One-way sensitivity analysis for stochastic cost effectiveness analysis: conditional expected incremental net benefit

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Abstract

Although stochastic analysis has become the accepted standard for decision analytic cost effectiveness models, deterministic one-way sensitivity analysis continues to be used to meet decision makers' need to understand the impact that changing the value taken by one specific parameter has on the results of the analysis. In this paper we review the reasons why deterministic one way sensitivity analysis will provide decision makers with biased and incomplete information. We then describe how stochastic one-way sensitivity analysis can be successfully implemented, and apply these methods to a previously published cost effectiveness analysis, to produce stochastic Tornado Diagram and the Conditional Incremental Net Benefit Curve. We then discuss how these outputs should be interpreted and the potential barriers to the implementation of stochastic one-way sensitivity analyses.

Introduction

The last two decades have seen rapid developments in the methods for cost effectiveness analysis in the context of health technology assessment.[i] Arguably the greatest developments have been seen in the area of analyzing the uncertainty relating to the expected costs and outcomes of alternative interventions.
[2 3 4 5 6 7]

Over the last decade, stochastic models have replaced by deterministic models for reference case analyses. Whilst the flawed nature of deterministic analyses has been accepted, submissions to HTA organisations continue to include a range of deterministic approaches to exploring decision uncertainty, notably one-way sensitivity analyses, and threshold analyses. The value of such analyses to decision makers is clear. They purport to address important questions such as the sensitivity of the result to changes in one or more components of the evidence. However, it is important to recognize that just as deterministic models of non-linear relationships will produce biased results; deterministic sensitivity analyses will also produce biased results. The move to eliminate deterministic sensitivity analyses from recognized good practice is an outstanding task in the drive to improve the methodological quality of the economic evaluations. To facilitate the final moves away from deterministic analyses it is necessary to provide alternative methods that meet the needs of decision makers to understand the importance of individual components of the evidence base for the decisions they are charged with making.

In this note we present a method for constructing stochastic equivalents to the conventional tornado diagrams that are typically used to report deterministic one-way sensitivity analyses. The remainder of the paper is structured as follows. In the next section we briefly describe deterministic one-way sensitivity analysis, its rationale and the reasons why it is both an inaccurate and incomplete response to decision makers' legitimate interest in the importance of specific components in the evidence base. We then describe the information that should be provided to decision makers to allow them to understand the importance of a specific parameter for the decision problem – the expected value of perfect parameter information (EVPPI). [8] We go on to explain why EVPPI is insufficient to construct a stochastic Tornado diagram before describing what is required and how such data can be obtained. The penultimate section of the paper provides an example of the stochastic Tornado Diagram using a previously published cost effectiveness analysis and introduces a novel graphical representation of stochastic one-way sensitivity analyses. The final section discusses some strengths, limitations and challenges of the proposed approach to stochastic one-way sensitivity analysis.

Deterministic One-way sensitivity analysis and Tornado Diagrams

Deterministic one-way sensitivity analysis (DOWSA) examines the impact on the predicted costs and outcomes of changing the value of the specified variable whilst holding all other variables constant at their expected value. The intent of undertaking DOWSA is to allow support the decision maker to consider the question – 'What if the specified variable took the a different value from the expected value used in the analysis?' Given that we are (almost) never certain of the true value of any parameter included in an economic evaluation, this is a sensible question for any decision maker to consider. However, there are two problems with the way that DOWSA addresses the question. First, in holding the value of all other parameters constant at their expected values, it assumes that the values of all the parameters are independent of each other. For example if the cost of managing an adverse event is increased compared to the expected cost used in the base case analysis, the quality of life impact (utility) of an adverse event will be unchanged. Intuitively, if adverse events are more expensive to treat than has been assumed, it is credible that the cost is higher because the adverse events are more severe and hence their impact on health related quality of life should also be greater. The DOWSA assumptions required for the value of parameter to change whilst others remain constant lacks face validity and the greater the change in the specified parameter, the less credible that assumption becomes. The estimated costs and outcomes produced by DOWSA are likely to be biased to the degree that the value taken by that parameter and the values of other parameters are correlated.

The second problem with DOWSA as a response to the decision makers' question is that it provides no information on how likely it is that the parameter will take a specific value. Observing that a there is a value that the parameter could take that would lead to a different recommendation, is useful, but it does not tell the decision maker how likely it is that the parameter will take that value. Theoretically possible but highly unlikely parameter values should not carry the same weight in decision making as those that are both possible and likely. Probabilistic analyses use probability density functions (PDFs) to incorporate the likelihood that each parameter will take on any specific value, and we do this because we know that not all *possible* values are equally likely to be the *true* value. To undertake DOWSA of a stochastic model is to throw away important information that is already included in the model. In summary DOWSA of a probabilistic model provides decision makers with unnecessarily incomplete and likely biased information.

Stochastic One-way Sensitivity Analysis (SOWSA).

Whilst DOWSA is a poor mechanism for addressing the decision makers' question about the impact of a specific variable taking a different value, the question is still important. It is incumbent on analysts to provide a complete and unbiased answer to this question. It is helpful for decision makers to have insights into the relationship between specific parameters and the expected costs and outcomes. What is required is a correct Stochastic One-way Sensitivity Analysis (SOWSA).

SOWSA requires that (a) the correlation between the value taken by the parameter of interest and other parameters in the model is reflected in the analysis; and (b) that the probability of the parameter takes a specific value (the uncertainty about the true value of the parameter) is promulgated through the model and reflected in the outputs from the analysis. Both of these objectives are achieved by running the analyses required for the conventional (2-step) methods for calculated the Expected Value of Perfect Parameter Information (EVPPI).[8] For the parameter of information, a value is randomly sampled from the parameter distribution. This value is then used as the fixed parameter value in a full simulation run of the model, in which the values for all other parameters are randomly sampled from the respective distributions for a sufficient number of simulations to provide a stable estimate of the expected costs and outcomes for the interventions being compared in the analysis. The results are then stored and the process repeated, with another value being randomly sampled from the distribution for parameter of interest. The first step is often referred to as the outer-loop and the second step is referred to as the inner loop. The process is repeated a sufficient number of times to establish stable estimates of the expected costs and outcomes over the range of possible values for the parameter of interest. As the stochastic model should have been constructed such that correlations between parameters are respected, the results of the SOWSA will also respect this correlation and hence produce unbiased estimates. Further, because the frequency with which a specific value is sampled from the parameter distribution, the output distributions will reflect the probability that any specific value is the true (observed) value.

This process produces an extremely large volume of data. The EVPPI aggregates this data and tells the decision maker, what would be the improvement in the expected net benefit from the new technology if they knew the value of the parameter of interest with certainty. This is different from telling the decision maker what the net benefit would be if the parameter took a specific value and how likely it is to take that value. Hence, whilst the data required for SOWSA is the same as for calculating EVPPI, the subsequent analysis of the data is different.

'Conditional Expected Net Benefit' and Stochastic One-Way Sensitivity Analysis

For each possible value of the parameter of interest, the above analysis provides the expected costs and outcomes for each technology being compared. For the purpose of a SOWSA, we wish to provide the decision maker with insight into the cost effectiveness of the technology for each possible value and the probability that the parameter takes a value at which the technology is cost effective/cost ineffective.

The limitations with Incremental Cost Effectiveness Ratios as a summary measure of a cost effectiveness analysis have been well described elsewhere. [9] One limitation that is particularly pertinent to the construction of Tornado Diagrams is that ICERs can be undefined when either the denominator or numerator take the value of zero i.e. the effectiveness or costs of the technologies being compared are equal. When costs and outcomes are transformed into the Net Monetary Benefit plane using the cost effectiveness threshold, this problem is eliminated. Given that the SOWSA allows for non-linear relationships between the value of a specific parameter and costs and outcomes; and it will typically examine many more possible values than DOSWA, the prior probability of encountering non-defined ICERs is higher and therefore we recommend plotting the Tornado diagram in Incremental Net Benefit space.

The first step in constructing the graphical representation of the SOWSA is to rank the simulated costs and outcomes by the sampled value from the parameter of interest; from highest to lowest or vice versa. Step Two in the analysis is to use the 'reference case' value of lambda (the cost effectiveness threshold) to calculate the Conditional Expected Incremental Net Monetary Benefit for each value of the parameter.

At this stage, it will be important to examine whether there is a continuous increasing/decreasing relationship between the value of the parameter and the Incremental Net Monetary Benefit. If this condition holds, then the construction of the SOWSA is straightforward, because the probability that the parameter takes values that give a positive incremental net benefit can be 'read off' from the cumulative density function of the distribution used in the stochastic analysis.

This information can be used to plot a Tornado Diagram where the bar plots the credible range for the cINMB between, for example, the 1st and 99th centile of the parameter distribution. The probability of observing a value that produces a positive or negative cINMB can be captured by recording the proportion of parameter distribution that lies either side of the parameter value at which cINMB is equal to zero. It would also be possible to mark the cINMB for each decile of the parameter distribution. An alternative way of presenting the same information is to plot a line graph of the cINMB against the centiles of parameter distribution. This avoids the need to manually mark the deciles points on the Tornado Diagram, and allows the decision maker to read off the probability that the parameter takes a value that is associated with either a positive or negative Incremental Net Benefit. In addition, such line graphs allow the decision maker to observe whether the relationship between the parameter and net benefit is positive or negative.

Stochastic One-way sensitivity analysis plots for Prosignia

We use a previously published cost effectiveness analysis from the Optima Prelim study. [10] The study compared the costs and outcomes of alternative chemo-sparing tests in the management of Early Breast Cancer.

We undertook SOWSA for 3 variables – the cost of chemotherapy, the utility for the health state 'distant recurrence' and the effectiveness of chemotherapy in preventing distant recurrence. The distributions for each parameter are described in Table 1.

Table 1: Parameter distributions

	Cost	Utility	Probability
Distribution	Normal	Beta	Beta
Mean	3555	0.5	0.298507463
SD	67	0.225	0.219
Alpha	N/A	2	1
Beta	N/A	2	2.35

The monte carlo simulations ran 4,000 outer loops and 10,000 inner loops; i.e. we sampled 4000 values from the distribution of each parameter and for each of these ran 10,000 simulations to estimate the *Conditional* Expected Costs and Outcomes for Oncotype Dx and Prosigna. We assumed Lambda (the cost effectiveness threshold) was equal to £30,000 per Quality adjusted Life Year (QALY), and used this to calculate the *Conditional* Expected Incremental Net Benefit, for each sampled parameter value. This process was repeated for all three parameters.

For each parameter we sorted the Conditional Expected Costs and Outcome data from the lowest to highest value of the parameter. We used the moments of the parameter distributions, (see Table 1) to identify the cumulative probability of observing each of the sampled values. This identifies the centile of the parameter distribution for each sampled value. At this point it is possible to construct Probability, Parameter and Conditional Expected Incremental Net Benefit Triads; i.e for each value of the parameter, the analyst can describe the Expected Incremental Net Benefit, conditional upon the parameter taking that value, and the probability that the parameter will take that value.

Figure 1 is a Tornado Diagram showing the 99% credible range for the cINMB for the three parameters. We can see that the largest proportion of the total range for the cINMB is greater than zero. This is also true for cost. In contrast, for the utility parameter the credible range is quite evenly distributed between positive and negative values. This does not mean that positive and negative incremental net monetary benefit estimates are equally likely. The Tornado Diagram has only plotted the credible range and therefore it does not provide information on how likely it is that any specific value in that range will be observed.

Figure 1: Stochastic One Way Sensitivity Analysis – Tornado Diagram

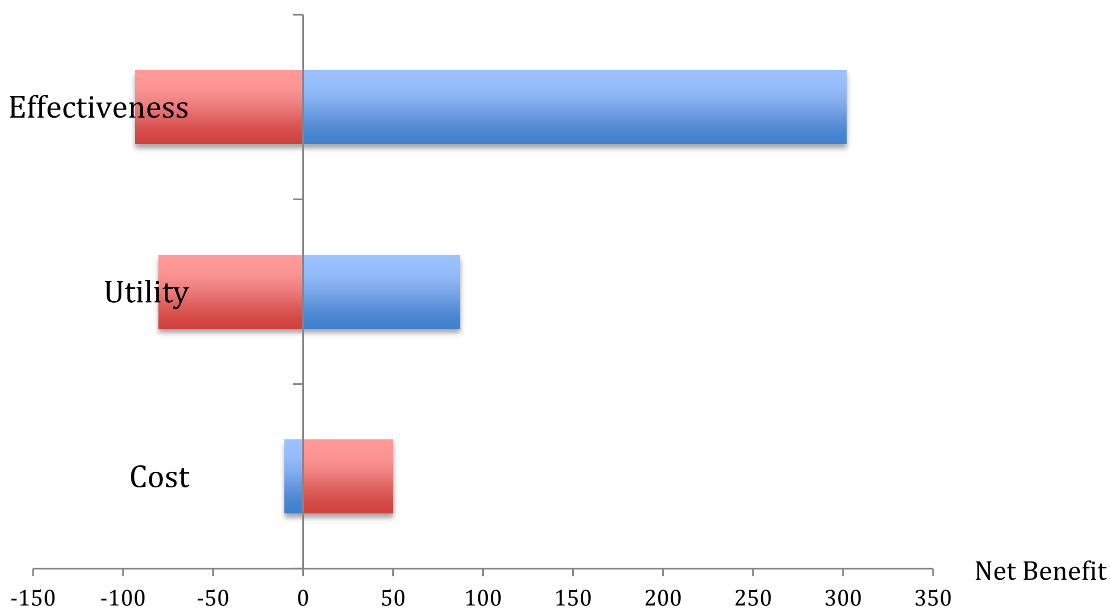
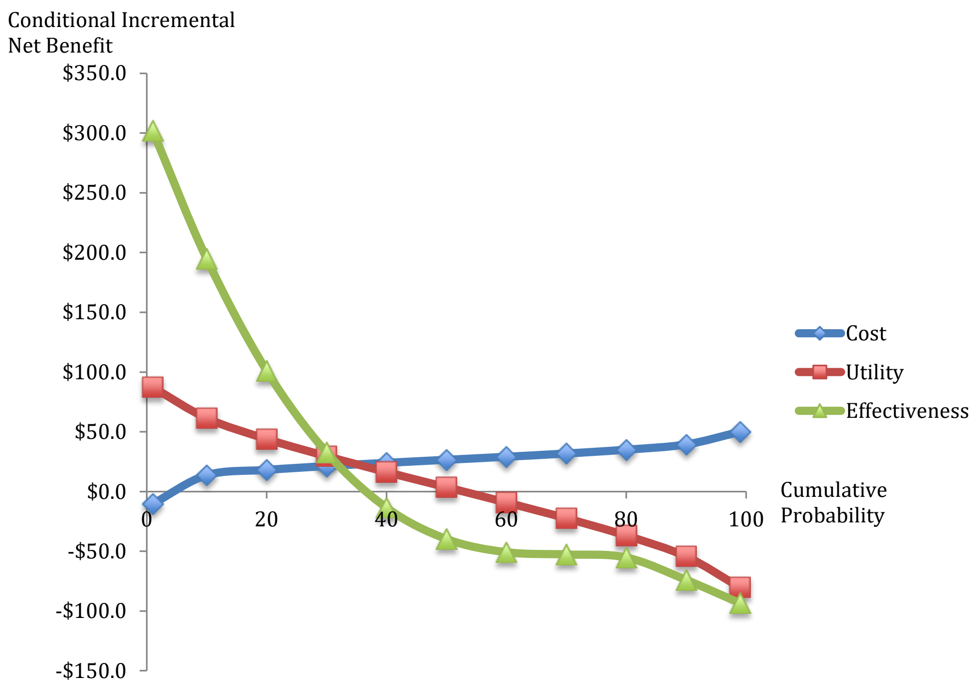


Figure 2 is a line graph plotting the cINMB for each parameter (cost, utility, effectiveness) against its probability distribution. For ease, we have only plotted the cINMB for the 1st and 99th centiles, as well deciles 1 to 9, but the graph could be constructing with centiles or even smaller probability increments. Examining Figure 2, we can see that whilst the majority of the credible range for the 'effectiveness' cINMB is positive, the probability that the parameter takes a value that leads to a positive cINMB is slightly less than 40%. This illustrates very nicely how the Tornado Diagram bar describing the credible range cannot be treated as a reliable indicator of the probability of specific values being observed.

Figure 2: Line Graph Stochastic One Way Sensitivity Analysis



Discussion

Decision makers have always been interested in the impact of specific parameters on the expected value of new technologies. Historically one-way sensitivity analysis has been the mechanism by which analysts have met the decision makers' information needs. Over the last decade deterministic cost effectiveness analyses have become increasingly recognized as flawed and a general consensus has emerged around the importance of stochastic analyses to provide decision makers with unbiased results. Stochastic models have also become more prevalent as they provide support to decision makers who wish to use more nuanced decision options such as Patient Access Schemes, Only in Research and Only with Research.[11] These developments in the methods and process of health technology assessment have not reduced the importance to decision makers of the impact of specific parameters, and hence analysts have continued to provide decision makers with deterministic one-way sensitivity analyses. Whilst such information is provided in response to decision makers' needs; it is actually misleading. The results of deterministic models are biased in the presence of non-linear relationships between parameters in the model. In addition, because deterministic one-way sensitivity analyses explore the impact of changing the value of a single parameter whilst holding all other parameters constant at their expected value, it ignores the correlations between parameters, which again will lead to biased estimates of cost and outcomes, and hence their sensitivity to changes in the value of the parameter. As well as producing biased estimates of the quantities that the decision makers are interest, deterministic one-way sensitivity analysis also throws away crucial information on the probability that the parameter will take a value that would change the decision. For these reasons the use of deterministic one way sensitivity analysis represents a retrograde step in the methodological quality of cost effectiveness analyses provided to decision makers, and increases the risk of both Type 1 and Type 2 errors in decision making.

The importance of individual parameters in stochastic cost effectiveness analysis has conventionally been characterized using the Expected Value of Partial Parameter Information. This statistic addresses the question 'What would be the valuable of eliminating uncertainty about the true value of the parameter?'. This is a different question from the one that reimbursement decision makers are interested in, which may be characterized as 'What is the probability that this parameter would take a value that change the decision?'. As we have described above, there is a substantial overlap in the analysis required to answer both of these questions, however, they differ in the final phases. For Stochastic One way Sensitivity Analysis the expected costs and outcomes for each outer-loop set of simulations is captured, along with the sampled value of the parameter and these are linked to the probability that the parameter takes that value – which can be read off the probability distribution for the parameter used in the stochastic analysis. The correct estimate of the credible range for the conditional incremental net benefit can then be plotted in a Tornado Diagram. However, the Tornado Diagram does not provide decision makers with information on the probability that parameter will take a value that will change the decision. This information can be presented to the decision makers using a line diagram that plots the cumulative probability of the parameter against conditional Incremental Net Benefit.

In the same way that stochastic analyses were initially resisted on the grounds of excessive computational burden.[12] it is likely that the some will resist moves to replace the biased deterministic one-way sensitivity analysis because of the need to undertake two-level simulations in order to produce the data required. However, we would argue that the computational power of modern computers and advances in the software that is available for constructing decision analytic cost effectiveness models mean that such criticisms are not supported by the evidence. A recently completed benchmark comparison of decision analytic modeling software found that 'R' and Matlab could run Value of Information analyses with 10,000 simulations in less than 1 minute running on a desktop PC.[13] The use of appropriate software means that the production of SOWSA can be accomplished in similar time periods to that required for stochastic analyses when it was initially advocated at the start of this century by organizations such as NICE.[6]

As with all developments in the presentation of analytic results to decision makers, care will be required to ensure that the decision makers understand the information provided to them. For the Tornado Diagram it will be important that decision makers are aware that the bar only shows the credible range for the conditional incremental net benefit; and that the underlying probability of observing a value that changes the recommendation i.e. shifts the expected net benefit from positive to negative, or vice versa; must be read-off from the line graph plotting cumulative probability against the conditional incremental net benefit.

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