Online Appendix II to "Economic Evaluation under Ambiguity and Structural Uncertainties" [Supplemental Information]

Author: Brendon P. Andrews

A. Practical Example

To demonstrate possible discordance between decision-making under CBA versus CEA objective functions, I use example data for incremental costs and incremental benefits (e.g. QALYs). Table O.II-A1 provides artificial data from a 'preferred' model and nine sensitivity analyses.[1] Among the ten models, the minimum increments in QALYs and costs are $\underline{Q} = 0.665$ and $\underline{C} = 33867$, respectively. The maximum increments in QALYs and costs are $\overline{Q} = 3.339$ and $\overline{C} = 53149$, respectively. Table O.II-A2 reports my calculations of ICERs and NMBs at NICE's standard £20,000 and £30,000 thresholds (NICE, 2013, p. 38), based on the incremental costs and benefits for each alternative model. Ambiguity in g is expressed by $\mathbb{G} = \{20000, 30000\}$.

[1] Incremental costs were randomly selected from the interval £25,000 to £65,000, except for analyses 1-2 in which they were restricted to be identical to the preferred model. Incremental benefits were randomly selected from the interval 0.5 to 3.5, with the restriction that Analysis 1 be "low-benefit" and Analysis 2 be "high-benefit."

Table O.II-A1: Example Data

Model	ΔC (£)	ΔQ (QALYs)
Preferred	35,400	1.630
Analysis 1	35,400	1.177
Analysis 2	35,400	2.336
Analysis 3	33,867	0.665
Analysis 4	50,868	2.748
Analysis 5	53,149	2.207
Analysis 6	43,732	3.339
Analysis 7	41,226	1.779
Analysis 8	52,585	1.430
Analysis 9	43,956	0.828

This is a hypothetical technology which has no true impact on welfare, but we shall assume that approval is the true welfare-maximizing decision. Then my results in Section 3 suggest that a regulator could make an error and reject it. I show below which decisions would be made under formalized decision rules under both CBA and CEA, and where the approaches differ, in a simplified appraisal process. The analyses assume a representative decision-maker had access only to data in Tables O.II-A1-O.II-A2, and no other information. These assumptions, while unrealistic, highlight the role of ambiguity on decision-making, avoiding contamination by the effects of other issues.

Table O.II-A2: CBA Net Benefits and CEA ICERs for Example Data

Model	CBA, Net Benefits £, (g=20k)	CBA, Net Benefits £, (g=30k)	CEA, ICER £
Preferred	-2,803	13,495	21,720
Analysis 1	-11,863	-94	30,080
Analysis 2	11,328	34,692	15,151
Analysis 3	-20,569	-13,920	50,935
Analysis 4	4,085	31,561	18,513
Analysis 5	-9,015	13,051	24,086
Analysis 6	23,052	56,445	13,097
Analysis 7	-5,636	12,159	23,167
Analysis 8	-23,989	-9,691	36,778
Analysis 9	-27,391	-19,108	53,071

Results from the 'preferred' model are presented in the top row of Table O.II-A2. Its ICER of £21,720 suggests that NICE should recommend this hypothetical technology at the £30,000 threshold but not at the £20,000 threshold. However, ICER estimates range between £13,097 and £53,071. Analyses 1, 3, and 8-9 are rejected using not only CEA at both threshold values, but also CBA. If the £20k threshold is used, analyses 5 and 7, as well as the preferred model, also suggest that NICE should not recommend this hypothetical technology for use. As demonstrated in Section 2.1, the choice between CBA and CEA is irrelevant for each model considered in isolation because the analyses are equivalent in unambiguous settings. Manufacturers often submit many estimates because *there is* ambiguity in model specification, which leads to considerable ambiguity in incremental costs and benefits.

Bayes: Denote the weight assigned by a Bayesian representative decision-maker to the preferred model by π_0 and to each sensitivity analysis s by π_s $\forall s = 1, \ldots, 9$. Table O.II-A3 provides results from a distribution π with $\pi_s = 1/10$ $\forall s = 0, 1, \ldots, 9$ in the top row. For ease of comparison, CBA welfare has been standardized to an ICER analogue using the results of Theorem 3 with a known g. For example, this Bayesian planner would select the alternative if and only if $E_\pi[\Delta C]/E_\pi[\Delta Q] < g$. I report the left-hand side of this inequality. Similarly, the column for CEA provides $E_\pi[\Delta C/\Delta Q]$. The CBA analysis yields a value of £23,462 while the weighted-average ICER yields £28,660. If the decision-maker's beliefs are represented by such a π, or if this hypothetical decision-maker considers the preferred model most likely and all other models equally likely such that $\pi_0 \geq 1/10$ (not in Table O.II-A3), they should recommend this technology when $g = 30,000$ but not when $g = 20,000$ no matter what weight $\pi_0 \geq 1/10$ is assigned.

Table O.II-A3 also demonstrates that this is not true for all possible π. Suppose instead that the representative decision-maker is skeptical about the technology's ability to produce benefits and places more weight on the model with the lowest incremental benefits reported, $\underline{Q} = 0.665$ in Analysis 3. Rows 2-6 of Table O.II-A3 report ICER analogues for CBA and CEA, varying $\pi_3 \in \{0.12, 0.14, 0.16, 0.18, 0.20\}$ where the remaining probability is divided equally among the other models. In this case, neither CBA nor CEA would recommend approving this technology if the threshold is strictly $g = £20,000$. If $g = £30,000$ is applied, the CBA method recommends approval at each of these five values for π_3 while the CEA method recommends approval if $\pi_3 \in \{0.12, 0.14\}$ and rejection if $\pi_3 \in \{0.16, 0.18, 0.20\}$.

There are therefore ranges of π_3 for which the methods disagree under a known threshold. It is possible to find an interval over which this disagreement occurs. The bottom two rows of Table O.II-A3 provide the minimum and maximum values of π_3 for which this discordance materializes: in an interval which contains $\pi_3 \in [0.1541487, 0.5140251]$. This is a non-trivial region of the set of possible π, and such disagreement regions can be relatively small or large depending on the example and the probabilities varied. For this reason, regulators facing ambiguity and deciding – whether implicitly or explicitly – to use a Bayesian decision rule should be careful to use the CBA objective function to avoid errors in judgment.

Table O.II-A3: Bayesian, Varying Weights on Analysis 3

		ICER Analogue	
π_3	$\pi_s,\ s \neq 3$	CBA	CEA
0.10	0.1000	23,462	28,660
0.12	0.0978	23,689	29,155
0.14	0.0956	23,923	29,650
0.16	0.0933	24,163	30,145
0.18	0.0911	24,411	30,640
0.20	0.0889	24,666	31,135
0.1541487	0.0940	24,092.0928	30,000.0025
0.5140251	0.0540	29,999.9983	38,907.1590

Notes: ICER analogues are based on the results of this paper when there is no ambiguity in the threshold g.

Maximin: The representative decision-maker might instead have used a maximin [MM] rule. Panel A of Table O.II-A4 shows how such a regulator would have rejected this hypothetical technology. For both standard thresholds, and when there is ambiguity in g, Panel A demonstrates that the minimum welfare under the alternative is negative for both CBA and CEA. By definition, welfare under the status quo is always zero. Thus, the decision-maker would reject the technology (the alternative) using either framework in all cases. This is not shocking: MM is known to be highly conservative and Theorem 4 demonstrated that a MM planner always selects the status quo under CBA and CEA.

Table O.II-A4: Minimax Regret and Maximin Analyses

Panel A: Maximin Analysis

	Minimum Welfare		
Threshold g	Status Quo	Alternative	Choice
(i) Cost-Benefit Analysis			
20,000	0	-27,391	Status Quo
30,000	0	-19,108	Status Quo
20,000 or 30,000	0	-27,391	Status Quo
(ii) Cost-Effectiveness Analysis			
20,000	0	-33,071	Status Quo
30,000	0	-23,071	Status Quo
20,000 or 30,000	0	-33,071	Status Quo

Panel B: Minimax Regret Analysis

	Maximum Regret		
Threshold g	Status Quo	Alternative	Choice
(i) Cost-Benefit Analysis			
20,000	23,052	27,391	Status Quo
30,000	56,445	19,108	Alternative
20,000 or 30,000	56,445	27,391	Alternative
(ii) Cost-Effectiveness Analysis			
20,000	6,903	33,071	Status Quo
30,000	16,903	23,071	Status Quo
20,000 or 30,000	16,903	33,071	Status Quo

Minimax Regret: The third well-known decision rule that the representative decision-maker might have implemented is minimax regret. Panel B of Table O.II-A4 shows the maximum regret under the status quo (in £) for CBA and CEA under both the £20,000 and £30,000 thresholds as well as the case where g is ambiguous. The regulator selects the option with the lesser maximum regret. In this case, both CBA and CEA recommend rejection in favor of the status quo when the threshold is known to be £20,000. By contrast, CBA recommends approval but CEA continues to favor the status quo when the threshold is ambiguous or known to be £30,000.

Summary: Using ratio-based CEA instead of the linear CBA-type analysis can lead to errors in judgment. Employing the CBA objective function is therefore critical when evaluating alternatives under ambiguity, and regulators should pay keen attention to the decision rules which they are implicitly applying. With that in mind, I stress that this is a simplified analysis designed to clarify the role of ambiguity. In real-world situations, supplemental information is considered and must be combined using more complex objective functions than those used by the representative decision-maker in the preceding analysis, who was exposed only to the information in Tables O.II-A1-O.II-A2.

B. Minimax Regret Analysis

In this online appendix, I continue the discussion of rectangular MMR analysis from Section 3.2 of the paper.

Corollary O.II-B1 *Suppose there is no dominant strategy,* $\mathbb{G} = \{g\}$*,* $\Delta Q \in \mathbb{Q}$*, and* $\Delta C \in \mathbb{C}$*, and the state space is "rectangular" such that* $\{(\overline{Q}, \underline{C}), (\underline{Q}, \overline{C})\} \in (\mathbb{Q}, \mathbb{C})$*. Then under an MMR planner:*

i. If CEA recommends the alternative, then CBA will recommend the alternative.

ii. If CBA recommends the status quo, then CEA will recommend the status quo.

Proof: Theorem B2 shows that CBA recommends the alternative if $\frac{\underline{C}+\overline{C}}{\overline{Q}+\underline{Q}} < g$. Additionally, it shows that CEA recommends the alternative if $\frac{\overline{CQ}+\underline{C}\underline{Q}}{2\underline{Q}\overline{Q}} < g$. Now consider that:

$$\frac{\underline{C} + \overline{C}}{\overline{Q} + \underline{Q}} \leq \frac{\overline{CQ} + \underline{C}\underline{Q}}{2\underline{Q}\overline{Q}}$$

$$2\underline{Q}\overline{Q}(\underline{C}+\overline{C}) \leq (\overline{C}\overline{Q}+\underline{C}\underline{Q})(\overline{Q}+\underline{Q})$$

$$2\underline{Q}\overline{Q}\underline{C}+2\underline{Q}\overline{Q}\overline{C} \leq \overline{C}\overline{Q}^2+\underline{C}\underline{Q}\overline{Q}+\overline{C}\overline{Q}\underline{Q}+\underline{C}\underline{Q}^2$$

$$\underline{Q}\overline{Q}\underline{C}+\underline{Q}\overline{Q}\overline{C} \leq \overline{C}\overline{Q}^2+\underline{C}\underline{Q}^2$$

$$\underline{Q}\underline{C}[\overline{Q}-\underline{Q}] \leq \overline{C}\overline{Q}[\overline{Q}-\underline{Q}]$$

$$\underline{Q}\underline{C} \leq \overline{C}\overline{Q}$$

which must hold. Therefore, (i) $\frac{\overline{C}\overline{Q}+\underline{C}\underline{Q}}{2\underline{Q}\overline{Q}} < g \Rightarrow \frac{\underline{C}+\overline{C}}{\overline{Q}+\underline{Q}} < g$; and (ii) $\frac{\underline{C}+\overline{C}}{\overline{Q}+\underline{Q}} > g \Rightarrow \frac{\overline{C}\overline{Q}+\underline{C}\underline{Q}}{2\underline{Q}\overline{Q}} > g$. ■

The MMR planner using CEA may be too conservative, and they will never be too aggressive in implementing a policy. Corollary O.II-B2 provides necessary conditions on g, $\mathbb{Q}$, and $\mathbb{C}$ for this dilemma to occur in this more simple setting.

Corollary O.II-B2 *If the state space is rectangular as defined in Corollary O.II-B1 and CBA recommends the alternative under the MMR rule, then it must be that*

$$0 < (1-\overline{Q})[g\underline{Q}-\overline{C}]+(1-\underline{Q})[g\overline{Q}-\underline{C}] \qquad \text{(O.II-B1)}$$

if the MMR rule recommends the status quo under CEA.

Proof: If the alternative should be approved under CBA, this implies that $0 < g(\overline{Q}+\underline{Q}) - (\underline{C}+\overline{C})$. If the status quo should be selected in CEA, then also $0 > 2\underline{Q}\overline{Q}g - \overline{C}\overline{Q} - \underline{C}\underline{Q}$. Consequently:

$$g(\overline{Q}+\underline{Q})-(\underline{C}+\overline{C}) > 2\underline{Q}\overline{Q}g-\overline{C}\overline{Q}-\underline{C}\underline{Q}$$

$$g(\overline{Q}+\underline{Q}-2\underline{Q}\overline{Q}) > (\underline{C}+\overline{C})-\overline{C}\overline{Q}-\underline{C}\underline{Q}$$

$$g(\overline{Q}+\underline{Q})-(\underline{C}+\overline{C}) > 2g\underline{Q}\overline{Q}-\overline{C}\overline{Q}-\underline{C}\underline{Q}$$

$$g(\overline{Q}+\underline{Q})-(\underline{C}+\overline{C}) > \overline{Q}[g\underline{Q}-\overline{C}]+\underline{Q}[g\overline{Q}-\underline{C}]$$

$$0 < (1-\overline{Q})[g\underline{Q}-\overline{C}]+(1-\underline{Q})[g\overline{Q}-\underline{C}]$$

This completes the proof. ∎

Recall that there is no dominant strategy. Consequently, the worst-case CBA welfare $[g\underline{Q} - \overline{C}] < 0$ and the best-case CBA welfare $[g\overline{Q} - \underline{C}] > 0$. The RHS of Inequality O.II-B1 is a "weighted" sum of the welfare in these extreme cases. While this is informative, it is only a necessary condition for disagreement between CBA and CEA and cannot be used to predict this qualitative result. I explore below when this disagreement is likely to occur in practice based on the orientation of $\overline{C}$, $\underline{C}$, $\overline{Q}$, and $\underline{Q}$.

When there is no ambiguity in the threshold g, the results of Theorem 5 imply that a MMR planner selects the alternative if and only if (a) under CBA, $(\overline{C} + \underline{C})/(\overline{Q} + \underline{Q}) < g$; and (b) under CEA, $(\overline{C}\overline{Q} + \underline{C}\underline{Q})/(2\underline{Q}\overline{Q}) < g$. I refer to the left-hand side of these expressions as "ICER analogues" because they can be compared directly with g in the same manner as a typical ICER.

Corollary O.II-B1 implies that $(\overline{C} + \underline{C})/(\overline{Q} + \underline{Q}) \leq (\overline{C}\overline{Q} + \underline{C}\underline{Q})/(2\underline{Q}\overline{Q})$, but I seek orientations of $\overline{C}$, $\underline{C}$, $\overline{Q}$, and $\underline{Q}$ which result in the left-hand side [LHS] of this expression falling below g simultaneously with the right-hand side [RHS] rising above g. Several characteristics make this qualitative results more likely. First, we require ambiguity in incremental benefits. In the absence of ambiguity, $\overline{Q} = \underline{Q}$ and the inequality can be replaced with a strict equality. Second, we require the denominator on the left to be relatively large and the denominator on the right to be relatively small. Given that $\underline{Q} < \overline{Q}$, this will tend to occur where $\underline{Q} << \overline{Q}$ and in particular where $\underline{Q}$ is *very* small and $\overline{Q}$ sufficiently large. If both $\underline{Q}$ and $\overline{Q}$ are too large or too small, then it becomes more likely that both the LHS and RHS are on the same side of the threshold g. Finally, it can be seen from the numerators that the impact of $\overline{C}$ and $\underline{C}$ on this result will depend on the values of $\overline{Q}$ and $\underline{Q}$. In particular, larger $\overline{C}$ ($\underline{C}$) makes this qualitative result more likely when $\overline{Q} > 1$ ($\underline{Q} > 1$) and smaller $\overline{C}$ ($\underline{C}$) makes this qualitative result more likely when $\overline{Q} < 1$ ($\underline{Q} < 1$). If both $\underline{C}$ and $\overline{C}$ are too large or too small, then it again becomes more likely that both the LHS and RHS are on the same side of the threshold

g.

To make this more concrete, Table O.II-B1 provides a breakdown of where neither CBA or CEA ("No"), where both CBA or CEA ("Yes"), and where only CBA ("CBA") recommends the alternative over varying orientations of $\overline{C}$, $\underline{C}$, $\overline{Q}$, and $\underline{Q}$. To match reasonable values in practice, I vary $\overline{C}$ and $\underline{C}$ over the set $\{20000, 35000, 50000, 75000\}$ subject to $\underline{C} \leq \overline{C}$, and I vary $\overline{Q}$ and $\underline{Q}$ over the set $\{0.5, 1, 2.5, 5, 10\}$ subject to $\underline{Q} < \overline{Q}$.[2] I set an unambiguous threshold $g = 25000$ to represent the midpoint between commonly asserted thresholds for decision-making in the UK.[3] Tables O.II-B2 and O.II-B3 present the relevant ICER analogues under each orientation of the data which underlie the predicted differences in behaviour. The errors in judgment predicted by Table O.II-B1, where the representative decision-maker using CEA fails to implement the alternative when they would have done so using the CBA objective function, roughly correspond to the discussion in the previous paragraph.

[2] I employ a strict inequality in this case because there can never be disagreement between CBA and CEA when $\underline{Q} = \overline{Q}$. See the discussion above.

[3] These are £20,000 and £30,000. See Section 4.1.

Table O.II-B1: Example Rectangular MMR Analysis, Approval Matrix

		$\underline{Q}$:	0.5	0.5	0.5	0.5	1	1	1	2.5	2.5	5
$\underline{C}$	$\overline{C}$	$\overline{Q}$:	1	2.5	5	10	2.5	5	10	5	10	10
20,000	20,000		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	35,000		No	CBA	CBA	CBA	Yes	Yes	Yes	Yes	Yes	Yes
	50,000		No	CBA	CBA	CBA	CBA	CBA	CBA	Yes	Yes	Yes
	75,000		No	No	CBA	CBA	No	CBA	CBA	Yes	Yes	Yes
35,000	35,000		No	CBA	CBA	CBA	Yes	Yes	Yes	Yes	Yes	Yes
	50,000		No	No	CBA	CBA	CBA	CBA	CBA	Yes	Yes	Yes
	75,000		No	No	CBA	CBA	No	CBA	CBA	Yes	Yes	Yes
50,000	50,000		No	No	CBA	CBA	No	CBA	CBA	Yes	Yes	Yes
	75,000		No	No	CBA	CBA	No	CBA	CBA	Yes	Yes	Yes
75,000	75,000		No	No	No	CBA	No	No	CBA	Yes	Yes	Yes

Notes: This table summarizes whether the ICER analogues in Tables O.II-B2 and O.II-B3 support the recommendation of the alternative when compared to the cost-effectiveness threshold $g = 25,000$. If both CBA and CEA recommend the alternative for the specified values of $\underline{C}$, $\overline{C}$,$\underline{Q}$, and $\overline{Q}$, then the corresponding cell reads "Yes." If both CBA and CEA recommend the status quo, the cell reads "No." If CBA recommends the alternative and CEA recommends the status quo, the cell reads "CBA."

Table O.II-B2: Example Rectangular MMR Analysis, CBA

		$\underline{Q}$:	0.5	0.5	0.5	0.5	1	1	1	2.5	2.5	5
$\underline{C}$	$\overline{C}$	$\overline{Q}$:	1	2.5	5	10	2.5	5	10	5	10	10
20,000	20,000		26,667	13,333	7,273	3,810	11,429	6,667	3,636	5,333	3,200	2,667
	35,000		36,667	18,333	10,000	5,238	15,714	9,167	5,000	7,333	4,400	3,667
	50,000		46,667	23,333	12,727	6,667	20,000	11,667	6,364	9,333	5,600	4,667
	75,000		63,333	31,667	17,273	9,048	27,143	15,833	8,636	12,667	7,600	6,333
35,000	35,000		46,667	23,333	12,727	6,667	20,000	11,667	6,364	9,333	5,600	4,667
	50,000		56,667	28,333	15,455	8,095	24,286	14,167	7,727	11,333	6,800	5,667
	75,000		73,333	36,667	20,000	10,476	31,429	18,333	10,000	14,667	8,800	7,333
50,000	50,000		66,667	33,333	18,182	9,524	28,571	16,667	9,091	13,333	8,000	6,667
	75,000		83,333	41,667	22,727	11,905	35,714	20,833	11,364	16,667	10,000	8,333
75,000	75,000		100,000	50,000	27,273	14,286	42,857	25,000	13,636	20,000	12,000	10,000

Notes: This table presents ICER analogues for the specified values of $\underline{C}$, $\overline{C}$,$\underline{Q}$, and $\overline{Q}$ based on the results of Theorem 5 when there is no ambiguity in the threshold g and the representative decision maker uses the CBA objective function.

Table O.II-B3: Example Rectangular MMR Analysis, CEA

		$\underline{Q}$:	0.5	0.5	0.5	0.5	1	1	1	2.5	2.5	5
$\underline{C}$	$\overline{C}$	$\overline{Q}$:	1	2.5	5	10	2.5	5	10	5	10	10
20,000	20,000		30,000	24,000	22,000	21,000	14,000	12,000	11,000	6,000	5,000	3,000
	35,000		45,000	39,000	37,000	36,000	21,500	19,500	18,500	9,000	8,000	4,500
	50,000		60,000	54,000	52,000	51,000	29,000	27,000	26,000	12,000	11,000	6,000
	75,000		85,000	79,000	77,000	76,000	41,500	39,500	38,500	17,000	16,000	8,500
35,000	35,000		52,500	42,000	38,500	36,750	24,500	21,000	19,250	10,500	8,750	5,250
	50,000		67,500	57,000	53,500	51,750	32,000	28,500	26,750	13,500	11,750	6,750
	75,000		92,500	82,000	78,500	76,750	44,500	41,000	39,250	18,500	16,750	9,250
50,000	50,000		75,000	60,000	55,000	52,500	35,000	30,000	27,500	15,000	12,500	7,500
	75,000		100,000	85,000	80,000	77,500	47,500	42,500	40,000	20,000	17,500	10,000
75,000	75,000		112,500	90,000	82,500	78,750	52,500	45,000	41,250	22,500	18,750	11,250

Notes: This table presents ICER analogues for the specified values of $\underline{C}$, $\overline{C}$,$\underline{Q}$, and $\overline{Q}$ based on the results of Theorem 5 when there is no ambiguity in the threshold g and the representative decision maker uses the CEA objective function.

References

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