The Implications of Parameter Independence in Probabilistic Sensitivity Analysis: An Empirical Test

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BACKGROUND AND OBJECTIVES

In probabilistic sensitivity analysis (PSA), it is typical to see distributions assigned to all (relevant) parameters in a model. However, attention is only usually paid to estimating covariance or interactions between a small number of parameters, if any at all. The study explores the impact of interaction and non-interaction assumptions on the outcomes of PSA.

METHODS

A simple, eight-state Markov model (including 'death') was developed, with hypothetical inputs, as shown in Tables 1 and 2 below. The model was built with a lifetime time horizon and generates costs and QALYs for two hypothetical treatments, 'Treatment' and 'Comparator'.

Table 1: Effectiveness inputs

Transition probability matrix ('Treatment')

	1	2	3	4	5	6	7	8 (Dead)
1	84%	5%	2%	0%	0%	0%	0%	0%
2	10%	79%	5%	2%	0%	0%	0%	0%
3	5%	10%	76%	5%	2%	0%	0%	0%
4	0%	5%	10%	76%	5%	2%	0%	0%
5	0%	0%	5%	10%	75%	5%	2%	0%
6	0%	0%	0%	5%	10%	78%	5%	0%
7	0%	0%	0%	0%	5%	10%	83%	0%
8 (Dead)	1%	1%	2%	2%	3%	5%	10%	100%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Transition probability matrix ('Comparator')

	1	2	3	4	5	6	7	8 (Dead)
1	77%	3%	1%	0%	0%	0%	0%	0%
2	15%	74%	3%	1%	0%	0%	0%	0%
3	7%	15%	72%	3%	1%	0%	0%	0%
4	0%	7%	15%	72%	3%	1%	0%	0%
5	0%	0%	7%	15%	71%	3%	1%	0%
6	0%	0%	0%	7%	15%	74%	3%	0%
7	0%	0%	0%	0%	7%	15%	86%	0%
8 (Dead)	1%	1%	2%	2%	3%	7%	10%	100%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Table 2: Costs and utility inputs

Health state	1	2	3	4	5	6	7	8 (Dead)
Annual cost	£0	£0	£1,000	£3,000	£5,000	£10,000	£50,000	£0
Utility	1.00	0.97	0.94	0.90	0.80	0.70	0.50	0.00

As well as producing a deterministic ICER, the model was developed to allow three different approaches towards the probabilistic sensitivity analysis, as described below. In all case, the distributions assumed a standard error equal to 10% of the mean parameter value.

Scenario 1: All parameters varied independently using individual 'seeds'

In this scenario, every single input in the model was varied as an individual parameter. For all parameters, probabilities were varied using beta distributions, cost were varied using gamma distributions and utility scores were varied using beta distributions. Because there are 8 health states in the model, the state transition probability matrix has 64 potential probabilities for each treatment. Combined with the cost and utility inputs, this meant that the model contains 144 individual parameters, each of which was varied independently.

Scenario 2: Single multiplier 'seeds' used for separate types of input

In Scenario 2, the effectiveness inputs for each treatment were varied using a single multiplier, based on a lognormal distribution with a mean of 1 and a standard error of 0.1. Probabilities that *improved* the patient's health state were multiplied by the 'multiplier', whilst probabilities that *worsened* the patient's health state were divided by the multiplier (no change was estimated using the residual probability). This way, a single seed for each treatment determined all inputs within each matrix. Similarly, all costs were varied using a single multiplier, and all utilities were varied using a (separate) single multiplier.

Scenario 3: One single multiplier 'seed' used for the whole model

The third scenario used a similar approach to Scenario 2, expect that *one single seed* was used to estimate all parameters in the model. Thus, one multiplier drove all effectiveness inputs for the 'Treatment', its inverse drove all effectiveness inputs for the 'Comparator', and the same multiplier drove the cost and utility inputs.

RESULTS

The mean outcomes from each approach are shown in Table 3 below. The standard deviations for each output are shown in Table 4.

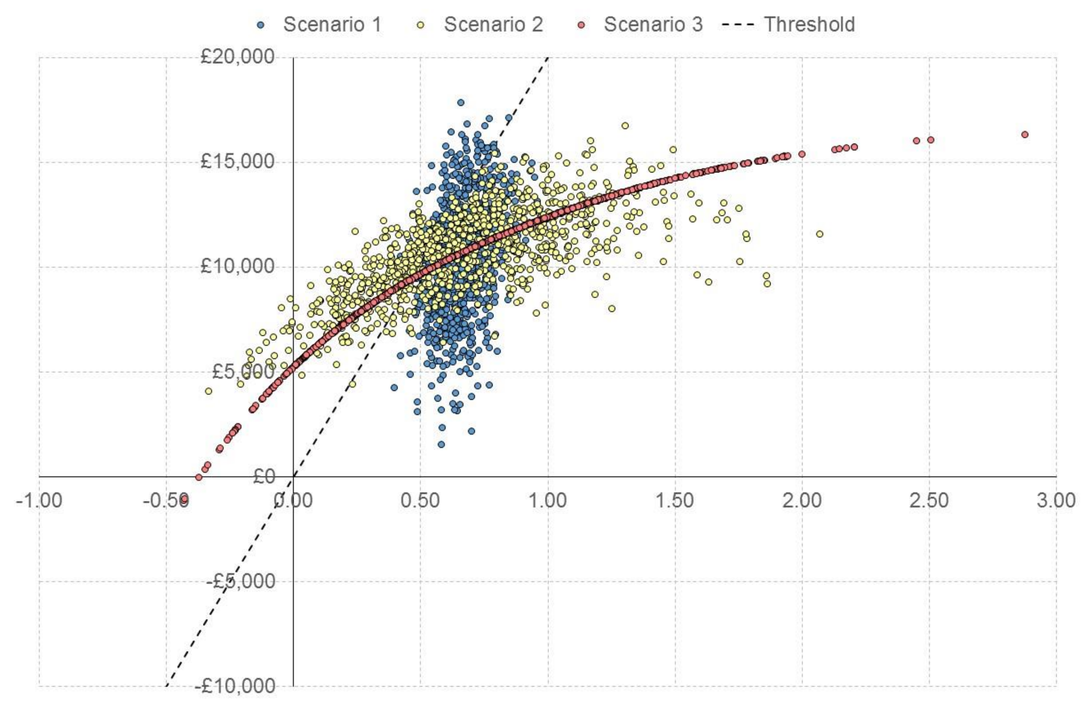
Table 3: Mean outputs

	Treat cost	Comp cost	Treat QALY	Comp QALY	Inc costs	Inc QALYs	ICER	NMB	%CE
Deterministic	£35,507	£24,866	1.910	1.249	£10,640	0.661	£16,095	+£9,193	n/a
Scenario 1	£35,626	£25,039	1.920	1.256	£10,588	0.664	£15,943	+£9,335	86%
Scenario 2	£35,392	£24,902	1.924	1.254	£10,490	0.671	£15,638	+£9,635	66%
Scenario 3	£35,403	£25,177	1.947	1.244	£10,226	0.703	£14,537	+£10,876	64%

Table 4: Standard deviations for each output

	Treat cost	Comp cost	Treat QALY	Comp QALY	Inc costs	Inc QALYs	ICER	NMB	%CE
Deterministic	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Scenario 1	£2,081	£2,868	0.104	0.068	£2,590	0.086	£3,815	£2,537	86%
Scenario 2	£2,184	£3,068	0.361	0.193	£1,988	0.361	£621,468	£6,028	66%
Scenario 3	£1,269	£4,298	0.464	0.048	£3,070	0.512	£319,474	£7,358	64%

Figure 1: Scatter-plots



It is noteworthy that Scenario 1 (where all parameters are varied independently) produces the highest ICER, but also displays the highest likelihood of being cost-effective (see highlighted areas in Table 3). This is because the variation across so many independent parameters tends to cancel itself out, producing very little variation in effectiveness (as shown in the highlighted area in Table 4 and in the blue scatter-plot). This suggests that the choice of approach in PSA can substantially affect the model's estimation of uncertainty.

CONCLUSIONS

This analysis demonstrates that, if a specific input parameter (such as 'effectiveness') is broken down into several components which are varied independently, then it is likely that the variation in each parameter will cancel out the effect of the changes in the other parameters. Indeed, the greater the 'granularity' of the input parameters, the greater the likelihood that the variations will offset each other, thus suggesting a false level of certainty in the PSA's results. This analysis demonstrates the outcomes of a PSA can be influenced by the level of detail that the modellers choose to include and, counterintuitively, modellers can create 'false' confidence in PSA results by including more parameters.

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