Probabilistic Analysis of Cost-Effectiveness Models: Statistical Representation of Parameter Uncertainty

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There was a time when a simple dichotomy characterized many health economic evaluations. On the one hand there were those economic appraisals that were conducted alongside clinical trials and which commonly employed statistical methods in so-called stochastic evaluations. On the other, there was the use of decision analytic modeling to synthesize data from secondary sources in order to estimate cost-effectiveness in a deterministic fashion. Now, however, the distinctions are becoming ever more blurred. The limitations of single trials as the sole vehicle for economic appraisal is widely reported [1] and, in particular, the continued need for modeling to adapt trial-based analyses is well understood [2]. Furthermore, the use of probabilistic sensitivity analysis to represent uncertainty in modeling studies offers the opportunity to make statistical statements about the impact of parameter uncertainty for cost-effectiveness estimates from deterministic models.

The trend toward a more statistical approach to handling uncertainty in cost-effectiveness models has been picked up in the new guidance from the National Institute for Clinical Excellence (NICE) in the UK. NICE now advocates the use of a reference case set of methods for those making submissions to its appraisal process [3]. Included within this reference case is the recommendation to use probabilistic sensitivity analysis to represent parameter uncertainty. Journal editors and reviewers too are becoming more stringent in their requirements to see the use of probabilistic methods to characterize parameter uncertainty. In this issue of *Value in Health*, Oostenbrink and colleagues [4] present a probabilistic model that typifies the approach to presenting uncertainty in such models. By characterizing the uncertainty in the input parameters of their model as probability distributions, the authors are able to propagate that uncertainty through the model using Monte Carlo simulation, thus generating a joint distribution in the incremental costs and effects that represents the consequences of the input parameter uncertainty. This is presented on the cost-effectiveness plane and can be summarized using cost-effectiveness acceptability curves just as any statistical analysis of costs and effects from a trial-based analysis.

Probabilistic methods are not universally accepted, however. A common criticism levied at the use of probabilistic analysis is that the choice of distribution is essentially arbitrary and generates another aspect of the analysis that must itself be subjected to sensitivity analysis. Although it is true that the literature contains many examples of probabilistic sensitivity analyses that employ arbitrary distributional forms, this is generally because the authors have not thought carefully about the uncertainty in the parameter they are seeking to capture. Although there are clearly a large number of potential distributions available in the software packages used to produce cost-effectiveness models, it does not follow that they are all candidate distributions for every possible parameter. For any given parameter in a decision model, the choice of distribution to characterize uncertainty in that parameter should be chosen from a small number of candidate distributions which will depend on the data from which the parameter is estimated and the method of estimation. For example, a normal distribution is always a candidate for any parameter based on expected values because of the role of the *Central Limit Theorem,* which essentially states that the sampling distribution of the mean will be normally distributed whatever the underlying distribution of the data with sufficient sample size. Of course, models will often be employed in situations where sample sizes of data informing parameter estimation cannot be relied on to be sufficient and other distributional forms are required. Probability parame-

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ters, for example, are constrained on the interval zero to one, and distributional forms that are consistent with this restriction should be chosen. If binomial data are available to estimate a simple proportion, then the Beta distribution is the obvious candidate distribution for the probability because of its special relationship with binomial data [5]. If the probability parameters are estimated from a logistic regression, then the appropriate assumption is normality on the log-odds scale. Similarly, single costs can be assigned a gamma distribution, or lognormal distribution if estimates of costs come from a log-scale regression model.

The point is that far from involving arbitrary assumptions and choices, application of probabilistic methods encourages the analyst to think carefully about the appropriate distribution and variance to represent the uncertainty in a given model parameter, based on the empiric data informing the estimation of that parameter. In general, these distributions will be the exact same distributions that form the basis of standard methods for confidence interval estimation for given parameter types that can be found in any medical statistics or econometric textbook. Appropriately undertaken, probabilistic analysis will give a more accurate depiction of the importance of parameter uncertainty for the results of the analysis in comparison, say, to simple univariate sensitivity analysis.

Although choice of distributional form and estimation of variance may be straightforward when primary data are available, what should the analyst do when primary data are not available—when parameters are informed by secondary information from the literature, or perhaps even by expert opinion? Is this a situation where univariate sensitivity analysis should be used? I would suggest not. Even in these situations, probabilistic methods can and should be used to characterize uncertainty. Inevitably, in the absence of primary data, the role of subjective opinion of the analysts will be greater in determining the variance of distributions. The choice of distributional form, however, should be guided by the type of parameter and the sort of primary data that would in principle be available to inform the estimation of the parameter if additional data collection was initiated.

A final thought on the use of probabilistic methods and the role of traditional sensitivity analysis: It is important to recognize that the use of probabilistic methods is primarily advocated for representing parameter uncertainty. Other types of uncertainty continue to be important, in particular, uncertainty relating to the structure and assumption of decision models [6]. In the article by Oostenbrink and colleagues [4], a series of sensitivity analyses is presented looking at the consequence of changing different assumptions and scenarios. This represents an important continuing role for traditional sensitivity analysis to be used alongside probabilistic methods.

References

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