Estimating the return from reducing bias in clinical trials

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Paper presented at 72nd Health Economists' Study Group meeting, Norwich, January 2008.

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Abstract

In this paper we begin by defining the research process as a cycle of systematic review and economic evaluation, followed by the adoption decision, and the decision to obtain further information through new trials and studies. We then summarise the methods for value of information analysis, and their use in valuing reductions in the variance of parameter estimates. Following this, we propose a method to extend these principles to valuing reductions in bias in those estimates. We do this by defining a theoretical 'gold standard' economic evaluation alongside a clinical trial of a treatment compared with current therapy (measuring every cost and every benefit to every agent over a lifetime horizon). This should provide an unbiased estimate of the incremental cost-effectiveness ratio and hence expected incremental net benefit.

Departures from this 'gold standard' will lead to a biased estimate of the expected net benefits of the comparators: for example, failure to collect all relevant cost data. This will lead to an increasing probability of making the 'wrong' decision. Investment in research to collect missing data will reduce the bias and hence probability of a 'wrong' decision, thus increasing the expected value of the decision. The value of the gain from investment in more detailed data collection can then be compared with the cost of obtaining it to guide trial protocol development.

This principle can be extended to other aspects of clinical trials, for example follow-up length and costing perspective.

Introduction

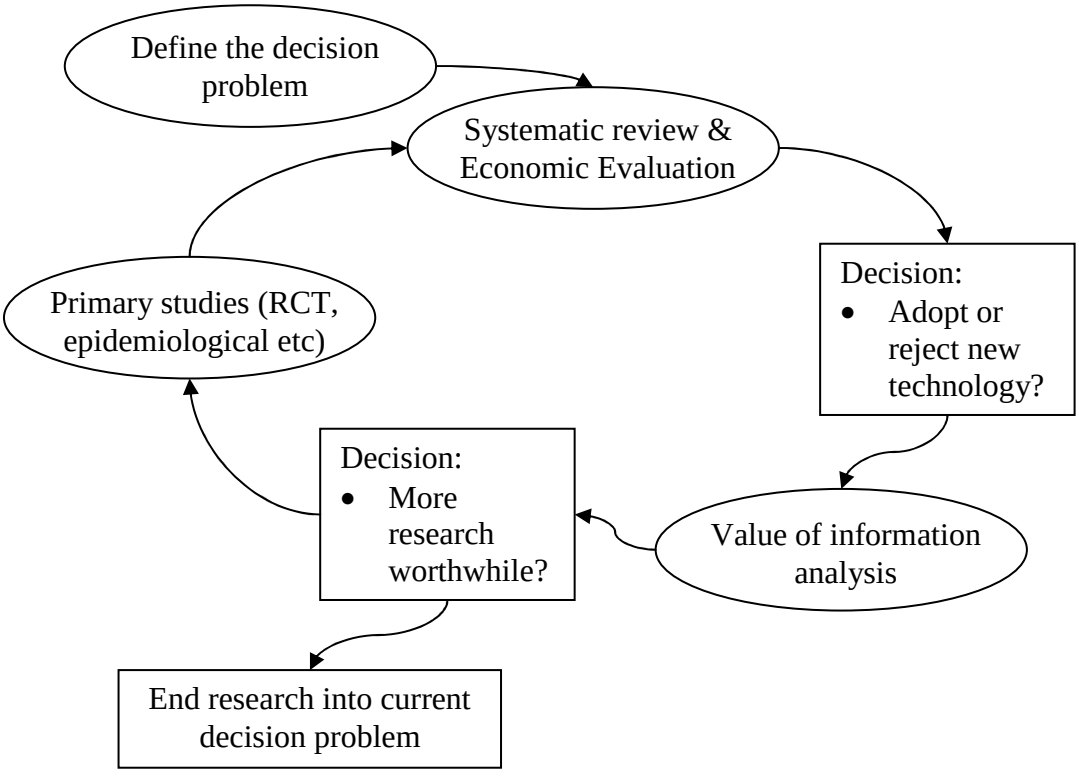
The purpose of much health services research is to assist in decisions as to whether or not to adopt a given technology (drug, device, programme or technique). In order to maximise expected health gain, a decision should be based on the highest expected net benefit to be gained from each alternative course of action.[1] (This is simply a rearrangement of the incremental cost-effectiveness ratio into the net benefit form). There will be uncertainty associated with this decision, typically expressed through the cost-effectiveness acceptability curve (or rather, frontier).[2] This uncertainty should be used to inform decisions as to whether to pursue future research.

This approach fits within a cycle of 'economics based medicine' (Figure 1), which begins with the definition of a specific decision question. This must be specified fully, for example "Is x cost-effective compared with y from perspective z". Following on from this, a systematic review of the existing literature should be carried out, and this evidence synthesised in a model-based economic evaluation. It is critical to specify appropriate input parameters and carefully estimate their mean values and characterise the uncertainty at this stage. Where no data exist for a particular parameter, expert judgement is required to define a likely range of values. Uncertainty within the model should be analysed with a probabilistic sensitivity analysis.

The expected incremental net benefit obtained from the model is used to make an adoption decision. At this stage, a value of information analysis is performed to judge whether further research into the decision question is warranted. If the cost of future research is predicted to exceed its value, then further research into this question would not be appropriate, and the decision should be based on existing knowledge. However, if the value of further research is greater than its cost, more information should be gathered, and synthesised back into the model. The cycle thus repeats itself.

Value of information analysis focuses on determining whether further research should be carried out into the decision question, and if so, which parameters should be examined. Finally, it provides an appropriate sample size for such studies. In the remainder of this paper, we summarise the methods of value of information analysis, and then consider an extension of these principles to other trial design issues, for example, the quality of resource use data required, follow-up length etc. Value of information as currently employed focuses on reducing variance in a parameter estimate. These other issues reflect reductions in bias.

Figure 1: "Economics Based Medicine"



Value of information analysis / Information theory

Information theory has its origins in the early 1960s in the work of Raiffa & Schlaifer,[3] but recently interest has grown in its application to healthcare decision making to inform future research. Value of information (VoI) analysis provides justification for whether future research should be conducted, and if so, on which uncertain parameters, and the appropriate sample size for such a study.[4-6] Pilot studies have been undertaken to inform future research priorities in the NHS Health Technology Assessment programme[7] and for the National Institute for Health and Clinical Excellence,[8] and VoI analyses are beginning to appear alongside published economic evaluations.[9 10]

Value of information analysis is a technique to value the returns from investment in further research to reduce decision uncertainty. It can be used in place of conventional power calculations to estimate the appropriate sample size for future trials of the technology under consideration, based on a comparison of the return from the marginal trial enrolee and the associated marginal cost of including her/him in the research.

Expected Value of Perfect Information

As stated in the introduction, the decision rule is to choose the option, j which maximises the expected net benefit, based on the input parameter set, θ:

$$\max_j E_\theta NB(j,\theta) \qquad (1)$$

The expected value of perfect information is the difference between the net benefit with perfect information and that with current information:

$$EVPI = E_\theta \max_j NB(j,\theta) - \max_j E_\theta NB(j,\theta) \qquad (2)$$

Where:

j = intervention (e.g. 1= current treatment, 2=new treatment)

θ = input parameters to model

NB(j,θ) = net benefit of intervention j with parameter set θ.

The maximum expected net benefit with current information is simply the outcome of the model [equation (1)]. The maximum net benefit with perfect information is unknown. However, the expected maximum NB can be estimated as the mean of the maximum NB observed from each iteration in the probabilistic sensitivity analysis.

Equation (2) is the EVPI per patient. This should be scaled up to the current and future population to provide an upper limit for the budget for future research in to the technology in question:

$$PopnEVPI = EVPI.\sum_{t=1}^{T}\frac{I_t}{(1+r)^t} \qquad (3)$$

Where:

I_t = incident population in time t.

r = discount rate

Expected value of perfect parameter information

The expected value of perfect information for a parameter (EVPPI) provides an upper bound to research expenditure in a particular parameter:

$$EVPPI_{\varphi} = E_{\varphi}\max_j E_{\psi|\varphi}NB(j,\varphi,\psi) - \max_j E_{\theta}NB(j,\theta) \qquad (4)$$

Where:

$\varphi \cup \psi = \theta$

(φ is a parameter or subset of parameters of interest, ψ is all the others in set θ)

Again, this should be multiplied by the incident population over an 'appropriate' time horizon to calculate the population EVPPI:

$$PopnEVPPI = EVPPI.\sum_{t=1}^{T}\frac{I_t}{(1+r)^t} \qquad (5)$$

Note the sum of EVPPIs is not necessarily equal to the EVPI due to interactions between variables.

These statistics, EVPI and EVPPI, are necessary, but not sufficient conditions for deciding to carry out a research project to reduce decision uncertainty around a given question.

The expected value of sample information (EVSI) provides the sufficient condition as to whether undertake a particular trial by estimating the return from the trial given a sample size n. For a single parameter this is:

$$E_D \max_j E_{\theta|D} NB(j,\theta) - \max_j E_\theta NB(j,\theta) \qquad (6)$$

Where

θ = single uncertain parameter

D = sampled value of θ from trial of size n

And for groups of parameters:

$$E_D \max_j E_{\psi,\varphi|D} NB(j,\varphi,\psi) - \max_j E_\theta NB(j,\theta) \qquad (7)$$

The expected net benefit of sampling (ENBS) is the EVSI less the cost of conducting the research with sample size n. If there is no positive sample size for which the ENBS is greater than zero, then additional research is not warranted, and there is sufficient evidence for decision making (i.e. the cost of future research would be greater than the value of the benefit).

Extending the principles to bias

The above techniques provide estimates as to the return from a clinical trial, epidemiological or cost study of sample size n. However, to our knowledge, this approach has not been extended to consider other aspects of trial design, such as follow-up length and how detailed a resource data collection instrument needs to be. Essentially, the techniques have been used to inform reductions in variance, but have not addressed bias, although the potential has been acknowledged.[11]

Bias is a systematic (as opposed to random) error leading to incorrect inferences as to the true value of a parameter. Many sources of bias have been identified in randomised clinical trials and epidemiological studies. These usually include (among other sources of bias):

- selection bias (systematic differences in comparison groups);
- performance bias (systematic differences in patient management other than the intervention being assessed);
- attrition bias (systematic difference in dropouts from a trial); and
- detection bias (systematic difference in interpretation or assessment of results).[12 13]

A solution to controlling for selection bias is the method for randomisation and blinding processes within a trial.[14-16] However, there are other sources of bias particularly pertinent to economic evaluations conducted alongside clinical trials. These include the follow-up length of the study, cost perspective and approach to resource use measurement and valuation. The results of systematic reviews are subject to publication bias in the source studies, and model-based economic evaluations are further subject to bias in the structural assumptions made in developing the model.

For the remainder of this paper, we will focus on bias caused by failure to collect all relevant resource use data. In a 'gold standard' economic evaluation alongside a clinical trial,[17] all resource use by all participants in the trial is measured, whether or not attributable to the intervention. This ensures that any 'unintended consequences' of an intervention (i.e. displacement of costs to other areas / sectors) are captured. Furthermore, in such a trial cost measurement commences prior to randomisation and continues for the full duration of trial follow-up. The follow-up period would be sufficient to capture all costs and outcomes to all parties affected by the intervention under consideration (potentially not only the lifetime of the patient, but also his/her family & friends, carers, employer, the treasury, health and social services etc). The perspective of this trial is thus societal. The sample size in this trial

provides adequate power to detect anticipated differences in both outcome and resource use.

The decision rule based on this trial is to adopt the technology with the highest expected net benefit (equation 1), or alternatively "adopt option 2 if the incremental net benefit over option 1 is greater than zero". Given a finite sample size, the trial would provide an unbiased estimate, ω, of the population INB, Ω:

$$E(\omega) = \Omega \qquad (8)$$

and

$$\omega \sim Dist(\Omega, \sigma^2) \qquad (9)$$

Value of Information analysis as currently applied focuses on reducing the variance, σ^2. However, it does not consider whether ω is biased, i.e. whether $E(\omega) \neq \Omega$.

A particular issue in the design of an economic evaluation alongside a clinical trial is the amount of detail required in resource use measurement; specifically whether a top-down approach is sufficient, or whether to attempt collection of 'difficult to obtain' data. This is particularly the case in social care interventions where resource use measurement is complicated by the multiplicity of agencies providing care, and the need for relatively long follow-up time. Failure to address these issues sufficiently could lead to systematic errors in calculating net benefit. Therefore there is a probability that the 'wrong' decision will be made, and hence foregone health benefit to the population. Investment in research to more closely match the gold standard will reduce the bias, and thus increase the probability of making the 'correct' decision. This therefore increases the expected value of the decision. However, more detailed resource use measurement or longer follow-up times increase the cost of the trial. The question is whether the value of this health gain exceeds the cost of performing the "less-biased" analysis.

Quantifying the gain from bias elimination ("expected value of bias elimination")

The existence of bias when sampling a parameter only matters when it affects the decision. Suppose a 'gold standard' clinical trial with piggy-backed economic evaluation was designed measuring a set of resource items X_1 = {all relevant resource items} such that an unbiased estimate of the net benefit was generated. The net benefit of the decision between technologies j=1,2 is thus:

$$\max_j NB(j, X_1) \qquad (10)$$

Suppose the analysis was performed with some of the resource items (φ) missing (i.e. unobserved). We call the reduced set X_2 such that $X_2 \cup \varphi = X_1$. Given the same state of the world, the decision would be:

$$\max_j NB(j, X_2) \qquad (12)$$

This will give a biased estimate of the NB. There is an opportunity loss if the decision with (11) is different from (12), equal to the incremental net benefit from each course of action as measured from the unbiased dataset, X_1:

$$L = abs(NB(1, X_1) - NB(2, X_1)) \mid D_U \neq D_B \qquad (13)$$

Where:
abs = absolute value
D_U = decision using unbiased dataset
D_B = decision using biased dataset

This represents just one possible state of the world. We do not know the true maximum benefit from each dataset, so we take the expectation of repeated samples:

$$L = E(abs(NB(1, X_1) - NB(2, X_1)) \mid D_U \neq D_B) \qquad (14)$$

This is the expected opportunity loss associated with a biased subset of resource items, and thus the maximum possible value of additional research to correct the bias. It is therefore directly analogous to the EVPI.

In order to calculate the expected maximum net benefit with set of resource items X_2, we need some prior information as to the mean and distribution of $NB(j,X_2)$ (i.e. the net benefit of each treatment when calculated using X_2).

A hypothetical example

Let us assume that we are looking at a new treatment for speeding up fracture healing time. Based on current information, (assume this is restricted to an NHS cost perspective), we estimate the following:

	Cost per patient	QALYs
New treatment	£10,000	5
Existing treatment	£6,000	4.8
Increment	£4,000	0.2
ICER:	£20,000	
Inc. net benefit | WTP of £30k	£2,000	

The input parameters to the model used to generate these figures were all assigned prior distributions, and a probabilistic sensitivity analysis conducted (results not shown). The incremental cost per QALY gained is £20,000, with a mean positive incremental net benefit, given a threshold (λ) of £30,000.

A new trial is planned evaluating the treatment, and we are planning to include NHS costs, but are considering whether or not to measure indirect costs. Assume that we think a patient with the new treatment (call this j=2) is likely to return to work earlier and earn around £900 extra, compared with a patient with treatment j=1 (e.g. let's say the average wage is £300 and the treatment allows the patient to get back to work three weeks earlier). The impact of this on mean net benefit is simply £900 (=λ(E2-E1)-(C2-C1-900) =

£2,900). However this does not take into account uncertainty in the indirect cost, or its impact on decision uncertainty.

We defined and estimated the parameters of a gamma distribution with a mean of £900 and 'reasonable' variance around it. In this case:

$$I \sim \Gamma(9,98) \qquad (15)$$

We then performed the Monte Carlo simulations, including sampling values for the indirect cost [equation (15)]. We calculated two estimates of the cost of treatment 2: the biased one (C_{2B}), and the unbiased one, which includes the indirect cost (C_{2U}). From this we get two decision problems: choosing the maximum of the biased net benefit estimates ($NB_{1|B}$ and $NB_{2|B}$), and the maximum of the unbiased ($NB_{1|U}$ and $NB_{2|U}$). Where both result in the same decision, there is no opportunity loss. However, where different decisions result, the opportunity loss is simply the incremental net benefit of the options estimated with the unbiased dataset.

In the sample simulation showing just 10 iterations (Table 2), the mean loss from the bias is estimated at £1,032. This is the per patient estimate, and must be multiplied up to the present and future population as for EVPI calculations. Based on an incidence of suitable fractures of 23 per 100,000[i], a UK population of 60m, a discount rate of 3.5%, and a relevant time horizon of 10 years, the population value of bias elimination is:

$$\sum_{t=0}^{10} 1032 * \frac{13800}{(1+0.035)^t} = £132.7m$$

In this case the population value is £132.7m. Assume the marginal cost of collecting and analysing these data is 0.5WTE researcher. Including overhead costs, this would sum to around £25,000, suggesting that collecting the additional data in this case is very worthwhile.

[i] This is an illustrative rate. Figure is based on the incidence of open fractures, Court-Brown et al. 1997

Table 2: Example simulation (WTP = £30,000)

#	C1	C_{2B}	C_{2U}	E1	E2	$NB_{1\|B}$	$NB_{2\|B}$	$NB_{1\|U}$	$NB_{2\|U}$	D_B	D_U	Opp loss
1	£5,834	£7,292	£5,818	4.830	5.113	£139,056	£146,092	£139,056	£147,566	2	2	0
2	£4,910	£5,073	£14,111	4.726	5.032	£136,860	£145,887	£136,860	£136,849	2	1	11
3	£4,346	£15,729	£8,789	4.880	4.787	£142,058	£127,870	£142,058	£134,810	1	1	0
4	£2,900	£3,979	£4,950	4.956	4.905	£145,791	£143,186	£145,791	£142,215	1	1	0
5	£4,313	£8,109	£11,401	4.727	5.043	£137,483	£143,176	£137,483	£139,884	2	2	0
6	£5,661	£14,988	£6,204	4.684	4.920	£134,859	£132,598	£134,859	£141,383	1	2	6523
7	£7,990	£13,102	£8,752	4.785	4.936	£135,550	£134,980	£135,550	£139,330	1	2	3781
8	£8,154	£6,873	£7,221	4.938	4.974	£139,974	£142,361	£139,974	£142,012	2	2	0
9	£4,039	£5,164	£6,470	4.673	4.941	£136,139	£143,077	£136,139	£141,770	2	2	0
10	£2,821	£13,838	£4,088	4.914	4.854	£144,593	£131,789	£144,593	£141,539	1	1	0
Mean												1032

Discussion

The work presented in this paper is at an early stage, and arose following involvement in a trial of a social care intervention with an extremely complex set of resource use instruments, requiring a great deal of time and effort to analyse and interpret. The question was whether a simpler approach would have sufficed.

We present here a proposed method to estimate whether investment in more detailed resource data collection is worthwhile. The metric presented, the "expected value of bias elimination" is directly analogous to the expected value of perfect information. We demonstrated its application with an example of whether to collect indirect cost data alongside a planned economic evaluation alongside a clinical trial. As for EVPI calculations, our metric provides a necessary, but not sufficient, condition as to whether or not it is worthwhile to collect more detailed resource use data.

The logical next steps are to extend this analysis to calculate analogous values of the EVPPI and EVSI. We envisage the latter as being a comparison of two proposed trials, one of which is more likely to be biased than the other. There is an opportunity loss when the difference in the results from each trial

is sufficient to result in different conclusions (i.e. $D_1 \neq D_2$). However, it is unknown whether either of the trials will be completely unbiased.

An issue for all information theoretic approaches is correlation between the expected net benefit from each intervention: it is reasonable to assume that if a patient does well on one treatment, they are likely to do well on the other too. Value of Information analysis assumes the correlation coefficient is zero, leading to an overestimate of the EVPI, and in this case, the expected value of eliminating bias. This does not affect interpretation of the EVPI or expected value of eliminating bias as they still set ceilings for future research budgets. However, the true value of the ceiling will be lower than this (given a correlation coefficient of 1, the EVPI will be zero).

Specific areas in which we would welcome discussion are:

* The plausibility and accuracy of the mathematics, and whether this has been done before.

* The relationship between the cost-effectiveness acceptability curve and bias: Correcting for bias will shift the curve, but can any conclusions be drawn from the degree or direction in which it is shifted?

Conclusion

We presented a method for estimating whether a more detailed resource use data collection instrument is likely to be value for money for research funds, based on the degree to which bias affects decision uncertainty. The question of scope and perspective of an economic evaluation (i.e. whether to undertake a societal or just health service perspective) are essentially the same question as to whether or not to collect a particular resource use variable.

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