A Novel Approach to Ranking Parameter Uncertainty in One-Way Sensitivity Analysis: What Tornado Diagrams Are Missing

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OBJECTIVE

- The objective of this work was to develop a new approach for ranking parameter uncertainty in one-way sensitivity analysis (SA) of economic evaluations.
- Our approach focuses first on identifying variables where uncertainty has the potential to change the cost-effectiveness (CE) conclusion, thus overcoming the shortcomings of traditional tornado diagrams in scenarios where uncertainty causes the incremental CE ratio (ICER) to change signs.

BACKGROUND

- Economic evaluations of health technologies rely on SA to examine the impact of parameter uncertainty on modeling outcomes.[1,2]
- In the words of the ISPOR-SMDM Modeling Good Research Practices Task Force, when studying the impact of uncertainty, "what investigators should examine are the conditions that alter the implications for the decision" at hand.[3]
- One-way, or univariate, SA considers parameters one at a time, comparing outcomes at the low and high ends of plausible ranges to identify the parameters where uncertainty has the potential to change the conclusion of the analysis.[2]

Traditional One-Way SA

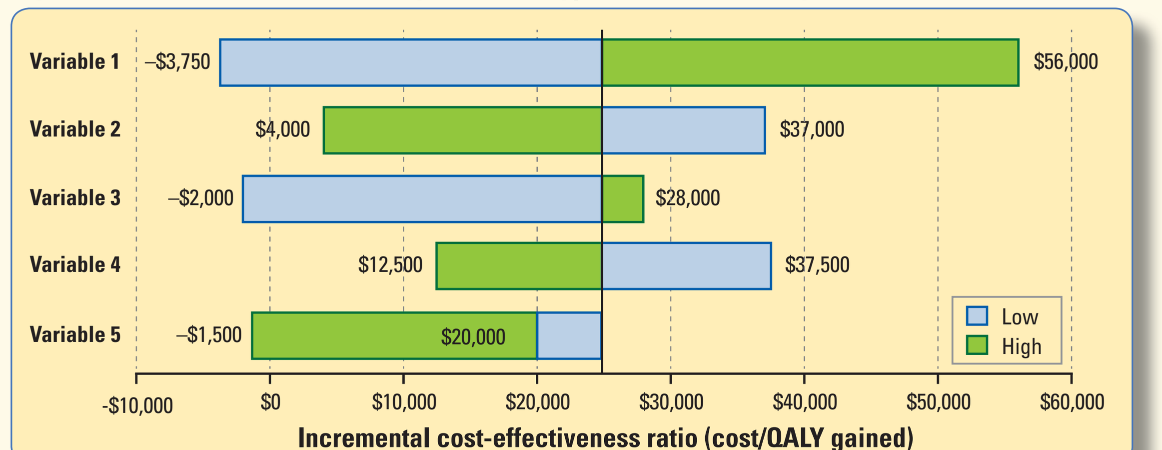
- Traditionally, one-way SA results are presented by ranking variables based on the absolute range of the ICER across their plausible values and displaying the top variables in a tornado diagram[4]; the use of tornado diagrams is recommended for inclusion in formulary submissions.[5]
- In the hypothetical one-way SA results presented in Table 1 and Figure 1, the traditional, ICER-based tornado diagram approach identifies variables 1 and 2 as the variables with the greatest ability to influence the results.
- In a scenario where all the one-way SA results remain in the first quadrant of the CE plane, and thus where the ICERs remain positive (Figure 2), this traditional approach is appropriate; however, this approach falls short when the results change quadrants in the CE plane.

Table 1. Cost and Health Outcomes for a Hypothetical One-Way SA

Variables	Low End of Range			High End of Range			Absolute ICER Range
	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	
Base case	$12,500	0.50	$25,000	–	–	–	–
Variable 1	-$3,000	0.80	-$3,750	$21,000	0.38	$56,000	$59,750
Variable 2	$18,500	0.50	$37,000	$2,000	0.50	$4,000	$33,000
Variable 3	-$500	0.25	-$2,000	$16,000	0.57	$28,000	$30,000
Variable 4	$12,500	0.33	$37,500	$12,500	1.00	$12,500	$25,000
Variable 5	$15,000	0.75	$20,000	$500	-0.33	-$1,500	$21,500

Δ = difference between the target and comparator technologies.

Figure 1. Traditional Tornado Diagram for a Hypothetical One-Way SA

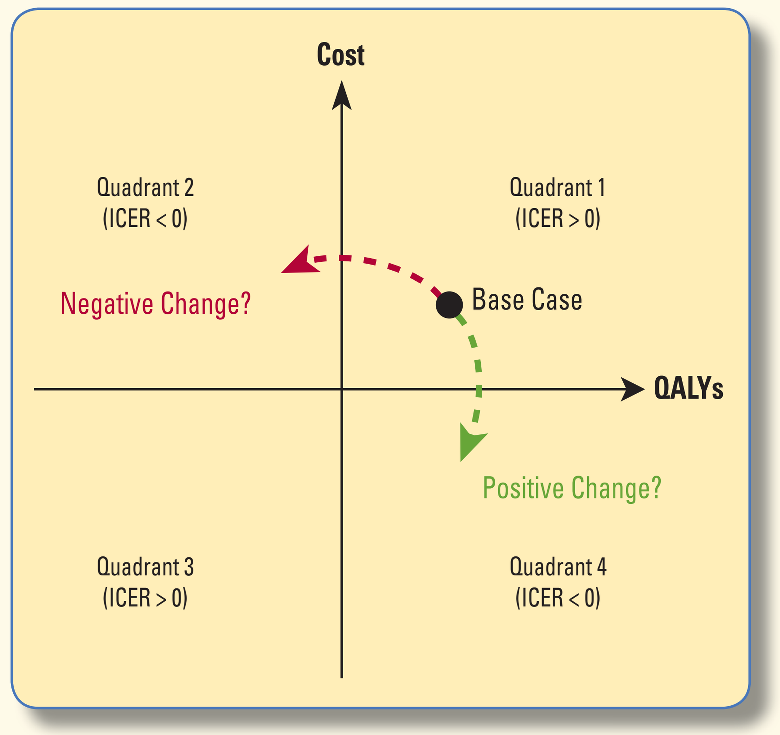


QALY = quality-adjusted life-year.

Shortcomings of Traditional Approach

- The traditional, ICER-based approach does not adequately identify or prioritize parameters where the range of uncertainty causes the results to change quadrants in the CE plane (often corresponding to a change of sign in the ICER).
- However, quadrant changes, which represent fundamental changes to the CE conclusion, are arguably more meaningful than changes in the ICER within a quadrant.
- In Figure 1, variables 1, 3, and 5 show the potential to change the ICER from positive to negative, but the tornado diagram format does not reveal the details of these quadrant changes:
  - Are the negative ICERS occurring because of an overall reduction in health (quadrant 2 in the CE plane) or a reduction in costs (quadrant 4) (Figure 2)?
  - In other words, do these variables have the potential to change the CE conclusion in a negative way or in a positive way?
- In analyses with large numbers of parameters, rankings based on absolute ICER ranges may lead to important, conclusion-changing variables being omitted from tornado diagrams, which often are limited to a subset of the most "influential" variables (with influence determined by the absolute ICER range).
- From the perspective of a health care decision maker, it is important that variables with the potential to change the overall CE conclusion are prioritized over variables with large ICER ranges that do not change the conclusion.

Figure 2. Ambiguity Related to the Change From a Positive to a Negative ICER



METHODS

- We developed a comprehensive, conclusion-based algorithm for ranking the parameters varied in a one-way SA that focuses on identifying parameters with the greatest potential to change the overall CE conclusion.
- The algorithm requires looking at the differences in costs and QALYs that lie behind the ICERS used to generate the tornado diagram (Table 1).

Algorithm Overview

- Parameters first are categorized based on whether they have the potential to change the CE conclusion both negatively and positively, negatively only, positively only, or not at all (the scenario in which a tornado diagram is most helpful) (Figure 3).
- Within each category, parameters are ranked primarily based on the impact of observed quadrant changes (ranking of potential quadrant changes shown in Table 2).
- Within each category, parameters are ranked secondarily based on the magnitude of changes to selected modeling outcomes (costs, QALYs, or ICERs).

Algorithm Details

- Step 1: For each parameter varied in the SA, identify whether results for at least one of the ends of the plausible range fall in a different quadrant of the CE plane than the base-case results.
- Step 2: Categorize each quadrant change identified in Step 1 as being a negative change or a positive change (Figure 3).
  - Negative changes are indicated by counter-clockwise moves, starting with quadrant 4 (where the target technology dominates the comparator technology) as the most desirable conclusion.
  - Positive changes are indicated by clockwise moves, starting with quadrant 2/3 (where the target technology leads to fewer QALYs than the comparator technology) as the least desirable conclusion.
- Step 3: Categorize each parameter varied in the SA as one of the following:
  - One end of the plausible range leads to a negative change in the CE conclusion, and the other end of the range leads to a positive change (**CONCLUSION±**).
  - One or both ends of the plausible range leads to a negative change in the CE conclusion, and neither end of the plausible range leads to a positive change in the CE conclusion (**CONCLUSION-**).
  - One or both ends of the plausible range leads to a positive change in the CE conclusion, and neither end of the plausible range leads to a negative change in the CE conclusion (**CONCLUSION+**).
  - Neither end of the plausible range leads to a change in the CE conclusion (**NEUTRAL**).
- Step 4: Within each of the categories identified in Step 3, rank the parameters based on the following primary and secondary rankings:
  - First, assign a level of impact to any observed quadrant changes and rank the parameters based on these levels (Table 2).
  - Second, break any ties in the primary ranking based on the magnitude of changes to selected modeling outcomes (costs, QALYs, or ICERs).

Figure 3. Augmented, Conclusion-Based CE Plane Used in One-Way SA Ranking Algorithm

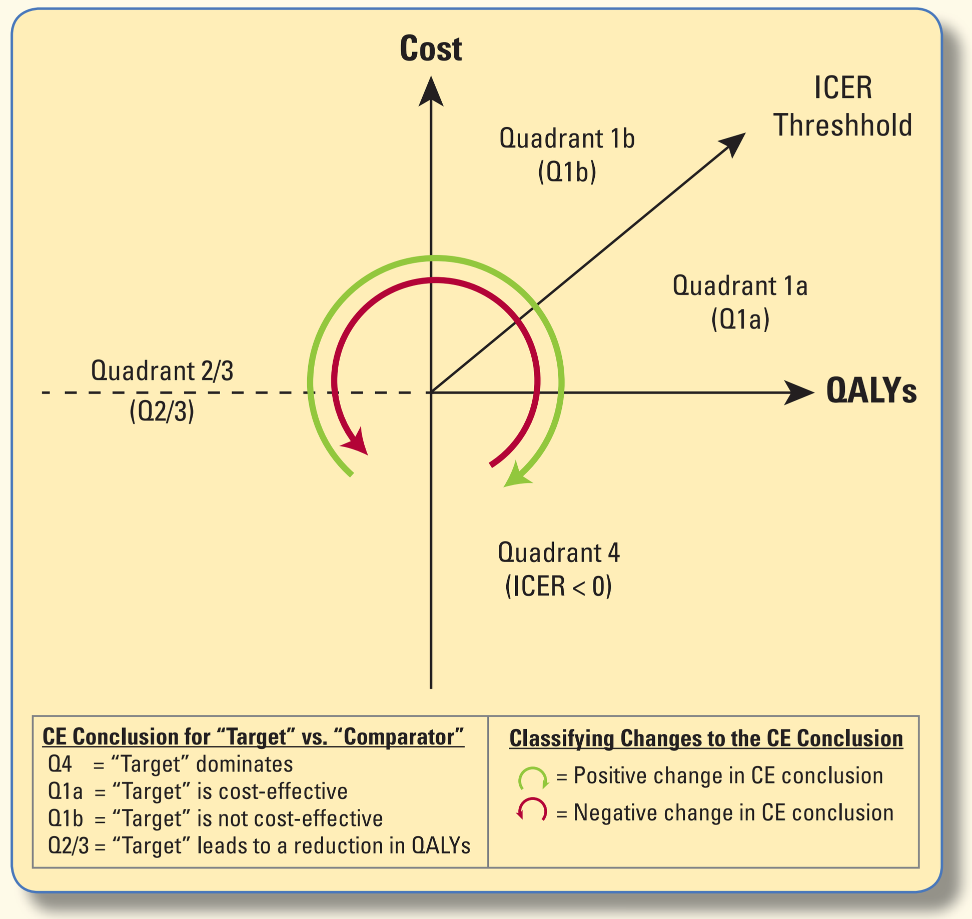


Table 2. Categorizing Quadrant Changes as Positive or Negative Changes From the Base-Case and Ranking Their Overall Impact

Level of Impact	Negative Quadrant Changes	Positive Quadrant Changes
Most impactful	Q4 → Q2/3	Q2/3 → Q4
	Q4 → Q1b	Q1b → Q4
	Q4 → Q1a	Q1a → Q4
	Q1a → Q2/3	Q2/3 → Q1a
	Q1a → Q1b	Q1b → Q1a
Least impactful	Q1b → Q2/3	Q2/3 → Q1b

Note: The order of the quadrant changes from most impactful to least impactful is determined by the location of the base-case results and the number of steps taken when moving counter-clockwise (negative changes) or clockwise (positive changes) around the augmented cost-effectiveness plane (Figure 3).

RESULTS

- When applied to the hypothetical data in Table 1, our conclusion-based approach identifies variables 1, 3, and 5 as having the potential to change the CE conclusion (due to a change in the sign of the ICER or a move from CE to not CE) and, importantly, characterizes the potential changes as negative or positive changes from the base case (depending on whether the change in ICER sign stems from a change in sign of the difference in costs or QALYs).
- Table 3 presents the same hypothetical results separated into conclusion-based categories and ranked using our algorithm.
  - The impact of uncertainty in variable 1 is observed on the low end of the range (highlighted in green), where reductions in cost have the potential to make the target technology cost-saving, and on the high end of the range (highlighted in red), where reductions in health have the potential to make the target technology dominated by the comparator.
  - The impact of uncertainty in variable 5 is primarily observed on the high end of the plausible range (highlighted in red).
  - In this example, we can see that the impact of uncertainty in variable 3 is primarily observed on the low end of the plausible range (highlighted in green).

Table 3. Cost and Health Outcomes for a Hypothetical One-Way SA Prioritized Using the Conclusion-Based Algorithm

Variables	Low End of Range			High End of Range			Absolute ICER Range
	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	
CONCLUSION±: Parameters where uncertainty has the potential to change the CE conclusion negatively or positively							
Variable 1	-$3,000	0.80	-$3,750	$21,000	0.38	$56,000	
CONCLUSION-: Parameters where uncertainty has the potential to change the CE conclusion only negatively							
Variable 5	$15,000	0.75	$20,000	$500	-0.33	-$1,500	
CONCLUSION+: Parameters where uncertainty has the potential to change the CE conclusion only positively							
Variable 3	-$500	0.25	-$2,000	$16,000	0.57	$30,000	
NEUTRAL: Parameters where uncertainty does not have the potential to change the CE conclusion							
Variable 2	$18,500	0.50	$37,000	$2,000	0.50	$4,000	$33,000
Variable 4	$12,500	0.33	$37,500	$12,500	1.00	$12,500	$25,000

Δ = difference between the target and comparator technologies.

Note: The ICER threshold for cost-effectiveness was assumed to be $50,000 per QALY gained.

CONCLUSIONS

- Our conclusion-based algorithm, which categorizes and ranks parameters based on the potential to change the CE conclusion, is an alternative method to a tornado diagram that provides a more appropriate assessment of the impact of uncertainty in individual parameter values on the CE conclusion.
- This algorithm can be used by researchers conducting one-way SA in scenarios where the associated cost and health outcomes result in ICERs that fall in multiple quadrants in the CE plane.

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