

How to do (or not to do) . . .

Allowing for uncertainty in economic evaluations: qualitative sensitivity analysis

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Sensitivity analysis allows analysts to explore the impact of uncertainty on their findings. It is an important part of any economic evaluation, and a lack of analysis is evidence of a poor quality study. Sensitivity analysis helps the analyst evaluate the reliability of conclusions for the context of the evaluation and can also facilitate consideration of the generalizability of results to other settings. The variety of one and multi-way sensitivity analyses offer simple and complementary approaches to evaluating the impact of uncertainty on the results and conclusions of economic evaluations. The paper begins with a brief discussion of the types of uncertainty that can arise in economic evaluation, and follows with suggestions of how to plan a justified sensitivity analysis. A number of specific techniques are worked through with examples, followed by a discussion of when it is best to use them. The main weakness associated with sensitivity analysis is the control that the analyst retains over three parts of the process: the choice of which variables to vary and which to treat as known or fixed; the amount of variation around the base value of the parameter that is considered clinically meaningful or policy-relevant; and the determination of what constitutes a sensitive or robust finding. It is therefore essential that the approach of the analyst is clear and justified. It is likely that the future will see further developments in the approaches and training of statistical analysis. But in the meantime, an increase in the number of evaluators undertaking a wider range of sensitivity analysis would improve the quality of evidence for, and outcomes of, decision-making.

1.0 Introduction

Structured methodological reviews of published economic evaluations have consistently pointed to inadequacies in the way that uncertainty is treated (e.g. Udvarhelyi 1992; Briggs and Sculpher 1995; Agro et al. 1997; Walker and Fox-Rushby 2000). The most common finding is that research results are not subject to any form of sensitivity analysis and, when sensitivity analysis has been undertaken, the dominant approach is an unjustified one-way analysis. Multi-way sensitivity analyses and statistical analyses are undertaken much less frequently.

Briggs and Sculpher (1995) attributed the state of analysis to the fact that '... few guidelines offer details on how exactly sensitivity analysis should be carried out', although, more recently, Mullins and Ogilvie (1998) found that different pharmaco-economic guidelines recommend quite different approaches. Brown (1999) has also suggested that researchers may feel unable to express doubts and uncertainties themselves because decision-makers may view uncertainty as a sign of weakness. Whatever the reason, the impact is that there can be a misplaced confidence in the results, which leads to bad decisions if point estimates of results are reported with

no recognition of the inherent uncertainty. Sensitivity analysis allows analysts to explore the impact of uncertainty on the findings.

This paper begins with a brief description of the types of uncertainty that can arise in economic evaluation, and follows with suggestions about how to plan a justified sensitivity analysis. A number of specific techniques are worked through with examples, followed by a discussion of when it is best to use them and their limitations.

2.0 Types of uncertainty

The two main taxonomies of uncertainty currently used were presented in the mid 1990s by Manning et al. (1996) and Briggs et al. (1994). Manning et al. (1996) distinguished two types of uncertainty: parameter and modelling. Parameter uncertainty is '... uncertainty about the true numerical values of the parameters used as inputs'. They argue it arises for several reasons:

- the size of key inputs (either their quantity or value of the quantity) in the economic evaluation are unknown or not

observable, e.g. how future technology may change or how prices of one input relative to another may change in the future;

- there is not a consensus about what value an input parameter should take. e.g. what the appropriate rate for social time preference is or which approach should be used to value the time of volunteers;
- there is uncertainty about the process behind variables, e.g. factors explaining utilization of services or aspects of the epidemiology of disease;
- sampling variability of parameters exists, e.g. estimates of the response to treatment;
- it is unclear how estimates relate to different populations, e.g. extrapolating costs or effects to/from a random, rather than convenience, sample.

Modelling uncertainty is broken down into 'model structure uncertainty' and 'modelling process uncertainty' (Manning et al. 1996). Model structure uncertainty concerns doubts about the correct method for combining the parameters of the costs, consequences and/or combinations of costs and consequences. This could include debates about: whether particular types of costs or effects should be included, e.g. productivity costs or decisions to include/exclude particular types of adverse reactions; and the functional form associated with effectiveness (e.g. the impact on disease of coverage of a population by a vaccine) or cost (e.g. the impact of scale of production on the various inputs costed) or the relationship between costs and effects. In all instances, questions of whether the parameters assume multiplicative or additive forms can influence the results. Modelling process uncertainty is the uncertainty introduced by the combination of decisions made by the analyst. The analyst retains the most influence over choosing what variable to include and how. For example, Busulwa et al. (2001) showed that the training and working pattern of economic evaluation students affects both the variables selected for analysis as well as results.

The taxonomy of uncertainty provided by Briggs et al. (1994) was based around four causes of uncertainty: variability in sample data on costs and effects of interventions within a population; methods used to measure and value costs and effects; extrapolation of results from intermediate outcomes to final outcomes or over time for the same population; and the extent to which the results are generalizable to other populations. Where these two taxonomies meet is a moot point. Ideas from both categorizations are contained within each and both provided guidance on methodological approaches for investigation, although Briggs et al. (1994) made a closer linkage between types of uncertainty and methods for analyzing uncertainty. On the whole Manning et al. (1996) raise more direct issues concerning the functional form and processes lying behind variables, although arguably this is implicit in Briggs et al.'s issues concerning generalizability if one assumes production processes change between settings. Briggs et al. (1994) explicitly discuss the issue of methodological uncertainty, which Briggs (2000) worked through later in his call for greater methodological comparability across studies.

All these types of uncertainty can be addressed through sensitivity or statistical analysis. This paper focuses on sensitivity analysis, which has been the main focus of activity in assessing the impact of uncertainty. Statistical analysis of uncertainty in economic evaluations incorporates sampling variability in parameter estimates and, whilst it has been the subject of much less research and fewer empirical applications in the economic evaluation of health interventions, interest is increasing, so we point readers to further literature in section 5.3.

3.0 Getting started: planning the sensitivity analysis¹

At this stage there are several steps that need to be performed prior to undertaking any type of sensitivity analysis. For each type of uncertainty (for costs and consequences) outlined in the previous section analysts need to:

- (1) Identify all the parameters or approaches to modelling that could be subjected to sensitivity analysis (in principle the model and all parameters are potential candidates);
- (2) Choose the input parameters or approaches to modelling that you feel are most important to subject to a sensitivity analysis from the list of possibilities, and justify the choices made. For example, you may consider those variables (for the quantity or price/value of costs and effects) or models that:
 - are the most uncertain;
 - have the greatest sampling variability;
 - are most in the control of policymakers;
 - influence the largest percentage of total cost/effects;
 - are more likely to differ from published data;
 - are subject to greatest disagreements amongst methodologists;
 - are key to explaining how costs and/or effects vary across settings.

Analysts should also justify why some parameters, if any, or different types of models, have not been subjected to sensitivity analysis. Reasons might include that parameter estimates are known with certainty² or that it only has a minimal impact on results³ (Drummond et al. 1997).

- (3) Choose the range of alternative values or models that you will substitute into the base-case analysis, justifying all choices made. The range of values adopted may be drawn from the literature, expert opinion accessed through consensus building techniques, sampling variation in the original data, or the researcher's own views. For parameter uncertainty, the following might be considered:
 - for deterministic data – high and low values of each key variable;
 - for stochastic data – the range, plus or minus one standard deviation of sampling error from clinical data, or the most often used 95% confidence intervals for key parameters to determine a plausible range for variation.

For modelling uncertainty, the following might be considered:

- using alternative functional forms for key variables;
- including/excluding particular types of costs/effects;

- asking another person/group to undertake the analysis with the same information.
- (4) Choose which techniques to use to analyze uncertainty (see section 4) and apply the sensitivity analysis to the evaluation. We suggest beginning with one-way analyses as a route to understanding the impact of individual variables/models prior to moving to multivariate analyses.
 - (5) The final step in a sensitivity analysis is to interpret the findings. The analyst must determine how much change from the base-case result is acceptable or constitutes a robust finding and/or the combination of parameter values required to achieve pre-determined incremental cost-effectiveness ratios (see section 5.2).

These steps show how much control the analyst retains. Whilst quantitative analysis is required, it remains an essentially qualitative analysis because of the element of choice in deciding what to vary, by how much, which technique to use and in determining what constitutes robust findings or not. It also shows how essential it is for the evaluator to justify all the choices involved before others can accept conclusions.

4.0 Techniques of sensitivity analyses

This section focuses on the techniques available for selection in the fourth step outlined above. The predominant focus is on approaches to estimating the impact of parameter uncertainty in one-way and multi-way sensitivity analysis using worked examples. All examples focus on treating pregnant women with antiretroviral therapy to reduce mother-to-child transmission of HIV and are illustrative rather than any reflection of reality.⁴ Section 4.3 focuses briefly on approaches to assess modelling uncertainty.

4.1 One-way (univariate) sensitivity analysis

The traditional approach to sensitivity analysis is to examine one variable at a time; one-way or univariate sensitivity analysis. The process is simple; after calculating the base-case scenario, the incremental cost-effectiveness ratio is re-calculated holding all parameters constant apart from the one parameter chosen which is varied over the specified, and justified, range. This process is repeated for as many parameters as desired, and ideally all of the model parameters.

Table 1 illustrates the results of a one-way sensitivity analysis, in which the HIV seroprevalence among pregnant women has been varied, from a base-case estimate of 20%, between 15% and 25%, representing low and high estimates that might have been obtained from the literature. Using a low estimate of seroprevalence resulted in a 36% divergence from the

base-case incremental cost-effectiveness⁵ of \$39 per disability-adjusted life year (DALY) averted to \$53 per DALY averted. The high estimate produced an 18% divergence from the base-case estimate resulting in an incremental cost per DALY averted of \$32. These results are illustrated graphically in Figure 1.

A second type of one-way analysis is a 'threshold analysis'. This concept is drawn from decision analysis, where the analyst varies the size of an input parameter over a range and determines the level above or below which the conclusions change, and hence the 'threshold' point at which neither of the alternatives are favoured over the other – where the decision is a 'toss-up' (Kassirer and Pauker 1981). This concept can be applied to economic evaluation. For example, analyses of antiretroviral therapies to reduce mother-to-child transmission of HIV might identify the 'threshold', or 'break-even', or 'switching', price of a new drug where it is and is not cost-effective to introduce it. However, we will also show that the decision rules used in cost-effectiveness analysis make threshold analyses more difficult to interpret relative to cost-minimization or cost-benefit analysis (Briggs et al. 1994; Karlsson and Johannesson 1999).⁶

Figure 2 illustrates a threshold analysis in which the costs, effects and cost-effectiveness of short-course antiretroviral therapy (using zidovudine) have been compared with the cost, effects and cost-effectiveness of ultra short-course antiretroviral therapy (using nevirapine), for a given population. In the first instance, ultra short-course antiretroviral therapy (USC₁) dominates the programme of short-course antiretroviral therapy (SC₁), i.e. it is more effective and less costly. However, it is possible to vary the price of zidovudine, until

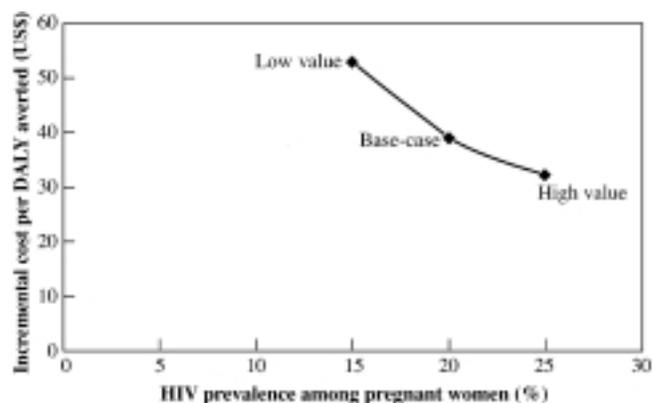


Figure 1. An illustrative example of one-way sensitivity analysis

Table 1. An illustrative example of one-way sensitivity analysis of incremental cost-effectiveness of short over long-course antiretroviral therapy

	HIV seroprevalence among pregnant women	Incremental cost-effectiveness ratio	% divergence from base-case
Low value	15%	\$53	+36%
Base-case estimate	20%	\$39	–
High value	25%	\$32	–18%

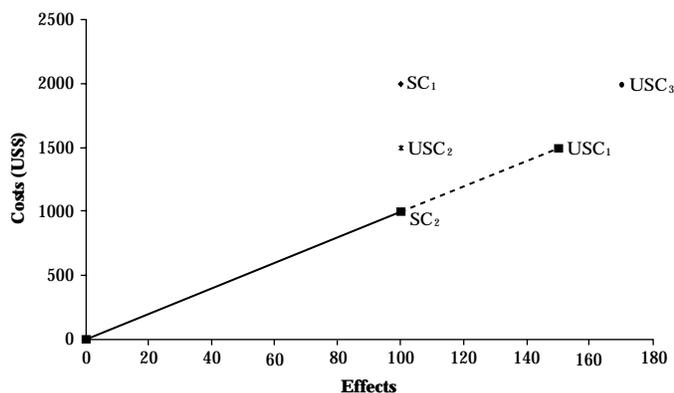


Figure 2. An illustrative example of threshold analysis

both alternatives have the same average cost-effectiveness ratio, i.e. SC_1 moves to point SC_2 and an average cost-effectiveness ratio of \$10 per unit of effect (\$1000/100). It may be tempting, on the basis of this evidence, to suggest that neither of the options being compared would be favoured over the other as the average cost-effectiveness of each regimen is equal. However, decisions should be made based on incremental cost-effectiveness ratios, which in this case is also \$10 per unit of effect, the same as the average cost-effectiveness ratios of the two interventions. Unfortunately, this information still does not provide sufficient information to guide decision-makers. To determine which intervention should be implemented based on cost-effectiveness, either a fixed budget or a price per unit of effectiveness must be introduced as the decision rule (Karlsson and Johannesson 1999). That is to say, if a budget of \$1000 were available, decision-makers would choose either part of USC_1 or SC_2 ,⁷ whereas if a budget of \$1500 were available, a decision-maker would prefer to introduce USC_1 as it results in greater effects, even though the average cost-effectiveness ratios are equal. In fact a decision-maker might prefer to introduce an intervention with a higher average cost-effectiveness ratio with a larger budget because of a desire to maximize effects given a fixed budget, e.g. USC_3 were a budget of \$2 000 available.

However, if the same problem was a cost-minimization analysis, it is possible to perform a threshold analysis that can be more readily interpreted. For example, if ultra short-course

antiretroviral therapy is at point USC_2 , a point at which both interventions accrue the same amount of effects, it is possible to identify the cost of short-course antiretroviral therapy required to result in this intervention being more cost-effective than ultra short-course antiretroviral therapy – essentially, this problem becomes one of cost-minimization. For example, say that the current cost of short-course antiretroviral therapy is \$20 per person. The cost for 100 individuals is therefore \$2000 (SC_1). If however, the cost of the therapy could be reduced to \$15 per person, the cost for 100 individuals would be \$1500 and in this instance a decision-maker would be indifferent between the two alternatives, given that they both cost the same amount and produce the same quantity of effects. Hence, we have identified the threshold value of short-course therapy, \$15, above which USC therapy is more cost-effective and below which short-course therapy is more cost-effective. A similar position exists concerning cost-benefit analysis, where the specific focus is the point where a technology offers a net benefit (Briggs et al. 1994).⁸

4.2 Multi-way (multivariate) sensitivity analysis⁹

There are several ways to deal with multiple sources of uncertainty or variability: two-way, three-way, n-way and scenario analyses (Briggs et al. 1994; Genugten et al. 1996; Petitti 2000). A two-way analysis varies two parameters, both of which are common to the interventions assessed, at the same time, and assesses the impact on the incremental cost-effectiveness ratios of two mutually exclusive interventions, e.g. short-course over long-course antiretroviral therapy. The first step is to construct a two-by-two matrix reflecting the incremental cost-effectiveness for every combination of the two variables of interest, in this case the price of AZT and HIV prevalence among pregnant women (holding all other parameters constant at their base-line values) (see Table 2). The second step is to identify the pairs of values that equalize a pre-determined willingness-to-pay for a unit of effect (\$60 per DALY averted in this example), i.e. the values of the two variables of interest at which the decision is a ‘toss-up’ given the threshold value chosen.¹⁰ Next, all those combinations of price and prevalence that result in these threshold cost-effectiveness ratios are identified and presented graphically.¹¹ Figure 3 shows that the region to the right of the line represents combinations of parameter values for which short-course antiretroviral therapy would be considered

Table 2. An illustrative example of two-way sensitivity analysis of incremental cost-effectiveness of short- over long-course antiretroviral therapy

Seroprevalence	Price of antiretroviral therapy (\$)									
	0.17	0.25	0.50	0.62	0.75	0.84	0.98	1.00	1.07	1.13
10%	60	65	72	80	97	110	125	150	172	200
15%	25	33	45	60	75	90	110	130	150	170
20%	15	17	20	45	52	60	75	90	110	130
25%	12	15	17	20	45	55	60	85	90	110
30%	10	12	15	17	20	30	45	50	60	85
35%	7	10	12	15	17	22	30	45	55	60
40%	5	7	10	12	15	20	25	30	35	45

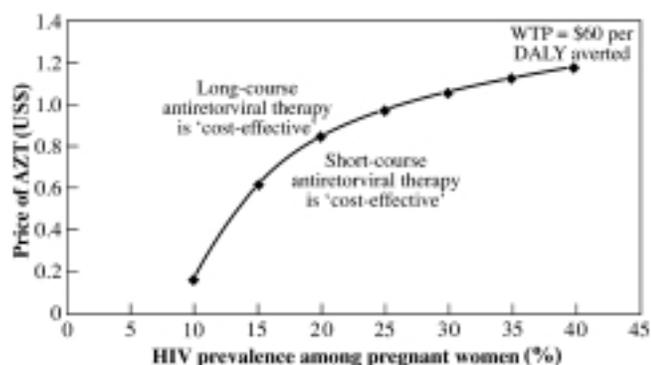


Figure 3. An illustrative example of two-way sensitivity analysis of short- over long-course antiretroviral therapy

cost-effective; and the region to the left illustrates combinations for which long-course therapy would be considered cost-effective.

In three-way sensitivity analysis, as the name suggests, the incremental cost-effectiveness is determined for combinations of estimates of three parameters (holding all other parameters constant at their baseline levels). This time a choice is made to hold one of the three variables at a particular level and to identify the combination of the other two variables that equal a pre-determined willingness-to-pay per unit of effect. This analysis is repeated according to the number of levels the analyst wants to hold the first choice variable at and/or number of different willingness-to-pay values the analyst wants to explore. Again, the interpretation of three-way sensitivity analyses is difficult without a graph. Figure 4 shows the case where the decision-maker's willingness-to-pay per unit of effect is \$60 per DALY averted and three parameters have been varied: price of AZT; HIV prevalence among pregnant women; and the percentage of women who subsequently breast-feed their children. Five lines are shown for five values representing the probability that women breast-feed their children. For each of these values, the line shows the combination of the price of AZT and HIV prevalence among pregnant women that would result in an incremental cost-effectiveness ratio equal to the pre-determined

value. To help understand how to interpret this graph, take the case where the probability of breast-feeding is 100%. All the space below the line represents the case when a short-course regimen would be considered cost-effective relative to long-course therapy given a threshold value of \$60 per DALY averted, and the area above the line is where long-course treatment would be considered cost-effective.

It is also possible to perform *n*-way sensitivity analyses, in which the expected cost-effectiveness is determined '... for every possible combination of every reasonable value of every variable' (Petitti 2000). This type of analysis is difficult to undertake and difficult to interpret; we will not be illustrating how to do this type of analysis in this paper.

The fourth type of multi-way sensitivity analysis is 'scenario analysis', of which there are many examples. There are also a variety of approaches that can be used to develop scenarios that encompass the researchers thinking through possible scenarios themselves, through to scenarios developed with consensus group techniques. We note three types of scenarios that might be used:

- Analysis of the set of extreme circumstances across parameters, also known as a 'max-min' analysis or 'worst/best' case analysis (Briggs et al. 1994). In this case the parameter values that yield the worst (highest) and the best (lowest) cost-effectiveness ratios are combined. For the purposes of illustration, we base this on two parameters (although in practice any number of parameters can be used). Using the same example, an HIV prevalence of 10% and a price of \$1.13 per dose of AZT might produce the worst scenario (\$200 per DALY averted), and a combination of 40% and price of \$0.17 the best scenario (\$5 per DALY averted) (see Table 2).
- Use of an agreed 'reference case' of methods by analysts. The most well-known reference case is described by Gold et al. (1996)¹² who set out the methodological guidance from the report of the Panel on Cost-Effectiveness and Medicine in the United States. It is particularly aimed at increasing the quality and comparability of results across interventions and reducing what Briggs et al. (1994) call 'methodological uncertainty'.
- Use of the 'null' set (Genugten et al. 1996). A case calling

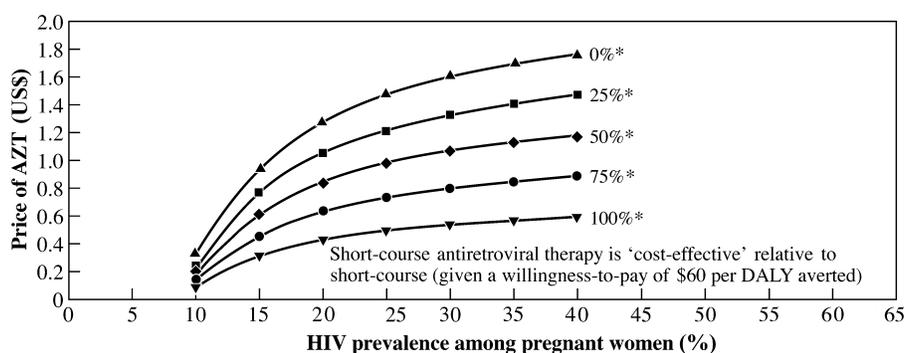


Figure 4. An illustrative example of three-way sensitivity analysis of short- over long-course antiretroviral therapy. *Note:* an asterisk signifies the percentage of women who subsequently breast-feed their children

for evaluating all cost-effectiveness ratios alongside a scenario assuming no interventions at all was recently set out by Murray et al. (2000). Using Murray et al.'s approach to defining a scenario for the null set would involve the development of natural history models to estimate the impact of disease without any formal sector health care interventions and redefining all interventions considered with respect to this null set. In particular it is argued that using a null set scenario will increase the generalizability of results across regions of the world.

4.3 Functional form sensitivity analyses

One-way and multi-way sensitivity analyses focus on the choice of values for parameters. They do not question the way that parameters are assumed to be related to each other in the underlying model. Computing incremental cost-effectiveness ratios using different types of models and comparing the impact on the final ratios is the only approach recommended to date (Manning et al. 1996). The two main approaches to this are either for the analyst to run alternative models or for different analysts or groups of analysts to run their own models on the same data. Examples of some of the structural issues that could be considered include:

- comparing simple and more complex models (e.g. judging the impact of increasing the ability to distinguish different types of patients);
- comparing the effect of using multiplicative or additive models of diseases, interventions evaluated and comorbidities when calculating age-sex specific hazard functions (Mandelblatt et al. 1996);
- changing the relationship between costs and number of 'events' throughout the model.

5.0 Discussion

Having set out why sensitivity analysis is needed, and how it might be planned and executed, it is important to reflect on when the alternative approaches might be used. Secondly, we consider how the results of sensitivity analyses might be interpreted. Finally, we indicate the value of statistical approaches that might be used to evaluate uncertainty, and provide a guide to further reading.

5.1 What are the advantages and disadvantages of the different types of sensitivity analysis?

Relative to the other techniques described, one-way sensitivity analyses are easy to use and provide flexibility in parameter choice. They are a logical, easy to grasp place to start to understand the structure of a particular cost-effectiveness analysis and provide the natural building blocks to do multi-way sensitivity analyses. They can shed light on whether any piece(s) of research could improve the outcome from a policy decision and whether it is worth waiting for this additional data. However, although insightful, one-way sensitivity analyses (including threshold analyses) by themselves are inadequate.

Looking at one source of uncertainty at a time in the model provides an incomplete and under-estimate of how uncertain the estimated overall cost-effectiveness ratio actually is (Agro et al. 1997). There are three related problems:

- the incremental cost and effectiveness depend on multiple parameters, not just one;
- the interaction of particular factors may imply that the total effect could be something quite different from the simple sum of individual contributions;
- the cost-effectiveness ratio is a ratio of two uncertain numbers, with the result that the uncertainty in the ratio may be substantially larger than that of either of its elements.

The various forms of multi-way analyses allow these aspects to be taken into account to some degree. Of these, possibly the 'max-min' is least useful, unless the results are insensitive to the extreme combination of parameter values considered (Agro et al. 1997). If the results are sensitive to the extremes, the results are not very useful bounds on the uncertainty in the cost-effectiveness ratio for two reasons: it is highly unlikely that all of the extreme values of key parameters will occur in any particular setting; and, under some circumstances, two or more sources of uncertainty may partially offset each other, due to the inherent structure of the problem. Two- and three-way sensitivity analyses can be helpful to identify the best scenario likely to appeal to decision-makers with a note of the reliability of such a situation, but they also suffer from some of the same problems of one-way sensitivity analyses; namely, that they may be difficult to interpret if the variables used are dependent on each other (Agro et al. 1997). In addition, these types of analyses become cumbersome if more than two inputs are varied simultaneously.

The 'reference case' as a type of scenario analysis may stimulate an improvement in the comparability and methodological quality of economic evaluations. However, the remaining uncertainty associated with the effects of applying different parameter estimates can only be handled using different tools, and the reference case requires that additional sensitivity analysis be undertaken. It is important to note also, that the reference case (as with the null set) has not yet been validated for low- and middle-income countries.

The variety of univariate and multivariate sensitivity analyses provides a range of complementary techniques for dealing with uncertainty. For this reason, we urge practitioners of economic evaluation of health care programmes to strengthen their research by performing a range of sensitivity analyses in order to best capture the extent to which uncertainty is present in their findings, and hence the robustness of their results and recommendations. The rather cursory section on functional form sensitivity analysis was a reflection of our desire for completeness in covering approaches to sensitivity analysis, and the paucity of methodological and empirical work in this area. We hope it encourages more people to consider how to undertake assessment of uncertainty in this area.

5.2 How should the results of sensitivity analysis be interpreted?

Following any sensitivity analysis, the first step is to note which variables cause the greatest and least change in the incremental cost-effectiveness ratio. The two main difficulties with this are deciding: what constitutes a large/small change, and how likely the change is to be. With a sensitivity analysis both these decisions are the analyst's own judgement and the basis of such decisions need to be open for readers (and policymakers) to assess and consider changing according to different views about the future. For example, threshold analyses of the price of antiretrovirals can help in identifying prices at which different therapies might be cost-effective in sub-Saharan Africa given knowledge of the size of the budget available or a decision-maker's willingness to pay per unit of effect. The analyst makes a judgement of how likely this is to be and therefore how robust conclusions about the base-case results are.

The implications of the results of the sensitivity analysis can be considered in terms of recommendations for policy and/or research. For example:

- results of a sensitivity analysis may show that collecting one type of data may make conclusions far more robust, and thus a decision may be better delayed until data are collected;
- decision-makers may take results from one type of sensitivity or scenario analysis dealing, for example, with a variable more in their control to set policy;
- decision-makers in different time periods or countries may also be able to draw alternative conclusions provided analysts have undertaken sensitivity analyses. For example, if the decision-maker's willingness-to-pay for a unit of effect was \$60, the breast-feeding rate was only 30%, price of AZT was \$1.0/dose and HIV prevalence was 0.3, then the illustrative example provided in Figure 4 would suggest, provided all other things were equal, that long-course treatment was cost-effective;
- estimates of the maximum willingness-to-pay by decision-makers for a unit of effect can be used to identify decisions. For example, \$50 per DALY averted has been adopted arbitrarily, by the World Bank (Jamison et al. 1993; World Bank 1993),¹³ as the threshold below which public-health interventions are deemed to be cost-effective in low-income settings.

Finally, as Manning et al. (1996) state, it is important that policy-makers understand that any '... particular analysis presented is but one sampled from a universe of possible analyst-analysis pairs'.

5.3 What other types of techniques exist to evaluate uncertainty?

In recent years, there has been an increased interest in developing and undertaking statistical analyses of uncertainty in the estimated incremental cost-effectiveness ratio. It is particularly aimed at evaluating uncertainty due to sampling variation of the input parameters. The advantages

are that all parameters can be varied simultaneously and, as it allows point estimates of cost-effectiveness ratios to be given confidence intervals, the likelihood of particular cost-effectiveness ratios occurring can be judged. A growing number of publications have addressed the application of statistical methods to pharmacoeconomics. Most of the literature is related to assessing the variability of cost-effectiveness ratios, calculation of confidence intervals and formal hypothesis testing with cost-effectiveness ratios (Mullins and Ogilvie 1998). This body of literature is likely to continue to evolve and be debated. Manning et al. (1996), Briggs (2000), Petitti (2000) and Hutubessy et al. (2001) all provide further details on methods for the interested reader.

6.0 Conclusions

Sensitivity analysis is an important part of any economic evaluation, and a lack of analysis is evidence of a poor quality study. Sensitivity analysis helps the analyst evaluate the reliability of conclusions for the context of the evaluation and can also facilitate consideration of the generalizability of results to other settings. The variety of one-way and multi-way sensitivity analyses offers simple and complementary approaches to evaluating the impact of uncertainty on the results and conclusions of economic evaluations. However, the main weakness associated with sensitivity analysis is the control that the analyst retains over three parts of the process: the choice of which variables to vary and which to treat as known or fixed; the amount of variation around the base value of the parameter that is considered clinically meaningful or policy-relevant; and the determination of what constitutes a sensitive or robust finding (Mullins and Ogilvie 1998). It is therefore essential that the approach of the analyst is clear and justified. It is also likely that the future will see further developments in the approaches and training of statistical analysis, but in the meantime an increase in the number of evaluators undertaking a wider range of justified sensitivity analysis would improve the quality of evidence for, and outcomes of, decision-making.

Endnotes

¹ Prior to undertaking a sensitivity analysis, it is important to have completed the base-case analysis of the evaluation and checked for potential errors. Detection of errors in the base-case analysis during the sensitivity analysis will mean that not only will the base-case analysis have to be re-calculated, but also that the sensitivity analysis will have to be re-worked.

² Although if authors are considering the generalizability of results and models across space and time, they may still wish to examine the impact of such uncertainty and choose a range of alternative parameter values.

³ This could, of course, be difficult to claim without having undertaken the analysis.

⁴ See Marseille et al. (1999), Söderlund et al. (1999) and Stringer et al. (2000) for examples of applications of sensitivity analysis to economic evaluations of strategies to reduce mother-to-child transmission of HIV among pregnant women in sub-Saharan Africa.

⁵ This is calculated as the difference in cost of two competing interventions divided by the difference in effectiveness of the same two competing interventions, e.g. long- and short-course antiretroviral therapy.

⁶ When an intervention is both more effective and less costly than the alternative, a state of dominance occurs, i.e. there is never a switching point at which an intervention is and is not cost-effective.

Issues of dominance are relevant only when interventions are mutually exclusive and can only be discussed after sensitivity analyses have been performed because initial decisions made on the basis of point estimates of cost-effectiveness may suggest that an intervention is dominant, when in fact this relationship may not hold true for other values of parameters.

⁷ This assumes constant returns to scale and perfect divisibility of inputs.

⁸ Nevertheless, it will still be necessary to apply decision rules to identify those interventions that should be implemented on the basis on cost-benefit analyses.

⁹ If an intervention dominates the alternative, it is not possible to perform a multi-way sensitivity analysis.

¹⁰ It is also possible to identify the pairs of values that result in an incremental cost-effectiveness ratio of zero (i.e. the average cost-effectiveness ratios of the two alternatives are equal), but as illustrated above, this provides no aid to decision-makers.

¹¹ It is difficult to interpret the results of a two-way sensitivity analysis without the aid of graphs.

¹² See their Appendix A and applications of the reference case given in Appendices B and C.

¹³ Alternative benchmarks have been suggested as well. For example, an intervention that results in a life-year saved for less than the per capita GNP is sometimes considered to be cost-effective (Miller and McCann 2000). Also note that benchmarks in developed nations will usually be several orders of magnitude greater than those for developing nations.

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