IVI INNOVATION AND VALUE INITIATIVE

VALUE BLUEPRINTS
Research Brief Series

The Impact of Structural Uncertainty on Cost-Effectiveness Estimates

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RESEARCH QUESTION

What impact can model design assumptions have on cost-effectiveness estimates?

KEY TAKEAWAYS

- Models are used to integrate relevant evidence and predict outcomes and costs for healthcare interventions over time.
- Choices made in determining the structure of a model can have an impact on the model's results, but this structural uncertainty is frequently overlooked when cost-effectiveness analyses are performed.
- Using the IVI-RA model, we demonstrated how different structural assumptions lead to varying cost-effectiveness estimates.
- Given the potential impact of structural assumptions, model-based cost-effectiveness analysis should explicitly incorporate and report effects of structural uncertainty to ensure that decision-makers relying on cost-effectiveness estimates to guide their decisions have complete information about the certainty of estimates.

MODELING AND STRUCTURAL UNCERTAINTY

To assess the value of a therapy relative to its alternatives, the findings from multiple scientific studies regarding its risks, benefits, and costs must be brought together in a model – i.e, a set of mathematical equations – designed to predict, as best as possible, the long-term expected benefits and costs of the therapy in the real world. However, how those models are developed, and the information that they are based on can significantly impact their results.

Two types of uncertainty exist in models. "Parameter uncertainty" arises when we do not know the exact values for a given model's input variables – for example, the probability of a treatment response or the costs associated with an adverse event. Model results are also affected by another type of uncertainty that is commonly overlooked, called "structural uncertainty."

Frequently, there are multiple scientifically-defensible model structures reflecting different "beliefs" regarding the appropriate, yet simplified, nature of the relationships between model input and model output. In cases where there is limited empirical evidence, it is particularly difficult to reject one structure in favor of another. These different defensible model structures can produce widely different results.

Unfortunately, this structural uncertainty is not always acknowledged when cost-effectiveness is estimated based on a model. Typically, only a single model structure

RHEUMATOID ARTHRITIS AND THE IVI-RA MODEL

Rheumatoid Arthritis (RA) is the most common autoimmune inflammatory arthritis in adults and often negatively impacts patients' quality of life and ability to perform daily activities. To help decision-makers understand the value of alternative treatment strategies for patients with RA, the Innovation and Value Initiative (IVI) created a model that simulates the lifetime costs and benefits of different strategies for treating patients with moderate to severe rheumatoid arthritis. The IVI-RA model is designed to provide flexibility in determining structural assumptions, allowing up to 384 different model structures. This flexibility allows us to explore the impacts of structural uncertainty on outcomes and estimates of value.[1]

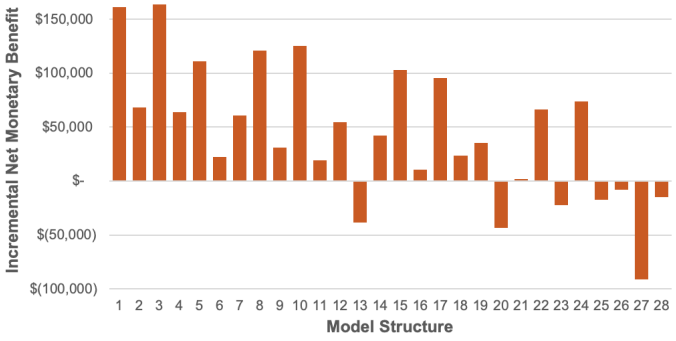
[1] Incerti DI, Curtis JR, Shafrin J, Lakdawalla DN, Jansen JP. A flexible open-source decision model for value assessment of biologic treatment for rheumatoid arthritis. *Pharmacoeconomics*. 2019;37:829-843.

is created, and the uncertainty in model results is evaluated by varying the model input parameters. In essence, the uncertainty in model results that is presented is conditional upon the model structure of choice. It is important to realize this limitation when interpreting model-based cost-effectiveness findings.

METHODS

Using the IVI-RA simulation model, we illustrate the potential impact of "structural uncertainty" on model outcomes and cost-effectiveness results.

FIGURE 1. Impacts of Structural Assumptions on Incremental Net Monetary Benefit (iNMB)



Note: iNMB calculated assuming a societal willingness to pay of $150,000 per QALY gained.

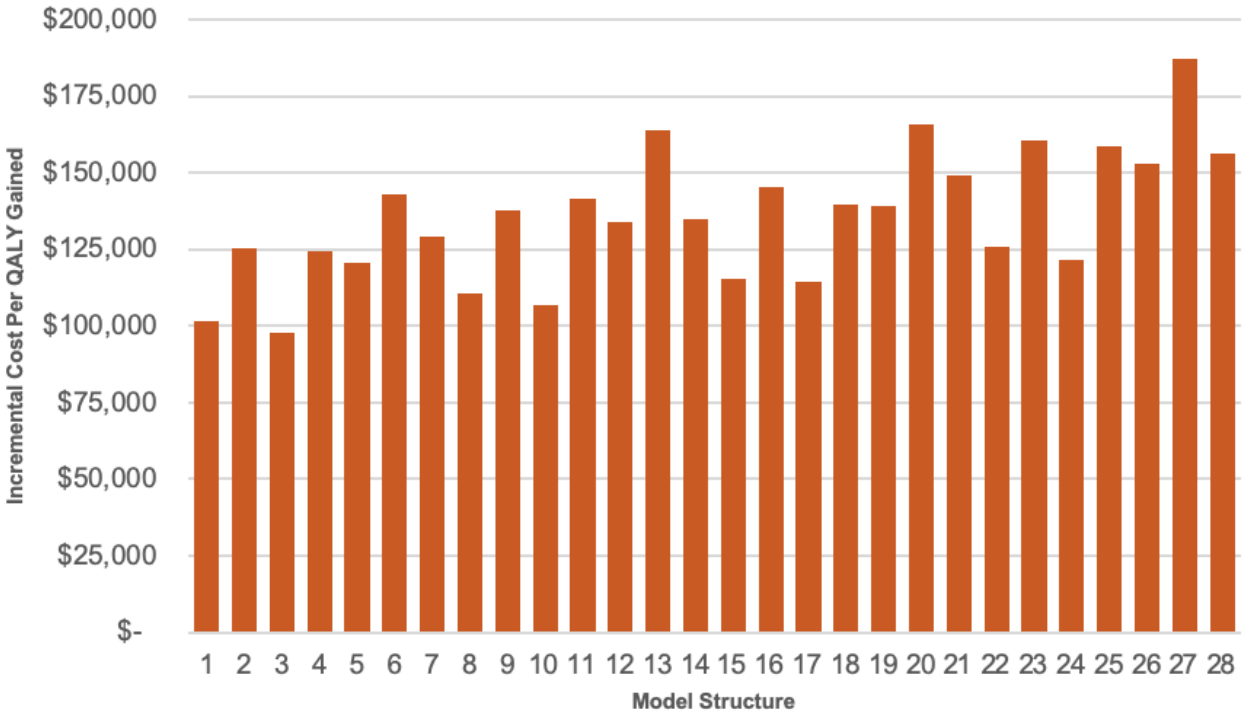
A total of 28 distinct model structures were created by varying four key structural assumptions: 1) the impact of a given treatment on functional status as measured with the HAQ (Health Assessment Questionnaire); 2) the way timing of treatment switching is determined; 3) how HAQ progresses over time; and 4) the approach used to translate HAQ scores into health state utilities needed to calculate quality-adjusted life years.[2]

For each selected model structure, we simulated the benefits and costs associated with sequential treatment with biologic disease-modifying anti-rheumatic drugs (DMARDs) relative to treatment with conventional DMARDs among moderate-to-severe RA patients in the United States.[3] Based on estimated total costs and Quality-Adjusted Life Years (QALYs), the incremental net monetary benefit[4] (iNMB) and the incremental cost-effectiveness ratio (ICER) were calculated as measures of value. For the iNMB, the societal willingness to pay for a QALY gained was assumed to be $150,000.

FINDINGS

Results of this basic analysis show that different model assumptions of the IVI-RA model lead to varying cost-effectiveness estimates. The iNMBs range from roughly -$90,000 to $160,000 (Figure 1). Twenty-one out of 28

FIGURE 2. Impacts of Structural Assumptions on the Incremental Cost-Effectiveness Ratio (ICER)



[2] For details, see the complete IVI-RA model documentation at: https://innovationvalueinitiative.github.io/IVI-RA/model-description/model-description.pdf.
[3] Simulated patients were assumed to have previously failed on conventional DMARDs and to have not yet been treated with a biologic DMARD.
[4] iMNB is Defined as (willingness-to-pay per QALY gained * incremental QALYs) – incremental costs.

TABLE 1. Number of Model Structures Considered Cost-Effective at Various Threshold Levels

Cost-Effectiveness Threshold	Number of Model Estimates (out of 28) Indicating Sequential Treatment with Biologic DMARDs is Cost-Effective
$100,000 per QALY	1
$125,000 per QALY	9
$150,000 per QALY	21
$175,000 per QALY	27

Note: Cost-effectiveness assessed relative to treatment with conventional DMARDs. Treatments are considered cost-effective if the incremental cost-effectiveness ratio (ICER) falls below the selected threshold.

analyses suggest the incremental benefits of the biologic DMARD intervention strategy exceed the incremental costs, whereas seven analyses suggest they do not. Incremental cost-effectiveness ratios range from just under $100,000 to almost $200,000 (Figure 2). Depending upon the cost-effectiveness threshold, the different estimates can lead to different conclusions as well (Table 1).

IMPLICATIONS FOR VALUE ASSESSMENT

The implications of structural uncertainty can be striking. As illustrated in Table 1, structural assumptions in modeling can substantially affect the estimates of value. Real-world decision-makers relying on cost-effectiveness estimates to guide their decisions about treatment options need to be aware of the potential implications of structural uncertainty.

For example, imagine a decision-maker using a cost-effectiveness analysis based on a model according to structure 13 to guide a coverage decision; the analysis indicates that sequential treatment with biologic DMARDs is not cost-effective at a $150,000 per QALY threshold (the decision-maker's guidepost). Had the decision-maker known that only seven out of the 28 of model structures support that conclusion, however, a different decision may have been reached.

Understanding the uncertainty that the choice of model structure introduces to these decisions is essential to the ongoing effort to ensure that value assessment is scientifically credible. To address this, changes in practice are needed in both analyses and the reporting of results. First, when conducting analyses using simulation models, the effect of using competing model structures should be examined – ideally by varying structures within the simulation itself, but at a minimum through a thoughtful review and consideration of other published approaches. Second, the results of this examination of structural uncertainty should be included in any report of results. These measures will enhance decision-makers' ability to see nuances between therapeutic alternatives and to understand the overall sensitivity of cost-effectiveness analysis to the choices made in the model's design and assumptions.

Furthermore, to reduce structural uncertainty over time, open discussion and collaboration among model designers and other stakeholders is needed to identify the model structures that best reflect current knowledge regarding the impact of treatment on outcomes, the progression of the disease over time, and associated treatment decisions. Open-source model development, such as that conducted by IVI through the Open-Source Value Project (OSVP), is an essential route to developing consensus on modeling approaches. Through open and iterative development, approaches like the OSVP increase transparency and foster collaboration on model structure and best methods for accounting for structural uncertainty.

CONCLUSION

An example evaluation using the IVI-RA model shows that decisions regarding model structure can have a substantial impact on the estimates of model-based cost-effectiveness analysis. Cost-effectiveness analyses to inform value assessment should not be limited to incorporating parameter uncertainty; the impact of structural uncertainty should be evaluated as well. This allows for a more accurate reflection of the uncertainty regarding the value of a treatment based on current insights and evidence available.

ABOUT THE INNOVATION AND VALUE INITIATIVE

IVI is a nonprofit research organization committed to advancing the science and improving the practice of value assessment in healthcare through collaboration among thought leaders in academia, patient organizations, payers, life science firms, providers, delivery systems and other organizations.

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