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Computing Expected Value of Partial Sample Information from Probabilistic Sensitivity Analysis Using Linear Regression Metamodeling

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Abstract

Decision makers often desire both guidance on the most cost-effective interventions given current knowledge and also the value of collecting additional information to improve the decisions made [i.e., from value of information (VOI) analysis]. Unfortunately, VOI analysis remains underutilized due to the conceptual, mathematical and computational challenges of implementing Bayesian decision theoretic approaches in models of sufficient complexity for real-world decision making. In this study, we propose a novel practical approach for conducting VOI analysis using a combination of probabilistic sensitivity analysis, linear regression metamodeling, and unit normal loss integral function – a parametric approach to VOI analysis. We adopt a linear approximation and leverage a fundamental assumption of VOI analysis which requires that all sources of prior uncertainties be accurately specified. We provide examples of the approach and show that the assumptions we make do not induce substantial bias but greatly reduce the computational time needed to perform VOI analysis. Our approach avoids the need to analytically solve or approximate joint Bayesian updating, requires only one set of probabilistic sensitivity analysis simulations, and can be applied in models with correlated input parameters.

Introduction

Decision makers often desire both guidance on the most cost-effective interventions given current knowledge and also the value of collecting additional information to improve the decisions made [i.e., from value of information (VOI) analysis]. VOI analysis has gained increased interest in clinical trial design and research prioritization.[1–25] However, it remains underutilized due to the conceptual, mathematical and computational challenges of implementing Bayesian decision theoretic concepts in models of sufficient complexity for real-world decision making.[26–28] A recent review reports a small number of practical

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applications of VOI in healthcare settings.[29] This study attributes this small number of applications to the technical and mathematical challenges involved in computing VOI, and highlights the importance of developing leaner approaches to conduct VOI analyses.

The most practical form of VOI analyses involves quantifying the amount of information an actual empirical study could generate. While VOI analyses can provide an upper bound on the value of conducting additional studies [i.e., expected value of perfect information on all parameters (EVPI) or expected value of partial perfect information on a set of parameters (EVPPI)], the expected value of sample information for a study of size (n) (EVSI) and its analog for sample information on some parameters (EVPSI) are clearly more useful for informing actual decisions to collect further information.[26]

Current methods for performing EVPSI are often challenging for real-world modeling problems, necessitating the further methodological development and are yet to be incorporated into the standard statistical and mathematical software packages [e.g., TreeAge, (TreeAge Software, Inc., Williamstown, MA)]. For example, the two level Monte-Carlo simulation[30] (2MCS) approach, which can be considered the gold-standard for computing EVPSI, consists of an outer and inner expectation. The outer expectation is computed through an outer loop to generate a large number of experimental datasets from the prior distributions. The inner loop samples from the posterior distribution generated from these datasets. However, if a conjugate prior does not exist for the likelihood function, then the posterior distribution must be obtained using techniques, such as the Markov chain Monte Carlo (MCMC). In addition to the computational demand, the 2MCS approach may require Bayesian updating of correlated parameters and calculating joint posterior distributions which are extremely difficult except in special cases. Thus, for a single parameter and with a sufficient number of model runs, this approach guarantees a precise estimate of EVPSI, however, it can be extremely difficult to compute EVPSI, especially for multiple correlated parameters.

Several shortcut techniques have been proposed to reduce the computational burden of the 2MCS approach. Some of these approaches are designed for specific applications. For example, Ades et al.[26] demonstrate an analytic approach to measure the EVPSI for parameter types common in clinical trials, such as rates and odds ratios; Welton et al.[31] compute EVPSI for cluster randomized multi-arm trials with binary outcomes; and Brennan and Kharroubi[32] illustrate a technique to compute EVPSI for survival data. Other proposed approximation techniques include Laplace approximation[33] and non-parametric regression[34] approaches to efficiently compute EVPSI. Most of these shortcut techniques offer significant reduction of the computation burden of the 2MCS approach by avoiding the inner expectation and the need for MCMC analysis. However, these approaches generally require additional development efforts, sometimes ignore correlations among various model parameters, and are often limited to calculating EVPSI for a single parameter at a time.

We describe a novel framework to compute EVPPI and EVPSI using the unit normal loss integral (UNLI) function and linear regression metamodeling (LRM). The UNLI is a parametric function for computing VOI from a model's outcome. This approach was originally proposed by Raiffa and Schlaifer[35–37] over fifty years ago. Since then many

researchers, including Claxton[7,38], Willan[16,39], Eckerman[16], Coyle and Oakley[40] have adopted this approach to compute EVPI, EVSI and to some extent EVPPI. In this study, we extend the UNLI function to compute EVPPI and EVPSI using LRM, which involves regressing the model's outcome on the input parameter values using a probabilistic sensitivity analysis (PSA) dataset.[41] In addition, we demonstrate the importance of correlation among model parameters in VOI analysis, and the flexibility of our approach in allowing the model parameters to be correlated. We highlight the assumptions of our approach and illustrate why our approach may still be appropriate for most healthcare applications despite these assumptions.

Methods

Incremental Net Benefit

Expected utility maximization involves choosing the strategy that has the highest expected net benefit. We use incremental net benefit (INB) as our measure of cost-effectiveness instead of the cost-effectiveness ratio because it has attractive statistical properties in our application.[42–14] INB measures the incremental net benefit of adopting the optimal strategy (t^*) relative to an alternative (t_*) based on the current evidence. An intervention's net benefit (B), when expressed in a monetary value, measures the savings from an intervention (t) relative to a marginally cost-effective intervention at a specified willingness to pay threshold.

Approximating Measures of VOI

To compute VOI measures, we first obtain the INB distribution via probabilistic sensitivity analysis (PSA). We can then apply the UNLI to compute EVPI and EVSI[35,36] using the INB distribution. Finally, we extend the UNLI approach to calculate EVPPI and EVPSI using linear regression metamodeling (LRM).[41]

1. EVPI—EVPI can be computed from the expected opportunity loss due to choosing t^* over t_* based on the current evidence. This loss (L) can be expressed as

$$L = \int_{-\infty}^{0} \mathrm{INB} f(\mathrm{INB}) d\mathrm{INB}, \quad (1)$$

where f is the density function of INB. The relationship of this opportunity loss to INB's distribution is further illustrated in Appendix A. When f is normally distributed, L can be computed from the UNLI function, such as

$$UNLI(\mu, \sigma^2) = \mu \Phi\left(-\frac{\mu}{\sigma}\right) - \frac{\sigma}{\sqrt{2\pi}} e^{-\frac{\mu^2}{2\sigma^2}}, \quad (2)$$

where μ and σ^2 are the mean and variance of the INB, respectively; and Φ is the cumulative density function of the standard normal distribution (for more detail, please refer to[35,36]).

Box 1 outlines the steps of computing EVPI using PSA and UNLI. First, obtain INB's distribution using PSA results.[45,46] We can think of the resulting distribution as the prior distribution of INB because it reflects the combined uncertainty from all the parameters in the model prior to conducting new research. EVPI is computed from the mean and variance of the INB distribution using the UNLI function (Equation 2). Note, we take the negative of the UNLI to express EVPI as a value instead of a loss.

2. EVSI—Box 2 outlines the steps of calculating EVSI using the UNLI approach.[35,36] This approach is similar to calculating EVPI. However, unlike EVPI which uses the *prior* distribution of INB, EVSI uses the *preposterior* distribution[35,36] of the INB. The preposterior distribution defines the distribution of the posterior mean INB which is derived from the INB's prior distribution and additional experimental "data" that are also simulated from the prior. Thus, the preposterior distribution defines the prior distribution of the posterior mean INB before collecting actual data, hence the name preposterior.

First, we compute the variance of the preposterior distribution of INB. When the prior distribution of INB is normally distributed, the preposterior variance of INB can be expressed as a fraction of the prior variance, such that $\sigma_1^2 = \sigma_0^2 \nu$, where ν is the variance fraction equal to $n / (n + n_0)$, n is the additional sample size, and n_0 is the prior sample size. n_0 can be arbitrary[35] or estimated from the prior distribution (For example, if a parameter is distributed as Beta(α, β), it can be shown[47] that $n_0 = \alpha + \beta$). Thus, if we assume that no additional sample to be collected ($n = 0$), the posterior INB will always be equal to the prior INB and the mean posterior INB is certain to be equal to the mean prior INB, which is known. Thus, there is no uncertainty about the posterior mean INB ($\sigma_1^2 = 0$), and there is no value for conducting additional research (EVSI = 0). However, if we imagine an experiment in which we take an infinitely large sample from each value of the prior ($n = \infty$) then for each prior sample, the posterior mean INB is certain to be equal to this sampled value of the prior INB. Repeating this exercise many times produces the posterior distribution of the mean INB (i.e., preposterior INB distribution) which will exactly follow that of the prior INB distribution. As a results, σ_1^2 equals σ_0^2 and EVSI equals EVPI.

3. EVPPI—Boxes 1 and 2 above review how to compute EVPI and EVSI using the UNLI function. Next, we focus on the main contribution of the current study which extends the UNLI function to computing EVPPI and EVPSI using the LRM approach.

Box 3 summarizes the steps to compute EVPPI, which are very similar to calculating EVPI. Unlike EVPI, which reflects prior uncertainties from all parameters in the model, EVPPI involves the uncertainty in the prior INB explained by a subset of parameters of interest. We denote this subset of parameters by $\boldsymbol{X}_I$, and the mean and variance of the distribution of INB | $\mathbf{X}_I$ by $\tilde{\mu}_0$ and $\tilde{\sigma}_0^2$, respectively. We use the LRM approach to compute $\tilde{\mu}_0$ and $\tilde{\sigma}_0^2$.

LRM involves regressing INB on the model inputs. Thus, LRM is the application of classical regression analysis post-simulation analysis, hence the name *metamodeling*. Metamodeling is widely used in engineering and physics, but remains underutilized in healthcare applictions.[41,48] By treating the INB as the dependent variable and the model input

parameters of interest ($\boldsymbol{X_I}$) as the independent variables, the resulting regression coefficients define the relationship between $\boldsymbol{X_I}$ and INB. We use these regression coefficients to compute EVPPI and EVPSI.

In EVPPI (and also in the EVPSI calculation described below) we adopt two approximations: (1) a normal approximation of $\boldsymbol{X_I}$, and (2) a linear approximation of the relationship between $\boldsymbol{X_I}$ and INB. It is important to note that unlike EVPI and EVSI, which assumes that the INB is normally distributed, when applying LRM, the INB does not need to be normally distributed as long as the prior or the preposterior distributions of $\boldsymbol{X_I}$ (for EVPPI or EVPSI, respectively) are normally distributed and their relationships with INB are approximately linear.[40] In addition, as we shall discuss later, the normality of $\boldsymbol{X_I}$ and the reliability of all VOI analyses are closely related per the Central Limit Theorem.

In the algorithm above, we use $\boldsymbol{X_I}$ instead of the full set of parameters ($\boldsymbol{X} = \{\boldsymbol{X_I}, \boldsymbol{X_C}\}$) to account for the potential correlations between the $\boldsymbol{X_I}$ and $\boldsymbol{X_C}$ parameters in the model. If such correlations exist, any additional information on $\boldsymbol{X_I}$ will impact our prior belief about $\boldsymbol{X_C}$. Since we are only interested in $\boldsymbol{X_I}$, we want this additional information to be captured by the regression coefficients of $\boldsymbol{X_I}$. However, regressing INB on the full set of parameters ($\boldsymbol{X}$) instead of $\boldsymbol{X_I}$ results in the regression coefficients of $\boldsymbol{X_C}$ capturing this additional effect which can bias the EVPPI and EVPSI values since the regression coefficients of $\boldsymbol{X_C}$ are not of interest and do not enter in the calculation of $\tilde{\sigma}_0^2$. As a result, $\tilde{\sigma}_0^2$ can be underestimated or overestimated depending on the nature of the existing correlation and the direction of the regression coefficients. [Please refer to Appendix B for further detail.]

4. EVPSI—Following the logic used to calculate EVSI and EVPPI, EVPSI can be computed from the preposterior variance for INB explained by $\boldsymbol{X_I}$ (Box 4). We denote this variance by $\tilde{\sigma}_1^2$. To obtain $\tilde{\sigma}_1^2$, we calculate $\tilde{\sigma}_0^2$ for $\boldsymbol{X_I}$ using LRM. Then we use the variance fraction ν to compute the preposterior variance. If the prior evidence (n_0) is the same across all $\boldsymbol{X_I}$ and the new study contributes equal additional samples (n) to these parameters, then $\tilde{\sigma}_1^2 = \nu\tilde{\sigma}_0^2$. However, if the n_0 varies among the parameters or if the proposed study adopts a heterogeneous design in which different samples contribute different information to the model parameters, then the prior variance must be adjusted by decomposing $\tilde{\sigma}_0^2$ and applying the appropriate variance fractions on the parameter level.

Thus, the computation for the various VOI analyses depend on the mean and variance of the INB as summarized in Table 1.

Case-studies—We illustrate our approach using two examples: A standard decision tree and a Markov model.

Example 1: Standard decision tree

The first example involves a decision model published by Ades et al. (2004)[26] (Appendix C). This model compares a new intervention to the standard of care in preventing a hypothetical critical condition. The new treatment reduces the risk of the critical event, but it may cause side effects. There are eleven parameters in the model, four of which are

uncertain and are represented by probabilistic distributions. Correlated parameters may represent a limitation of computing EVPSI.[26] However, in practical applications, uncertainties of model parameters are rarely independent. These correlations may reflect subjective uncertainty about joint parameter distributions or may be induced as a result of statistical analyses.[26,49] We introduce correlation between the treatment's side effects (p_{SE}) and the risk of the critical events (OR) using a previously developed sorting algorithm[50]. We vary the correlation between these parameters from −1 to +1 and examine the resulting EVPSI of these two parameters combined for various study sample sizes.

Example 2: Markov model

The second example involves a Markov model which defines a more complex relationship between INB and the model parameters compared to the first example. This model involves computing the most cost-effective alternative for treating a 50-year old cohort of newly diagnosed cancer patients (Appendix D). The treatment choices are either to receive chemotherapy or perform a surgical resection of the tumor. There are three Markov health states in the model (cancer-free, cancer and dead). If cured the quality of life increases from 0.8 to 1, but the probability of cure depends on the intervention chosen. If cured, the patients are assumed to remain cancer-free for the remainder of their lives. Annual mortality rates are calculated from the US life tables and an additional cancer specific mortality which is uncertain. In addition, we use a one-year cycle length, a lifetime horizon and a discounting rate of 5% annually for the benefits and costs.

Results

Example 1: Standard decision tree

Our implementation of the Ades model produces results and estimates of VOI that are similar to the analytical method proposed by Ades et al (2004)[26] (Table 2). The EVPI, probability of the new treatment not being optimal, and the EVPPI for the listed parameters are comparable between both methods. The relative contribution of various parameters to decision uncertainty and hence to EVPPI is also preserved. Uncertainty regarding the probability of side effects is the most important followed by the odds ratio of the critical event, and the quality of life after the critical event. There are slight variations in the estimated EVPPI using the LRM compared to the analytic approach, which may be due to a combination of violating the normality and linearity assumptions.

Our estimates of EVPSI also compare favorably to the analytic approach. The EVPSI is shown for p_{SE} and Q_E (Figure 1) and the combination of p_{SE}, Q_E and LOR (Figure 2). Our exploration of EVPSI's asymptotic properties follows the theoretical predictions. Again, our approach slightly overestimates the EVPSI for the quality of life after the critical event (Q_E) and underestimates the EVPSI of the odds ratio of the event for the treatment (OR); however, the sample sizes are relatively small ($n_0 = 12$). Larger sample sizes may increase the normality of the preposterior distribution and the accuracy of our approach.

Next we demonstrate the flexibility of our approach to incorporate correlations among model parameters (Figure 3). Varying correlation between the treatment's probability of

causing side effect (p_{SE}) and the odds ratio of the critical event (OR) from −1 to +1 results in a 6-fold increase in EVPPI from $2,000 to $12,000, indicating the potential impact of correlation between model parameters on their EVPPI and EVPSI.

Example 2: Markov Model

Although the probability of failing chemotherapy (pFailChemo) is expected to have a non-linear relationship with INB, we found a nearly linear relationship (R^2 = 98.3%), indicating that linear approximation may be appropriate in this model. We chose to demonstrate the VOI analyses and compare the results of our LRM approach to the 2MCS approach. We conducted the 2MCS computations using a server with 128 gigabytes of memory and 12 processing cores that were used simultaneously in parallel to increase the speed of the computations. We used a single processing core to conduct LRM.

The EVPPI for the probability of failing chemotherapy is $18,050 and $17,800 using the 2MCS and the LRM methods, respectively. Figure 4 compares the performance of the LRM and the 2MCS approaches.

The LRM computation took only 1.6 milliseconds on a single core compared to more than 25 minutes for the 2MCS approach using 12 threads in parallel, a 20,000 fold gain in computation time compared to the 2MCS approach. It is important to mention that this may underestimate the potential gain in the computation time of the LRM approach relative to the 2MCS because we used a beta prior distribution and a binomial data likelihood function. This conjugate prior/likelihood combination has resulted in a significant gain in the computation time compared to situations in which a conjugate prior may not exist.

Discussion

We describe a practical and feasible method to estimate the EVPSI, which enables such calculations in models whose complexity would have previously rendered methods to estimate EVPSI intractable. Our method combines standard tools and concepts including the UNLI, developed by Raiffa and Schlaifer for EVPI and EVSI; PSA, which is now performed for most models; and linear regression metamodeling, which only requires standard statistical software and the outputs of the PSA. LRM allows us to extend Raiffa and Shlaifer's past application to EVPPI and EVPSI. We illustrate our approach with a case study of a simple decision tree and a more complex Markov model.

The LRM approach is extremely efficient, flexible and easy to implement. This approach consists of a set of simple equations using a single dataset of PSA results. [In Appendix F, we provide a sample code to compute EVPSI using Microsoft Excel and R]. This approach resulted in more than 20,000 folds decrease in computation time when compared to the 2MCS approach using a Markov model. Higher performance improvements are expected in more complex models and for non-conjugate prior/likelihood combinations which may require additional MCMC simulations.

In addition, the LRM approach can be easily extended to calculate the EVPPI and EVPSI for a combination of multiple parameters, when correlations exist among the parameters of

interest, the complementary set of parameters and between these two sets of parameters. Furthermore, this approach can also be used for heterogeneous trial designs that involve various sample allocations to the individual parameters.

Our approach has several limitations. First, we adopt a normal approximation of the prior and preposterior distributions for the parameters of interest in EVPPI and EVPSI computations, respectively. This approximation can bias the results if these parameters are "severely" non-normal. However, normal approximation as shown by Raiffa and Schlaifer[35] and Schlaifer[37] is an excellent approximation to a large number of real distributions of practical importance. If the parameter distribution is based on bootstrapping the sample mean or published estimates of a sufficiently large sample size, then a normal approximation of the parameter's estimate is perhaps sufficient per the Central Limit Theorem. In some cases, however, the parameter's estimates may not be normally distributed, especially in the case of subjective estimation of uncertainty, limited prior evidence (e.g., $n_0 \leq 10$), or when meta-analyzing treatment effects from heterogeneous and inconsistent data sources.[51–57] Most of these cases are perhaps instances of less accurate specification of the prior uncertainties, which may compromise the reliability of all VOI analyses because these analyses are inherently dependent on how "accurately" these prior uncertainties are specified.

Second, our approach may be limited to models in which the relationship between INB and $\boldsymbol{X_I}$ are approximately linear. Although some decision models are generally non-linear (e.g., Markov models), we illustrated with a Markov model that this relationship can be well approximated with a linear relationship. Because we lack empirical evidence that quantifies the degree of non-linearity in various model types, the level of linearity should be determined on case-to-case bases. In fact, many decision models used in healthcare application can be approximated well with an LRM. For example, Coyle and Oakley[40] show that regressing the INB on the model parameters of a Markov model produces an R^2 of 0.985. In addition, Tappenden et al.[58] find a strong linear relationship ($R^2 = 0.93$) between the model parameters and the resulting net benefit values in a complex model.

This high degree of linearity can be explained by several factors: (1) INB may be locally linear because its functional form is assessed only over a parameter's uncertainty range (Figure 5a), (2) the difference between the individual net benefits functions (INB) of the compared interventions may produce a linear benefit function even if the net benefit (NB) of these interventions are individually non-linear (Figure 5b), and (3) discounting future rewards may also contribute to increased linearity of INB. This is because each benefit function is the aggregation of future rewards weighted by the probability of being in a Markov state. Although the functional form of these probabilities increase in non-linearity in future cycles, they become rapidly less impactful when the future rewards are discounted. In all cases, we recommend that a model's linearity should be assessed visually and with a goodness of fit statistics (e.g., R^2). Both case-studies in this manuscript reveal high degrees of linearity (R^2 of 94.7% and 98.3% for case-studies 1 and 2, respectively). Further research is needed to assess the performance of our approach on less linear and more complex models.

Higher order polynomials (e.g., x^2 and x^3) terms can improve the overall fit of the LRM, but care must be given when using these higher order terms in LRM with UNLI. For example, if a parameter x is normally distributed, then the UNLI function can be applied because y is normally distributed in $y = \beta_0 + \beta_1 x$. In contrast, even if $y = \beta_0 + \beta_1 x + \beta_2 x^2$ provides a better fit, it may not increase the overall accuracy of the value of information calculation because x^2 may not be normally distributed. Further research is needed to extend the LRM approach using polynomial regression analysis.

Third, an important limitation of the UNLI function is that it is designed for models that involve two strategies only. We propose two alternatives in case of models that involve three or more strategies (multiple-action models): (1) The overall INB can be defined as $INB = B(t^*, \boldsymbol{X}) - B(t_2^*, \boldsymbol{X})$, where t_2^* refers to the second best alternative. If a density plot, for example, reveals this new variable to be approximately normally distributed, then the researcher may proceed with the algorithms above using this new definition of INB. It must noted, however, that this approach may bias the VOI analysis because the parameter of interest may have a stronger correlation with a third strategy that is not captured by this definition of the INB. (2) If the calculated INB is not approximately normal, then the UNLI method can still be applied for a single parameter, but it requires additional complexity. First, INB must be computed for each strategy relative to the optimal strategy, such that $INB_t = B(t^*, \boldsymbol{X}) - B(t, \boldsymbol{X})$, then the UNLI function can be applied for each INB_t over each strategy's (t) dominance region with respect to the parameter of interest. Next, the algorithms above are applied for all INB_t in each region. The overall value of information is computed as the aggregate of the individual opportunity losses in each of these regions [Appendix E generalizes the UNLI technique to models that involve three or more strategies. Further research is needed to extend this approach to multiple parameters.]

Finally, while multicollinearity is a potential limitation of linear regression analysis it may not be as important in metamodeling. Multicollinearity can theoretically increase the standard error of the LRM coefficients, thus affecting the stability of these coefficients when the model parameters are highly correlated. In practice, multicollinearity are less of an issue due to the vast improvement in computational precision. We found no evidence of multicollinearity (results are not shown) in LRM except when the parameters were in near perfect correlation. Clearly perfect correlation does not apply to decision modeling because if two parameters are perfectly correlated, only one of them will be necessary in the model.

Conclusion

EVPSI has many potential applications in healthcare, but it is one of the most challenging measures to quantify both methodologically and computationally. We propose an approximation technique to conduct VOI analysis. Our approach performs best if (1) the preposterior distribution of the model parameters of interest are approximately normally distributed, an assumption strongly tied to the reliability of the VOI analysis, and (2) the relationship of the parameters of interest and the INB are approximately linear which is common in many simulation models in healthcare, including Markov models. Because our approach is simple, flexible and extremely efficient, we propose it as an additional tool for analysts wishing to conduct VOI analyses.

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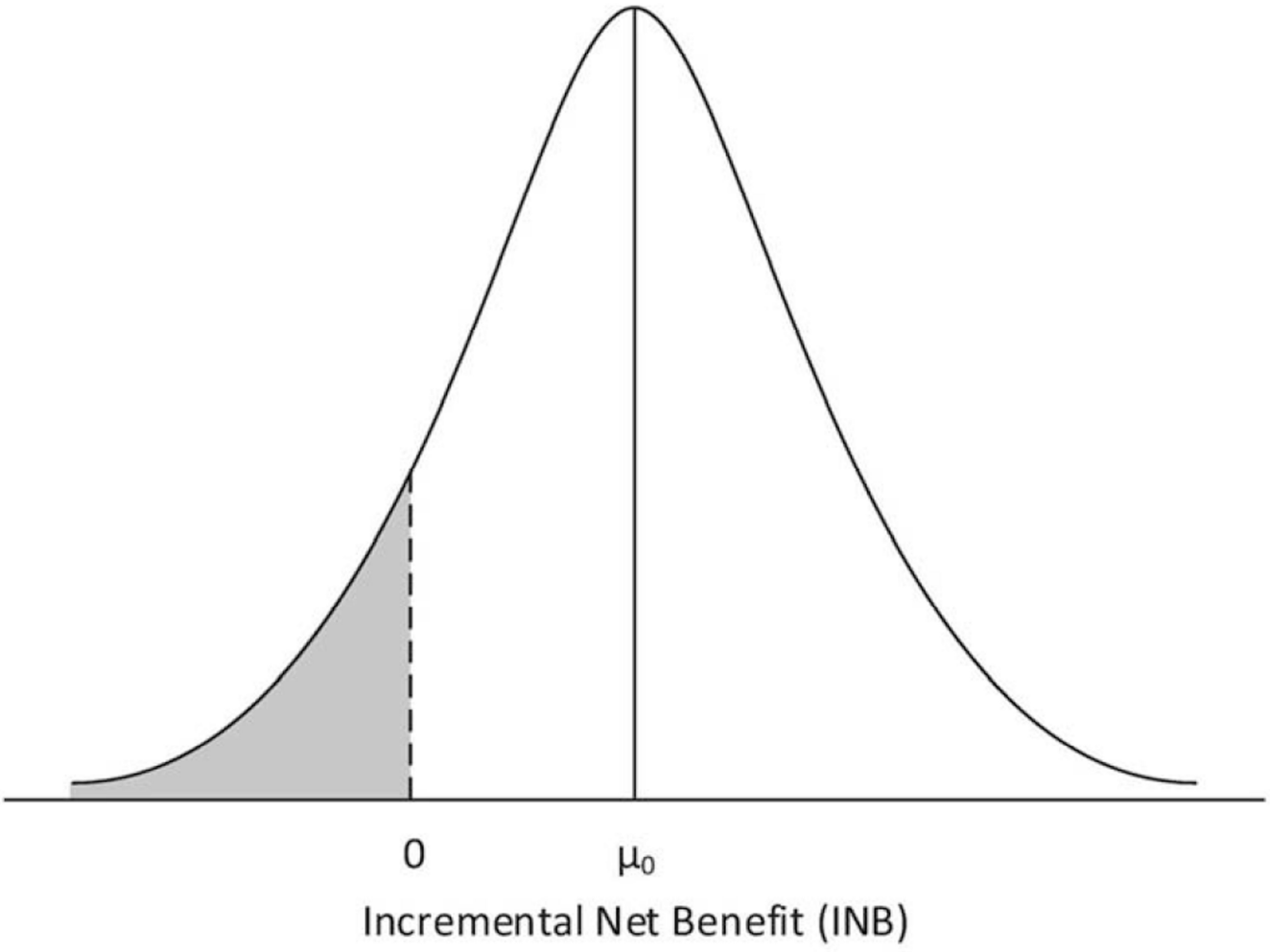
Appendices

Appendix A

The figure below illustrates the distribution of the incremental net benefit (INB) of the optimal treatment (t^*) relative to the alternative strategy (t_*) based on the prior evidence. The opportunity loss due to choosing t^* is represented by the grey area (INB<0). When the INB is normally distributed the expected value of this loss can be quantified from the mean and variance of the INB distribution using the unit normal loss integral (UNLI) function.



Appendix A Figure 1: The relationship between the opportunity loss from choosing the optimal strategy and the distribution of the incremental net benefit.

Appendix B

For computing EVPPI and EVPSI we regress the incremental net benefit on the parameters of interest ($\boldsymbol{X_I}$) instead of the full set of parameters ($\boldsymbol{X} = \{\boldsymbol{X_I}, \boldsymbol{X_C}\}$), where $\boldsymbol{X_C}$ is the complimentary set of parameters. Excluding $\boldsymbol{X_C}$ from the regression ensures that the regression coefficients $\boldsymbol{\beta_{X_I}}$ capture both the effect of $\boldsymbol{X_I}$ on INB and the partial effect of $\boldsymbol{X_C}$ on INB (through their correlation with $\boldsymbol{X_I}$). Ignoring this correlation biases the value of information analysis. To illustrate this concept further, we assume that $x_1 \in \boldsymbol{X_I}$, $x_2 \in \boldsymbol{X_C}$ and x_1 and x_2 are correlated. Thus, a regression that includes both parameters will be in the form

$$y=\beta_0+\beta_1 x_1+\beta_2 x_2+e.$$

Obviously computing the expected value of information as a function of β_1 alone is biased because, a clinical trial that informs about x_1 also adds information regarding x_2 which is not directly measured in the trial and is not reflected in β_1.

The correct approach is to use only x_1. To demonstrate this mathematically, we first define x_2 as a function of x_1, such that:

$$x_2=\alpha_0+\alpha_1 x_1+u,$$

where $\alpha_1 \neq 0$ because x_1 and x_2 are correlated as stated above. By substituting x_2 in the first equation, we obtain

$$y=\beta_0+\beta_1 x_1+\beta_2(\alpha_0+\alpha_1 x_1+u)+e.$$

Rearranging the terms results in:

$$y=(\beta_0+\alpha_0\beta_2)+(\beta_1+\alpha_1\beta_2)x_1+(e+\beta_2 u).$$

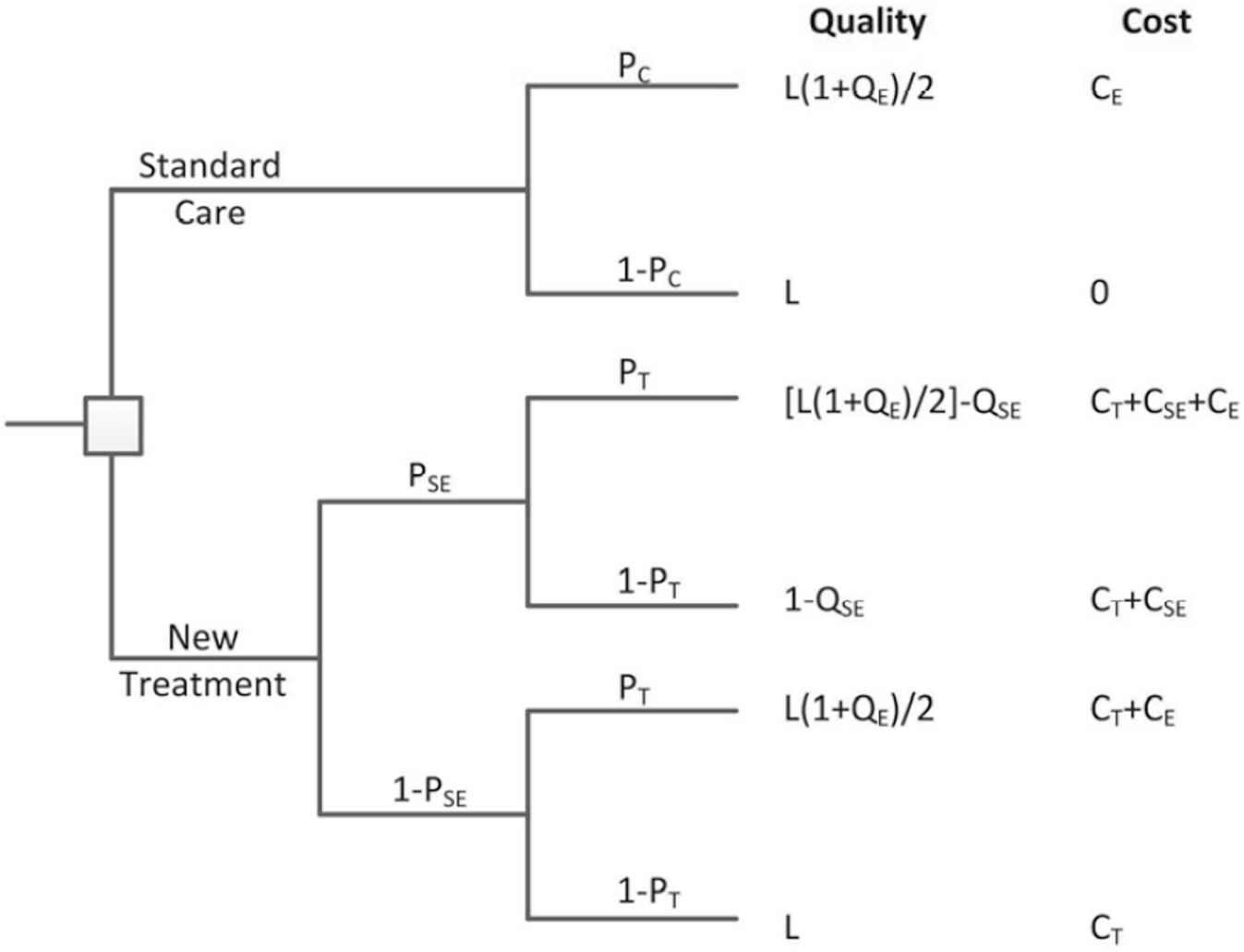
The new coefficient ($\beta_1 + \alpha_1\beta_2$) correctly captures the effect of x_1 on y and the effect of x_2 on y through its correlation with x_1. Thus, the equation above can be further simplified to

$$y=\gamma_0+\gamma_1 x_1+\varepsilon,$$

where γ_1 can be obtained from a regression that excludes x_2.

Appendix C

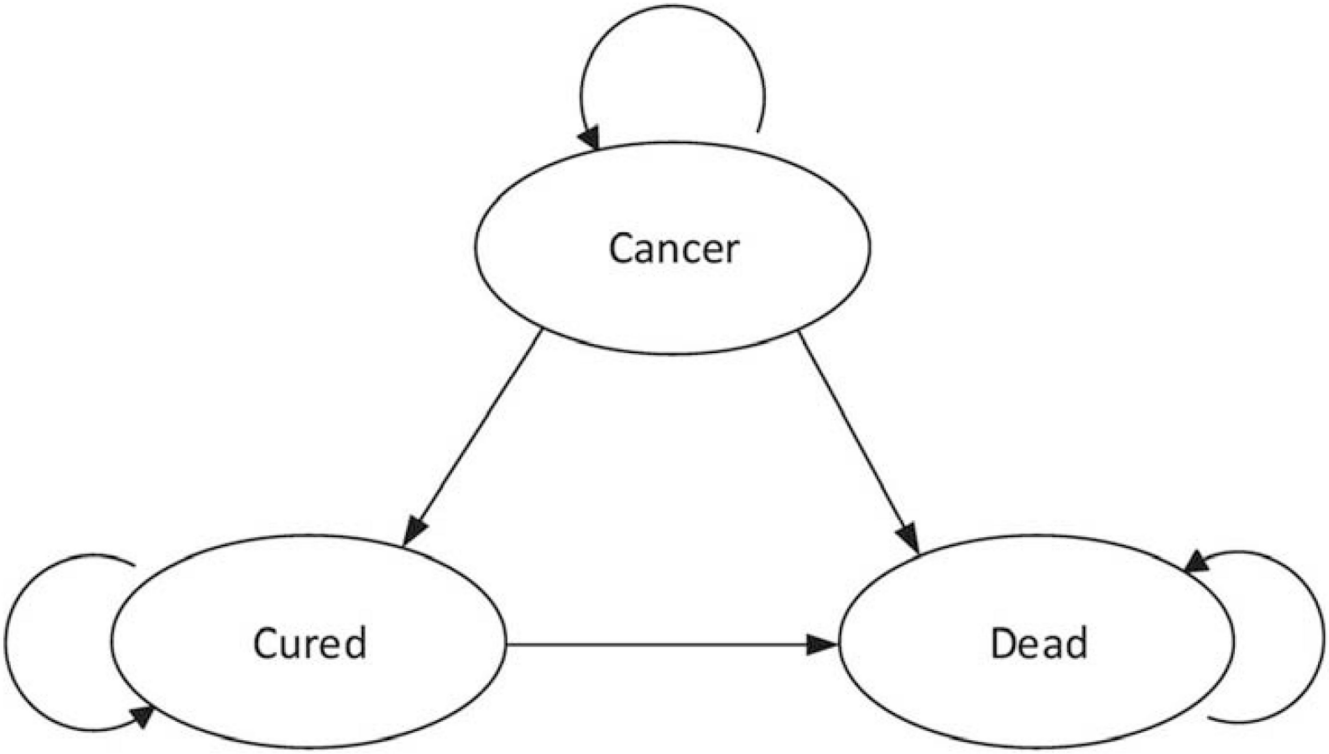
Model outline and parameter descriptions adapted from Ades et al (2004)[26]. This model compares the costs and benefits of a new treatment to the standard of care for a hypothetical condition. The new treatment is more effective, but associated with an additional risk of adverse events. The model consists of eleven parameters, four of which are uncertain in the primary analysis.



Appendix C Figure 1: A diagram representing the decision tree example. Adapted from Ades et al (2004).

Appendix D

Example 2: Model description and input parameters Adapted from Jalal et al (2013)[41]. The ovals represent the Markov health states, and the arrows represent the allowed transitions.



Appendix D Figure 1: A simplified diagram of the Markov model example. Adapted from Jalal et al (2013). The ovals represent the mutually exclusive health states and the arrows represent the allowed transitions.

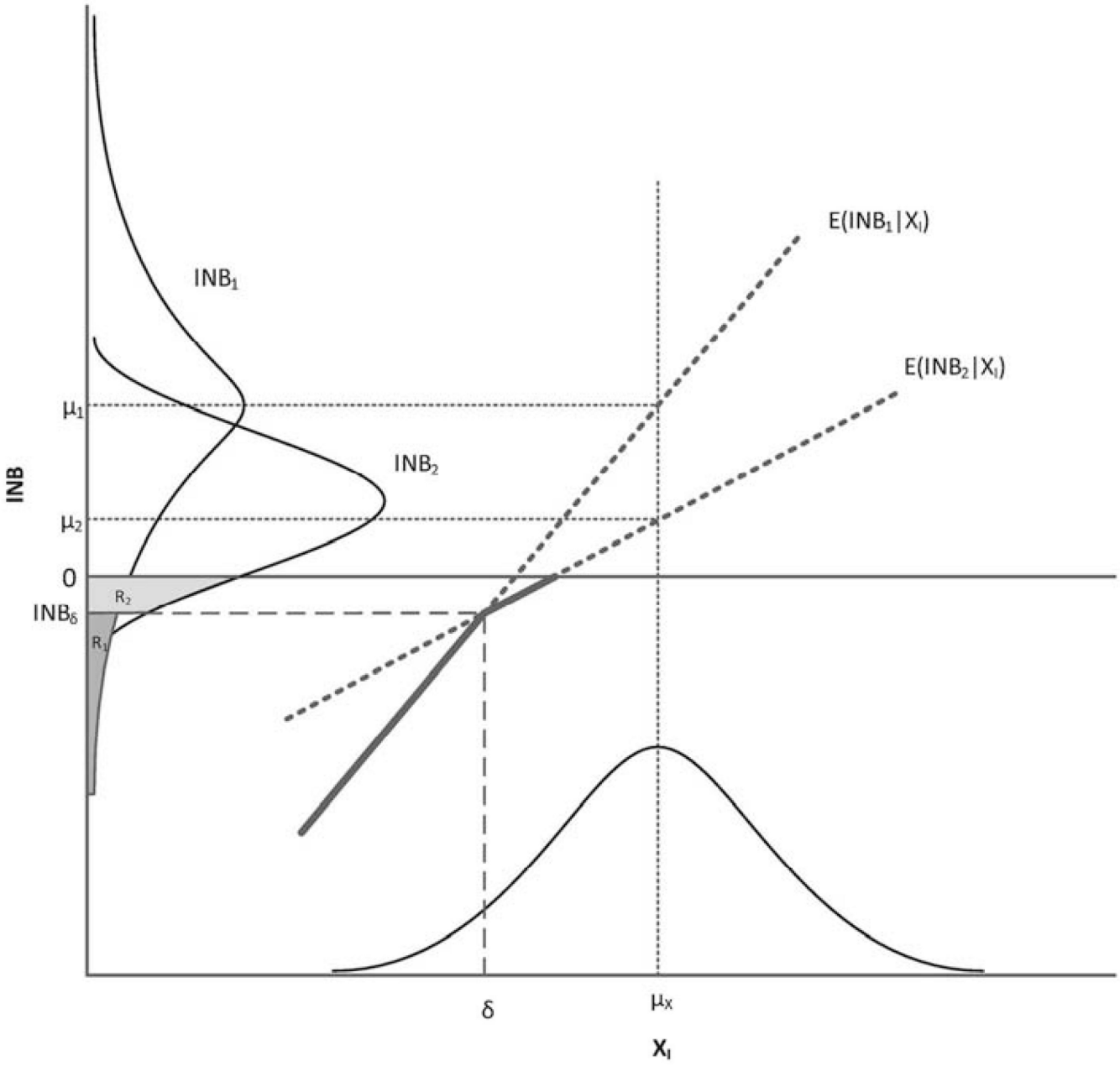
Appendix E

In this section we propose a technique to extend the LRM approach to multiple strategies (Figure). A parameter's value (X_I) is plotted on the X-axis and the INB is plotted on the Y-axis. The distribution of X_I, and that of two INB variables are shown which represent the INB of the dominant strategy compared to the first alternative (INB_1) and a second alternative (INB_2). These two vectors have a linear relationship with X_I. In this example the dominant alternative changes as shown by the solid line which is the farther from the y-axis. As a result, we must calculate the opportunity loss for each alternative while considering the threshold value (INB_δ) at which the dominant alternative changes.

The algorithm involves determining the region on the Y-axis in which each strategy is optimal, then estimating the UNLI separately for INB_1 and INB_2 in each region (R_1 and R_2), respectively. Next we determine the minimum (most negative) opportunity loss in each region. Finally, the sum of these two values estimate the opportunity loss (L) which equates to the value of information, such that

$$L = \int_{-\infty}^{INB_\delta} INB_1 f_{INB_1}(INB_1) dINB_1 + \int_{INB_\delta}^{0} INB_2 f_{INB_2}(INB_2) dINB_2.$$

This approach can be readily extended to decision models that involve more than three strategies.



Appendix E Figure 1: A visual representation of an alternative approach to extend the unit normal loss integral (UNLI) approach to multiple strategies. (Please refer to the text for a description of the parameters in this diagram.)

Appendix F

In this appendix we provide a code example that illustrates how to compute EVPPI and EVPSI for two parameters combined from PSA results using Microsoft Excel and R (R

version 3.0.2). The code first imports the input parameter estimates and the resulting net benefit values from a Microsoft Excel workbook (MarkovModel.xlsx) from a previously built model. The first spreadsheet of the file contains 10,000 PSA samples of four input parameter, and the second sheet contains the resulting 10,000 net benefit of the two strategies.

Table

Description of the model parameters. Adapted from Ades et al (2004)[26]

Description	Parameter	Mean	Distribution
Mean remaining lifetime	L	30	Constant
QALY after critical event, per year	Q_E	0.6505	Logit(QE) ~ N (0.6, 0.17)
QALY decrement due to side effects	Q_{SE}	1	Constant
Cost of critical event	C_E	$200,000	Constant
Cost of treatment	C_T	$15,000	Constant
Cost of side effects	C_{SE}	$100,000	Constant
Monetary value of 1 QALY	W	$75,000	Constant
Probability of critical event, no treatment	p_C	0.15	Beta(15,85)
Probability of treatment side effects	P_{SE}	0.25	Beta(3,9)
Odds ratio, PT $(1-P_C)/(P_C(1-P_T))$	OR		log(OR) ~ N (−1.5, 0.34)
Probability of critical event on treatment	P_T	0.0440	

Table

Case study 2: input parameter

Description	Parameter	Mean	Distribution
Cancer-specific mortality rate	mCancer	0.398	Log-normal(−l, 0.4)
Annual probability of failing chemotherapy	pFailChemo	0.7	Beta(14,6)
Probabilty of failing surgery	pFailSurg	0.4	Beta(4, 6)
Probability of dying due to surgery	pDieSurg	0.05	Beta(0.5, 9.5)
Annual Chemotherapy cost($)	cChemo	$3000	Constant
Surgery cost	cSurg	$15,000	Constant
Willingness to pay threshold	wtp	$50,000 /QALY	Constant

```
setwd("C:/") # Set the working directory
# The ULNI function, inputs mu and sigma, and outputs the expected opportunity loss.
UNLI <- function(mu, sigma){
  prob=pnorm(-mu/sigma) # The probability of choosing the wrong decision.
  evi=mu*prob - (sigma/sqrt(2*pi))*exp(-mu^2/(2*sigma^2)) # expected value of information
  return(evi)
}
## Install required packages
install.packages("gdata")
install.packages("xlsx")
install.packages("matrixStats")

library(matrixStats)  # for colMins
library(gdata)
library(xlsx)

## Load model inputs and outputs
Xdata <- read.xlsx ("MarkovModel.xlsx", 1, header = FALSE) #Read model inputs (sheet 1)
Ydata <- read.xlsx ("MarkovModel.xlsx", 2, header = FALSE) #Read model outputs (sheet 2)
X <- as.matrix(Xdata) #convert inputs into a matrix X
Y <- as.matrix(Ydata) #convert outputs into a matrix Y
nParam <- ncol(X) # No. of parameters
nSim <- nrow(X) # No. of PSA simulations.
dStar <- which.max(colMeans(Y)) #Index of the optimal strategy
inb <- Y[,dStar] - Y[,3-dStar] #INB = optimal strategy - the other strategy
X0 <- rep(1, nSim) # a vector of constants (intercept term)

## Computing EVPPI for the 3rd and 4th parameters combined:
p <- c(3,4) #selected parameter are #3 and #4
nParamInterest <- length(p)
Z <- cbind(X0, X[,p]) # add the constant vector
Bhat <- solve(t(Z) %*% Z) %*% t(Z) %*% inb # multivariate linear regression
mu0tilde <- Bhat[1] + colMeans(X[,p]) %*% Bhat[2:(nParamInterest+1)]
Sigma <- cov(X[,p])
sigma0tilde <- sqrt(t(Bhat[2:(nParamInterest+1)]) %*% Sigma %*% Bhat[2:(nParamInterest+1)])
evppi <- -UNLI(mu0tilde, sigma0tilde)

## Computing EVPSI for the 3rd and 4th parameters combined.
n0 <- 1 #prior sample size
n <- 60 #additional sample size
v <- sqrt(n/(n+n0)) #variance reduction coefficient
sigma1tilde <- sqrt(v) * sigma0tilde  #posterior variance of mean INB explained by Xp
evpsi <- -UNLI(mu0tilde, sigma1tilde) #value of information
```

Box 1

EVPI Algorithm

1.1: Probabilistic sensitivity analysis (PSA):

- Assign appropriate distributions for the uncertain input parameters to reflect their uncertainties.
- Sample m values from each parameter, and obtain a matrix $\boldsymbol{X}$ of input parameter values, where x_{ij} represents the i^{th} value ($i = 1 \ldots m$) of the j^{th} parameter.
- Determine the optimal strategy (t^*) that maximizes the net benefit (B) over all parameter uncertainties $\max_t E_{\boldsymbol{X}} B(t, \boldsymbol{X})$.
- For each set of parameter values ($\boldsymbol{x}_i$), compute INB_i, as the difference between the net benefit of the optimal strategy (t^*) less that of the alternative strategy (t_*), such as

$$INB_i = B(t^*, \boldsymbol{x}_i) - B(t_*, \boldsymbol{x}_i).$$

- Compute μ_0 and σ_0^2 as the mean and variance of the INB 's prior distribution.

1.2: UNLI

- Use equation (2) to compute EVPI, such as:
  - $$EVPI \approx -UNLI\left(\mu_0, \sigma_0^2\right).$$

Box 2

EVSI Algorithm

1.1: PSA (follow 1.1).

- Compute μ_0 and σ_0^2.

1.2: Calculate the preposterior variance of INB (σ_1^2):

- Calculate the variance fraction ν:
  - $$\nu = \frac{n}{n+n_0}$$
  - $$\sigma_1^2 = \sigma_0^2 \nu$$

1.3: Compute EVSI:

- $$\mathrm{EVSI} \approx -\mathrm{UNLI}\left(\mu_0, \sigma_1^2\right).$$

Box 3

EVPPI Algorithm

3.1: PSA (follow 1.1)

3.2: LRM: Compute the prior mean ($\tilde{\mu}_0$) and variance ($\tilde{\sigma}_0^2$) of INB explained by the parameters of interest ($\boldsymbol{X_I}$)

- Regress only the subset of parameters of interests ($\boldsymbol{X_I}$) on the prior INB, such as:
  - $$\mathrm{INB} = \alpha + \mathbf{X}_\mathbf{I}\boldsymbol{\beta} + e,$$

where α is the regression intercept, $\boldsymbol{\beta}$ is a vector of regression coefficients, and e is the regression's residual term.

- Compute $\tilde{\mu}_0$:
  - $$\tilde{\mu}_0 = \alpha + E(\boldsymbol{X_I})\boldsymbol{\beta},$$
- Compute $\tilde{\sigma}_0^2$:
  - $$\tilde{\sigma}_0^2 = \boldsymbol{\beta}'\boldsymbol{\Sigma}\boldsymbol{\beta},$$

where $\boldsymbol{\Sigma}$ is the covariance matrix of $\boldsymbol{X_I}$.

3.3: UNLI: use $\tilde{\mu}_0$ and $\tilde{\sigma}_0^2$ in A.2 to compute EVPPI:

- $$\mathrm{EVPPI} \approx -\mathrm{UNLI}\left(\tilde{\mu}_0, \tilde{\sigma}_0^2\right).$$

Box 4

EVPSI Algorithm

4.1: PSA (follow 1.1)

4.2: LRM (follow 3.2)

4.3: Compute $\tilde{\sigma}_1^2$

- If n_0 and n are the same for all $\boldsymbol{X_I}$, then compute $\tilde{\sigma}_1^2 = \nu\tilde{\sigma}_0^2$.
- Otherwise, in a heterogeneous design, compute a vector of variance fractions ($\boldsymbol{\nu}$), such as: $\nu_j = n_j/(n_j + n_{0j})$, where ν_j represents the variance fraction for x_j, $x_j \in X_I$, and n_j and n_{0j} represent the sample sizes for the prior and additional samples for x_j, respectively. Then, compute $\tilde{\sigma}_1^2 = \boldsymbol{\beta}' \left(\sqrt{\boldsymbol{\nu}\boldsymbol{\nu}'} \circ \boldsymbol{\Sigma} \right) \boldsymbol{\beta}$.

4.4: Finally, compute $EVPSI \approx -UNLI\left(\tilde{\mu}_0, \tilde{\sigma}_1^2\right)$

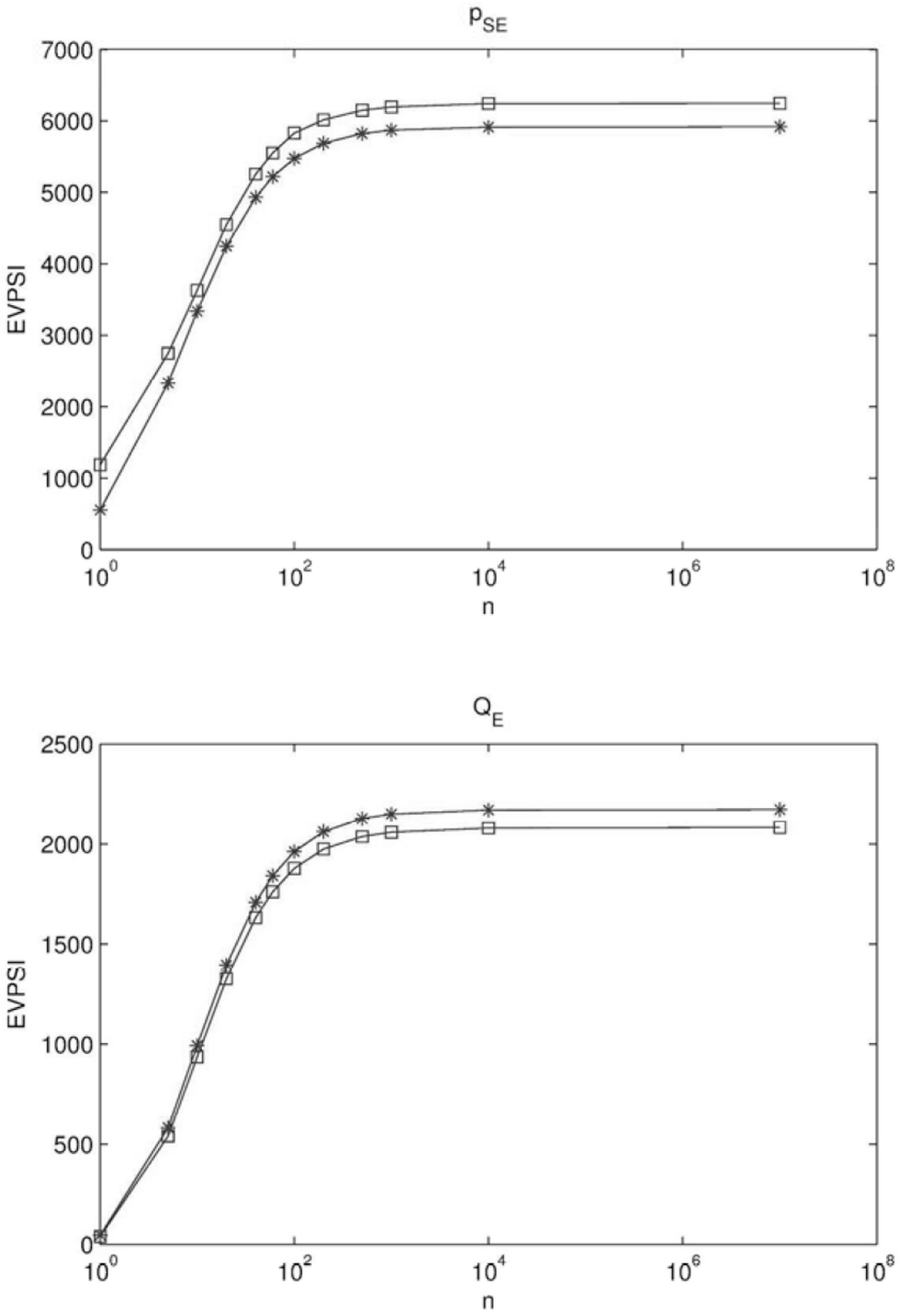


Figure 1.

Comparing the results of the LRM and analytic approaches from Example 1. The EVPSI is shown for the probability of the new treatment causing side-effects (p_{SE}) and the quality of life after the event (Q_E). [Note LRM = linear regression metamodeling, EVPSI = expected value of partial sample information]

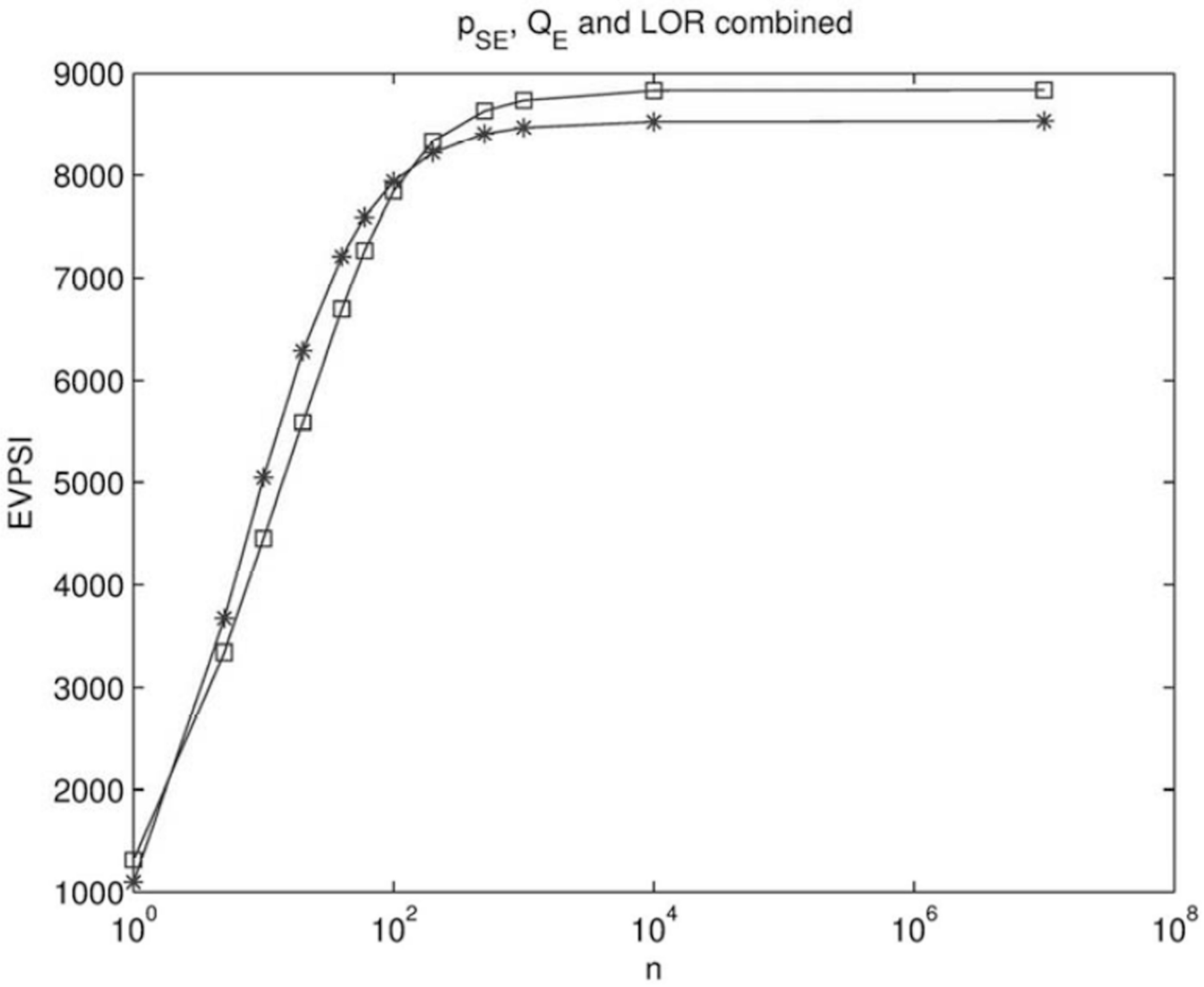


Figure 2.

Comparing the results of the LRM and analytic approaches from Example 1. The EVPSI is shown for a combination of parameters: probability of the new treatment causing side-effects (p_{SE}), the quality of life after the event (Q_E), and the log odds ratio of the new treatment causing the event relative to the standard treatment (LOR). [Note LRM = linear regression metamodeling, EVPSI = expected value of partial sample information]

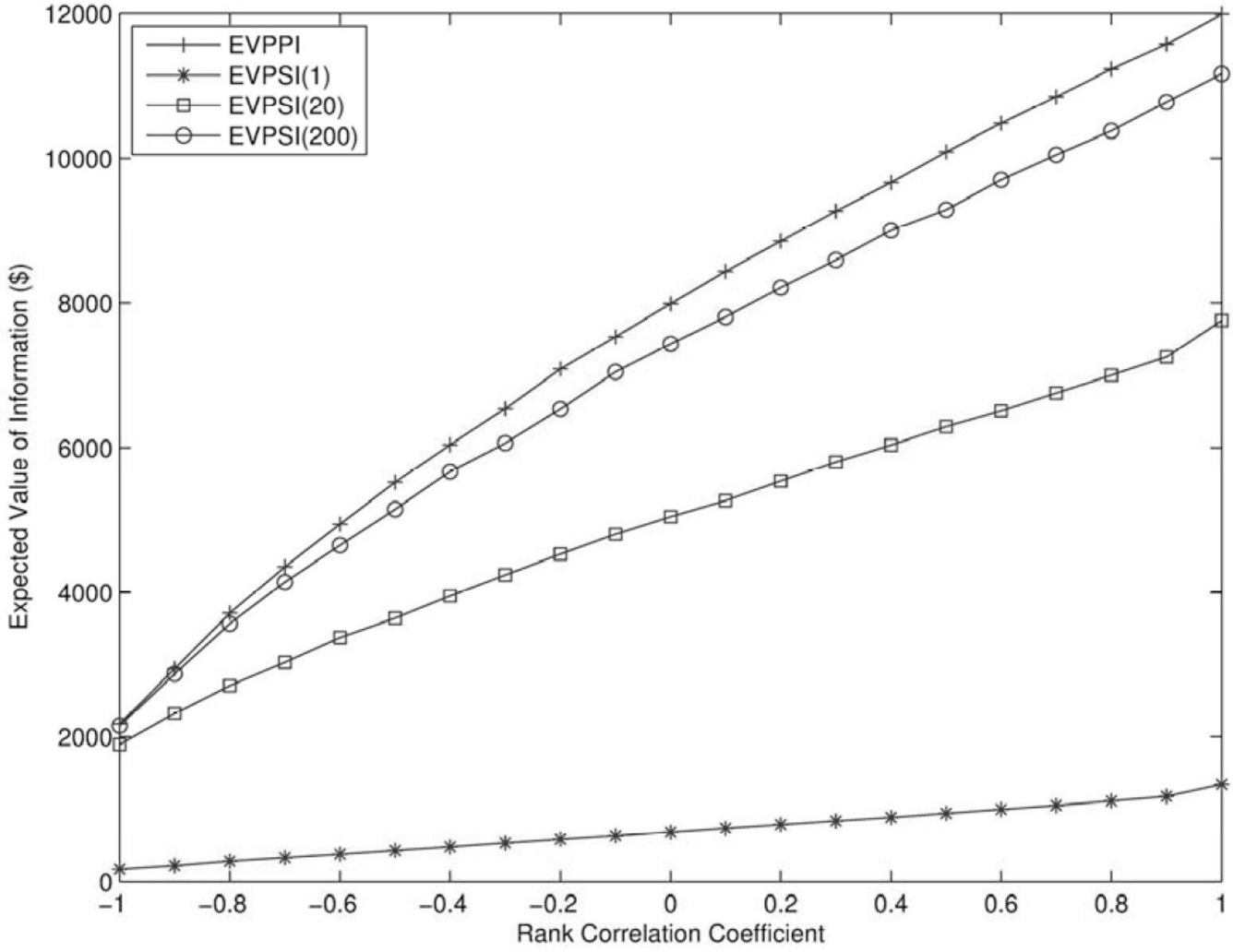


Figure 3.

The impact of correlation between the probability of side effects (p_{SE}) and the odds ratio of the critical event (OR) on the EVPPI and EVPSI of these two parameters combined in Example 1. The EVPSI is shown for three sample sizes n = 1,20 and 200. Correlation has a significant impact on EVPPI and EVPSI, this impact is proportional to the sample size. [Note EVPPI = expected value of partial perfect information and EVPSI = expected value of partial sample information].

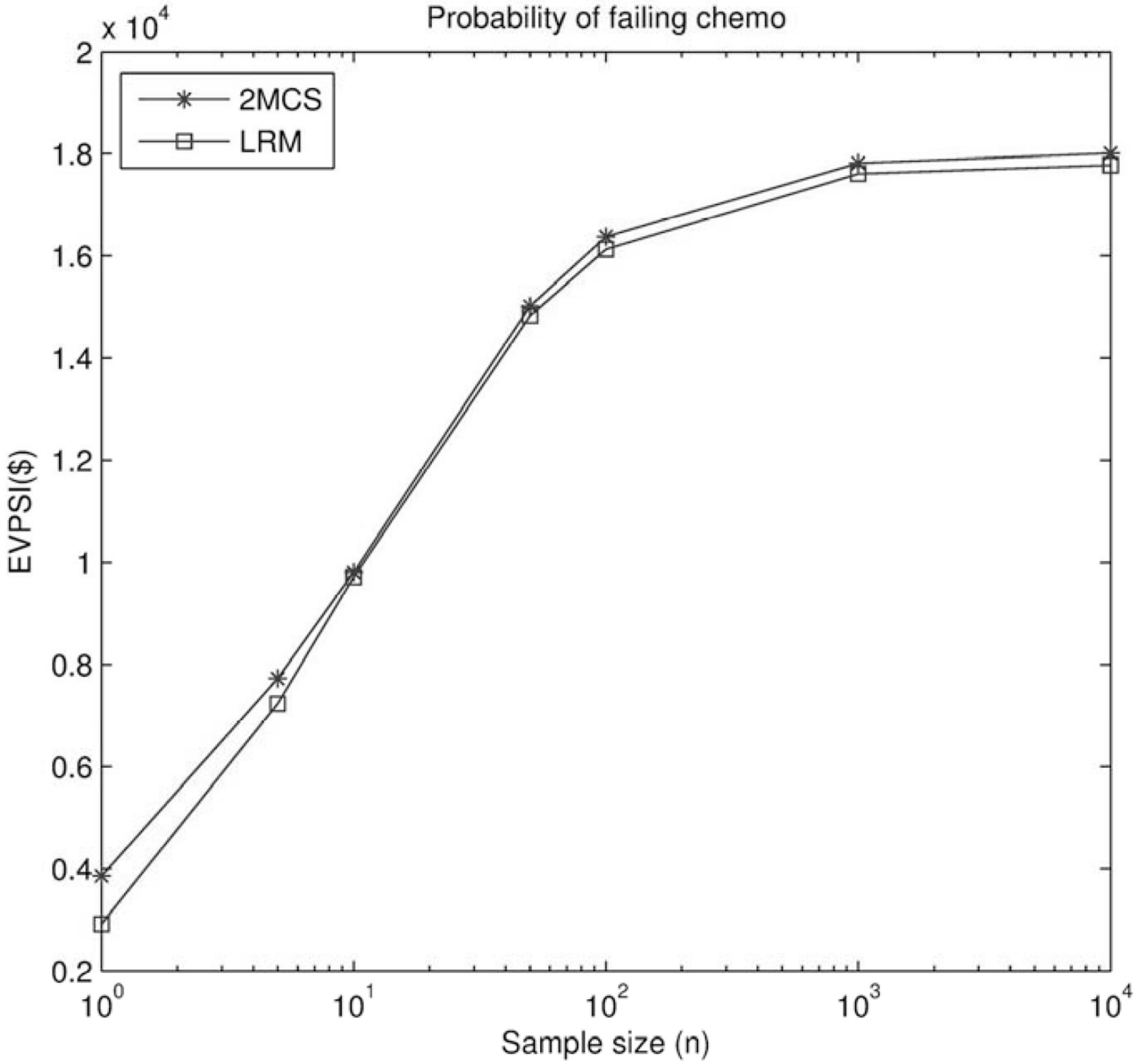


Figure 4.

Results from Example 2 comparing the LRM and 2MCS approaches. The EVPSI for the probability of failing chemotherapy (pFailChemo) is shown. [Note LRM = linear regression metamodeling, 2MCS = two-stage Monte-Carlo simulation, EVPSI = expected value of partial sample information].

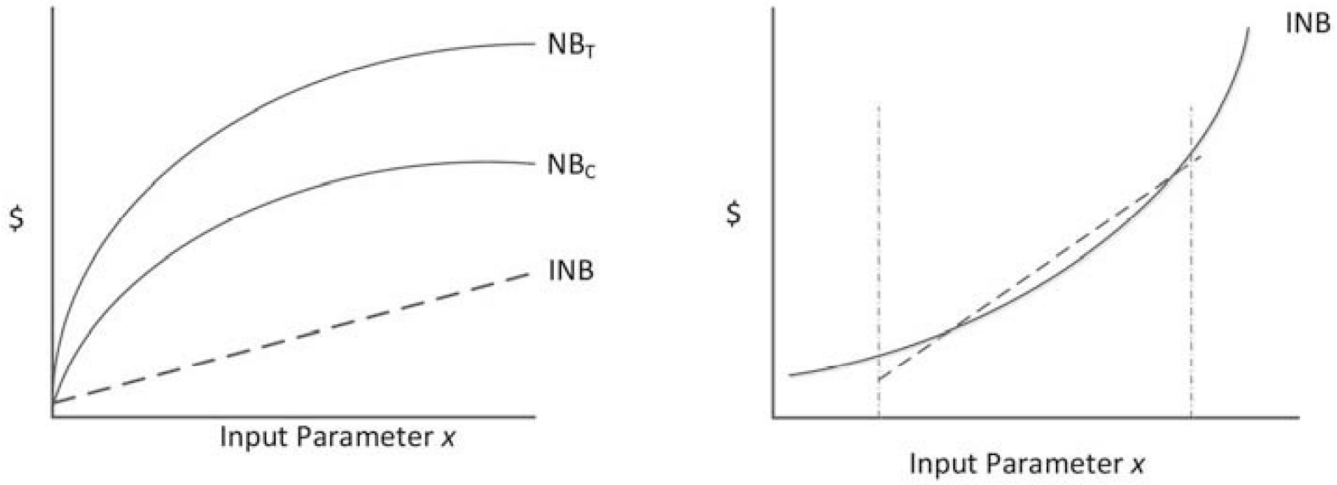


Figure 5.

The linearity assumption: (A) A local linear relationship is shown between INB over a parameter's (x) uncertainty range (marked by the vertical dashed lines). (B) A potential linear relationship between INB and x can be the result of the difference between the net benefits of the optimal treatment (t^*) and the alternative (t_*) strategies. [Note INB = incremental net benefit].

Table 1

Summary of the mean and variance used in the UNLI function by type of VOI measure.

	All Parameters	**Subset of Parameters (X_I)**
Perfect information. Infinite sample (∞)	*EVPI* Prior mean of INB (μ_0) Prior variance of INB (σ_0^2)	*EVPPI* Prior mean of INB explained by X_I $(\tilde{\mu}_0)$ Prior variance of INB explained by a subset of parameters of interest $(\tilde{\sigma}_0^2)$
Sample information (n)	*EVSI* Prior mean of INB (μ_0) Preposterior variance of INB (σ_1^2)	*EVPSI* Prior mean of INB explained by X_I $(\tilde{\mu}_0)$ Preposterior variance of INB explained by X_I $(\tilde{\sigma}_1^2)$

UNLI = unit normal loss integral; VOI = value of information; EVPI = expected value of perfect information; EVPPI = expected value of partial perfect information, EVSI = expected value of sample information; EVPSI = expected value of partial sample information, INB = incremental net benefit.

Table 2

The EVPI and EVPPI results of the current approach compared to Ades et al. (2004)[26]

	Current Approach	Ades et al. (2004)
EVPI	$10,200	$10,140
Decision change probability	0.431	0.428
EVPPI		
Probability of treatment side effects (p_{SE})	$6,000	$6,240
QALY after critical event, per year (Q_E)	$2,180	$2,080
Odds ratio of critical event while on treatment relative to the control (OR)	$3,800	$3,890
EVPPI of OR, p_{SE} and Q_E combined	$8,840	$8,770

EVPI = expected value of perfect information, EVPPI = expected value of partial perfect information, QALY = quality-adjusted life year.