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Decision-Analytic Modeling: Past, Present, and Future

Multivariable and Structural Uncertainty Analyses for Cost-Effectiveness Estimates: Back to the Future

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ABSTRACT

Background: In this commentary, celebrating the 20th anniversary of the journal Value in Health, I present a brief overview and illustration of the evolution over the past 20 years of the methodological literature providing guidelines for multivariable and structural uncertainty analysis for cost-effectiveness estimates.

Methods: To illustrate the impact of the guidelines for uncertainty analyses, I show how the inclusion of multivariable and structural uncertainty analyses in cost-effectiveness analyses published in Value in Health changed over the past 20 years using publications from 1999/2000, 2007 and 2017.

Results: The commentary is organized in three sections: past, focusing on the development and use of methods for multivariable uncertainty analysis; present, focusing on the growing awareness of the need for structural uncertainty analysis, suggested frameworks for structural uncertainty analysis and how it is currently implemented; and future, considering different methods for combining multivariable and structural uncertainty analyses over the next decades.

Conclusions: I conclude by suggesting how the continued evolution of uncertainty analyses in published studies and health technology assessment submissions can best take into account an important goal of cost-effectiveness analyses: to provide useful information to decision makers.

Keywords: multivariable, probabilistic sensitivity analysis, structural, uncertainty analysis.

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Introduction

In this commentary, written to celebrate the 20th anniversary of the journal *Value in Health* (*ViH*), I present a brief overview of the evolution over the past 20 years of recommended methods for multivariable and structural uncertainty analyses for cost-effectiveness estimates. To illustrate the impact of these recommendations, I show how multivariable and structural uncertainty analyses in cost-effectiveness analyses (CEAs) published in *ViH* changed over the past 20 years. The commentary is organized into 3 sections: *past* (focusing on the development and use of methods for multivariable uncertainty analysis from 1997 to 2007 and illustrated by multivariable uncertainty analyses in CEA publications in *ViH* in 1999/2000 [volumes 2/3] and in 2007 [volume 10]), *present* (focusing on the growing awareness of the need and suggested frameworks for structural uncertainty analysis from 2003 to 2018 and illustrated by how multivariable and structural uncertainty analyses were included in CEA publications in *ViH* in 2017 [volume 20]), and *future* (focusing on proposals for combining multivariable and structural uncertainty analyses over the next decades to ensure that CEAs continue to provide useful information to the decision makers who are responsible for making decisions about formulary approval or reimbursement).

The CEA publications appearing in the *ViH* print journal in 2017 (volume 20) were identified using the following keyword search strategy on MEDLINE: “Value Health”, “2017” and “cost-effectiveness.” A similar set of keywords was used for 1999, 2000, and 2007. A list of the studies identified in these searches is included in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.11.013. The CEA publications in *ViH* are not presumed to be representative of CEA publications in all journals.

In this commentary, *multivariable uncertainty analysis* is defined as the combined impact on model results of the uncertainty about the values of all the inputs (observed clinical outcomes and costs) used in the model.[1] The 2 types of multivariable uncertainty analysis are probabilistic sensitivity analysis (PSA) and bootstrap analysis using patient-level data. *Structural uncertainty analysis* is defined as the impact on model results of “the assumptions inherent in the decision model.”[2]

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Past

The first methodological discussion of multivariable sensitivity analysis in *ViH* was an article by Hay[3] published in 1998 in which a regression-based approach was proposed for estimating the impact of uncertainty of multiple input values simultaneously on the incremental cost-effectiveness ratio (ICER). In this article, Hay suggested that such an analysis would enable decision makers to understand the impact of changes in these parameter values on the ICER.[3] Hay suggested changing values simultaneously, either randomly or systematically, from plausible ranges of input parameter values including "drug prices, disease risks, survival, quality of life weights, discount rates, healthcare utilization and costs, treatment efficacy and safety parameters, etc." The different sets of input values would be used to populate an economic model and generate multiple alternative values for the ICER. The alternative values of inputs and ICERs could then be used in a regression analysis relating the ICER with alternative values for the input parameters. Hay concluded that the resulting regression equation would allow those using the models for decision making to readily estimate the expected cost effectiveness of a new product given a set of input variable values relevant for their decision context.

About the same time that the Hay article was published in *ViH*, articles were published in other journals proposing multivariable uncertainty analysis using a probabilistic approach (ie, PSA) (eg, Hunink et al,[4] Glick et al,[5] Briggs et al,[6] and Baltussen et al[7]) and suggesting presentation of the results as cost-effectiveness acceptability curves (CEACs) (eg, van Hout et al,[8] Briggs and Fenn,[9] Fenwick et al,[10] O'Brien and Briggs[11]). Other articles presented different methods for estimating the impact of multivariable uncertainty on the ICER (eg, Parmigiani et al[12]) or on net benefits estimated using a threshold value reflecting willingness to pay for an additional unit of health (eg, Stinnett and Mullahy[13]). Parmigiani et al[9] suggested Bayesian inference or bootstrapping methods for estimating the impact of input values on the ICER. Stinnett and Mullahy[13] concluded in their study that PSAs based on net benefit estimates are easier to interpret than those for the ICER, especially when the joint distribution of incremental costs and benefits lies in more than 1 quadrant of the cost and effectiveness plane and/or when there are multiple comparators in the analysis.

In 1999 to 2000, 6 of the 7 CEAs published in *ViH* included only deterministic 1-way sensitivity analyses of input values. The exception was the study by Pechevis et al[14] who used Monte-Carlo simulation to compute the costs, outcomes, and cost-effectiveness ratios by taking 1000 random draws from probability distributions for each of the input parameter values. In their article, they presented estimates of the lower 5th percentile, median, and upper 95th percentile for the ICER on the basis of 1000 runs of the model[14] Limited structural sensitivity analysis for 1 or more of the model assumptions was included in the 1-way sensitivity analyses in all but the analysis by Lecomte et al.[15]

By 2007, 9 of the 12 CEAs published in *ViH* (volume 10) either included a PSA (6 studies) or used bootstrapping (3 studies), allowing multiple input values to vary simultaneously for their sensitivity analyses, with only 3 of the 12 including only 1-way sensitivity and/or scenario analyses to estimate the impact of input uncertainty. In addition, all the 2007 studies, except 1 study,[16] included some structural variables in their 1-way sensitivity or scenario analyses. For example, in a CEA of second-line treatment for hyperphosphatemia, Brennan et al[17] assumed an average relative risk of mortality for all those with hyperphosphatemia that remained constant over time. In structural sensitivity analysis, they allowed the relative risk of mortality to decrease over time as those with higher risk left the population.

In my 2010 *ViH* editorial,[18] I noted that although the journal's editorial board had discussed whether a PSA should be required for all submitted CEAs, they decided that the journal should not require a PSA to allow for variability in methods. Nevertheless, journal reviewers had started to question the completeness of those submissions that did not include a PSA or bootstrap analysis, and in these cases, inclusion of a PSA or an equivalent form of multivariable uncertainty analysis addressing input parameter uncertainty became a de facto criterion for acceptance for publication because of the need for authors to respond to all reviewer comments. Nevertheless, structural uncertainty analysis was not a concern generally raised by reviewers at that time, and the CEAs published in *ViH* did not systematically test the impact of changes in all the model assumptions on the results in 1-way sensitivity analyses. None of the CEAs tested the impact on the results of changes in all the model assumptions together or the impact of changes in structural assumptions and input values combined.

Present

Methodological discussions about how to include uncertainty analysis in CEAs continued between 2003 and 2016. Although multivariable uncertainty analysis for inputs continued to be recommended, methodological publications during this period pointed out that other sources of uncertainty such as structural uncertainty (ie, model design and structural assumptions) can be just as impactful as input uncertainty on the ICER or net monetary benefits outcome measure (eg, Brisson and Edmunds[19] and Claxton[20]). Bayesian techniques were proposed to generate estimates of the impact of these multiple causes of uncertainty (eg, Spiegelhalter and Best[21]). Some researchers described the limitations of the CEAC for communicating uncertainty to decision makers and proposed a return to the estimation of confidence or credible intervals for the cost-effectiveness ratio using the results from the PSA along with estimates of the value of additional information for uncertain input values (eg, Groot Koerkamp et al[22]). An International Society for Pharmacoeconomics and Outcomes Research modeling task force report[2] on uncertainty analysis published in *ViH* in 2012 considered both structural and input uncertainty. In this report, the authors first recommended a calibration approach in which the outcomes from alternative model structures and assumptions are tested against observational real-world data and the results are used for guiding the final choice of model structure and assumptions. Then, once the best-fitting model has been selected, both 1-way sensitivity analysis and multivariable PSA should be used for a determination of the impact of input uncertainty. The report also recommended reporting the results of a PSA as a CEAC supplemented by estimates of the value of information for the most uncertain parameters.

By 2017, 17 of the 25 CEAs published in *ViH* included a PSA in which ICERs or net monetary benefit outcomes were estimated using input values taken from multiple random draws from probability distributions for each input. In addition, 4 articles used a nonparametric bootstrap analysis using patient-level data to assess multivariable input uncertainty. Nevertheless, 4 articles did not include any multivariable sensitivity analyses. One of the 4 studies without a formal PSA[23] included an analysis of first-order uncertainty to capture the variability in the input parameters. A second study[24] generated an estimate of the uncertainty of the ICER using upper and lower confidence limits for all the clinical inputs. Two studies[25,26] focused their uncertainty analysis on structural uncertainty only. Of the 21 studies that included multivariable uncertainty analysis, 18 presented in the main text a cost-effectiveness or net monetary benefits acceptability curve. A value of information estimate was presented in only 3 studies.[27-29]

In contrast to the systematic exploration of multivariable uncertainty, structural uncertainty was not systematically explored in any study published in 2017 in *ViH*. Nevertheless, many elements of structural uncertainty relating to model structure and assumptions were included either in the 1-way sensitivity analysis or in scenario analyses in all the studies. However, the interpretation of the results of these analyses was not made clear and no attempt was made to generate combined estimates including all elements of structural uncertainty or combined estimates of structural and multivariable uncertainty. A stepwise approach starting with calibration of the structural model to observational data, followed by a PSA, as recommended in the International Society for Pharmacoeconomics and Outcomes Research task force report,[2] was not used in these published studies, nor were alternative structural assumptions tested using a PSA.

Three recent publications provide interesting empirical demonstrations of the impacts of structural uncertainty on the CEA results by comparing the results from hypothetical models with different structural assumptions. An article by Ride[30] on setting boundaries for CEA demonstrated that for CEAs of postpartum depression, including a longer time horizon for the effects of the depression and including impacts on the whole family as well as the mother made a large difference in the cost-effectiveness estimates for treatments of postpartum depression. Penaloza-Ramos et al[31] tested the impact of the inclusion of different health states in cost-effectiveness models of primary care interventions for hypertension. The authors showed that increasing or decreasing the number of possible cardiac events associated with hypertension and/or allowing for secondary events after the first event did not materially affect the results of the CEA. Nevertheless, a study by Frederix et al[32] showed that differences in the included events in a breast cancer model did have an impact on the cost-effectiveness results. Differences in input values also had an impact on the results. Frederix et al concluded that there should be disease-specific model standardization and improved guidance for identifying data sources.

Several methodological reviews of CEAs have also demonstrated the impact of structural uncertainty on the results. In a systematic literature review of schizophrenia CEAs published in 2014,[33] we compared the cost-effectiveness results from multiple published studies that compared the same 2 drugs for the same patient populations. We showed that where conflicting results were found, the differences between them were not related to the modeling technique used (ie, Markov model or discrete event simulation). Rather, the differences were driven by differences in the model structural assumptions, such as how discontinuation, response, and relapse rates were included in the model, and differences in input values and data sources. A recent review by Silva-Illanes and Espinoza[34] on colorectal cancer screening models also showed that differences in structural assumptions across the studies had a significant impact on the estimated ICERs. A review by Le[35] on economic analyses in advanced breast cancer also found significant differences in the estimated ICERs in models with different health states. The evidence from these 3 reviews indicates that the results of a CEA may be sensitive to the disease states or events included in the model and other structural assumptions as well as the input values and data sources.

It is clear from the empirical demonstrations and methodological reviews and from the 1-way sensitivity analyses in the CEAs published by *ViH* described earlier that both model structural assumptions and model input estimates can have a large impact on cost-effectiveness estimates. PSA or bootstrap multivariable analysis methods use a systematic approach to provide a decision maker with estimates of the impact of uncertainty about input estimates on the magnitude of the ICER or net monetary benefit outcomes. But at present, the impact on these outcomes of all model structural assumptions is not systematically tested in the analyses provided to decision makers. In addition, a PSA representing multivariable uncertainty is typically run using a base-case set of structural assumptions and so does not take into account the impact of structural uncertainty.

Recently, a group of researchers has presented a framework that could be used to develop guidelines for the systematic assessment of structural uncertainty.[1,36-40] Bojke et al[36] identified 4 different categories of structural uncertainty: (1) inclusion of relevant comparators, (2) inclusion of relevant events, (3) alternative statistical estimation methods, and (4) clinical uncertainty. Relevant events might include choice of health states or outcomes impacted by the comparators. An example of such a structural uncertainty analysis was illustrated by Rognoni[41] comparing the impact on the ICER of using health states defined by best radiological response (stable, complete, or partial) according to the mRECIST criteria rather than health states defined as stable or progressing disease in a CEA of treatments for hepatocellular carcinoma. Alternative statistical methods might include accounting for missing data from a clinical trial using imputation rather than performing the analysis using only those patients who completed the trial. An example of such a structural uncertainty analysis was tested in a bootstrap analysis of the CEA by Seidl[42] of nurse case management for patients with myocardial infarction. Clinical uncertainty might include assumptions about duration of treatment, treatment efficacy, and discontinuation rates beyond the trial time period or treatment sequencing after initial treatment failure or the use of different data sources for the efficacy or effectiveness outcomes. Some of these types of clinical uncertainty were tested in 1-way structural analyses of alternative assumptions about discontinuation rates and extrapolation of efficacy beyond the trial time horizon in a CEA of a treatment for chronic heart failure by Ramos[29] The impact of the use of progression-free survival patient-level data from different clinical trials was tested in a CEA of treatments for pancreatic cancer in a 1-way sensitivity analysis.[43]

These researchers[1,36-40] suggest 3 methods for systematically assessing the impact of all categories of structural uncertainty and uncertainty combined: (1) selecting the model that best fits the observed data (similar to the suggestionof model calibration by Briggs et al[2]) and running the input PSA using this model; (2) using model averaging[44] (running the model including the PSA with alternative structural assumptions and averaging the results using weights developed either from likelihood estimates or from expert opinion); and (3) expanding the model structure to include all possible alternative structures in the same model and parameterizing the uncertainty in all the model inputs, including the structural inputs, using appropriate probability distributions and including them in the PSA.[36]

Future

Looking into the future, how should uncertainty analysis in the next generation of CEAs differ from those illustrated by the *ViH* 2017 publications to ensure that the information provided is useful to healthcare decision makers? One simple change in the presentation of the uncertainty analysis could be to have the 1-way sensitivity analyses presented in separate sections, highlighting the impacts on the CEA results separately for model structural assumptions and input parameter ranges. All model structural assumptions could be included in the 1-way sensitivity analyses covering the 4 different categories of structural variability that have been identified in the articles recommending methods for structural uncertainty analyses.[1,36-40] Also, if it is clear from the 1-way analyses that 1 or more of the structural assumptions have a large impact on the CEA results, then the authors either should include the results from more than 1 PSA run using models with the alternative assumptions or should use one of the approaches to estimate the joint impact of structural and multivariable uncertainty (ie, best-fit, averaging, or expanded model structure) that have been suggested.[1,36-40]

Alternatively, another approach to address model structural uncertainty when comparison of modeling results for treatments of only the same disease is of interest would be to have "disease-specific model standardization and improved guidance" for the structural assumptions as suggested in the article by Frederix et al.[32] An example of a standardized disease-modeling approach was presented in a systematic review of economic evaluations in chronic pain by Sullivan[45] They identified choice of time horizon and treatment pathways as key drivers of model results. They then provided an "open source code" model that was available to all researchers, which they recommended should be used for standardized economic evaluations comparing alternative chronic pain treatments.

In recent articles, Ghabri et al[1] and Afzali et al[40] suggest that clear guidance on how to present estimates of structural uncertainty in CEAs is needed and should be developed by the health technology assessment (HTA) agencies. Figure 1 in the study by Jackson et al[37] provides a detailed flowchart for assessing the impact of structural parameters on the CEA that could serve as a starting point for the development of such guidance.

Conclusions

Published and HTA guidance for performing and reporting multivariable uncertainty analysis has led to a more comprehensive and consistent approach to multivariable uncertainty analysis over the past 20 years in the *ViH* publications reviewed. In addition, 1-way sensitivity or scenario analyses in the *ViH* publications reviewed include selected structural assumptions one at a time, but their combined impact on the outcomes is not considered.

It is quite likely that HTA guidance for a systematic approach to structural uncertainty on the basis of the frameworks that have already been proposed may be developed over the next decade and added to the guidance for estimating multivariable uncertainty. My concern is that healthcare decision makers may have increasing difficulty using the results of CEAs that follow such guidance. This will be because of the added volume and complexity of the sensitivity analyses and the added uncertainty about the likely predictive validity of the results. Most PSAs include at least some distributions for input parameters that are not derived from observed variability but are based on assumptions or expert opinion. In addition, lack of correlation among the included variables in a PSA is generally assumed even when this might not be true in all cases. Adding a systematic approach for including structural uncertainty analyses in 1-way sensitivity analyses, scenario analyses, or an expanded PSA will result in even more uncertainty as to the predictive validity of the results and, hence, may reduce their value to decision makers.

Two of the approaches described in this commentary could avoid this added concern about the complexity of the analyses and the predictive validity of the results and increase the credibility and usefulness of the results: (1) demonstration that the selected model structural assumptions and input values produce outcomes that match current observational data[2] and (2) development of standardized and validated "open source–coded" disease models and inputs.[32,45]

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