WHO'S BETTER NOT BEST: APPROPRIATE PROBABILISTIC UNCERTAINTY ANALYSIS

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Abstract

The use of probabilistic analysis as a means for analyzing uncertainty within economic analysis has grown in popularity in recent years as it has been recognized as the most complete method for propagating uncertainty with respect to input parameters in terms of uncertainty about outcomes of interest. The World Health Organization (WHO) in a series of recent reports and publications have recognized the role of probabilistic analysis in what they term generalized cost-effectiveness analysis. However, there are fundamental problems with the analysis and the interpretation of such analysis as proposed by WHO. This study highlights three specific points for concern and offers constructive criticism by recommending more appropriate approaches.

Keywords: Economic analysis, Uncertainty, Probabilistic analysis

The use of probabilistic analysis as a means for analyzing uncertainty within economic analysis has grown in popularity in recent years, because it has been recognized as the most complete method for propagating uncertainty with respect to input parameters in terms of uncertainty about outcomes of interest (3). Furthermore, probabilistic analysis allows the avoidance of potential nonoptimal decisions, which can be generated from simple deterministic analysis (20) and can be used in Bayesian sensitivity analysis, whereby the value of further information with respect to individual input parameters can be ascertained (6;11;12).

The World Health Organization (WHO), in a series of recent reports and publications, has recognized the role of probabilistic analysis in what they term generalized cost-effectiveness analysis (2;14;17). However, there are fundamental problems with the analysis and interpretation of such analysis as proposed by WHO. This study highlights three specific points for concern and offers constructive criticism by recommending more appropriate approaches.

ESTIMATING INCREMENTAL COST-EFFECTIVENESS RATIOS FROM A MONTE CARLO SIMULATION

Monte Carlo simulation analysis (MCS) requires the specification of probability distributions for all pertinent input parameters (9;10). Analysis involves the repeated sampling from each input parameter's probability density function to allow the creation of a set of outcome parameters of interest. This can facilitate both a precise estimate of the outcome and a measure of its dispersion.

Stinnett and Paltiel (19) have categorized two available approaches for estimating a incremental cost-effectiveness ratio (ICER) based on the results of a MCS: the mean ratio approach and the ratio of means approach. A recent WHO study proposes the use of the mean ratio approach in terms of obtaining the expected value of an incremental cost-effectiveness

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ratio (ICER) (2). This is estimated as follows:

$$ICER = \sum_{i=1..R} \left(\frac{C_{A_i} - C_{B_i}}{E_{A_i} - E_{B_i}} \right) \Big/ R$$

where C_{A_i} and C_{B_i} and E_{A_i} and E_{B_i} are the costs and effectiveness of therapies A and B based on the ith replication and R is the total number of MCS replications.

For the ratio of means approach, the *ICER* is estimated as follows

$$ICER = \frac{\sum_{i=1..R} C_{A_i} - C_{B_i}}{\sum_{i=1..R} E_{A_i} - E_{B_i}}$$

Unlike the mean ratio approach, the ratio of means approach has been shown to have strong theoretical foundations based on both constrained optimization and individual utility maximization (19). The mean ratio approach, however, has no theoretical basis and is internally consistent primarily due to the ambiguity of ICERs without knowledge of their location on the cost-effectiveness plane (19).

Table 1 presents a reanalysis of data from a recent WHO publication (Data used are from Baltussen et al. [2]. Data used assume four options for therapy: no therapy, B1, B2, B3. The incremental costs compared with no therapy for B1, B2, and B3 are 180, 325, and 600, respectively, with incremental effects of 200, 300, and 400 units. For all variables the standard deviation is assumed to be 100). Analysis was conducted based on the original data using an excel spreadsheet with the Crystal Ball enhancement to facilitate MCS. The expected value for the ICER clearly differs by the method adopted demonstrating the potential bias of adopting the mean ratio method. The recent WHO study included a comment on the relative instability of estimates of the ICER as a function of the number of replications within the MCS. However, Figure 1 demonstrates that such a finding is as a result of the method of calculating the ICER. Estimates of ICER based on the ratio of means approach are shown to have considerable stability with respect to the number of replications.

CONFIDENCE INTERVALS AROUND THE ICER

WHO recommends the use of a percentile method for estimating the confidence interval around an ICER (2). The method proposed is to take percentile values of the distribution of ICER based on the replications from the MCS (2;3). However, this method again ignores the ambiguity of an ICER when the location of the ICER on the cost-effectiveness plane is ignored.

For example, two replicates can have the same positive ICER but be located on different quadrants of the plane. Thus, the relative desirability of these replicates will not simply be function of the ICER but a function of the ICER, the quadrant, and a decision makers

Table 1. Estimates of the Incremental Cost Effectiveness Ratio Based on the Mean Ratio and the Ratio of Means

Comparison	ICER based on mean ratio	ICER based on ratio of means
B1 vs. no intervention	0.90	0.88
B2 vs. B1	3.78	1.52
B3 vs. B2	1.15	2.75

ICER, incremental cost-effectiveness ratio.

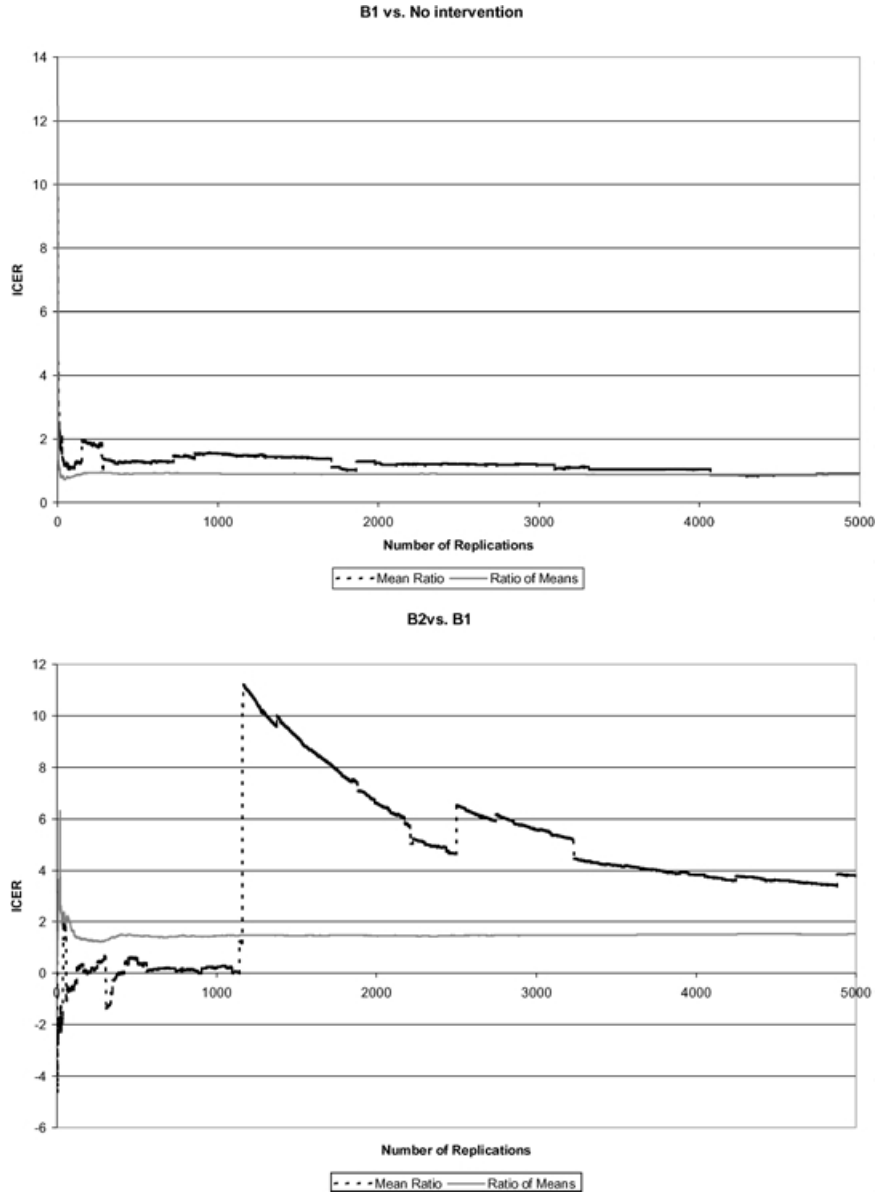

Figure 1. Incremental cost-effectiveness ratio (ICER) based on the mean ratio and the ratio of means as a function of the number of replications.

willingness to pay for a unit of health benefit. Furthermore, two replicates can have the same negative ICER, but one may estimate therapy as both cost saving and more effective and the other may estimate therapy as more costly and less effective.

The recent WHO study discusses other methods for generating confidence intervals around ICER; especially nonparametric bootstrapping (2). However, there is confusion within this discussion primarily because of a failure to distinguish between methods designed for economic analysis alongside clinical trials, which requires the bootstrapping of individual patient data, rather than methods designed for the analysis of economic analysis based on decision analysis and MCS, which provide a set of estimates at the population level.

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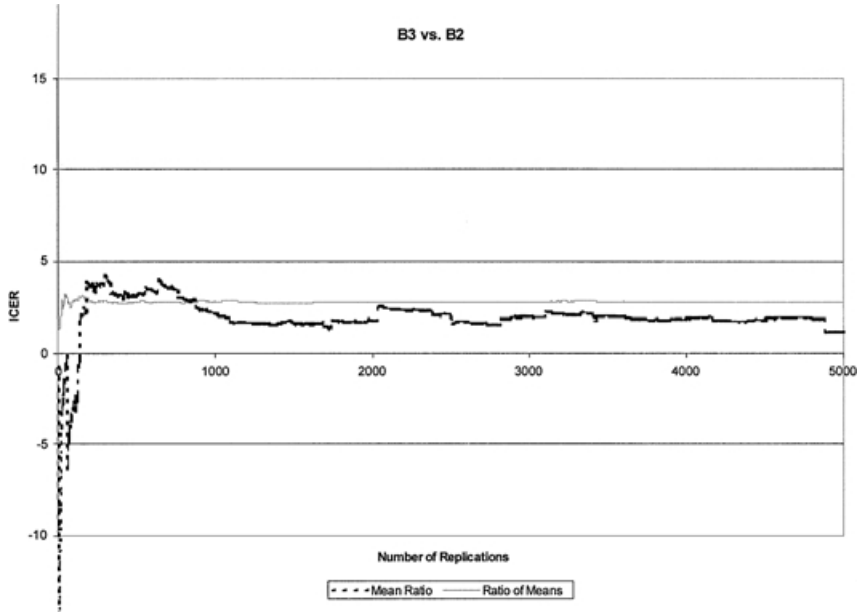

Figure 1. *(Continued).*

The net benefit approach is an alternative approach for presenting the cost-effectiveness of a technology and for characterizing the uncertainty around this value (18). This approach avoids the potential ambiguities of approaches based on the ICER and allows a simple formulation of a confidence interval around a measure of cost-effectiveness. Net benefit can be expressed in either monetary (NMB) or health (NHB) terms. NMB requires weighting the incremental effectiveness of a therapy by a decision makers willingness to pat for a unit of health benefit (λ). Thus, if the value of the incremental effectiveness is greater than the incremental costs, therapy can be deemed cost-effective. NMB is estimated from the results of a MCS as follows:

$$NMB = \sum_{i=1..R} \frac{\left(E_{A_i} - E_{B_i}\right)^* \lambda - \left(C_{A_i} - C_{B_i}\right)}{R}$$

A confidence interval around estimates of NMB obtained from a MCS is estimated by taking the $100.(\alpha/2)$ and $100.(1-(\alpha/2))$ percentiles from the distribution of NMB.

A drawback with the NMB approach is that the value for λ in most cases is uncertain. Thus, results should be presented for a range of values, which will facilitate interpretation by decision makers. Figure 2 presents estimates of NMB and the associated 95% confidence interval based on one comparison from the original data from the WHO study. However, it must be stated that there are convincing arguments against the consideration of statistical inference when making decisions within a public health care system which would negate the need for confidence intervals (1;7).

STOCHASTIC LEAGUE TABLES

Recent reports from the WHO have suggested a further approach for characterizing uncertainty: stochastic league tables (2;14). In this approach, it is assumed that the "optimal" intervention for each disease area can be determined by the probability of an intervention being the most cost-effective. Thus, the results of the MCS are presented in terms of the

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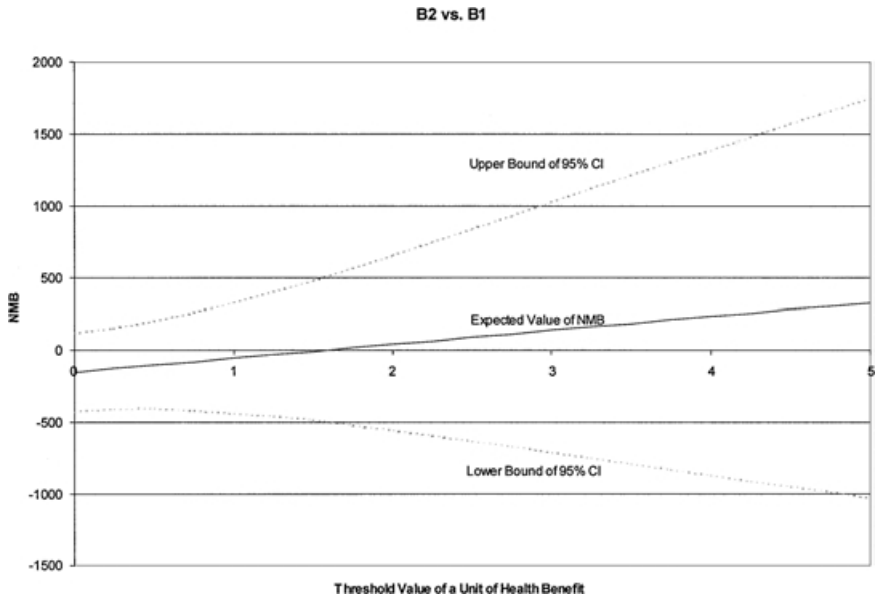

Figure 2. Estimate of net benefit based on alternate threshold values for a unit of benefit. NMB, net monetary benefit; CI, confidence interval.

probability of a specific intervention being chosen given its ICER and a prespecified budget limit.

This approach has been criticized in detail elsewhere (8). To summarize the approach has two fundamental problems. First, the approach can lead to an "optimal" combination of interventions, which exceeds the prespecified budget limits. Second, the approach can lead to "optimal" combinations which do not maximize the net benefit obtained as the approach fails to consider the shadow price of a unit of health benefit, thus ignoring the opportunity costs of the decisions made.

An alternative, simpler approach to determining the optimal combination of interventions has been proposed which avoids the potential criticisms of stochastic league tables (8). The cost-effectiveness of different combinations of therapies can be measured by their NMB. The NMB for each combination is simply the sum of NMB for each intervention within the package. If the threshold value for a unit of health gain is known, the optimal combination is that with the greatest net benefit; with expected costs within the budget limit. If the threshold value for a unit of health gain is unknown, then results can be presented for a range of potential threshold values.

DISCUSSION

Recent reports from the WHO are a welcome recognition of the need to conduct probabilistic uncertainty analysis. Whoever, there are fundamental concerns with certain of the approaches adopted. These relate to the estimation of the ICER, the calculation of 95% confidence intervals around the ICER and the use of what is termed stochastic league tables.

Several recent articles have addressed the interpretation of results under uncertainty (e.g., 2;4;7;13). Several of these articles have highlighted the irrelevance of focusing on inference and, thus, the irrelevance of confidence intervals, with respect to such decisions within a public health care system (e.g., 7). Such arguments lead to Bayesian approaches to

deal with such issues (3;4;6;13;15;16) which highlight the need to consider both the optimal treatment choice and the value to be obtained from further information (6;11;12).

The criticisms of the WHO-recommended approach are intended to be constructive and are based on a strong theoretical basis consistent with the arguments outlined in the paragraph above. It is hoped that the WHO reconsider their approach to probabilistic uncertainty analysis and focus on approaches with stronger theoretical underpinnings, which will lead to optimal decision making both in terms of therapeutic choices and further research priorities.

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