Impact of correlated outcomes in probabilistic analyses when treatment effects are derived from a network meta-analysis

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Background

Common approaches to the development of cost utility models include decision trees, markov models, and microsimulation approaches. In many cases these models are non-linear functions of parameters (eg, treatment effects) that are measured with uncertainty. In these cases, the use of deterministic model inputs (eg, mean or median odds ratios) will lead to biased estimates of net monetary benefit since the expected value depends on the full joint distribution of uncertainty in parameters. For this reason, the base case is typically to conduct a probabilistic sensitivity analysis (PSA), in which inputs to the model are assigned probability distributions, rather than fixed values.

An under appreciated consequence of non-linear models is that the expected value of net monetary benefit will also depend on the correlation between parameters. This is most commonly considered with respect to the correlation in regression coefficients for risk equations, or in relative effects estimated from network meta-analyses. A generally ignored issue is the potential for correlation in treatment effects across outcomes (eg, progression free survival and OS, or different measures of disease activity) which may introduce bias. This correlation could be accounted for through routine implementation of multivariate approaches to evidence synthesis (Bujkiewicz S 2019), although this is rarely conducted owing to the increased complexity of implementation.

Objective

The objective of this project was to explore the potential impact of accounting for correlation in treatment effects across multiple outcomes when model results are some non-linear function of these inputs.

Methods

For simplicity we consider a case where a validated meta-model can accurately reproduce the estimates from a cost-effectiveness analysis. Meta-models are a useful approach to reduce computational complexity of evaluations of cost utility models, and can be a useful tool when trying to understand the degree to which a model may be a non linear function of inputs. The analysis considers only a single therapy, with the goal of exploring how correlation in the absolute estimates of two continuous outcomes could meaningfully bias estimates of net monetary benefit if unaccounted for.

We specify outcomes as arising from a bivariate normal distribution specified as follows.

$$\begin{pmatrix} Y_1 \\ Y_2 \end{pmatrix} \sim \mathcal{N}\left[\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2\rho \\ \sigma_1\sigma_2\rho & \sigma_2^2 \end{pmatrix} \right]$$

Where $\mu_1 = 2$ and $\mu_2 = 3.5$, $\sigma_1 = 1$, $\sigma_2 = 1.75$ and ρ is varied from -0.9 to 0.9. The expected total utilities from the meta-model are Poisson distributed with

$$Y \sim \text{Poisson}(\lambda)$$
$$log(\lambda_{\text{utilities}}) = 0.1 + Y_1 1.5 + Y_2 2$$
$$log(\lambda \text{costs}) = 0.1 + Y_1 3 + Y_2 5$$

This model structure means that utilities and costs are non-linear functions of outcomes and would be expected to provide a biased estimate of true costs and utility if correlation is not appropriately modeled.

Results

As expected, failure to capture correlation results in bias that varies from small to large, depending on the degree of correlation (Table 1). The effects also appear to be sensitive to the scale of the relevant model output, so that differences are larger for costs than for quality adjusted life years. This suggests that the relative magnitudes of outputs may provide some sense of the importance of capturing parameter correlation.

Table 1: Mean utilities and costs across correlations

Correlation	Utilities	Cost
-0.9	3.71	$1,499
-0.5	4.51	$5,202
-0.3	4.99	$9,522
0.0	5.75	$21,539
0.3	6.66	$62,353
0.5	7.37	$101,074
0.9	8.97	$328,741

When evaluating the expected value over a range of willingness to pay thresholds, we also see that the bias increases as willingness to pay increases.

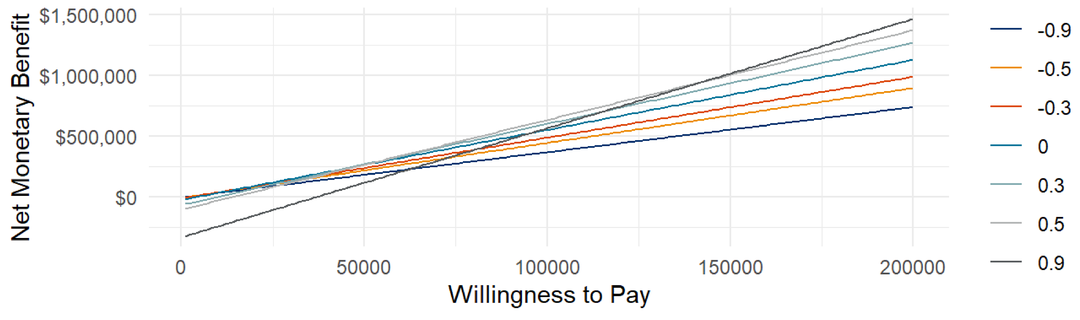

Figure 1: Net monetary benefit across different correlations

Conclusions

We found that models in which costs/QALYs are non-linear functions of parameters across multiple outcomes can give biased estimates if correlations are assumed to be zero as is most often the case. We did not explore the potential impact on comparative benefits between therapies, but this may be an interesting avenue for future research. Based on the trends observed in the present study we might expect the largest biases to be seen in therapies with the most benefits and/or higher costs, which may have important implications for decision-making.

References

Bujkiewicz S, Papanikos T, Achana F. 2019. “Nice Dsu Technical Support Document 20: Multivariate Meta-Analysis of Summary Data for Combining Treatment Effects on Correlated Outcomes and Evaluating Surrogate Endpoints.”