DETERMINING THE THRESHOLD FOR ACCEPTABILITY OF AN ICER WHEN NATURAL HEALTH UNITS ARE USED

Helen Lee Hyewon[1], Mitchell Levine[1,2]

[1]Centre for Evaluation of Medicines, St Joseph's Healthcare Hamilton; [2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton

Corresponding Author: levinem@mcmaster.ca

Key Words: *ICER; threshold; value*

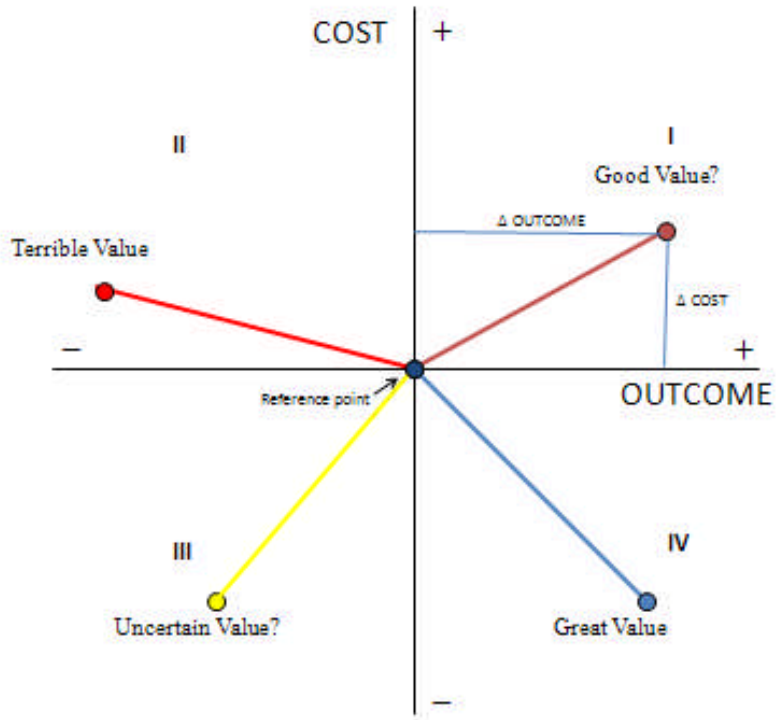
In health care, policy makers and clinicians need information to help determine the allocation of resources and the distribution of care. This can be achieved through health economic evaluations. One method of economic evaluation is the Cost-Benefit Analysis (CBA). In CBA, a demonstration of acceptable value is when the monetary value of the benefits exceeds the cost.[1] However, the ability to convert clinical benefits into a monetary value is not easily justified and the CBA does not take into account benefits that have no financial value. Hence, the most common approach in conducting a health economic evaluation is the cost-effective analysis (CEA).[2] However, the CEA, unlike the CBA, relies on arbitrary standards for acceptability and does not provide an explicit threshold for acceptable value.[1]

Cost-effective analyses assess the level of resource inputs (in the numerator) and health outputs of the health program (in the denominator) and this is expressed as a cost-effectiveness ratio[3]. The analytical unit of the CEA is the Incremental Cost Effectiveness Ratio (ICER), calculated as the difference in costs between two health care programs divided by the difference in outcomes[4]. The types of outcomes that can be used in an ICER include mortality, clinical events, or Quality Adjusted Life Years (QALYs).[4] The decision to adopt or not to adopt a program or intervention may be determined by the program's ICER, and as the ICER increases the likelihood of rejection on grounds of cost-effectiveness rises.[5] The ICER can be represented in a cost-effectiveness plane (CE plane), as shown in Figure 1. There are four quadrants in the CE plane: I- the intervention is more effective and more costly than the control; II- the intervention is less effective and more costly than the control; III- the intervention is less effective and less costly than the control; and IV- the intervention is more effective and less costly than the control. Quadrants II and IV are also known as the 'dominant quadrants', because decision making in terms of cost-effectiveness would be definitive (you should always reject programs in quadrant II and always adopt programs in quadrant IV). However, it is the non-dominant quadrants (I and III) that bring uncertainty to the use of the cost-effective analysis in decision making. Such uncertainty is due to the fact that the acceptability of the cost-effective ratio is dependent upon the decision maker's value of what would be an appropriate ICER threshold.

For non-dominant ICERs that use QALYs there are several approaches in which one can attempt to discern the value (or acceptability) of the ICER. One approach involves attaining a consensus regarding what is an acceptable cost per QALY. From a review of evaluations and guidelines, Laupacis, Feeny, Detsky, and Tugwell stated that $20,000 CAN per QALY was a reasonable threshold.[6]

Alternatively, $50,000 to $100,000 US per QALY has been presented as a range for acceptability.[7] However, there is no universal justification for these standard values in terms of the opportunity cost of marginal health care resources. Another method is the use of league tables, where different health services and programs are ranked in the order of their incremental cost effectiveness (cost per QALY) and the programs with the lower ICER values are implemented first, i.e., representing better value.[5] Further, by extrapolation the last program selected by policy makers from a league table could be considered as the acceptable threshold value. Unfortunately league tables are not ideal for many methodological reasons and have had limited use.[8]

FIG. 1 The Cost-effectiveness Plane



Trying to determine whether a non-dominant ICER involving natural health units (e.g. clinical events) represents acceptable value is even more difficult than an ICER involving a QALY. Because there is no common outcome one cannot create league tables; nor is it feasible to obtain consensus about what represents good value for thousands of potential clinical outcomes. This paper will describe a method that could provide guidance as to what would be an acceptable or unacceptable ICER in circumstances of non-dominance where the outcomes are represented by natural health units.

The approach that we propose is to compare the incremental cost-effectiveness results obtained with a new intervention relative to average cost-effectiveness results of an existing intervention, where the latter has implicit acceptable value since the latter intervention has already been implemented by the health care system or society. Thus, we are proposing a method where the "added value" of a new program or intervention would be judged against the "value" of the program or intervention it would be replacing.

The Relative Value Index takes the average cost-effectiveness ratio (ACER) of the existing (ex) intervention and divides it by the incremental cost-effectiveness ratio (ICER) of the new intervention:

Relative Value Index (RVI) = ACERex / ICER

ACERex = COSTex / EFFECTex

$$\textbf{ICER} = \frac{\textbf{(COSTnew – COSTex)}}{\textbf{(EFFECTnew – EFFECTex)}}$$

The ACERex in the numerator represents the average cost-effectiveness ratio of the existing program that has already been implemented; and therefore, implicitly represents acceptable value and is used as a representation of the society's minimum threshold for acceptable value for the type of program being assessed. The ICER for the new program (in the denominator) reflects the additional benefit and additional cost associated with the implementation of the new program in place of the existing program. A Relative Value Index (RVI) greater than 1 would mean that the incremental cost per incremental outcome gained with the new program (compared to the existing program) is lower than the cost per outcome attainable with the existing program. As the latter reflects established values, the new intervention would provide new outcomes at a lower incremental cost per outcome than the cost per outcome obtained with the existing program; therefore, the new program is offering additional outcomes at an "acceptable" cost, and should be implemented. To the contrary, when the RVI is substantially less than 1 and closer to 0 this would mean that the additional outcomes associated with the new intervention would cost more than the previously "accepted value" of a cost per outcome. The adoption of the new program would not be supported on economic grounds and would require other factors to support adoption.

To demonstrate how the RVI could be applied to existing literature we identified a number of health economic analyses as illustrative examples. Yao *et al.* studied the cost-effectiveness of nebivolol compared with standard care in elderly patients with heart failure.[9] Clinically, there was a 3% reduction in all cause mortality with nebivolol compared to standard care. The ICER was €87,862 per death averted. Is this acceptable value? The RVI in these circumstances is 0.09. As this number is less than 1.0 it suggests that the incremental cost per death averted is considerably greater than the costs to avoid a death that is already obtained with standard care. Therefore, the findings of RVI suggests that nebivolol provides less "added value" than the value of existing standard care and might not be viewed as acceptable value (see Table 1).

TABLE 1 Nebivolol compared to standard care in elderly patients with heart failure

	Standard	Nebivolol	Δ*
Cost (€)	6740	9288	2548
Alive	0.816	0.845	0.029
ACER	8260	-	
ICER	87862		
RVI	0.094		

*Differences in costs or effects of the new intervention compared to the existing program

Ramsey *et al* studied the cost-effectiveness of atorvastatin in preventing cardiovascular events in patients with type 2 diabetes[10]. At 10 years of treatment the ICER to prevent a CV event would be $3,117. Is this acceptable value? The RVI for preventing a CV event is 3.41, a number higher than 1.0. An ICER of $3,117 to prevent a CV event is considerably less than the average cost of $10,627 per CV event free person in the placebo group i.e. what is being expended in current healthcare practices (see Table 2).

TABLE 2 Atrovastin compared to no statin therapy for prevention of cardiovascular events in type 2 diabetes

	Placebo	Atrovastatin	Δ*
Cost ($)	8820	9007	187
CV events absent	0.83	0.89	0.060
ACER	10627	-	
ICER	3117		
RVI	3.41		

*Differences in costs or effects of the new intervention compared to the existing program

Orme *et al.* conducted a cost-effectiveness study comparing tacrolimus to cyclosporine for the prevention of graft rejection following renal transplantation.[11] At 1 year the ICER for tacrolimus is an additional $11,700 to achieve one additional graft survival. The RVI at one year is 0.90 (less than, but close to 1.0) suggesting that any "extra" clinical benefits with tacrolimus are obtained at an incremental cost that reflects just a slightly lower value than the costs per benefits attained with cyclosporine. Then at year 5 and year 10 the RVI is greater than 1 demonstrating an acceptable value of the therapy with long term use (see Table 3).

TABLE 3 Tacrolimus compared to cyclosporine for prevention of graft rejection following renal transplantation

		Cyclosporine	Tacrolimus	Δ*
Year 1	**Cost ($)**	9783	9900	117
	% Survival	0.93	0.94	0.010
	ACER	10519	-	
	ICER	11700		
	RVI	0.90		
Year 5	**Cost ($)**	1501	1560	59
	% Survival	0.76	0.85	0.090
	ACER	1975	-	
	ICER	656		
	RVI	3.01		
Year 10	**Cost ($)**	965	1023	58
	% Survival	0.56	0.64	0.080
	ACER	1723	-	
	ICER	725		
	RVI	2.38		

*Differences in costs or effects of the new intervention compared to the existing program

In conclusion, the absence of a QALY, or similar standard outcome unit in the denominator of an ICER, makes the determination of what would be an acceptable threshold very problematic in the non-dominant situation. In this paper we have presented an idea that may reduce the uncertainty about the value of an ICER by using an implied accepted threshold for the ICER, i.e., the average cost-effectiveness of the currently adopted intervention or program. Further work in this area is still needed, particularly a comprehensive assessment of the utility of the RVI. This could be done in circumstances where both clinical events and QALY outcomes are reported in a cost-effectiveness analysis and a comparison is made between the RVI and the cost per QALY (where an *a priori* designated cost per QALY threshold of acceptability has been determined). Finally, there is a limitation that we have not addressed in this paper. It is possible that decision makers may choose to override inferences derived from the RVI and adopt programs despite a low RVI because some resource allocation decisions are made using information or values that are unrelated to traditional health economics.

REFERENCES

1. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a Quality-Adjusted Life Year: in search of a standard. Med Decis Making 2000;20:332-42.
2. Bleichrodt H, Quiggin J. Life-cycle preferences over consumption and health: when is cost-effectiveness analysis equivalent to cost-benefit analysis? J Health Econ 1999;18:681-708.
3. McGregor M, Caro JJ. QALYs: are they helpful to decision makers? Pharmacoeconomics 2006;24(10):947-52.
4. Raisch DW. Understanding Quality-Adjusted Life Years and their application to pharmacoeconomic research. Ann Pharmacother 2000;34:906-14.
5. Smith RD, Richardson J. Can we estimate the 'social' value of a QALY? Four core issues to resolve. Health Policy 2005;74:77-84.
6. 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. CMAJ 1992;146:473-81.
7. Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ 2010;19:422-37.
8. Drummond M, Torrance G, Mason J. Cost-effectiveness league tables: more harm than good? Soc Sci Med 1993;37(1):33-40.
9. Yao G, Freemantle N, Flather M, Tharmanathan P, Coats A, Poole-Wilson PA. Long-term cost-effectiveness analysis of nebivolol compared with standard care in elderly patients with heart failure. Pharmacoeconomics 2008;26(10):879-89.
10. Ramsey SD, Clarke LD, Roberts CS, Sullivan SD, Johnson SJ, Liu LZ. An economic evaluation of atorvastatin for primary prevention of cardiovascular events in type 2 diabetes. Pharmacoeconomics 2008;26(4):329-39.
11. Orme ME, Jurewicz WA, Kumar N, McKechnie TL. The cost effectiveness of tacrolimus versus microemulsified cyclosporin: a 10-year model of renal transplantation outcomes. Pharmacoeconomics 2008;21(17):1263-76.