Does One Comparator Fit All Scenarios? An Example from the Institute for Clinical and Economic Review's 2023 Assessment of Relapsing-Remitting Multiple Sclerosis

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Introduction/Objectives

In 2023, the Institute for Clinical and Economic Review – ***the organization (ICER-O)***, an influential US health technology assessment (HTA) body, published a report, concluding that dimethyl fumarate was cost-effective in Relapsing Remitting Multiple Sclerosis and that four monoclonal antibodies it assessed were not. In making this determination it did not include all relevant alternatives nor did it analyze heterogeneous subgroups it acknowledged elsewhere in the report, separately (as would be appropriate,[1] despite acknowledging the existence of patient heterogeneity. It also assessed cost reductions needed to make the monoclonal antibodies cost-effective. We examine only whether dimethyl fumarate was the appropriate comparator for all treatments examined (as ICER-O's analysis suggests) across different willingness-to-pay (WTP) thresholds. We do not explore the implications of the reduced set of treatment alternatives or the presence of patient heterogeneity as we lacked data to do so.

Methods

We reviewed this model according to long-standing, accepted and published methods for health economic evaluation, focusing on the calculation of appropriate Incremental Cost-effectiveness Ratios (ICERs). This literature is aligned in the view that treatment alternatives should not be compared to one common alternative as this can mislead. Cost and QALY data from the report (treatments ordered, here, by QALYs) are presented in Table 1, where treatments are assigned a letter (A-E) to facilitate presentation. We illustrated data in an Incremental Cost-Effectiveness (ICE) plane (Figure 1) and calculated the appropriate ICERs and Net Monetary Benefit (NMB) values for various WTP threshold scenarios to determine whether/when ICERs versus dimethyl fumarate were appropriate. NMB is defined for each treatment, i, as $WTP*QALYs_i - Costs_i$. The cost-effective (CE) choice is always that with the maximum NMB for a given WTP.

We calculated the cost reduction for treatment B that would make it cost-effective. We did this by reducing costs of B sufficiently so that B had the same NMB value as the optimal treatment for a given WTP. The calculation is also possible using correctly calculated ICERs, but is more complex as the appropriate ICER can change with the WTP if the optimal treatment changes. ICER-O's method of reducing B's cost so that its ICER vs the common comparator, A, is equal to the WTP value fails to yield the correct answer in some cases since the common comparator ceases to be relevant at some WTP values.

Results

Figure 1 shows an ICE Plane (Costs, QALYs based on Table 1) with 2 WTPs (dotted lines). This indicates that B, D and E are technically inefficient (strongly*/weakly** dominated and cannot be CE. At a $200K WTP (the highest ICER-O examined), A is CE; at $300K, C is CE. ICER-O failed to identify any treatments as inefficient, instead calculating ICERs for all treatments vs. one alternative - A. All those ICERs exceeded $200K WTP, so it concluded that only A was CE - and this is correct for WTPs it explored.

If strongly dominated alternatives (D & E) are eliminated, ICERs for the remaining contiguous alternatives[2] indicate that B is weakly dominated and may also be eliminated. $ICER_{CA}$ (= $292K) is the only decision-relevant ICER. Conclusions are identical to those in Figure 1.

Table 2 shows results of ICER-O's and our NMB method of calculating cost reductions needed to make B CE. Those reductions are identical for WTPs of $200K and $292K ($ICER_{CA}$). Figure 2 shows the ICE plane with only treatments A, various points B' ($B'=B^1$-B^4) and C. If the cost of B is reduced to correspond to point B^1 on the line indicating a $200K WTP or to B^2 on the line indicating WTP=$292K, ICER-O's method works because these two new B' points are appropriate to compare to A. $B'=B^1$ indicates indifference with A as being CE for $200K WTP. $B'=B^2$ indicates indifference for treatments A, B^2 and C at the WTP = $292K = $ICER_{CA}$ = $ICER_{B'A}$ = $ICER_{CB'}$. ICER-O's and the NMB method do not give the same answers for WTP greater than $292K. ICER-O's method would suggest B^3 representing the cost reduction needed for $300K. Note however that this point is still weakly dominated (as was B in the first place). The NMB method indicates that the costs must be reduced to point B^4 for B to be CE. The cost reduction (Table 2) is not $207K ($B^3$) but $229K ($B^4$). ICER-O would claim B to be CE at B^3, but only treatment C is. The NMB method indicates indifference between B^4 and C. We note in Figure 2, the ICER that is relevant to making B^4 CE is $ICER_{CB'}$ which is equal to the $300K WTP (parallel line to $ICER_{B'A}$) at B^3.

Figure 1: Incremental Cost-Effectiveness Plane

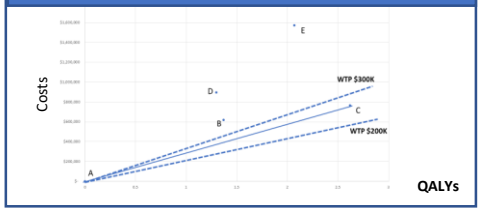

Figure 2: ICE Plane Based on Incremental Costs and QALYs vs. Treatment A with Various Cost Reductions for Treatment B to various B' (B^1 – B^4) to Attempt to Make B Cost-Effective

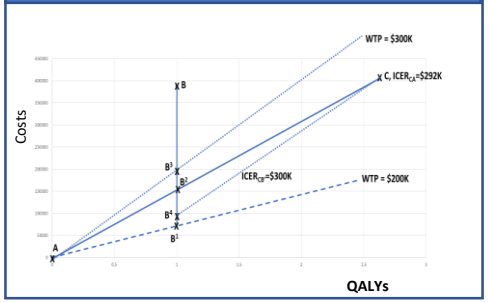

Table 1 Cost and Effectiveness Data from ICER-O Report, Ordered by Effectiveness

Treatment	TC	QALYs
Dimethyl Fumarate (A)	$ 1,065,000	11.27
Ofatumumab (D)*	$ 1,960,000	12.57
Ublituximab (B)**	$ 1,683,000	12.64
Natalizumab (E)*	$ 2,636,000	13.34
Orcelizumab (C)	$ 1,829,000	13.89

Table 2: Cost Reductions at which Ublituximab (Treatment B) Is Cost-Effective: Comparison of ICER-O's Method Using ICERs and the NMB Method

WTP	ICER-O Method	NMB Method	Cost-Effective Treatment(s)
$200K ($B^1$)	$344K	$344K	A and B^1
$292K ($B^2$)	$219K	$219K	A, B^2 and C
$300K ($B^3$)	$207K*	NA	C only
$300K ($B^4$)	NA	$229K	C and B^4

Discussion

It is not clear for certain what ICER-O's conclusions would have been at WTP=$300K. It did not explore this WTP level and, therefore, did not make claims based on that, so our claims about its likely errors in methods may appear unproven. However, the choice to always calculate ICERs against a common alternative (A) suggests that ICER-O would conclude at WTP = $300K, that C was CE *and* that, at even higher WTPs (greater than other treatment ICERs vs. A, ***multiple treatments were CE***.

Further supporting our claim is that in ICER-O's Obesity report, it does exactly this, claiming that 2 alternatives were CE based on their ICERs vs a common alternative being less than the WTP. It further shows the cost reduction needed to make an initially not CE treatment CE and does this by reducing costs to make that non CE treatment ICER vs the common alternative equal to the presumed WTP.[4] Instead, it should be calculating the cost reduction that makes the ICER *vs. the cost-effective alternative* equal to the WTP. That cost reduction is much greater.

Conclusions

ICER-O limited its CEA to a subset of relevant treatments and it ignored patient heterogeneity that it acknowledged elsewhere in its report. Both simplifications violate accepted principles.[3] We lacked data to address those concerns, but were able to assess ICER-O's methods, CE conclusions and price reductions for non-CE alternatives needed to make them CE. Using the WTP values it explored, ICER-O conclusions were correct, but we have shown its methods (ICERs vs a common (A) alternative) are not robust to a wider range of WTP values. As a premier HTA organization, its methods need to be unassailable and its accuracy not serendipitous.

Additional text?

References

[1]Heterogeneity paper – Briggs
[2]Glick, 2007
[3]Joint SMDM/ISPOR publication
[4]ICER Obesity Report