# A BAYESIAN APPROACH TO STOCHASTIC COST-EFFECTIVENESS ANALYSIS

#### ANDREW H. BRIGGS\*

Health Economics Research Centre, University of Oxford, UK

#### SUMMARY

The aim of this paper is to briefly outline a Bayesian approach to cost-effectiveness analysis (CEA). Historically, frequentists have been cautious of Bayesian methodology, which is often held as synonymous with a subjective approach to statistical analysis. In this paper, the potential overlap between Bayesian and frequentist approaches to CEA is explored—the focus being on the empirical and uninformative prior-based approaches to Bayesian interpretation for decision-making while retaining the robustness of the frequentist approach is equivalent to a Bayesian approach assuming no prior information, while where there is pre-existing information available from which to construct a prior distribution, an empirical Bayes approach is equivalent to a frequentist approach based on pooling the available data. Cost-effectiveness acceptability curves directly address the decision-making problem in CEA. Although it is argued that their interpretation as the probability that an intervention is cost-effective given the data requires a Bayesian interpretation, this should generate no misgivings for the frequentist. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS - Bayesian decision theory; cost-effectiveness analysis

# INTRODUCTION

The aim of this paper is to explore how Bayesian methods might be used in stochastic cost-effectiveness studies. It is sometimes thought that Bayesians and frequentists inhabit different scientific paradigms that exclude any middle ground. In particular, frequentists are often concerned that Bayesian analysis is too sensitive to the chosen prior, leading to a lack of robustness compared with the classical approach. However, there is an increasing acceptance of the fact that it is possible to exploit the natural interpretation associated with a Bayesian approach to statistical analysis while retaining the robustness of the frequentist approach [1].

Bayesian methods might usefully be classified into three main types, dependent on the approach to prior information. Empirical Bayes describes the approach of estimating prior distributions on the basis of previously available statistical information. A second approach to Bayes would be to assume no information concerning the parameter of interest. The third approach could be described as subjective Bayes, where prior information is elicited (in a coherent fashion) from experts on the basis of their personal beliefs. This classification emphasizes that only the third type of ap-

Contract/grant sponsor: UK MRC/Anglia Contract/grant sponsor: Oxord Region Training Fellowship

Received 30 September 1998 Accepted 7 December 1998

<sup>\*</sup> Correspondence to: Health Economics Research Centre, Institute of Health Sciences, University of Oxford, Headington, Oxford OX3 7LF, UK. Tel.: +44 1865 226847; fax: +44 1865 226842; e-mail: andrew.briggs@ihs.ox.ac.uk

proach is synonymous with the subjective approach commonly considered (by frequentists) to introduce a lack of robustness to statistical analysis.

In this paper the emphasis is on the overlap between the frequentist approach and Bayes methods employing empirical or uninformative priors, rather than on the subjective Bayes methods. First, the standard frequentist approach to handling uncertainty in economic evaluation is introduced. including the representation of uncertainty as a cost-effectiveness acceptability curve. Since the interpretation of such curves is most natural using a Bayesian approach, the third section considers a Bayesian approach to cost-effectiveness analysis (CEA). The final section offers a discussion of the issues raised in this paper. The focus is on the intuitive appeal of the Bayesian approach rather than the technical aspects: statistical formulae and data are, therefore, omitted.

# HANDLING UNCERTAINTY IN CEA

In a trial situation, on the basis of data collected from two groups of patients receiving alternative therapies, the incremental cost-effectiveness ratio (ICER) can be estimated by

$$\hat{R} = \frac{\bar{C}_T - \bar{C}_C}{\bar{E}_T - \bar{E}_C} = \frac{\Delta \bar{C}}{\Delta \bar{E}}$$

where  $\bar{C}_T$  and  $\bar{C}_C$  are the mean costs in the treatment and control arms of the trial, respectively, and  $\bar{E}_T$  and  $\bar{E}_C$  are the mean effects. A traditional approach for handling uncertainty due to sampling variation would be to estimate the confidence interval for the ICER and compare the interval to the maximum or ceiling cost-effectiveness ratio appropriate for decision-making,  $R_c$ . If the estimated interval excludes  $R_c$  then the intervention is significantly cost-effective/cost-ineffective.

Ratio statistics pose particular problems for standard methods of calculating confidence intervals when there is a non-negligible probability that the denominator of the ratio can take a very small value. Application of non-parametric bootstrapping [2,3] has shown the sampling distribution of the ICER statistic may not follow a well-defined parametric distribution.

Recently, a net-benefits approach to handling uncertainty in CEA has been suggested that can be employed when the ceiling ratio appropriate for decision-making,  $R_c$ , is known [4,5]. The approach involves using the value of  $R_c$  to rescale either the effect difference or the cost difference in order to provide a net-benefit statistic on the cost [5] or the effect scale [4]. For this paper, the net-benefits on the cost scale are used and defined as

$$NB = R_c \cdot \Delta \bar{E} - \Delta \bar{C}.$$

Positive net-benefits for an intervention indicate that the intervention represents good value for money. Therefore, the standard statistical approach would be to estimate the confidence interval for net-benefits and to see whether that interval excludes zero. An advantage of the netbenefit statistic is that, in contrast to the ICER, the variance of the net-benefit statistic is mathematically tractable and, with sufficient sample size, its sampling distribution is normal.

Despite the desirable properties of the net-benefit statistic, the interpretation of the net-benefits statistic is problematic due to the assumption that the ceiling ratio appropriate for decision-making,  $R_{\rm c}$ , is known. One solution to this problem of interpretation is to plot the (one-sided) confidence level at which the estimated net-benefit statistic is just significantly different from zero, as a function of  $R_c$ . This is the cost-effectiveness acceptability curve initially described in relation to cost-effectiveness ratios and the cost-effectiveness plane [6] and which has been argued to address the fundamental decision-making problem facing policymakers [7]. A strict frequentist interpretation of cost-effectiveness acceptability curves is possible, since one minus the confidence level for net-benefits gives the p value for net-benefits and the curve is, therefore, equivalent to plotting the p value as a function of  $R_{c}$ . However, just as the p value is often misinterpreted (in a strictly frequentist sense) as a probability of the hypothesis given the data, so cost-effectiveness acceptability curves presented in the literature to date [6-8] (being based on frequentist analyses) have been interpreted as the probability that the intervention is cost-effective. This natural interpretation is only possible with a Bayesian approach.

#### BAYESIAN METHODS FOR CEA

Under a Bayesian interpretation, parameters of interest are ascribed a distribution reflecting un-

certainty concerning the true value of the parameter. For mathematical convenience, it is common for prior distributions to be specified in terms of a distribution that is conjugate to the likelihood function based on the observed data since the use of a conjugate prior leads to a posterior distribution from the same family of distributions [9]. In particular, the normal distribution is self-conjugate such that a normal prior and a normal likelihood function lead to a normal posterior distribution.

For CEA, it is clear that the net-benefits statistic will be much more convenient to handle in a Bayesian analysis than would the ICER statistic. Figure 1 presents a Bayesian analysis of net-benefits. Three distributions are shown: the prior distribution of net-benefits: the likelihood function estimated from the observed data: and the posterior distribution of net-benefits based on the likelihood function, updated to account for the prior distribution using Bayes' theorem. Where the prior distribution is estimated from existing statistical information available prior to the study being undertaken, this is the empirical Bayes approach introduced above. An alternative would be to employ an uninformative prior such that the posterior distribution produced is dominated by the observed data. The posterior distribution based on the uninformative prior is the same as the likelihood function for the case of normally distributed net-benefits. It is clear from Figure 1 that incorporating the prior information reduces the variance of the posterior distribution, but that the point estimate of net-benefit is weighted most heavily toward the likelihood function from the existing data. This is because the empirical Bayes approach weights the prior information in relation to its variance compared to the observed data.

Having estimated the prior and posterior distributions for net-benefits using Bayesian methods, these can then be plotted as a function of  $R_c$  in order to generate cost-effectiveness acceptability curves—see Figure 2. The cost-effectiveness acceptability curve based on the likelihood function is equivalent to using an uninformative prior. Therefore, the presentation of cost-effectiveness acceptability curves in the context of a typically frequentist analysis [6,8] is equivalent to a Bayesian analysis of cost-effectiveness assuming an uninformative prior.

# DISCUSSION

The emphasis in this paper has been on the middle ground between Bayesian and frequentist



Figure 1. Bayesian approach to CEA based on the distribution of net-benefits.

Health Econ. 8: 257-261 (1999)

Copyright © 1999 John Wiley & Sons, Ltd.



Figure 2. A Bayesian approach to CEA presented as cost-effectiveness acceptability curves.

methods for CEA. The applications of empirical Bayes methods or Bayes methods employing an uninformative prior are largely uncontroversial. Indeed, it has been argued that Bayesian analysis based on uninformative priors is equivalent to a frequentist analysis based on the observed data (while allowing the more natural Bayesian interpretation associated with distributions of parameters). Similarly, empirical Bayes methodology is equivalent to a frequentist approach based on pooling available data. Because of this close relationship with the frequentist approach, some Bayesians would argue that the methods illustrated in this paper are not in fact Bayesian at all since no subjective beliefs are employed. For example, Spiegelhalter et al. [10] argue that while previous results should form the basis of prior distributions those results should not specify the distribution completely since to do so would be to treat historical and current data as exchangeable, which is in essence equivalent to simply pooling the results.

One way in which subjective beliefs could be incorporated in a way that may be acceptable to frequentists would be to weight prior information. In the present analysis, the two logical extremes are presented. Using data from another study to describe the prior distribution in the Bayesian analysis gives equal weighting to the prior and observed data (while giving more weight to the data with the least variance). On the other hand, using a non-informative prior distribution where data are available from a previous study effectively gives no weight to this prior data. In practice, it may be that statistical information available from previous studies could be used as a basis for the prior distribution, but that less weight could be given to these prior data. Such an approach has been illustrated by Brophy and Joseph [11]. They looked at the effect on the conclusions reached by the GUSTO investigators [12] of using information from three previous trials of thrombolytic therapy as a basis for a prior distribution with various weightings attached to the previous data. Their Bayesian reanalysis suggested that the clinical benefits of tissue-type plasminogen activator over and above those of streptokinase remain uncertain.

The characterization of the outcome of a CEA as a cost-effectiveness acceptability curve is only half the story. A full Bayesian analysis would involve using the decision-makers' loss function in order to examine the consequences of decisionmaking under uncertainty and to provide decision-making recommendations. However, in the absence of such information, cost-effectiveness acceptability curves represent an important first step for handling uncertainty in cost-effectiveness results. It is also clear that this information could be used by decision-makers, with knowledge of their own loss functions, to make decisions.

At present, few stochastic CEAs have been reported and similar studies applied to the same intervention are rare. However, as more economic analyses are undertaken alongside clinical trials, Bayesian methods may prove powerful in conducting cost-effectiveness meta-analyses, with the potential to update our degree of belief concerning the cost-effectiveness of an intervention as new studies become available.

This paper has demonstrated how Bayesian methods can be used in a way entirely consistent with the desire by frequentists for a robust approach to statistical analysis. In particular, the Bayesian approach allows a more natural way of interpreting cost-effectiveness acceptability curves. It would be unfortunate if the potential for Bayesian methods were cast aside due to the prior beliefs of frequentists that the methods are necessarily subjective.

#### ACKNOWLEDGEMENTS

This paper has benefited greatly from Dr Alastair Gray's comments and from discussion with Sir David Cox. The comments from two anonymous referees are also acknowledged. Responsibility for all remaining errors is of course my own. Funding comes from a joint UK MRC/Anglia and Oxford Region Training Fellowship in Health Economics and Medical Statistics.

# REFERENCES

1. Carlin, R.P. and Louis, A.T. *Bayes and empirical Bayes methods for data analysis.* London: Chapman & Hall, 1996.

- Chaudhary, M.A. and Stearns, S.C. Estimating confidence intervals for cost-effectiveness ratios: An example from a randomized trial. *Statistics in Medicine* 1996; 15: 1447–1458.
- 3. Briggs, A.H., Wonderling, D.E. and Mooney, C.Z. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Economics* 1997; **6**: 327–340.
- 4. Stinnett, A.A. and Mullahy, J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Medical Decision Making* 1998; **18**(2 Suppl): S65–S80.
- Tambour, M., Zethraeus, N. and Johannesson, M. A note on confidence intervals in cost-effectiveness analysis. *International Journal of Technology As*sessment in Health Care 1998; 14: 467–471.
- van Hout, B.A., Al, M.J., Gordon, G.S. and Rutten, F.F. Costs, effects and C/E-ratios alongside a clinical trial. *Health Economics* 1994; 3: 309–319.
- Briggs, A. and Fenn, P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Economics* 1998; 7: 723-740.
- Raikou, M., Gray, A., Briggs, A., Stevens, R., Cull, C., McGuire, A., Fenn, P., Stratton, I., Holman, R. and Turner, R. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *British Medical Journal* 1998; 317: 720–726.
- 9. Rice, J.A. *Mathematical statistics and data analysis*, 2nd edition. Belmont: Duxbury Press, 1995.
- Spiegelhalter, D.J., Freedman, L.S. and Parmar, M.K.B. Bayesian approaches to randomised trials. *Journal of the Royal Statistical Society, Series B* 1994; 157(Part 3): 357–416.
- Brophy, J.M. and Joseph, L. Placing trials in context using Bayesian analysis. GUSTO revisited by Reverend Bayes. *Journal of the American Medical Association* 1995; 273: 871–875.
- 12. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *New England Journal of Medicine* 1993; **329**: 673–682.