Knowing What You Don't Know: Bayesian Approaches to Uncertainty in Economic Evaluations

INTRODUCTION

The science of decision analysis can help patients and physicians choose the best treatment when outcomes are uncertain. We say that randomness exists whenever intrinsically unobservable factors influence outcomes. Consider a simple coin flip. In comparison to the complex biomedical processes of disease and treatment, the physics of flipping coins is relatively straightforward. Nevertheless, whether the coin lands heads up depends on the exact physical state of the coin and the environment, which is unknowable. Imperfect foresight of random outcomes is referred to as "first-order" uncertainty (see Briggs[1] for discussion of types of uncertainty).

If the coin is fair, half of the flips will turn up heads in the long run. Using classical statistics, the frequency of long-run events can be converted into the probability of an event occurring in a given instance (i.e., the probability of a fair coin turning up heads is one-half). But what if you don't know whether or not the coin is fair? If a bet were to be placed on heads or tails, which would you choose? If a very large (nearly infinite) number of coin flips could be observed prior to placing a bet, and 75% came up heads, it wouldn't be a bad idea to bet on heads! This situation would be similar to choosing between 2 treatments after the "perfect" head-to-head randomized clinical trial. While individual outcomes remain uncertain, at least we have (almost) perfect knowledge about their probabilities.

It is also (almost) certain that no perfect head-to-head clinical trial has ever been conducted. Physicians and patients must make treatment decisions based not only on imperfect foresight but also on imperfect knowledge. Not only are the probabilities of treatment success, failure, side effects, etc. uncertain, but so are the consequences of these events in terms of costs and outcomes.

In decision analysis, such event probabilities and consequences are referred to collectively as the "parameters" of the decision model. Knowledge about parameters comes from real-world controlled trials, observational studies, expert opinion, etc. Such imperfect investigations will always leave some statistical margin of error. "Second-order" uncertainty refers to imperfect knowledge of the true value of the model parameters.

Decision analyses should reflect how second-order uncertainty affects the decision-maker's ability to choose the optimal treatment. Unfortunately, published decision analyses often report base-case incremental cost-effectiveness ratios as if they were known with certainty. While researchers often use one-way, deterministic sensitivity analysis to test the model's robustness to variation of single parameters, they often do not assess globally the influence of second-order uncertainty on the decision-maker's ability to choose the optimal treatment.

Bayesian Uncertainty Analysis

Measures of second-order uncertainty derived from Bayesian statistics can help us to "know what we don't know" in a decision analysis. In contrast to the classical statistics approach based on long-run frequencies (the perfect clinical trial), Bayesian statistics establishes how more can be learned about an unknown parameter as new data are observed piece by piece (the real world of clinical studies). Bayes' Law is the cornerstone of Bayesian statistics. It relates what we know about a random parameter after observing new data to what we knew beforehand and the likelihood of observing the data we actually observed. The state of knowledge before observing new data is called the "prior", the state of knowledge afterwards is called the "posterior."

What if nothing was known beforehand about the probability that a new treatment would be successful? One might represent such (lack of) knowledge with a uniform probability distribution ranging from zero to one. For example, suppose that a case series of 9 individuals under treatment is observed: 6 successes and 3 failures. Using "conjugate" analysis (where the posterior distribution is easily calculated given the prior and the observed data), the posterior distribution can be calculated using Bayes' Law. The prior and posterior distributions are plotted in Figure 1. Note the posterior distribution has ruled out zero and one (since both successes and failures were observed). The most likely success probability is two-thirds = 6/9 (which would be the classical maximum likelihood estimate). We still do not know the true probability of success with certainty — it may still be 0.1 or 0.95 (or any other number other than zero or one), although 0.66 is more likely to be true given the current state of knowledge. The level of certainty about an unknown parameter can be visualized as the "tightness" of its distribution (Figure 1).

Decision Acceptability

Monte Carlo simulation can help identify how second-order uncertainty influences the decision-maker. The standard methods of calculating expected incremental cost and effectiveness from decision trees are used. However, rather than using the base-case set of parameters, we use a computer to draw a pseudo-random set of parameters from the probability distributions reflecting our current state of knowledge (ideally, Bayesian posterior distributions). The incremental cost and effectiveness pair resulting from this random parameter "draw" can be plotted on the incremental cost-effec-

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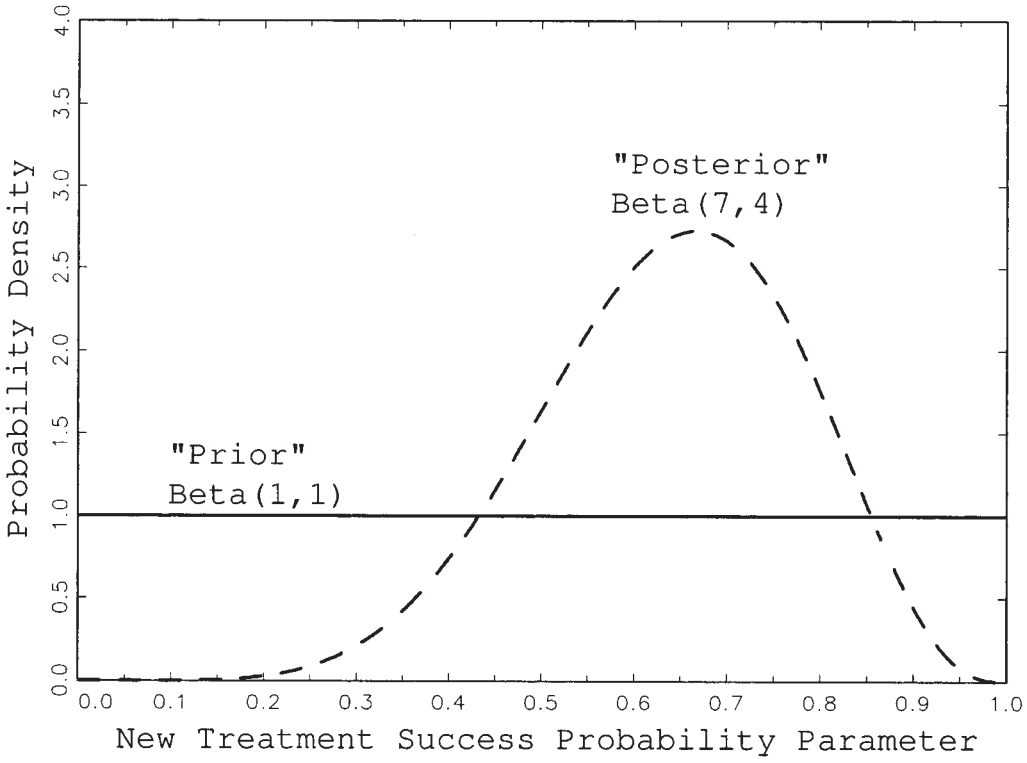

Figure 1. Prior and posterior distributions for an unknown treatment success rate.

tiveness plane (see Briggs, *et al*[3]). Given a threshold value of willingness to pay for a unit outcome improvement (for example, $50,000 per quality-adjusted life year), we can plot a line through the origin with that slope. If the point lies below and to the right of that line (i.e., more effective and/or less expensive) that would be evidence in favor of the new treatment. Doing this exercise repeatedly (say, 10,000 times) would yield a cloud of points in the cost-effectiveness plane (Figure 2).

By counting the number of points below the line and dividing it by the total number of points, we can derive a measure of the "acceptability" of the decision to the decision-maker. If, for example, after considering all uncertainty, 90% of the simulations favored the new treatment, this would be more acceptable to a decision-maker than if it were "50/50." Acceptability depends on the threshold value for cost-effectiveness. Plotting acceptability as a function of the threshold value yields an "acceptability curve"[4].

The Value of Information

Bayesian decision analysis can also explicitly assign value (even monetary value) to information. While beyond the scope of this short introduction, it is worthwhile to consider 2 concepts: the "expected value of perfect information" (EVPI) and the "expected value of sample information" (EVSI)[5]. Assuming there is a penalty for making a wrong decision, it is logical to ask, "How much would a decision-maker be willing to pay to know the true value of all unknown parameters?" In the coin-flip example, if a person were about to place a bet on heads, how much would they be willing to pay to know, for certain, the exact probability of the coin coming up heads? That amount would be the EVPI — it would depend on the size of the bet and current knowledge about the probability of heads. If the bet is small or if one is almost certain of the fairness of the coin, then EVPI would be small. In medical decision-making exercises, EVPI is high when little is known about parameters that strongly influence the decision and the penalty of making the wrong decision is high. All else being equal, research questions with high EVPI may be given higher priority over questions with low EVPI.

But, is perfect knowledge really the relevant concept? The absolute truth is rarely learned all at once; rather, we learn sequentially by observing samples. It might be more instructive to ask, "How much would a person be willing to pay to see 10 flips of the coin before they had to place a bet on the 11th flip?" That amount describes the EVSI. When combined with the cost of sampling, it can be used to determine the optimal design of a clinical study[8].

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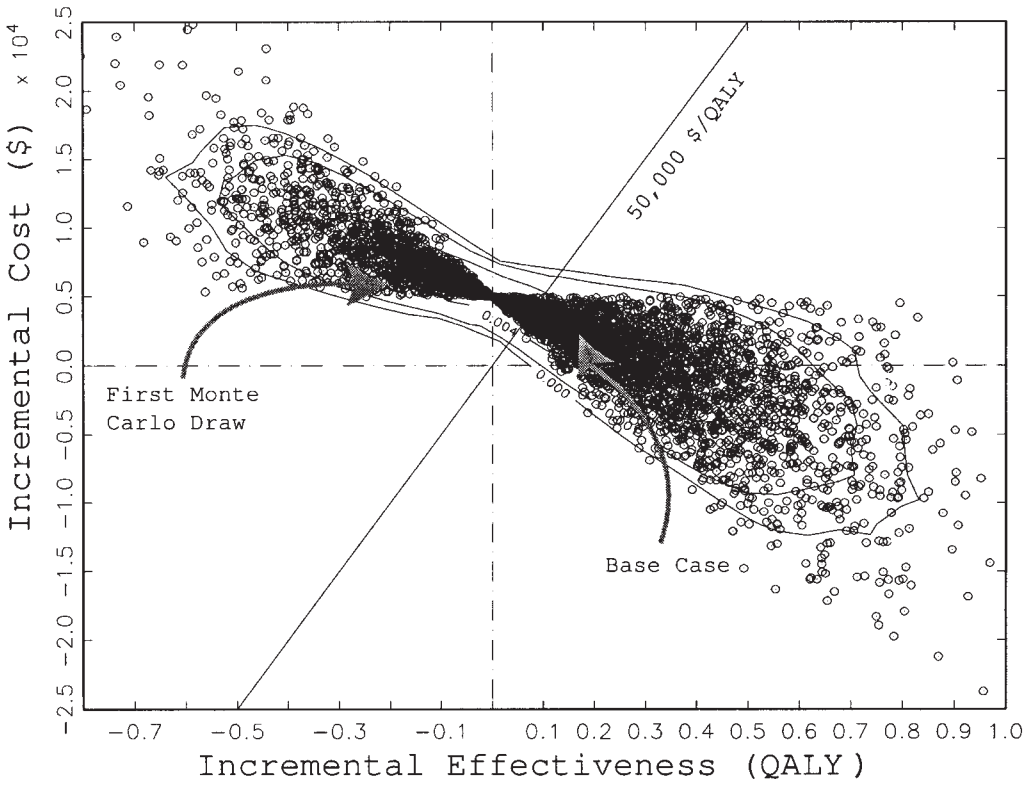

Figure 2. A second-order Monte Carlo simulation plot on the cost-effectiveness plane.

CONCLUSION

In summary, there are 4 key messages to take away from this discussion:

1. Parameter estimates used in decision analyses are random variables.
2. Uncertainty can be represented by probability distributions (whether asymptotic or Bayesian posterior, subjective, or systematic).
3. Uncertainty affects the ability to make clear decisions; Monte Carlo simulation can be used to visualize that effect.
4. The value of information can be quantified from the decision-maker's point of view; this can help prioritize future research.

It is hoped that this short introduction will spark the interest of readers to pursue more knowledge about Bayesian decision analysis (Spiegelhalter, *et al*[6] and Felli and Hazen[7] are excellent starting points).

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REFERENCES

1. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000;17:479-500.
2. Gelman AB, Carlin JS, Stern HS, Rubin DB. Bayesian data analysis. Boca Raton: Chapman & Hall/CRC; 1997.
3. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost effectiveness studies. Annu Rev Public Health 2002;23:377-401.
4. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10:779-87.
5. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999;18:341-64.
6. Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Methods in health service research: an introduction to Bayesian methods in health technology assessment. BMJ 1999;319:508-12.
7. Felli JC, Hazen GB. A Bayesian approach to sensitivity analysis. Health Econ 1999;8:263-8.
8. Kadane JB. Bayesian methods and ethics in a clinical trial design. New York: John Wiley & Sons, Inc.; 1996.

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