Presenting evidence and summary measures to best inform societal decisions when comparing multiple strategies

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Abstract

The aim of this paper is to consider how cost and effect evidence under uncertainty can be best presented and summarized to inform societal decision making in comparing multiple treatment strategies for defined patient populations.

Presenting distributions on the cost-disutility plane with costs measured relative to the cheapest strategy and outcomes measured relative to the most effective strategy is shown to overcome confounding of effect and cost inference across multiple strategies on the incremental cost-effectiveness plane. However, further analysis is required to inform societal decision making, as assessing cost-effectiveness requires joint consideration of costs and effects and societal decision making asymptotes towards risk neutrality with risk spreading under the Arrow-Lind theorem.

Cost-effectiveness acceptability (CEA) and expected net loss (ENL) curves and frontiers have been proposed as summary measures in comparing multiple strategies. When informing risk neutral societal decision making ENL curves and the ENL frontier are demonstrated to have distinct advantages over their CEA counterparts by explicitly comparing expected net benefit rather than probabilities of maximizing net benefit. If societal preferences are somewhat risk averse then optimal reimbursement decisions can diverge from the ENL frontier where tradeoffs arise between the strategy maximising expected net benefit and strategies with higher probability of maximising net benefit. Presenting ENL curves supplemented by trade-offs, over localized threshold regions where they occur, between incremental ENB and incremental probability fully informs societal decision making. Deriving incremental
probabilities for such trade-offs from bilateral CEA curves is shown to avoid confounding inherent in multiple strategy CEA curves.
1 Introduction: Comparing multiple strategies under uncertainty

Cost-effectiveness acceptability (CEA) curves (van Hout, et al., 1994; Fenwick, Claxton and Sculpher et al., 2001) and frontiers (van Hout, et al., 1994; Fenwick, Claxton and Sculpher et al., 2001), and more recently expected net loss (ENL) curves and frontiers (Eckermann, Briggs and Willan, 2008) have been proposed as summary measures for comparing multiple strategies under uncertainty in informing societal decision making.

Claxton (1999) argues that societal decision making with respect to reimbursement in health technology assessment (HTA) should be based on expected values, consistent with risk neutrality of societal decision making. The Arrow-Lind theorem (Arrow and Lind, 1970) suggests risk preference approaches neutrality where risk associated with a public investment are publicly borne, due to risk spreading across large numbers of individuals. However, Graff Zivin and Bridges (2002) suggest preferences for societal decision making in HTA may be somewhat more risk averse given individual health outcomes may not be diversifiable and risk spreading may be limited in private markets affected by HTA decisions. Hence, in general, societal decision making is best characterised as either risk neutral or somewhat risk averse.

This paper critically examines what CEA and ENL curves and frontiers represent and consequently how they can be interpreted and might be best used in aiding societal decision making with risk neutral or somewhat risk averse preferences. We first demonstrate that in comparing multiple strategies presentation of joint distributions of costs and effect evidence on the cost disutility plane has distinct advantages over the incremental cost effectiveness plane in illustrating clinical and cost inference, while
further analysis is required to inform societal decision making based on cost-effectiveness. Construction of cost effectiveness acceptability (CEA) and expected net loss (ENL) curves and frontiers are then critically examined in relation to their ability to inform risk neutral or somewhat risk averse decision making. For risk neutral decision making ENL curves and frontiers are shown to have advantages over the CEA frontier in directly presenting differences in expected net benefit (ENB), rather than the partial solution provided by CEA frontiers by identifying the strategy which maximizes ENG, while still presenting the probability of maximizing NB. For somewhat risk averse decision making, calculating the probabilities of maximizing NB in multiple strategy CEA curves are shown to be confounded by strategies not relevant to the comparison. However the ENL frontier supplemented by incremental tradeoffs between ENB (ENL curves) and probabilities from bilateral CEA curves is shown to overcome these problems. Based on these findings, recommendations are made about the presentation of distributions and use of summary measures in informing decisions for multiple strategies where degree of risk aversion is unknown, and contrasted with those for two strategies.

To illustrate decision making with multiple strategies we consider the comparison of one year costs and effects for six gastro-espohageal reflux disease (GERD) strategies introduced by Goeree et al. (1999), modelled under uncertainty by Briggs, Goeree et al. (2002) and previously considered on the cost-disutility plane by Eckermann (2004) and Eckermann, Briggs and Willan (2008). Effects framed from a utility bearing perspective were estimated as the number of weeks free of GERD to one year, while equivalently from a disutility perspective they were measured as weeks with GERD to one year. To allow for uncertainty Briggs et al. (2002) modelled joint cost and
effects of alternative strategies (A=intermittent PPI, B=Maintenance PPI, C = Maintenance H2RA, D=step down maintenance PA, E=Step-Down maintenance H2RA and F=step down maintenance PPI) to one year with 1000 replicates constructed from Monte-Carlo Simulation.

The joint distribution of cost and effects across GERD strategies are shown in Figure 1 on the cost disutility plane. Following Eckermann, Briggs and Willan (2008) costs are measured incremental to the cheapest strategy in each replicate and effects framed from a disutility perspective (i.e. weeks with GERD over 1 year) are measured relative to the most effective strategy (i.e. lowest weeks with GERD) in each replicate. Comparing the six GERD strategies with this presentation on the cost-disutility plane it becomes clear that strategy B (Maintenance PPI) has the highest effect in every replicate since its entire distribution lies on the vertical axis with 0 incremental weeks of GERD relative to the most effective strategy in each replicate.

This inference cannot be made with an alternative presentation on the incremental cost effectiveness (ICE) plane in Figure 2, where the horizontal axis represents effects incremental to a single strategy, in this case strategy C. The inference on the ICE plane is hidden by the relationship across replicates for incremental effect between strategies B, E and F, since effects are measured incremental to a single comparator rather than the highest effect strategy in each replicate. That is, the lowest incremental cost for B across all replicates is not higher than the highest incremental cost for each of E and F on the incremental cost effectiveness plane. Similarly, visual inference in relation to costs can always be made on the cost disutility plane by the proportion of distributions with 0 incremental costs. Such valid inferences are
Presentation of multiple strategies on the cost disutility plane was previously shown to have advantages to the analyst in allowing efficiency methods to be used in constructing efficiency frontiers and to the decision maker in permitting degree of dominance to be estimated (Eckermann, Briggs and Willan, 2008). Here we have demonstrated further advantages to the decision maker in allowing visual inference for cost and effects. Never-the-less, inferences in relation to ‘cost-effectiveness’ are prevented in both the ICE and cost-disutility planes when comparing multiple strategies, given covariance (links) between the net benefit of joint distributions are hidden in each case. Further analysis is required to interpret what joint distributions of cost and effect across multiple strategies imply for societal decision making about their ‘cost effectiveness’, where CEA and ENL curves and frontiers have been proposed as summary measures to aid decision making.

2 What do CEA and NL curves & frontiers represent?

When comparing multiple strategies both CEA and ENL curves make use of the net benefit (NB) statistic (Stinnett and Mullahy, 1998), which for any strategy can be expressed in monetary terms as:

\[ NB = k \times E - C, \]  

(1)

where \( C \) and \( E \) are respectively mean costs and effects per patient and \( k \) represents the threshold value of a unit of effect. Following the net benefit criteria of Graham (1992), \( k \) should reflect the marginal rate of transformation with available technology in production of effects to enable budget constrained health maximization. Net
benefit is additively separable implying that the $NB$ statistic from equation (1) allows consistent ordering of, and differences across, multiple strategies in any given replicate regardless of comparator, unlike the incremental cost effectiveness ratio (Stinnett and Paltiel, 1997). Hence, the probability of maximizing $NB$ (CEA curves) or differences in $NB$ (ENL curves) at any given threshold value is independent of the comparator used.

2.1 CEA curves and frontiers

CEA curves represent the probability (proportion of replicates for which) a particular strategy maximizes $NB$ relative to other strategies, as a function of threshold values for effects (Briggs, 1999; Briggs and Gray, 1999; Lothgren and Zethraeus, 2000; O'Hagan, Stevens et al. 2000; Fenwick, Claxton and Sculpher, 2001; Fenwick, O'Brien and Briggs, 2004). Figure 3 illustrates CEA curves for the six GERD strategies. The CEA curves imply that the following strategies have the greatest probability of maximising $NB$ of the six compared across the indicated range of threshold values:

- Strategy C from 0 up to $10.85 per week of GERD avoided;
- Strategy A from $10.85 up to $34.60 per week of GERD avoided;
- Strategy E from $34.60 up to $272.56 per week of GERD avoided; and
- Strategy B for $272.56 or greater per week of GERD avoided.

However, while CEA curves compare the probability of maximizing $NB$ across all strategies, they do not compare expected net benefit (ENB). Comparing ENB requires taking expectations across replicates rather than considering the proportion of replicates maximizing $NB$ as in CEA curves. This distinction does not make a difference to decision making in the comparison of two strategies provided the distribution of prior incremental $NB$ is symmetric, a safe assumption where there is
enough evidence to support the central limit theorem. However, the distinction can be particularly important in comparing more than two strategies given correlations between strategies can have significant influence on the probability of a particular strategy maximising NB, while not influencing the ENB. For example, with comparison of three strategies, a strategy can maximize ENB but have no replicates in which it has highest NB and hence a 0 probability of maximising net benefit, where there is a strong negative correlation between NB of the other two strategies. Hence, when comparing three or more strategies, a strategy can have a CEA curve which remains at 0 (a flat line) despite maximizing ENB for all values.

Recognising the value to societal decision making of presenting ENB rather than the probability of maximizing NB, Fenwick, Claxton and Sculpher et al. (2001) suggested construction of a cost-effectiveness acceptability (CEA) frontier. For each threshold value the CEA frontier identifies which strategy maximises ENB but presents its probability of maximizing NB. At any given threshold value, the strategy that maximises ENB will not necessarily be the strategy that has the highest probability of maximizing NB. Hence, the CEA frontier does not necessarily follow the upper bound of CEA curves, with discontinuities where strategies have the highest probability of maximizing NB, but not the highest expected net benefit. For example, discontinuities in the CEA frontier for GERD strategies in Figure 4 arise at:

(i) \( k = \$10.26 \) per week of GERD where A maximizes ENB while C has the highest probability of maximizing NB;

(ii) \( k = \$35.02 \) per week of GERD where A maximizes ENB while E has the highest probability of maximizing NB and;
(iii) k=$265.79 per week of GERD where B maximizes ENB while E has the highest probability of maximizing NB.

These discontinuities, and the indirect nature of identifying strategies which maximising ENB by presenting their probability, can easily confuse risk neutral or risk societal decision makers as to what the CEA frontier represents. More importantly, even if decision makers understand how the CEA frontier is constructed and what it represents, it provides only a partial solution to informing risk neutral or risk averse decision making. While a CEA frontier identifies strategies maximizing ENB, it actually presents the probability of maximizing NB for these strategies rather than differences in ENB between strategies.

For risk neutral societal decision making the CEA frontier lacks transparency in not presenting differences in ENB to explain why a given strategy maximises expected net benefit across strategies. Choosing the optimal strategy based on maximising ENB when presented with a CEA frontier becomes an article of trust, with the CEA frontier effectively a black box in indicating strategies maximizing ENB but failing to explain why.

For somewhat risk averse societal decision making, information on differences in ENB is required to inform trade-offs between ENB and the probability of maximizing NB (Bala, Zarkin and Mauskopf, 2007). By presenting probabilities to indirectly indicate strategies maximising ENB rather than differences in ENB the CEA frontier does not inform such tradeoffs. Consequently, whether societal decision making is risk neutral (only interested in ENB) or somewhat risk averse (interested in tradeoffs), there are advantages to including summary measures that present differences in ENB.
Incremental net benefit (INB) curves are recommended for comparing two strategies (Willan and Lin, 2001; Briggs, O'Brien and Blackhouse, 2002; Groot Koerkamp et al., 2007). However, INB curves rely on a single comparator, and for multiple non-dominated strategies no one strategy will be the appropriate comparator at every threshold value and in every replicate. Hence INB curves do not allow joint representation of uncertainty for multiple strategies, as noted by Fenwick and Briggs (2007) in debating Groot Koerkamp et al. (2007) on the relative merits of CEA and INB curves. However, expected net loss curves (Eckermann, Briggs and Willan, 2008) do allow comparison of ENB across multiple strategies.

2.2 Expected net loss curves and frontiers

Expected net loss (ENL) curves for each strategy represent the expected value across replicates of loss in NB relative to the NB maximizing strategy in each replicate at any threshold value (Eckermann, Briggs and Willan, 2008). The net benefit loss for strategy \( i \) and replicate \( j \) (\( \text{NBL}_{ij} \)) can simply be expressed as:

\[
\text{NBL}_{ij} = \text{NB}_{ij} - \text{NB}^*_j
\]  

(2)

Where \( \text{NB}_{ij} \) is the net benefit for strategy \( i \) for replicate \( j \) and \( \text{NB}^*_j \) is the maximum \( \text{NB}_{ij} \) over compared strategies (\( i=1,..,n \)) for replicate \( j \).

\( \text{NBL}_{ij} \) is non-negative in each replicate (0 if strategy \( i \) has the maximum NB in that replicate and positive otherwise) and hence the average across replicates will also be non-negative, and 0 only if strategy \( i \) maximizes NB in all replicates. By varying the threshold value and re-calculating the average net loss for each strategy, ENL curves are formed. Constructing ENL curves is no more onerous than construction of CEA curves for multiple strategies, which similarly require
determining the strategy maximising expected net benefit in each replicate for a given
threshold value then calculate proportions rather than differences.

Figure 5 illustrates ENL curves for each GERD strategy. The ENL frontier is the
lower bound of ENL curves and identifies the strategy with the lowest ENL, and hence
highest expected net benefit (ENB), across replicates at any given threshold value. For example, Figure 5 shows that ENL is minimized, and hence ENB
maximized, with: strategy C from $0 to $10.26 per week of GERD avoided; strategy
A from more than $10.26 to $35.02; strategy E for more than $35.02 to $265.79; and
strategy B for more than $265.79.

The ENL frontier also informs the decision maker of the expected value of perfect
information (EVPI) from choosing the optimal strategy in comparing strategies with
current evidence, at the same time as identifying the strategy maximising expected net
benefit (Eckermann, Briggs and Willan, 2008). For example, at a threshold value of
$100 strategy E minimizes ENL at $4.90 per patient. However, adopting strategy E is
associated with an expected opportunity loss of $4.90 per patient since strategy E does
not have the maximum net benefit in 111 of the 1000 replicates. If we had perfect
information this loss of $4.90 could be avoided. Hence, in informing decisions of
whether future research is optimal the ENL frontier has advantages to decision makers
over the CEA frontier in providing information on EVPI and consequently the
potential value of future research (Claxton, 1999; Willan and Pinto, 2005; Eckermann
and Willan, 2007; Eckermann and Willan, 2008a; Eckermann and Willan, 2008b). It
should be noted that Eckermann and Willan (2007) (2008a) (2008b) show that
optimal decision making requires joint consideration of research and reimbursement
decisions within or across jurisdictions, something that the ENL frontier further supports. However, in the remainder of this paper we focus on how ENL and CEA curves and frontiers can be best used to inform the reimbursement decision in isolation, implicitly assuming that the choice is restricted to adopting or rejecting with no additional trial or other information considered.

3 Informing reimbursement decisions conditional on risk preference

Risk neutral decision making is based on maximizing ENB, not on the highest probability of maximizing NB. ENL curves and the ENL frontier directly inform risk neutral decision making by comparing ENB across two or more strategies for any given threshold value, while CEA curves and the CEA frontier do not. The CEA frontier, while indicating strategies maximizing ENB actually presents their probability of maximising NB. Hence the CEA frontier can confuse risk neutral decision making firstly by failing to explain why strategies maximise ENB at any given threshold value and secondly by presenting probabilities of maximizing NB rather than differences in ENB. The ENL frontier avoids such confusion, allowing direct comparison of ENB to transparently inform risk neutral decision making.

Decision making with somewhat risk averse preferences is influenced by trade-offs, where they exist, between ENB and the probability of maximising NB. CEA curves are based on the highest probability of maximum NB, while ENL curves are based on minimizing ENL or equivalently maximising ENB under the net benefit correspondence theorem (Eckermann 2004; Eckermann, Briggs and Willan, 2008). Hence, the preferences for somewhat risk averse societal decision making can be characterized as lying between those based on ENL frontiers and those based on CEA curves. As the degree of risk aversion in societal decision making increases,
preferences move from those based on maximizing ENB inherent in the ENL frontier towards those based on minimizing probabilities of losses (CEA curves).

What does the distinction in advice for risk neutral or somewhat risk averse preferences imply for decision making where we do not know the degree of risk aversion? The distinction between preferences based on the ENL frontier (risk neutral) and CEA curves (completely risk averse) only becomes important to decision making at the threshold values for effects where there is a trade-off between choice of strategies in incremental ENB and the incremental probability of maximizing NB. There is no trade-off for threshold values where a given strategy both maximizes ENB and the probability of maximizing NB. Hence, when comparing decisions based on the ENL and CEA curves there are regions of the threshold value for which the optimal strategy is the same regardless of risk aversion. For the remaining regions, trade-offs between differences in ENB and probability of maximizing NB can be presented to inform somewhat risk averse decision making.

In the case of GERD, comparing maximizing ENB (ENL frontier in Figure 5) and maximizing probability of maximizing NB (CEA curves in Figure 3), the regions for which optimal strategies are identified to be the same are:

- Strategy C from $0 up to $10.26 per week of GERD avoided;
- Strategy A from $10.86 up to $34.60 per week of GERD avoided;
- Strategy E from $35.02 up to $265.79 per week of GERD avoided and;
- Strategy B for $272.56 or more per week of GERD avoided.
Focusing on the remaining regions, trade-offs for risk averse decision makers are suggested to be between:

1. A maximizing ENB and C with higher probability of maximizing NB from $10.26 to $10.86 per week of GERD avoided;
2. A maximizing ENB and E with higher probability of maximizing NB from $34.60 to $35.02 per week of GERD avoided and;
3. E maximizing ENB and B with higher probability of maximizing NB from $265.80 to $272.56 per week of GERD avoided.

In each of these regions the relevant trade-offs between incremental probability and incremental expected value is restricted to comparison of two strategies of interest. However, the probability of maximizing NB in the CEA curves in Figure 3 is across all strategies and hence can potentially be confounded by strategies irrelevant to the decision in these regions.

There is no potential for confounding in the first two trade-offs between C and A for threshold values from $10.26 to $10.85 and between A and E from $34.56 to $35.02, given all other strategies have a 0 probability of maximizing NB in these regions (Figure 3). Figures 6 and 7 illustrate the trade-offs between incremental ENL versus incremental reduction in the probability of maximising NB across the relevant regions for C versus A and E versus A, respectively. In Figure 6 from $10.26 to $10.85 per week of GERD strategy C has higher probability of maximising NB than A (measured on the left hand side vertical axis) but lower ENB (measured on the right hand side vertical axis). Similarly, in Figure 7, E has higher probability of maximising NB than A (measured on the left hand side axis) but lower ENB (measured on the right hand side vertical axis).
However, at around a threshold value of $265.80, comparing the probabilities of strategies E and B maximizing NB from the CEA curves in Figure 3 is potentially confounded by strategy F. Strategy F has a non-zero probability of maximizing NB for a threshold value around $265.80, but is not a relevant strategy for comparison in trade-offs between maximizing ENB and maximizing the probability of highest NB. Restricting CEA curves to the comparison of two strategies for the range of threshold values in which trade-offs takes place is recommended. This allows the estimation of the relevant incremental probability for decision making in such cases. Hence, any confounding impact of strategy F can be eliminated by comparing the NL frontier around $265.80 per week of GERD with the CEA curve restricted to E and B, as shown in Figure 8.

The comparison of Figure 8 with Figure 3 makes clear that strategy F confounds the probability of maximizing NB in the relationship of interest between strategies E and B for threshold values around $265.80. Removing strategy F, the threshold value at which E and B have an equal probability of maximizing NB in Figure 8 is $266.95, compared with $272.56 in Figure 3 where F was included. Consequently, advice for risk averse decision making should be revised around the upper threshold between B and E to strategy B being the preferred strategy for threshold values higher than $266.95, rather than $272.56. Figure 9 presents the remaining trade-off of interest to somewhat risk averse decision making for threshold values from $265.80 up to $266.95 between higher ENB for B and higher probability of maximizing NB for E. Table 1 combines final advice for GERD with risk averse societal decision making.
4 Advice when comparing two and more than two strategies

Table 2 summarises and contrasts the recommended presentation of evidence and use of summary measures in informing societal decision making when comparing two or more than two strategies. Comparing multiple strategies on the cost-disutility plane allows inference in relation to cost and effect, unlike the cost-effectiveness plane where such inference is confounded. This inferential advantage arises because on the cost-disutility plane cost are measured relative to the cheapest strategy in each replicate and effects relative to the most effective, while on the ICE plane costs and effects are always measured relative to the same comparator strategy.

If societal decision making is based on risk neutral preferences, then ENL curves directly inform the decision to reimburse by comparing differences in the ENB, unlike CEA curves of the CEA frontier which present the probabilities of the maximizing NB. If societal decision making is based on somewhat risk averse preferences then trade-offs between maximizing ENB and the probability of maximizing NB can occur around regions of threshold values where the strategy minimizing ENL changes. Somewhat risk averse decision making is best informed with ENL curves supplemented by information on such trade-offs, where they exist, between the strategy maximising ENB and strategy with the highest probabilities of maximising NB. Such trade-offs should be considered pair-wise, with incremental probabilities from bilateral CEA curves to avoid confounding across strategies inherent in CEA curves for multiple strategies. This provides a focused analysis in discrete regions of threshold values for effect between strategies of interest, clarifying the trade-offs relevant to decision making where societal preferences may be somewhat risk averse.
Inference in the face of uncertainty with respect to costs, effects and ‘cost-effectiveness’ at a threshold value is problematic with comparison of three or more strategies on the ICE plane. However, such inference can be validly made in comparing two strategies. Covariance between costs and effect for two strategies reduces to one distribution on the ICE plane and at a given threshold value acceptance and rejection region can be delineated with a ray through the origin, unlike the cost-disutility plane where two distributions are still presented. Hence, where two strategies are compared, we suggest that evidence under uncertainty is presented on the ICE plane.

In considering summary measures with comparison of two strategies CEA curves naturally link to inference on the ICE plane. Such CEA curves do not face the confounding of incremental probabilities between potentially optimal strategies that often occurs with comparison of more than two strategies with multilateral CEA curves. The incremental net benefit curve representing expected net benefit of the new strategy relative to the comparator as a function of threshold value and its uncertainty (95% CI or its distribution across replicates) can also be presented for the comparison of two strategies to inform decision makers of differences in ENB. ENL curves provide the same information on differences in ENB as the INB curve in comparing two strategies, but the ENL frontier as the lower bound of ENL curves additionally provides the EVPI.

For somewhat risk averse decision making, trade-offs between incremental ENL and incremental probabilities of making the wrong decision should additionally be presented. The CEA frontier by not presenting differences in expected net benefit
does not represent these trade-offs, however the probabilities for decision making are
at least not confounded with CEA curves in the comparison of two strategies.
Consequently, while there are problems of confounding with INB and multiple
strategy CEA curves and frontier in informing decision making across multiple
strategies, the INB curve and CEA curves and frontiers are suggested as valuable
summary measures in informing decision making with comparison of two strategies.
Expected net loss (ENL) curves and frontier are suggested as generally valuable to
informing risk neutral or somewhat risk averse decision making in comparison of two
or more strategies.

5 Conclusion

When comparing the cost and effects of multiple strategies under uncertainty, the
approach suggested in this paper to best inform societal decision making where
degree of societal risk aversion is unknown is to present:

1. joint distributions for strategies on the cost-disutility plane where for each
   replicate costs are measured relative to the cheapest strategy and effects
   framed from a disutility perspective are measured relative to the most
   effective strategy;

2. ENL curves for each strategy representing the expectation of the reduction
   in NB relative to the NB maximizing (net loss minimizing) strategy,
   conditional on threshold values and;

3. trade-offs where they exist over discrete regions of threshold values
   between incremental ENB (ENL curves) and incremental probability of
   maximizing NB constructed from the relevant bilateral CEA curves.

In relation to 1, comparing joint distributions for multiple strategies on the cost
disutility plane has been shown to have distinct advantages over the ICE plane in
allowing inference with respect to the probability of maximizing effects and minimizing costs. Such inference is prevented on the incremental cost effectiveness plane, as shown in comparison of Figures 1 and 2. This advantage of presenting distributions on the cost-disutility plane is in addition to those previously identified for allowing easier construction of efficiency frontiers and estimating degree of dominance identified by Eckermann, Briggs and Willan (2008).

In relation to 2, the ENL curves and their lower bound, the ENL frontier (Figure 5), have been shown to directly inform risk neutral societal decision, unlike CEA curves (Figure 3) or the CEA frontier (Figure 4). While the CEA frontier indicates the strategy which maximises ENB, they present the probability that the strategy maximises NB, and hence fail to explain why ENB is maximised and can confuse decision making. Further, the ENL frontier has been shown previously to represent EVPI at the same time as comparing ENB and hence inform the need for further research in addition to reimbursement decisions (Eckermann, Briggs and Willan, 2008).

In relation to 3, somewhat risk averse decision making is best informed with ENL curves supplemented by tradeoffs, where they exist, for discrete regions of the threshold value, between the strategy maximising ENB (ENL frontier) and the strategy with higher probabilities of maximising NB (e.g. Figures 6, 7 and 9). Such trade-offs should be considered pair-wise with incremental probabilities from bilateral CEA curves (Figure 8), to prevent confounding across strategies inherent in CEA curves for multiple strategies.
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Table 1: Advice to somewhat risk averse societal decision making on optimal strategies conditional on k ($ per week of GERD)

<table>
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<th>Regions of k ($ per week of GERD)</th>
<th>Optimal strategy</th>
<th>k</th>
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<tr>
<td>k ≤ $10.26</td>
<td>Strategy C</td>
<td></td>
</tr>
<tr>
<td>$10.26 &lt; k ≤ $10.85</td>
<td>Tradeoff between A (higher ENB) and C (higher P[max NB])</td>
<td></td>
</tr>
<tr>
<td>$10.85 &lt; k ≤ $34.60</td>
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<td></td>
</tr>
<tr>
<td>$34.60 &lt; k ≤ $35.02</td>
<td>Tradeoff between A (higher ENB) and E (higher P[max NB])</td>
<td></td>
</tr>
<tr>
<td>$35.02 &lt; k ≤ $265.79</td>
<td>Strategy E</td>
<td></td>
</tr>
<tr>
<td>$265.79 &lt; k ≤ $266.95*</td>
<td>Tradeoff between B (higher ENB) and E (higher P[max NB])</td>
<td></td>
</tr>
<tr>
<td>k &gt; $266.95*</td>
<td>Strategy B</td>
<td></td>
</tr>
</tbody>
</table>

* Advice differs from that based on CEA curves in Figure 3, due to confounding by strategy F of incremental probabilities across the relationship of interest between strategies E and B, as demonstrated in Figure 8.
Table 2: Informing reimbursement decisions comparing two and more than two strategies where degree of risk aversion is not known

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<th>Presentation and summary measures for more than two strategies</th>
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<td></td>
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<td>CEA frontier* (Figure 4)</td>
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<td><strong>Completely risk averse</strong>&lt;br&gt;Maximise P[max NB]</td>
<td>C-DU plane (Figure 1)</td>
<td>CE plane &amp; threshold</td>
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<td></td>
<td>CEA curves (Figure 3)</td>
<td>CEA curves</td>
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<td><strong>Somewhat risk averse</strong>&lt;br&gt;Trade off ENB and P[max NB]</td>
<td>C-DU plane</td>
<td>CE plane &amp; threshold</td>
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<td></td>
<td>ENL curves (Figure 5) plus tradeoffs in regions where they occur between maximising ENB and P(max NB)^ (Figures 6, 7 &amp; 9)</td>
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<td>CEA curves</td>
<td>ENL curves and CI</td>
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<td>CEA frontier*</td>
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* The CEA frontier, while indicating the strategy maximising ENB at any k presents the probability of maximising net benefit for these strategies, and hence does not explain why ENB is maximized. This prevents use in informing trade-offs for risk averse decision making and can confuse decision making more generally.

^ CEA curves across multiple strategies can confound the incremental probability of maximising NB between strategies of interest relevant to decision making at any given threshold value.
Figure 1: Bivariate distributions for GERD strategies on the cost-disutility plane.
Figure 2: Bivariate distributions for GERD strategies on the cost-effectiveness plane
Figure 3: Cost effectiveness acceptability curves for GERD strategies
Figure 4: Cost effectiveness acceptability frontier for GERD strategies
Figure 5: Net loss curves and the net loss frontier for GERD strategies

![Net loss curves and the net loss frontier for GERD strategies](image-url)
Figure 6: Risk averse decision maker trade-off from $10.26 to $10.85 per week of GERD between A with higher incremental ENB and C with higher $P(\text{max NB})$.
Figure 7: The risk averse decision maker trade-off from $34.60 to $35.02 per week of GERD avoided between A with higher ENB and E with higher P(max NB)
Figure 8: CEA curves for E vs B (removing the confounding impact of F)
Figure 9: The risk averse decision maker trade-off from $265.79 to $266.95 per week of GERD avoided between B with higher ENB and E with higher P(max NB)