the given set of interventions.

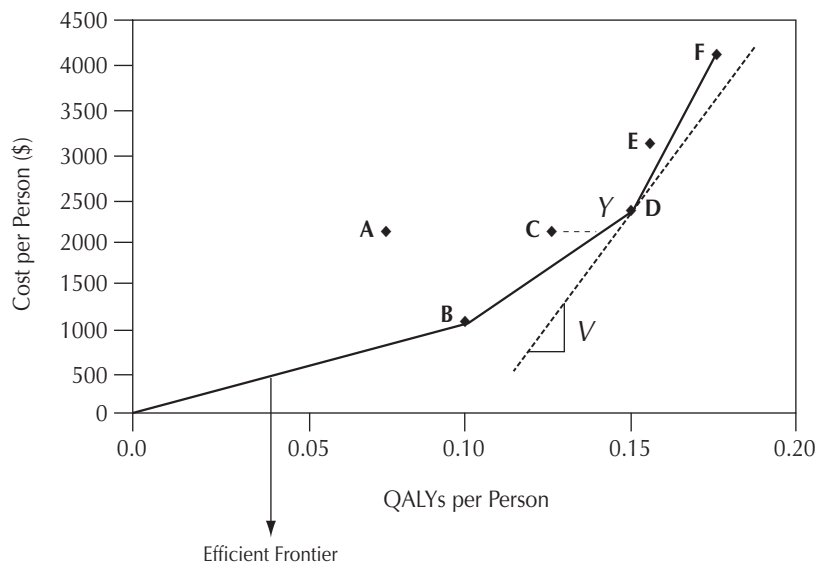
The interventions that are excluded from the efficient frontier correspond to those that are referred to in health economic literature as *dominated interventions*. There are 2 types of dominance: strict dominance and extended dominance. An intervention is said to be strictly dominated if there exists another intervention that is both cheaper and more effective. For instance, intervention A is strictly

dominated because B is both cheaper and more effective than A. In our graphic method A is excluded from the efficient frontier because it lies directly above the line segment joining baseline (origin) and B. Extended dominance is said to occur when the ICER does not increase with increasing effectiveness.¹⁶ In other words, an intervention is dominated in an extended sense if its ICER is higher than that of the next most effective treatment.¹⁶ For example, in **Figure 2**, C is more effective than B, and D is more effective than C. However, the ICER of C compared with B (\$16,000 per QALY) is higher than the ICER of D compared with C (\$15,000 per QALY), resulting in extended dominance. In this case C is said to be dominated in an extended sense. In our graphic approach, C is excluded because it lies directly above the line joining B and D. Similarly E is dominated in an extended sense, and in the graphic approach E is excluded because it lies above the line joining D and F.

None of the interventions that are excluded from the efficient frontier would qualify to be chosen. This decision is obvious in the case of strict dominance, since one would never choose an intervention if there existed another that was both cheaper and more effective. Let us examine why this is the case for interventions that are dominated in an extended sense. For instance, let us examine why the intervention C, which is dominated in an extended sense, would never be chosen. If the ICER of C compared with B (which is \$16,000) is less than V , the ICER of D compared with C (which is \$15,000) would also be less than V . V is a number chosen by the decision maker. So, if decision makers would choose C over B, they would also choose intervention D over intervention C, because if they were willing to pay \$16,000 for a QALY they would also be willing to pay \$15,000 for a QALY.

Alternatively, we can show that more QALY gain can be achieved for the same dollar amount that is spent on C by treating some patients with B and the rest with D. In **Figure 2**, the point Y on the line joining B and D has the same cost as C, but a higher QALY gain. The per-person cost and QALY gain

Figure 2. Choosing an Intervention in the Case of Implicit Budget Constraint



QALYs = quality-adjusted life-years; A–F = six hypothetical interventions to treat a given condition; V = the maximum amount that the decision maker is willing to pay for 1 additional QALY; Y = the point of intersection of the horizontal line through C and line segment

corresponding to Y can be achieved on average by treating some of the patients with B and the rest with D (we will examine this in more detail below in the section on decision rules for the explicit budget constraint scenario). Thus, intervention C would never be chosen under either budget constraint scenario, as long as the decision maker is free to treat different patients in the same disease population with different interventions. However, if the decision maker is required to treat all patients in a disease population with the same treatment, C could indeed be the treatment that should be chosen under the explicit budget constraint scenario, as discussed below in the section on decision rules for the explicit budget constraint scenario.

As we move up the efficient frontier, patients are switched from a less effective intervention to a more effective one. This increases the total effectiveness within that patient population, but the incremental cost per gain in effectiveness increases as we move up the efficient frontier. For example, as patients are switched from the baseline intervention (origin in the figure) to intervention B, there is a gain in effectiveness of 0.1 QALYs for an expenditure of \$1000; thus, the cost for every QALY gained with B is \$10,000. As patients are switched from intervention B to intervention D, the effectiveness increases by 0.05 QALYs (.15 – .10) for an additional expenditure of \$1250 (\$2250 – \$1000). The incremental cost of switching from B to D is \$25,000 (\$1250/0.05) per QALY gained. Similarly, the ICER of switching from D to F is \$70,000 per QALY gained.

In the next 2 sections we will examine how to use the efficient frontier to determine which intervention(s) should be chosen for a disease.

Decision Rules for the Implicit Budget Constraint Scenario

As noted earlier, under the implicit budget constraint, the decision maker is willing to pay up to, but no more than V dollars for every QALY gained. The objective of the decision maker is to choose the most effective intervention for which the incremental cost per QALY gained compared to the next best intervention is less than V . The intervention that should be chosen under this scenario is the one such that if we were to draw a line of slope V passing through this intervention, all other interventions would lie above this line. If the efficient frontier were a smooth curve, the intervention that should be chosen would lie at the point of tangency of the efficient frontier and a line of slope V . Using Figure 2 we will illustrate how to choose the intervention for the

example in the Table, when V is set equal to \$50,000 per QALY. The intervention that should be chosen in this case is D, because all other interventions lie above the line of slope V passing through D.

Let us see why D is indeed the intervention that should be chosen. The incremental cost per QALY of intervention D compared with intervention B ($\text{Slope}_{DB} = \$25,000$ per QALY) is less than V . The incremental cost per QALY of intervention F compared with intervention D ($\text{Slope}_{FD} = \$70,000$ per QALY) is greater than V . Hence, D is the most effective intervention for which the cost per QALY compared with the next best intervention is less than or equal to V . If the decision maker were to choose B rather than D, he or she would be missing the opportunity to purchase additional QALYs at a cost of only \$25,000 per QALY. The value of V of \$50,000 indicates that the decision maker is paying \$50,000 for a QALY somewhere else. In switching from B to D 2 QALYs would be gained for every \$50,000 spent. Because the decision maker is purchasing just 1 QALY for \$50,000 elsewhere, the overall QALYs in the population would be increased by using this money to purchase D rather than B. However, if the decision maker were to choose F instead of D, the decision maker would be purchasing QALYs at a cost of \$70,000 per QALY. Because this choice would require the diversion of dollars that were purchasing QALYs at the rate of \$50,000 per QALY, this decision would result in a decrease in overall QALYs gained. Hence, intervention D is indeed the intervention that should be chosen.

The graph in Figure 2 allows the decision maker to determine the sensitivity of the allocation decision to the value of V . For instance, the decision maker can determine from the graph that D is the intervention that should be chosen for any value of V between the slope of line segment BD (\$25,000 per QALY) and slope of line segment DF (\$70,000 per QALY). Thus, the decision maker can easily determine from the graph the range of values of V for which a given intervention will be chosen.

It is useful to examine why the intervention with the lowest cost-effectiveness ratio compared with baseline (ie, average cost-effectiveness ratio) is not the most desirable intervention from a cost-effectiveness perspective under the implicit budget constraint. As noted earlier, under this constraint, society is better off as long as every additional QALY gained costs no more than V dollars. Consider the case in which all patients are being treated with B, as recommended by decision maker D1 in the hypothetical debate, and let us assume that V is \$50,000.

Now, if the patients were switched from B to D, the expected QALY gain per patient is 0.05 for an additional cost of \$1250. Thus, the cost per QALY gained is \$25,000, which falls below \$50,000. Hence, society is better off, and D is a more desirable intervention than B, based on this decision criterion.

Decision Rules for the Explicit Budget Constraint Scenario

In this case, a fixed amount of money has been allocated for treating the specific disease. Once again, we use the efficient frontier to determine the allocation of resources that maximizes net benefit. We assume that the decision maker has a maximum of L dollars to spend per patient with the given disease. The objective now is to maximize the QALYs that can be generated using the available budget. The intervention (or mix of interventions) that should be chosen under this scenario corresponds to the point on the efficient frontier at which the cost is L . If this point does not correspond to any single intervention, the cost and QALY corresponding to this point on the efficient frontier can be achieved by treating patients with 2 drugs that have different cost and effectiveness. In Figure 3, we illustrate how to determine resource allocation when the per-

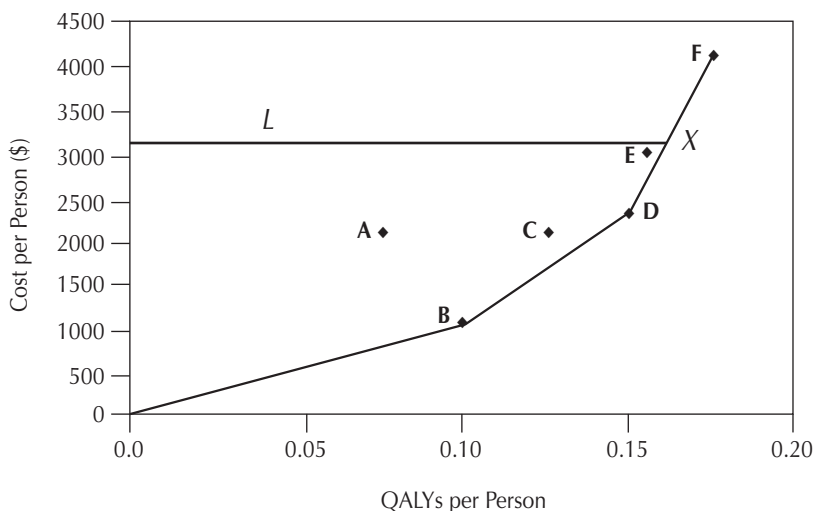
son available budget is \$3150. The optimal resource allocation in this case corresponds to the point X in Figure 3, where the budget constraint intersects the efficient frontier. The cost and effectiveness corresponding to X can be achieved by XF/DF proportion of the patients receiving intervention D, and DX/DF proportion of the patients receiving intervention F. Because X is half-way between D and F, the cost and QALYs corresponding to X can be achieved by treating half the patients with D and the other half with F.

Note that, as in the above case, the optimal allocation decision under the explicit budget constraint scenario may involve treating different patients in the same disease population with drugs of different efficacy. In some cases, it may not be feasible to treat 2 patients with the same disease with interventions of different efficacy. For equity consideration, some healthcare systems may prefer to treat all patients in a disease population with the same intervention.¹⁷ If the decision maker is forced to treat all patients with the same drug due to equity considerations, the optimal solution is to treat the entire disease population with the most effective drug with a cost below the budget constraint. This is the highest effectiveness that can be achieved with a single intervention with-

in the given budget. This intervention may be dominated, and hence may not lie on the efficient frontier. For instance, in Figure 3 the single drug that can provide the maximum effectiveness within the budget constraint is drug E, which does not lie on the efficient frontier.

Once again, it is useful to examine why the intervention with the lowest cost-effectiveness ratio compared with baseline is not the most desirable intervention from a cost-effectiveness perspective under the explicit budget constraint. As noted earlier, under this constraint, the objective is to maximize health gain within the available budget. In our example, it could be argued that the best decision is to keep treating patients with B until the money runs out. However, this decision assumes that the available per-person budget is less than the cost of B (\$1000), ie, the budget constraint line intersects the efficient frontier

Figure 3. Choosing an Intervention in the Case of Explicit Budget Constraint*



QALYs = quality-adjusted life-years; A-F = six hypothetical interventions to treat a given condition. L = the maximum amount that the decision maker can spend per patient; X = the point on the efficient frontier where the per person cost is L .

*The mix of interventions that should be chosen corresponds to the point of intersection of the efficient frontier and the budget constraint.

along the line segment joining the origin and intervention B in Figure 3. Indeed, if this were the case, the decision should be to treat as many patients as possible with B. However, if more than \$1000 were available per person to treat these patients, health gains can be maximized by treating at least some patients with an intervention other than B. The decision rule provided above describes how to identify the specific drug (or mix of drugs) that will maximize health gain within the available budget.

Applying the Decision Rules: An Example

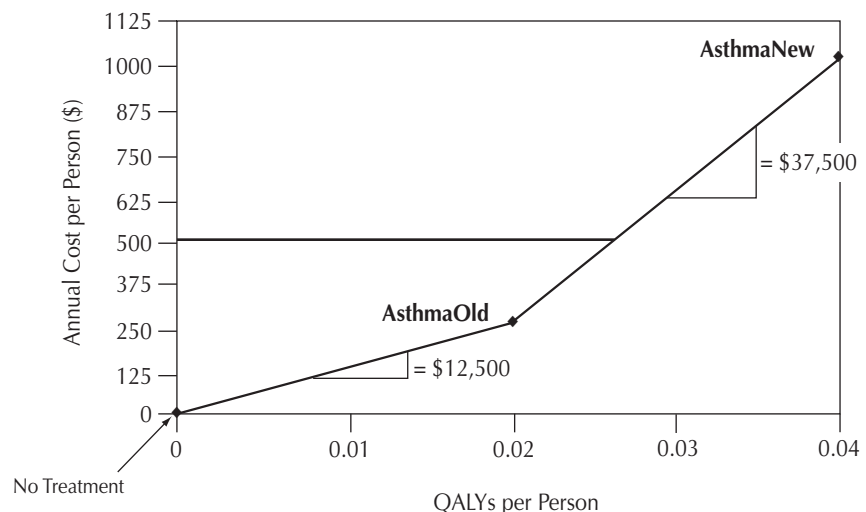
Consider a decision maker who is responsible for the pharmacy budget within an organization, such as a hospital, managed care organization, or a national health system. We examine how this decision maker could apply the rules described in this report to a potential decision-making problem that he or she may face in practice regarding asthma maintenance therapy. Assume that the decision maker is at the start of the budget cycle. The annual cost for the preferred drug (let us call this *AsthmaOld*) is \$250 per year per patient. However, a new product (*AsthmaNew*) that costs \$1000 per year has been approved. As is often the case, no data are available from trials directly comparing *AsthmaNew* with *AsthmaOld*, even though data from placebo-controlled trials seem to suggest that *AsthmaNew* is more effective. Given the uncertainty regarding the comparative efficacy of the 2 products, the decision maker budgets \$500 per year per patient for asthma maintenance therapy, to meet expected demand for the new product from patients and physicians.

At the start of the new year, data become available regarding the comparative efficacy of the 2 products from a head-to-head trial, and *AsthmaNew* is found to be more effective than *AsthmaOld*. The efficacy difference translated into a gain of 0.02 QALYs per patient for 1 year of treatment, and the efficacy difference was seen consistently in all subgroups of patients. **Figure 4** shows the cost and efficacy of *AsthmaOld*, *AsthmaNew*, and no treatment (the origin). However, the budget for this therapeutic class has already

been allocated for the year, and the decision maker has little flexibility to increase the budget at this point. Thus, the decision maker is in the explicit budget constraint scenario in which a limited amount (\$500 per patient) is available to spend on drugs for asthma maintenance. The budget line intersects the line joining *AsthmaOld* and *AsthmaNew* one third of the way between the 2 interventions. Applying the decision rule for the explicit budget constraint scenario as described above, the decision should be to provide *AsthmaNew* to one third of the patients and *AsthmaOld* to the other two thirds.

When estimating the budget for the following year, the decision maker must determine the appropriate budget for this drug category. To calculate this estimate, the decision maker must determine whether the incremental clinical benefit of *AsthmaNew* compared with *AsthmaOld* is worth its incremental cost. The manufacturers of *AsthmaOld* claim that the cost-effectiveness ratio for their drug compared with placebo is only \$12,500 per QALY gained, whereas *AsthmaNew* costs \$18,750 per QALY gained compared with placebo. Hence, they submit to the decision maker that their product should continue to be the preferred product, because *AsthmaOld* is more cost effective. However, the decision maker recognizes that the average cost-effectiveness ratio is not the appropriate metric for comparing *AsthmaNew* with *AsthmaOld*. Instead, the decision maker needs to calculate the ICER of

Figure 4. Cost and Efficacy for the Asthma Example



QALYs = quality-adjusted life-years.

AsthmaNew compared with AsthmaOld. The decision problem corresponds to the implicit budget constraint scenario, and thus the decision rule for the implicit budget constraint scenario as described above should be applied. In Figure 4, the ICER of AsthmaNew compared with AsthmaOld is \$37,500. If the decision maker's V is higher than \$37,500, then all patients should be treated with AsthmaNew. However, if the decision maker's V is less than \$37,500 but more than \$12,500 ($\$250/0.02$), then all patients should be treated with AsthmaOld. If V is lower than \$12,500 per QALY, then patients should not receive either treatment.

Conclusion

There has been considerable debate in the health economics literature regarding the appropriate use of cost-effectiveness results in making healthcare policy decisions. Studies that examine multiple interventions for a given disease often attempt to determine which one is most "cost effective" based on the average cost-effectiveness ratio. We have demonstrated herein why, when evaluating multiple interventions, the intervention that should be chosen is not necessarily the one with the lowest average cost-effectiveness ratio. We have provided a review of the decision rules described in the health economics literature for choosing an intervention from among multiple options, based on cost-effectiveness results. We have also described how to apply the rules using a simple graphic framework. The graphic framework described herein should allow decision makers to view the entire decision-making problem and examine the impact of different budget constraint assumptions on resource allocation.

We have presented rules for decision making using QALYs as the measure of outcome. However, QALYs are not a universally accepted measure of outcome. Furthermore, QALY data may not always be available for a new product. For example in the case of asthma, efficacy may be presented in terms of an alternate outcome variable such as symptom-free days. In this case, the decision maker can attempt to convert the gain in symptom-free days into an equivalent gain in QALYs. However, this approach may not be easily applicable if multiple efficacy and toxicity measures have to be considered. In the absence of QALY data, the methodology we have presented cannot be used unless the decision maker can derive another composite measure that incorporates all the different outcome variables.

Whether working in a competitive or nationalized healthcare system, the healthcare decision maker

usually attempts to allocate resources to maximize benefits for the participants in the health system. Under these circumstances, the decision rules we have presented using a simple graphic framework should be of assistance to decision makers in making their allocation decisions. Cost effectiveness usually forms just 1 of the inputs that decision makers consider in their decision process. Several other factors such as acceptability among customers and payers play a major role. However, cost-effectiveness results, if interpreted and used correctly, can form an important and useful tool to aid decision making.

... REFERENCES ...

1. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
2. Birch S, Gafni A. Cost-effectiveness/utility analysis: Do current decision rules lead us where we want to be? *J Health Econ* 1992;11:279-296.
3. Johannesson M, Weinstein MC. On the decision rules of cost-effectiveness analysis. *J Health Econ* 1993;12:459-467.
4. Karlsson G, Johannesson M. The decision rules of cost-effectiveness analysis. *Pharmacoeconomics* 1996;9:113-120.
5. Birch S, Gafni A. Changing the problem to fit the solution: Johannesson and Weinstein's (mis) application of economics to real world problems. *J Health Econ* 1993;12:469-476.
6. Laska EM, Meisner M, Siegel C. Statistical inference for cost-effectiveness ratios. *Health Econ* 1997;6:229-242.
7. Briggs A, Fenn P. Trying to do better than average: A commentary on "statistical inference for cost-effectiveness ratios." *Health Econ* 1997;6:491-495.
8. Laska EM, Meisner M, Siegel C. The usefulness of average cost-effective ratios. *Health Econ* 1997;6:497-504.
9. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;146:473-481.
10. Drummond MF, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd ed. Oxford, UK: Oxford University Press; 1997.
11. Eddy DM. Cost-effectiveness analysis: A conversation with my father. *JAMA* 1992;267:1669-1675.
12. Gafni A, Birch S. Guideline for the adoption of new technologies: A prescription for uncontrolled growth in expenditures and how to avoid the problem. *Can Med Assoc J* 1993;148:913-917.
13. Johannesson M. The relationship between cost-effectiveness analysis and cost-benefit analysis. *Soc Sci Med* 1995;41:483-489.
14. Anderson JP, Bush JW, Chen M, Dolenc D. Policy space areas and properties of benefit-cost/utility analysis. *JAMA* 1986;255:794-795.
15. Black WC. The CE plane: A graphic representation of cost-effectiveness. *Med Decis Making* 1990;10:212-214.
16. Cantor SB. Cost-effectiveness analysis, extended dominance, and ethics: A quantitative assessment. *Med Decis Making* 1994;14:259-265.
17. Ubel PA, DeKay ML, Baron J, Asch DA. Cost-effectiveness analysis in a setting of budget constraints. *N Engl J Med* 1996;334:1174-1177.