A Computationally Efficient Alternative Method for Probabilistic One-way Sensitivity Analysis

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POSA315

Introduction

- McCabe et al. 2020[1] proposed probabilistic one-way sensitivity analysis (POSA) to replace traditional one-way sensitivity analysis (OWSA). POSA incorporates the whole distribution of uncertain parameters, not only their extreme values, and better reflects the impact of a given parameter on the expected net benefit compared with deterministic sensitivity analysis.
- In POSA, the one-way analyses are implemented as probabilistic analyses. In traditional OWSA, only one parameter is changed at a time, and in traditional probabilistic sensitivity analysis (PSA), all uncertain parameters are varied at the same time according to an assumed joint distribution. PSA thus incorporates the potentially non-linear and interdependent uncertainty of all model parameters.
- However, it is unable to analyze the model outcomes' sensitivity to each parameter and identify the key model drivers, which is the aim of OWSA. POSA merges the two approaches. Each uncertain parameter is fixed one-by-one as in OWSA, while all other parameters are varied synchronously as in PSA. The result of a POSA scenario is a distribution of model outcomes similar to PSA that must be aggregated to support decision-making.
- McCabe et al. 2020[1] recommends the conditional mean incremental net monetary benefit (iNMB), E(iNMB), and the probability of a positive iNMB, Prob(iNMB>0) as the statistics to be most helpful for health technology assessment and decisions based on cost-effectiveness models.
- Importantly, McCabe et al. 2020[1] also recommends that the selected parameter is not only fixed to one or two of its extreme values, but to several points that span its whole distribution (e.g., at its deciles). This facilitates a sanity check on the model and would reveal any non-monotone or non-linear behavior with respect to the selected parameter and helps identify the threshold for significant impact (if any) for any given parameter.
- PSA bears a significant computational burden. Practically, they are based on the repetition of deterministic model calculations and runs, using in each run a different set of parameters.
- As most health economic models are developed in software not optimized for speed, calculation run-time may render repeating PSA of more complex analyses unfeasible. For a realistic, complex cohort, spreadsheet-based model, a single run may take a tenth of a second. For a patient-level simulation model, a single run-time may be in the order of tens of seconds.
- For POSA as suggested by McCabe et al. 2020[1], each parameter (p), quantile (q), and probabilistic simulation (n) require a deterministic run. With a typical setup of 100 uncertain parameters, 10 quantiles, 1,000 PSA trials, it requires a million deterministic model runs. That is in the order of a day for a cohort model and weeks for patient-level models, that is not practically feasible.

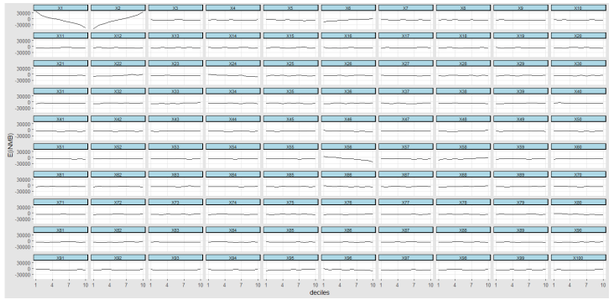
Objective

- We propose an alternative, simple, computationally more efficient analysis approach that can provide the same insight as POSA.

Methods

- Instead of running a PSA for each parameter of interest and each quantile, we propose to run just one PSA with a sufficiently large number of trials and analyze its results to obtain the data required by POSA. This analysis would mean that for each parameter and each quantile we select the PSA trials where the parameter fell in the given quantile (of its own distribution) and report E(iNMB) and Prob(iNMB>0) for the selected trials.
- To have n PSA trials for each parameter and each quantile, with this method only $\mathbf{q} \times \mathbf{n}$ deterministic runs are required, as opposed to POSA with $\mathbf{p} \times \mathbf{q} \times \mathbf{n}$ runs.
- Indeed, the economy of the method is that it reuses the PSA trials across parameters, thus there is no need to repeat the time-consuming PSAs for the number of parameters of interest. At the same time, the analysis can focus on the same ranges of the selected parameter's distribution, but instead of fixing its value as in OWSA or POSA, a sample is gathered from a large pool of PSA trials, where the given parameter has fallen in the range of interest.
- For the purposes of this exercise, a simplified and anonymized but still reasonably complex partitioned survival oncology model was used. It has been built in Microsoft Excel® and submitted for health technology assessment in recent years worldwide. A PSA was run with 10,000 trials to generate 1,000 observations in each decile of the parameter distributions. We were able to run the PSA within an hour. As we included 100 parameters in the analysis, the same analysis with the original POSA recommendation would have taken over three days.
- We have analyzed the data generated with Microsoft Excel® in R that is convenient to visualize information in a multifaceted dataset. We have plotted the effect of each 100 parameters on E(iNMB). This allowed us to identify, quickly and visually the parameters with important impact, or the ones that behave unexpectedly, practically taking the function of the tornado diagram in traditional OWSA.

Figure 1. Expected iNMB per Deciles of Each Parameter; Drug A vs. Drug C at WTP Threshold of $100,000



- We can then select the most important parameters and compare their effect on E(iNMB) and Prob(iNMB>0) in more detail.

Figure 2. Expected iNMB per Deciles of Three Key Comparators; Drug A vs. Drug C at WTP Threshold of $100,000

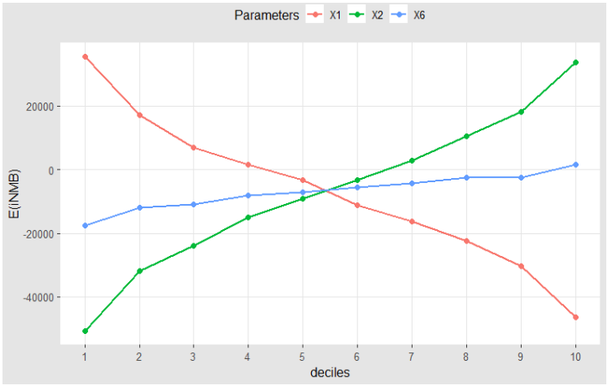
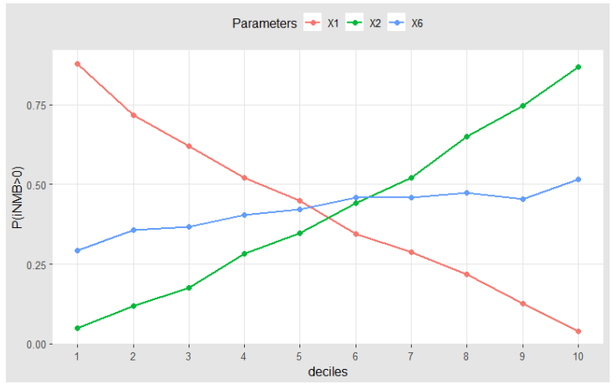


Figure 3. Probability of Positive Net Benefit per Deciles of Three Key Parameters; Drug A vs. Drug B at WTP Threshold of $100,000

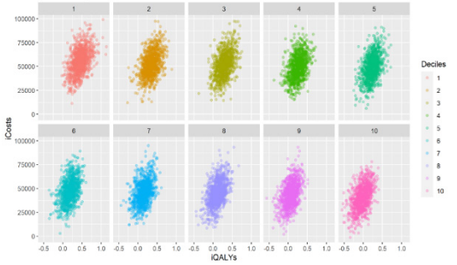


References

1. McCabe C, et al. One-Way Sensitivity Analysis for Probabilistic Cost-Effectiveness Analysis: Conditional Expected Incremental Net Benefit. *PharmacoEconomics*. 2020;38:135–141.

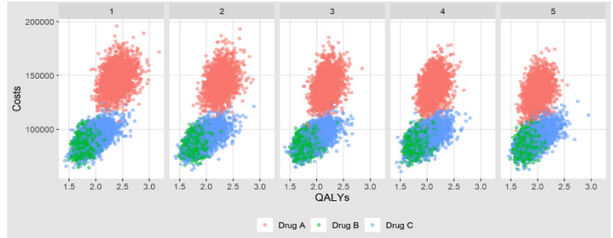
- It is also possible and worthwhile to visualize parameters' effect on the cost effectiveness plane and see how pronounced it is relative to the variation of PSA trials, how much a specific parameter is able to dominate the effect of other parameters. In our example, parameter X1 (that was an overall survival [OS] hazard ratio [HR]) has a more distinct effect (not only because the magnitude), than X6 (that was a progression-free survival [PFS] HR).

Figure 4. Cost-effectiveness Plane Sensitivity per Deciles



- Many additional options for visualization exist; multiple comparisons can be placed on the same graph, and quintiles can be presented, to investigate impact across comparisons.

Figure 5. Cost-effectiveness Plane Sensitivity per Quintiles



Conclusions

- The original criticisms of OWSA inspiring POSA are valid; however, its execution may be prohibitive in many larger models.
- With our proposed method, in a model of average complexity, with 100 uncertain parameters, only 1% of the run-time is required to generate POSA results. Results will not be identical, since the quantiles of parameters will be different when set up as proposed for POSA, vs. defining them post-hoc from a large run of initial PSA. Nevertheless, they should achieve the same objective. Additionally, we propose ways to visualize the results of such analyses, to help better understand models and roles of its parameters.

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