Expected Value of Sample Information with correlated parameters

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Abstract

Value of information analysis is a means to estimate the return from investment in research. The expected value of perfect information (EVPI) is the expected loss from making the 'wrong' decision. The expected value of sample information (EVSI) is the expected reduction in EVPI from additional information about incremental net benefit, or a component thereof (e.g. effectiveness of an intervention, resource use estimates). The expected net benefit of sampling (ENBS) is the EVSI less the cost of sampling, and is a function of the sample size, n, of the proposed study, as well as the threshold, λ.

If two parameters, A and B, are correlated, gathering information about parameter A should also provide some information about parameter B, hence reducing the EVSI of B. Therefore the EVSI of B, conditional on A may be lower than the unconditional EVSI of B. The implications are that consideration of the EVSI of A and B separately may suggest it is efficient to gather information on B, but taking into account correlations, it may be more efficient to gather information on A alone.

In this paper we explore whether this is a reasonable proposition, and if so, how to adjust VoI statistics with application to a previously collected dataset.

1. Introduction

Information theory has its origins in the work of Raiffa and Schlaifer[1] 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, based on a comparison of the return from the marginal trial enrolee and the associated marginal cost of including her/him in the research.[2-4] It therefore presents an alternative to classical frequentist sample size calculations.

Pilot studies have been undertaken to inform future research priorities in the NHS Health Technology Assessment programme[5] and for the National Institute for Health and Clinical Excellence,[6] and VoI analyses are beginning to appear alongside published economic evaluations.[7-17]

The key statistics in VoI analysis are the expected value of perfect information (EVPI), the expected value of perfect parameter information (EVPPI), the expected value of sample information (EVSI) and expected net benefit of sampling (ENBS). References to 'VoI' in this paper refer to all these statistics collectively.

Most examples of value of information analyses in the literature are restricted to calculating the EVPI and EVPPI, with only one example of an EVSI and ENBS calculation.[18] A likely reason for this is 'computational expense': most VoI analyses are performed on a decision analytic model such as a decision tree or Markov chain, and solved numerically (that is, by Monte Carlo simulation), rather than analytically (that is, by solving the equations). For anything but the simplest of models this requires nested iterations of the simulation, which can very easily consume considerable computer processing time.

A key strength of decision analytic models as a tool is that they draw on a variety of sources of information to inform the decision: a single trial is highly unlikely to capture all relevant costs and consequences.[19] For example, the relative risk of successful treatment or adverse event may be taken from a meta-analysis of clinical trial(s), baseline risks from epidemiological studies, and unit costs, resource quantities and

health state utilities from a combination of routine databases, surveys, and even expert opinion.

This heterogeneous data is also a key drawback of decision models as the interactions between the input variables (that is, the variance-covariance matrix) is unknown and probably unknowable for two reasons: firstly, as data are from different samples, there is no correlation observed between the parameters, yet it is reasonable to believe that high values of one (e.g. cost) may be associated with, for example, low values of another (e.g. utility / health-related quality of life / QALYs). Secondly, where parameters are observed in the same sample, analysts may not have access to the individual patient data, and so rely on what is reported in the write-up, which may be insufficient.

For these reasons, most decision models assume independence between input parameters. This has implications for the value of information, as the VoI is a function of the variance of incremental net benefit (INB). Ignoring correlations between input parameters may over or underestimate the variance of INB, thus over or underestimating the VoI.

The purpose of this paper is to explore the implications of correlations between input parameters on the value of information. We begin by assuming we have data from a single two-arm trial reporting mean cost per patient and mean QALYs per patient in each arm, and that this is the totality of evidence into this decision problem. Given a fixed willingness to pay for a QALY, incremental net benefit, b, can be calculated from the data, and it is defined solely in terms of ΔE and ΔC (the incremental QALYs and cost respectively). We also assume that b, ΔE and ΔC are normally distributed.

This setup allows us to calculate analytic solutions to VoI on b, ΔE and ΔC without concern for the parameters 'behind' ΔE and ΔC (e.g. health state utilities, unit costs, resource quantities etc), or the structure of a decision model. Both the implications of structural uncertainty and the random 'noise' of numeric solutions are therefore avoided.

Structure and purpose of paper

Our starting proposition is that VoI may be used to reach a decision to gather data on ΔE and ΔC. However, given the correlation between ΔE and ΔC, a scenario could be envisaged where it may be more efficient to gather data on ΔE alone: the

information on ΔE provides some information on ΔC, negating the need to collect data on ΔC. We do this by calculating the VoI on b, ΔE and ΔC before introducing some 'new' data on ΔE. We then recalculate the VoI on b, ΔE and ΔC.

The next section describes an analytic solution to EVPI, EVPPI and EVSI,[3 20] and applies this to data from a recent randomised controlled trial (patient level data on QALYs and cost). These data are assumed to comprise the totality of relevant evidence for the decision problem at that point.

We then introduce some additional data on effectiveness (incremental QALYs, ΔE), incorporate these into the prior data and re-estimate the VoI statistics. For the purpose of this paper, we assume the additional data yields a sample mean for ΔE (call this ΔE_n) and sample variance ($s^2_{\Delta En}$) identical to the prior mean and variance (ΔE_0 and $V(\Delta E_0)*N$). (The reason for this and the consequences are explained in the discussion).

The new data do indeed reduce the EVSI of yet more data on ΔE, but we then discuss whether it is reasonable to suppose that additional information on ΔE also gives us some information about ΔC. This would require some correlation not only between the means of ΔE and ΔC, but between the *variance* of ΔE and the *variance* of ΔC. If so, we propose a method for incorporating this to revise our estimate of the variance of ΔC, and hence our estimate of the value of additional information on ΔC. This then has consequences on the optimal sample size of a study on ΔC.

2. VoI Analysis

Method

We define incremental net benefit as the value of the difference in outcome less the difference in cost between two interventions ('New' and 'Old') (equation 1).

$$b = \lambda \Delta E - \Delta C \qquad [1]$$

where:

b = incremental net benefit
λ = willingness to pay threshold
ΔE = incremental outcome (QALYs)

ΔC = incremental cost

The data used in this paper are cost and QALYs gained per patient in two arms of a recent trial-based economic evaluation. These are assumed to comprise the totality of evidence on costs and outcomes. Critically, we also assume b, ΔE and ΔC are normally distributed. This allows us to use the 'unit normal loss integral' (UNLI) method to estimate VoI. See Appendix 1 for details of the method.

In this paper we estimate:

* the expected value of perfect information (EVPI) associated with b ($EVPI_b$ or just EVPI);
* the expected value of perfect parameter information (EVPPI) of ΔE and ΔC ($EVPPI_{\Delta E}$ and $EVPPI_{\Delta C}$);
* the expected value of sample information associated with b ($EVSI_b$ or just EVSI); and
* the 'partial' EVSI associated with ΔE and ΔC ($EVSI_{\Delta E}$ and $EVSI_{\Delta C}$).

Following this, we assume a new trial is conducted reporting only ΔE. We incorporate this information and then re-estimate the six statistics.

Results

Data

Data are taken from a recent study of the cost-effectiveness of a befriending intervention on the quality of life of carers of people with dementia.[21] Data are the total NHS cost and QALYs gained over 15 months of 105 intervention and 113 control subjects. The original results are based on an analysis incorporating Rubin's multiple imputation technique for missing data.[22] This replicates the dataset a number of times, with predicted values for missing data inserted for each replication. For the purpose of this analysis, we make use of only the first imputed set, thus treating the data as 'complete'. The estimates of incremental cost and outcome therefore also differ from those reported in the source study.

Summary statistics from the data are in Table 1, and net benefit calculated assuming a threshold of £30,000 per QALY.

The point estimate ICER is:

$$\frac{£979.95}{0.019} = £52{,}746$$

and the Incremental net benefit (at threshold of £30,000):

$$\hat{b} = 30000 * 0.019 - £979.95 = -£422.59$$

with a variance:

$$\hat{V}(\hat{b}) = £5{,}120{,}370$$

(figures sensitive to rounding)

On this basis, the decision would be to reject the intervention. The distribution of INB is plotted in Figure 1.

We now define these data as our prior estimates of ΔE, ΔC, b etc. Thus:

$$b_0 = \hat{b} = -£422.59$$

$$v_0 = v(\hat{b}) = £5{,}120{,}370$$

$$etc.$$

Using the UNLI method, the per patient EVPI, $EVPPI_{\Delta E}$ and $EVPPI_{\Delta C}$ at a £30,000 threshold are £707.14, £232.03 and £517.00 respectively (Table 2, column 'initial data'). As the majority of the uncertainty in b_0 is due to ΔC_0, $EVPPI_{\Delta C0}$ is correspondingly higher than $EVPPI_{\Delta E0}$. Figure 2 plots $EVPI_0$, $EVPPI_{\Delta C0}$ and $EVPPI_{\Delta E0}$ for a range of thresholds.

The EVSI of a trial of sample size n=100 in each arm gathering data on b is £436.50. As the sample size approaches infinity, the EVSI of b approaches the EVPI of b (Figure 3). The partial EVSIs of ΔE or ΔC (that is, of trials reporting only ΔE or ΔC, and of n=100 in each arm) is £120.41 and £308.28 respectively (Final three rows, column 'Initial Data', Table 2). These too approach their EVPIs as n tends to infinity ($EVPI_{\Delta E}$ and $EVPI_{\Delta C}$ not shown).

These per patient EVSIs in themselves cannot be used to make a research funding decision. This should be based on the expected net benefit of sampling (ENBS), which is the per patient EVSI multiplied by the total (present and future, discounted) patient population, less the cost of sampling (i.e. the cost of the trial). The ENBS

maximising point is where the marginal return from the last patient enrolled is equal to the marginal cost of sampling.

We do not calculate the ENBS as it is a function of total population size and the cost of sampling, which will vary from location to location. However, it should be noted that reducing the EVSI at a given sample size will reduce the ENBS at that sample size. This could reduce the sample size at which ENBS is maximised.

Now suppose an effectiveness trial was undertaken reporting only ΔE of sample size n=100 in each arm. Call the result of this trial $\hat{\Delta}E_n$ (the incremental QALYs observed in the new trial).

For the purpose of this paper, we assume the trial data reports identical results to the prior data (note the variance of the mean is slightly higher than the prior due to the smaller sample size (218 vs 200):

$$\hat{\Delta}E_n = 0.019$$

$$V(\hat{\Delta}E_n) = \sum_j \frac{s^2(E_j)}{n_j} = \frac{0.060}{100} + \frac{0.067}{100} = 0.00127$$

Combining these data together with the prior using Bayes rule (as per Spiegelhalter et al.[23] p63) yields the posterior distribution of ΔE:

$$\hat{\Delta}E_1 = \frac{n_0\Delta E_0 + m\Delta E_n}{n_0 + m} = \frac{(105+113)*0.019 + (100+100)*0.019}{(105+113+100+100)} = 0.019$$

$$V(\hat{\Delta}E_1) = \frac{V(\Delta E_0)n_0}{(n_0 + m)} = \frac{0.0012(105+113)}{(105+113+100+100)} = 0.00061$$

where m is the total number of patients enrolled in the new trial (100 in each arm).

Table 2, column 'with additional data on ΔE' shows the posterior estimates of ΔE, b and the VoI statistics. Note the correlation between ΔE and ΔC is not observed in the new data (it collected only ΔE). Therefore the 'best estimate' of the correlation is used, which is based on the original data alone, -0.252. We return to this issue in the discussion.

As expected, the new data have reduced the variance of incremental net benefit, thus reducing the overall EVPI (from £707 to £639) and EVSI (from £437 to £367). $EVPPI_{\Delta E}$ and $EVSI_{\Delta E}$ are reduced, however, $EVPI_{\Delta C}$ and $EVSI_{\Delta C}$ are unchanged.

3. Adjusting distribution of ΔC in the light of additional information on ΔE.

According to the Bayesian statistical approach, the distributions of ΔE and ΔC represent our belief about the likely values of the two. To say that they are correlated (in this case, negatively) means that if ΔE actually has a higher than expected value, ΔC is more likely to take on a lower than expected value. Correspondingly, when we revise our belief about ΔE upwards, we should revise our belief about ΔC downwards (and vice versa).

This paper extends that proposition to argue that revising our belief about the range of plausible values for ΔE should lead us to revise our belief about the range of plausible values for ΔC: if we can reduce the likelihood of some extreme values of ΔE, we should also be able to reduce the likelihood of some extreme values of ΔC.

This depends on whether the *variance* of ΔE is correlated with the *variance* of ΔC. We therefore need to consider the sampling distributions of V(ΔE) and V(ΔC).

Suppose many trials were undertaken of sample size n=105 and 113 in each arm respectively (as per the prior data in this example). We would have many estimates of the variance of ΔE and ΔC, which form a (bivariate) sampling distribution of v(ΔE) and v(ΔC). If they are correlated it should be possible to predict v(ΔC) from v(ΔE). The bivariate distribution of v(ΔE) and v(ΔC) is "not easy to find",[24] but can be estimated empirically by simulation.

We performed a Monte Carlo simulation of 5000 iterations on the original data, recording the v(ΔC) and v(ΔE) each time to build up an empirical distribution of each. There does not appear to be a clear relationship between v(ΔC) and v(ΔE), however the correlation coefficient is estimated at approximately 0.04 (Figure 4). Repeating the MCS 10 times yielded a mean correlation coefficient of 0.036 (range: 0.017, 0.057).

If we are reasonably confident the correlation between v(dE) and v(dC) is not zero, we may be able to predict v(ΔC) for a given v(ΔE). Standard errors are distributed χ^2, however for a large enough sample size, it may be expedient to rely on the central limit theorem and assume approximately normal distributions. This could be the case here (see Figures 5a and 5b).

Based on this, and assuming a linear relationship between v(ΔC) and v(ΔE), we can use OLS regression to predict v(ΔC) (Table 3). We can now revise our estimate of v(ΔC) in the light of the posterior estimate of v(ΔE), which falls from £3,152,467 to £3,078,425. $EVSI_{\Delta C}$ therefore also falls. Depending on the cost of sampling, this could reduce the optimal sample size of a study on ΔC.

4. Discussion

This work is at an early, exploratory stage, and should be considered an exposition of ideas, rather than concrete methodological recommendations. The original idea was to explore the impact of correlations between parameters on the value of information. In the process, a number of issues came to light.

Firstly, this work is a simple application of an analytic solution to VoI. Willan and Briggs[20] show a solution to calculate the EVPI and EVSI of an entire decision problem (that is, the EVPI and EVSI associated with uncertainty in incremental net benefit, b, alone). We extend this to calculate the partial EVPI and EVSI (that is, EVPI and EVSI associated with uncertainty in ΔE and ΔC; see Appendix 1). This is only valid where ΔE and ΔC are normally distributed and there is a linear relationship between ΔE, ΔC and b.

Secondly, this work demonstrates that VoI can apparently rise with additional data. This was the reason for the 'new' data, $\Delta\hat{E}_n$, being 'fixed' at the prior mean, ΔE_0. Originally, we sampled a value for $\Delta\hat{E}_n$ from the prior distribution of ΔE. By chance this yielded a value for ΔE_n lower than ΔE_0. Combining the new data with the prior did indeed reduce uncertainty in ΔE and b (i.e. the variance of ΔE and b respectively), so reducing the VoI. However, the new trial data also shifted the posterior distribution of b to the right (closer to zero). This increases the proportion of the distribution to the right of the y-axis and thus *increases* the value of future information. If the latter effect outweighs the former, the EVPI rises (Figure 6). A practical explanation for this is that we had simply underestimated EVPI with the prior data alone: it is itself a random variable subject to sampling error. By setting $\Delta\hat{E}_n$ equal to the prior mean, ΔE_0, we excluded this effect.

Thirdly, (and the key question of this paper), we propose that if it is reasonable to suppose a correlation between two input parameters in a decision question (in this case ΔE and ΔC), is it reasonable to suppose that gathering information about one

yields information about the other? That is, is there a correlation between v(ΔE) and v(ΔC)?

If this is a reasonable proposition, the next issue is how to estimate it. We present a very crude approach here: the OLS regression isn't a particularly good fit, and the coefficient on v(ΔE) is not statistically significant (but does this matter?). An obvious improvement would be to use a GLM to estimate the relationship between v(ΔE) and v(ΔC), with consideration given to find the best fit model. Time constraints did not permit this here, but are a necessary next step.

Other discussion points include:

* It was probably unnecessary to calculate the EVSI to illustrate the point of this paper: showing changes in EVPI and EVPPI would have shown it equally well. However it may aid the explanation to calculate the ENBS and consequent optimal sample sizes of studies (so a reduction in optimal sample size could be demonstrated). This would require assumptions about the cost of a study collecting data on b (that is, collecting both ΔE and ΔC), and two separate studies collecting only ΔE or ΔC.

* We assumed that the Pearson correlation coefficient between ΔE and ΔC was constant at the observed value from the original data (-0.252). This affects the estimate of covariance in the posterior distributions and hence the estimated variance of b. Is it reasonable to assume this is constant? It is our 'best guess', based on the original data, but not observed in the new as this only collected data on ΔE.

5. Conclusion

This paper explores some issues in undertaking VoI analyses, specifically whether, given two correlated parameters, it is reasonable to revise our belief about the range of plausible values on one parameter based on additional information about another.

Tables

Table 1: Summary statistics

	Intervention	Control	Increment
N	105	113	
$\hat{E}_j$	0.948	0.930	$\hat{\Delta}E = 0.019$
$\hat{C}_j$	£12,830.66	£11,850.72	$\hat{\Delta}C =$ £979.95
NB_j	£15,614.48	£16,037.07	$\hat{\Delta}NB = \hat{b} =$ -£422.59
$S^2(E_j)$	0.060	0.067	
$S^2(C_j)$	£198,836,610.32	£142,242,745.65	
$S^2(NB_j)$	£303,453,614.52	£252,027,922.22	
$V(\hat{E}_j)$	0.00057	0.00059	$V(\hat{\Delta}E) = 0.00117$
$V(\hat{C}_j)$	£1,893,682.00	£1,258,785.36	$V(\hat{\Delta}C) =$ £3,152,467.36
$\rho(\hat{E}_i, \hat{C}_i)$	-0.24	-0.27	$\rho(\hat{\Delta}E, \hat{\Delta}C) =$ -0.252
$V(NB_j)$	£2,890,034.42	£2,230,335.59	$V(\hat{\Delta}NB) = V(\hat{b}) =$ £5,120,370.02

Table 2: Prior, posterior and revised posterior VoI

	Initial data	With additional data on ΔE	With additional data on ΔE, adjusted v(ΔC)
$\hat{\Delta}E$	0.019	0.019	0.019
$\hat{\Delta}C$	£979.95	£979.95	-£162.85
$V(\hat{\Delta}E)$	0.0012	**0.0006**	**0.0006**
$V(\hat{\Delta}C)$	£3,152,467	£3,152,467	**£3,078,425**
$Corr(\hat{\Delta}E, \hat{\Delta}C)$	-0.252	-0.252	-0.252
$\hat{\Delta}NB(=\hat{b})$	-£422.59	-£422.59	-£422.59
V(b)	£5,120,370	£4,362,673	£4,288,630
EVPI	£707.14	£638.97	£632.02
$EVPPI_{\Delta E}$	£232.03	£130.96	£130.96
$EVPPI_{\Delta C}$	£517.00	£517.00	£508.87
$EVSI_b$ (n=100 in each arm)	£436.50	£366.88	£359.88
$EVSI_{\Delta E}$ (as above)	£120.41	£34.86	£34.86
$EVSI_{\Delta C}$ (as above)	£308.28	£308.28	£299.99

Table 3: OLS regression of v(dE) on v(dC)

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	3032147.90	51062.46	59.38	0
v(dE):	75954294.05	43612232.17	1.742	0.082

Figures

Figure 1: (prior) incremental net benefit

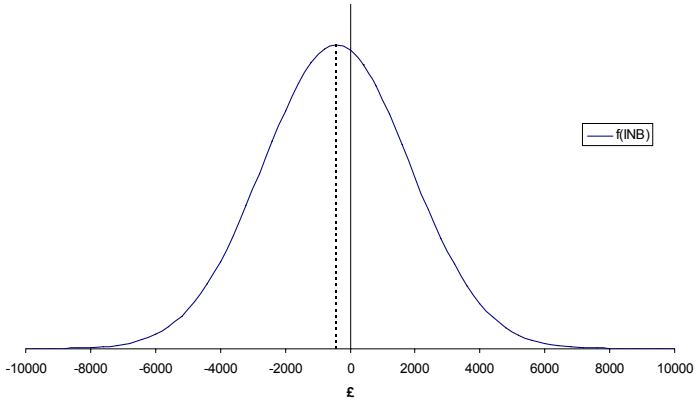


Figure 2: $EVPI_0$, $EVPPI_{\Delta C0}$ and $EVPPI_{\Delta E0}$ by willingness to pay for a QALY

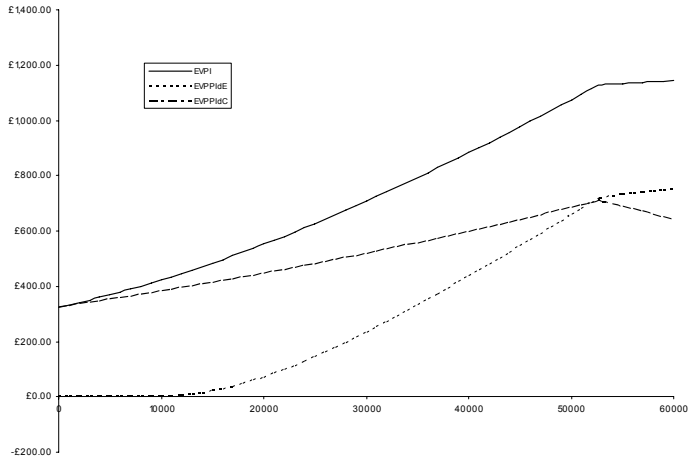


Figure 3: EVSI and EVPI (£30,000 threshold)

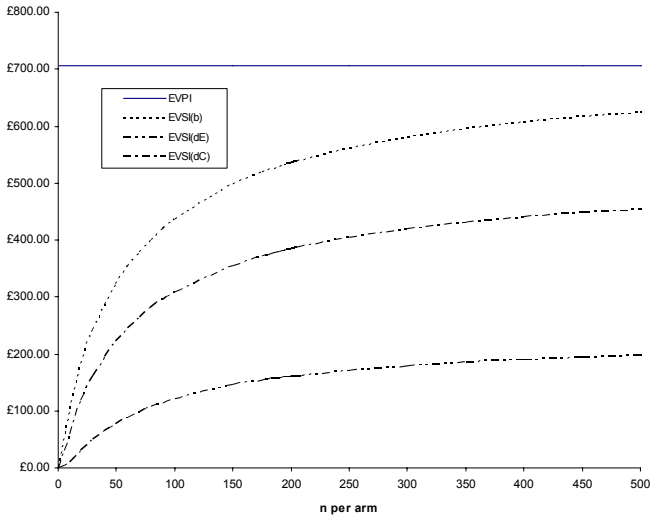


Figure 4: Scatter plot of v(dC) vs v(dE)

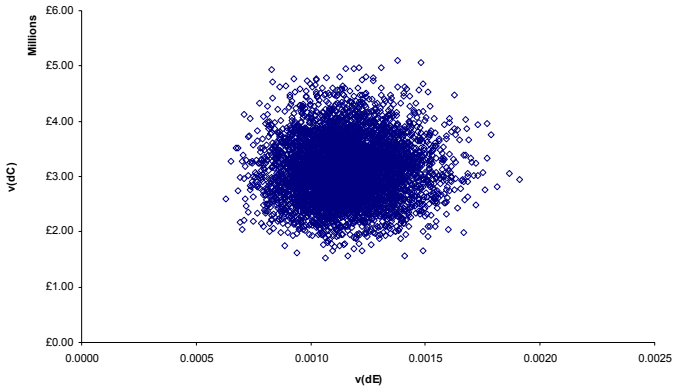
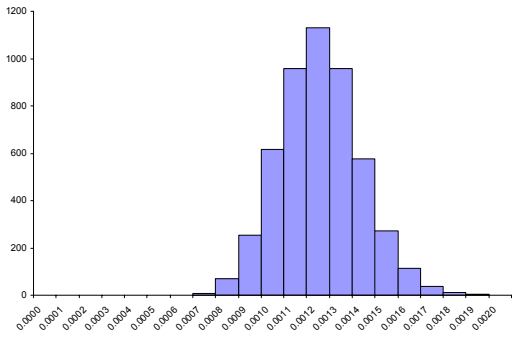


Figure 5: Histograms of (a) v(ΔE) and (b) v(ΔC)

a)



b)

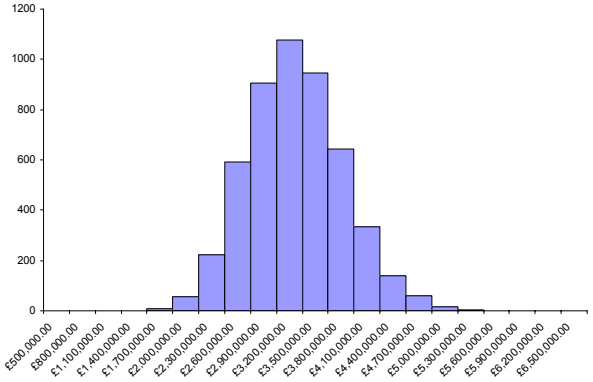
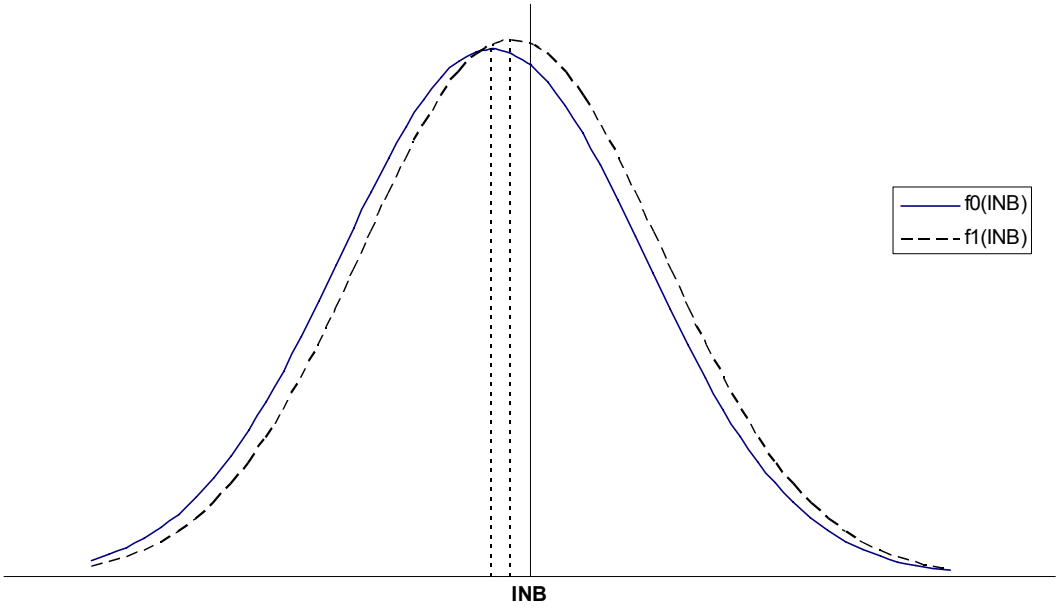


Figure 6: Prior and posterior INB showing increase in EVPI



(not to scale)

Appendix 1: Method for estimating VoI

A1.1 Expected value of perfect information

As we are assuming incremental net benefit is normally distributed, we can use the "unit normal loss integral" (UNLI) method for estimating EVPI as described by Willan and Briggs.[20] Conceptually this is the probability of making the 'wrong' decision multiplied by the associated loss. EVPI is an equation of two halves, depending on whether mean incremental net benefit, b_0, is greater or less than zero (equation A1).

$$EVPI_0 = N\left[I\{b_0 \geq 0\}\int_{-\infty}^{0} -bf_0(b)db + I\{b_0 < 0\}\int_{0}^{\infty} bf_0(b)db \right] \qquad [A1]$$

Where:

$EVPI_0$ = (prior) expected value of perfect information

b_0 = (prior) mean incremental net benefit

N = total population (present and future) who can benefit from one or the other treatment.

I{.} is the indicator function (returns 1 if the condition {.} is satisfied, otherwise 0).

$f_0(b)$ = prior density function of b.

Thus $\int_{-\infty}^{0} -bf_0(b)db$ is the expected opportunity loss (per patient) from adopting New in place of old. Similarly $\int_{0}^{\infty} bf_0(b)db$ is the expected opportunity loss per patient from retaining Old and rejecting New.

An analytic solution to [A1] is equation [A2].[20]

$$EVPI_0 = N\left[\sqrt{\frac{v_0}{2\pi}}.e^{\left(-\frac{b_0^2}{2v_0}\right)} - b_0\left[\Phi\left(\frac{-b_0}{\sqrt{v_0}}\right) - I\{b_0 < 0\} \right] \right] \qquad [A2]$$

Where

v_0 = variance of mean incremental net benefit, b_0

$\Phi(.)$ is the standard normal cumulative distribution function.

For the purpose of this analysis, we assume N = 1. That is, we are only considering the *per patient* value of information, not population.

A1.2 Expected value of perfect parameter information

The EVPPI is the expected loss resulting from uncertainty in a particular parameter or group of parameters. It can be estimated by assuming all other parameters are known with certainty (constants at their mean values). This is valid in this case because we are assuming b, ΔE and ΔC and normally distributed, and there is a linear relationship between all parameters (equation [1]). Therefore the EVPPI of ΔE can be estimated as follows.

The variance of mean incremental net benefit, v_0 is defined as the sum of the variances of ΔE_0 and ΔC_0 less twice the covariance (note λ^2 converts the v(ΔE) into monetary units; equation A3).

$$v_0 = \lambda^2 v(\Delta E)_0 + v(\Delta C)_0 - \lambda 2Cov(\Delta E, \Delta C)_0 \qquad [A3]$$

If ΔC_0 is known with certainty, then $v(\Delta C)_0=0$ and $Cov(\Delta E, \Delta C)_0 = 0$, thus we can simply substitute $\lambda^2 v(\Delta E)_0$ for v_0 in equation [A2] (equation [A4]. N is dropped for clarity).

$$EVPPI_{\Delta E_0} = \sqrt{\frac{\lambda^2 v(\Delta E)_0}{2\pi}}.e^{\left(-\frac{b_0^2}{2\lambda^2 v(\Delta E)_0}\right)} - b_0\left[\Phi\left(\frac{-b_0}{\sqrt{\lambda^2 v(\Delta E)_0}}\right) - I\{b_0 < 0\}\right] \qquad [A4]$$

and likewise for $EVPPI_{\Delta C}$:

$$EVPPI_{\Delta C_0} = \sqrt{\frac{v(\Delta C)_0}{2\pi}}.e^{\left(-\frac{b_0^2}{2v(\Delta C)_0}\right)} - b_0\left[\Phi\left(\frac{-b_0}{\sqrt{v(\Delta C)_0}}\right) - I\{b_0 < 0\}\right] \qquad [A5]$$

A1.3 Expected Value of Sample Information

Total EVSI

Willan and Briggs[20] define the expected value of sample information as the difference between the posterior EVPI (that is, with the additional sample information and denoted $EVPI_1$), and the prior EVPI (denoted $EVPI_0$).

$EVPI_1$ is uncertain as it is conditional on the trial information, which is unknown. Therefore the expected $EVPI_1$ is the $EVPI_1$ for a particular sample result, $\hat{b}$, multiplied by the probability of observing that result (equation [A6]).

$$E(EVPI_1) = \int_{-\infty}^{\infty} EVPI_1 \hat{f}(\hat{b}) d\hat{b} \qquad [A6]$$

The EVSI is thus the difference between prior EVPI and expected posterior EVPI (equation [A7]).

$$E_{\hat{b}}EVSI(n,\hat{b}) = EVPI_0 - \int_{-\infty}^{\infty} EVPI_1 \hat{f}(\hat{b})d\hat{b} \qquad [A7]$$

Willan and Pinto[3] provide an analytic solution to the expected posterior EVPI, $\int_{-\infty}^{\infty} EVPI_1 \hat{f}(\hat{b})d\hat{b}$, as $I_1+I_2+I_3$, where:

$$I_1 = D\sqrt{\frac{2\pi}{A}}e^{\left(\frac{B^2}{(8A)}-\frac{C}{2}\right)} \qquad [A8]$$

where:

$$A = \frac{v_1 n^2}{4\sigma^4} + \frac{1}{\sigma_{\hat{b}}^2}$$

$$B = \left(\frac{v_1 n}{v_0 \sigma^2} - \frac{2}{\sigma_{\hat{b}}^2}\right) b_0$$

$$C = \left(\frac{v_1}{v_0^2} + \frac{1}{\sigma_{\hat{b}}^2}\right) b_0^2$$

$$D = \frac{1}{2\pi}\sqrt{\frac{v_1}{\sigma_{\hat{b}}^2}}$$

$$\sigma_{\hat{b}}^2 = V(\hat{b}) = v_0 + \frac{2\sigma^2}{n}$$

$$I_2 = \sqrt{v_1}\left[b\Phi\left(\frac{b}{\sqrt{a^2+1}}\right) + \frac{a^2}{\sqrt{2\pi(a^2+1)}e^{\left(-\frac{b^2}{2(a^2+1)}\right)}}\right] \qquad [A9]$$

where:

$$a = \frac{n\sqrt{v_1\sigma_{\hat{b}}^2}}{2\sigma^2}$$

$$b = -\frac{n\sqrt{v_1}\sigma_{\hat{b}}^2 b_0}{2\sigma^2 v_0}$$

and

$$I_3 = b_0\Phi\left(-\frac{b_0\sqrt{\sigma_{\hat{b}}^2}}{v_0}\right) - \frac{v_1 n\sqrt{\sigma_{\hat{b}}^2}}{\left(2\sigma^2\sqrt{2\pi}\right)e^{\left(-\frac{b_0^2\sigma_{\hat{b}}^2}{2v_0^2}\right)}} \qquad [A10]$$

σ^2 is the between-patient variance of net benefit, which is assumed constant and equal between treatment arms. (Note that $2\sigma^2$ can be interpreted as the sample

variance of incremental net benefit. As we have full patient level data available, we can make use of this by defining $2\sigma^2$ simply as the sum of the variance of net benefit in the intervention and control arms, that is the sum of the row '$S^2(NB_j)$' in Table 1.

Partial EVSI

From equations [A4] and [A5], it was noted that $EVPPI_{\Delta E}$ and $EVPPI_{\Delta C}$ were estimated simply by assuming ΔC and ΔE respectively were constants. Following the same logic, to estimate $EVSI_{\Delta E}$, we assume ΔC is constant (that is, $v_{\Delta C} = cov(\Delta C, \Delta E) = 0$), and vice versa.

Therefore:

$$v_0 = \lambda^2 v(\Delta E)_0 + v(\Delta C)_0 - \lambda 2Cov(\Delta E, \Delta C)_0 = \lambda^2 v(\Delta E)_0 + 0 - 0 = \lambda^2 v(\Delta E)_0 \quad [A11]$$

$$\sigma^2 = \lambda^2 \sigma_j^2 + \omega_j^2 - 2\rho_j \sigma_j \omega_j \lambda = \lambda^2 \sigma_j^2 \quad [A12]$$

$$\sigma_{\hat{b}}^2 = v_{\hat{b}} = v_0 + \frac{2\sigma^2}{n} = \lambda^2 v_{\Delta E} + \frac{2\lambda^2 \sigma_T^2}{n} \quad [A13]$$

where

σ_j^2 = variance of QALYs in intervention or control group (assumption is both are equal)

ω_j^2 = variance of cost in intervention or control group (assumption is both are equal)

and similarly to estimate $EVSI_{\Delta C}$ we assume ΔE is constant ($v_{\Delta E}=0$)

$$v_0 = \lambda^2 v(\Delta E)_0 + v(\Delta C)_0 - \lambda 2Cov(\Delta E, \Delta C)_0 = 0 + v(\Delta C)_0 - 0 = v(\Delta C)_0 \quad [A14]$$

$$\sigma^2 = \lambda^2 \sigma_j^2 + \omega_j^2 - 2\rho_j \sigma_j \omega_j \lambda = \omega_j^2 \quad [A15]$$

$$\sigma_{\hat{b}}^2 = v_{\hat{b}} = v_0 + \frac{2\sigma^2}{n} = v_{\Delta C} + \frac{2\omega_T^2}{n} \quad [A16]$$

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