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Calculating Value of Information Measures for Health Economic Evaluations within R

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Abstract

Health economic evaluations involve synthesising information across different sources to evaluate the costs and consequences of a number of health care interventions with the aim of deciding on the "optimal" intervention. Health economic decisions are typically subject to parametric uncertainty. Thus, practitioners are encouraged to investigate how this uncertainty affects the decision-making process. Value of Information measures evaluate the economic cost of parametric uncertainty and can determine whether future research is required to reduce parametric uncertainty. In addition to this, they can prioritise research questions and design data collection exercises. Broadly, computational issues have hindered their widespread implementation but recent methodological developments have significantly reduced the computation time required. In this paper, software developed to implement these Value of Information computation methods in R is presented. This will continue to lower the barrier to the implementation of Value of Information methods in practice. This paper focusses on two R packages, **BCEA** and **EVSI**. These packages can be used to calculate different Value of Information measures are used at different points in the research design cycle. Additionally, **BCEA** and **EVSI** provide standardised graphics for the presentation of Value of Information analysis to increase their applicability in decision-making and research design in health economic evaluations.

Keywords: Value of Information, Health Economic Evaluation, Trial Design, Probabilistic Sensitivity Analysis.

1. Introduction

Health economic evaluations utilise a range of approaches to assess the costs and clinical consequences of health care interventions. The aim of these evaluations is to maximise health

gains across a population given finite monetary resources for health care spending. Within publicly funded health care systems, such as those in the UK or Canada, these evaluations provide guidance for policy decisions by determining which treatment is "optimal" among a set of alternative treatments (National Institute of Health and Care Excellence 2013; Canadian Agency for Drugs and Technologies in Health 2019). This means that new and existing treatments for a specific health indication are compared by synthesizing evidence across a range of different sources including the published literature, individual patient data from trials and administrative databases. Thus, it has been argued that health economics is a branch of applied statistics (Baio 2012; Willan and Briggs 2006).

The process of health-economic evaluations involves the identification of suitable measures of clinical benefits (generically termed as "effectiveness") and costs associated with an intervention. The total cost for an intervention (e.g. a drug) usually includes the cost of its acquisition and implementation, along with societal costs such as those related to number of days off work or social care. As for the clinical benefits, they can be a "hard" measurement (e.g. number of cases averted), but are, most often, considered in terms of *Quality Adjusted Life Years* (QALYs) (Loomes and McKenzie 1989), combining the quantity and the quality of life provided by a given intervention. Individual level variability in the costs and effectiveness is normally expressed in terms of a joint probability distribution, indexed by a set of population level parameters.

Across a range of jurisdictions, health economic evaluations require an assessment of the impact of uncertainty in these population level parameters on the decision making process (Canadian Agency for Drugs and Technologies in Health 2019; Department of Health and Ageing 2008; National Institute of Health and Care Excellence 2013; EUnetHTA 2014). Within the health economic literature, this process is known as Probabilistic Sensitivity Analysis (PSA) (Claxton, Sculpher, McCabe, Briggs, Akehurst, Buxton, Brazier, and O'Hagan 2005). To undertake PSA, the current level of uncertainty in the model parameters are represented by statistical distributions. This directly defines a distribution for cost and effectiveness outcomes for the different treatments, which, in turn, can lead to uncertainty in the decision-making process. By assessing parametric uncertainty using statistical distributions, health economic evaluations are implicitly undertaken using a Bayesian approach (O'Hagan and Stevens 2001; O'Hagan, Stevens, and Montmartin 2001; Spiegelhalter, Abrams, and Myles 2004; Baio 2012).

Value of Information (VoI) (Raiffa and Schlaifer 1961; Felli and Hazen 1998) is a concept from decision analysis and is defined as the amount a decision maker should be willing to pay to reduce/eliminate parametric uncertainty before making a decision (Willan and Pinto 2005). We can combine VoI with probabilistic health economic decision models to quantify the return on medical research investment. By targeting research to areas with a high return on investment, VoI then supports a comprehensive, principled method for research prioritisation and trial design (Minelli and Baio 2015). VoI also assumes that that information collected in a future trial will be added to the current body of evidence to support decision-making. Thus, VoI is an inherently Bayesian approach to research prioritisation and trial design.

VoI has long been touted as a method for clinical research design (Willan and Pinto 2005). However, computational issues, alongside a lack of visibility in the clinical community, have largely prevented the widespread implementation of VoI methods (Steuten, van de Wetering, Groothuis-Oudshoorn, and Retèl 2013). Traditionally, the VoI measures with the greatest potential as a tool for research design have been estimated using computationally costly

nested simulation (Felli and Hazen 1998; Ades, Lu, and Claxton 2004). Recently, a number of methods have been developed to overcome these computational barriers and, thus, unlock the potential of VoI (Strong, Oakley, and Brennan 2014; Strong, Oakley, Brennan, and Breeze 2015; Heath, Manolopoulou, and Baio 2016, 2017, 2018, 2019; Jalal, Goldhaber-Fiebert, and Kuntz 2015; Jalal and Alarid-Escudero 2018; Menzies 2016).

While these methods have decreased the computational time required to estimate these key VoI measures, their implementation is still a barrier to their widespread usage. Thus, we have developed two packages in R to further simplify the use of VoI methods in practice. The package **BCEA** is used to post-process the results of a Bayesian health economic model by producing advanced analysis and standardised output (Baio, Berardi, and Heath 2017). Within this package, two functions are available to compute standard VoI measures. These are accompanied by standardised graphics. The **EVSI** package has been developed to support trial design using VoI methods by implementing a method developed in Heath *et al.* (2018); Heath and Baio (2018); Heath *et al.* (2019). Using VoI for trial design requires a number of additional assumptions which can be explored using a number of graphics provided in the **EVSI** package and supported within a **shiny** interface to further ease presentation (Chang, Cheng, Allaire, Xie, and McPherson 2017).

2. Notation and Key Concepts

Health economic decision making is concerned with determining the *optimal* intervention for a specific health state, among $T + 1$ alternative options. In general, the current standard of care (with the index $t = 0$) is compared with T alternative treatments. Theoretically, health economic models can be developed to compare a large number of alternative interventions but in practice T is rarely greater than 5.

Health economic models determine the optimal intervention by estimating the effectiveness and costs for each treatment under consideration, denoted by the pair (e_t, c_t). These two health economic outcomes are then combined into a *utility function* that values each of the treatments. The treatments are typically valued in terms of the monetary net benefit (Stinnett and Mullahy 1998)

$$nb_t = ke_t - c_t.$$

Generally, (e_t, c_t) will be associated with variability at the individual level, expressed by a joint probability distribution $p(e_t, c_t \mid \boldsymbol{\theta})$ conditional on a set of model parameters $\boldsymbol{\theta}$. The parameter k is known as the *willingness-to-pay* and represents the amount of money the payer, i.e. the person/organisation that is paying for the treatment, is willing to spend to extend someone's life by 1 year in perfect health. This is typically set externally by the HTA body, such as the National Institute of the Health and Care Excellence (NICE) in the UK.

In a Bayesian setting, it is possible to rank the treatment options by computing the overall expectation of this utility function over both individual variability and parameter uncertainty

$$\mathcal{NB}_t = k\mathrm{E}[e_t] - \mathrm{E}[c_t],$$

i.e. the expectation here is taken with respect to the joint distribution $p(e, c, \boldsymbol{\theta}) = p(e, c \mid \boldsymbol{\theta})$ $p(\boldsymbol{\theta})$. A risk-neutral decision-maker would then deem that the option t associated with the maximum overall expected utility $\mathcal{NB}^* = \max_t \mathcal{NB}_t$ is "cost-effective", given current evidence.

Evidently, the ranking of the treatments can change depending on the value of the willingness-to-pay value k. In general, the willingness-to-pay is defined as an interval and standard health economic analysis requires a sensitivity analysis across different values of k. However, as the utility function is linear in k, this sensitivity analysis can be performed easily.

2.1. Probabilistic Sensitivity Analysis

Probabilistic Sensitivity Analysis (PSA) assesses the impact of parametric uncertainty on the decision-making process. Thus, to perform PSA, we consider the monetary net benefit as a function of $\boldsymbol{\theta}$ only by averaging out individual level uncertainty:

$$\mathrm{NB}_t(\boldsymbol{\theta}) = k\mathrm{E}[e_t \mid \boldsymbol{\theta}] - \mathrm{E}[c_t \mid \boldsymbol{\theta}]. \tag{1}$$

As in Baio (2012), this is known as the "known-distribution" net benefit. In the above expression, we take expectation with respect to the conditional distribution $p(e_t, c_t \mid \boldsymbol{\theta})$. Thus, decision making is concerned with the deterministic quantity $\mathcal{NB}_t$ and PSA is concerned with the random variable $\mathrm{NB}_t(\boldsymbol{\theta})$ where $\mathrm{E}\left[\mathrm{NB}_t(\boldsymbol{\theta})\right] = \mathcal{NB}_t$.

PSA is usually based on a simulation approach (Baio and Dawid 2011; Baio 2012; Andronis, Barton, and Bryan 2009). When the distribution $p(\boldsymbol{\theta})$ is conditional on data, Bayesian models are normally estimated using a simulation approach, e.g. MCMC and therefore the known-distribution net benefit values are created as a by-product of the health-economic analysis. If $p(\boldsymbol{\theta})$ is available in analytic form, then PSA proceeds by simulating from this prior distribution and calculating the known-distribution net benefit values. We denote $\boldsymbol{\theta}_s$, $s = 1 \ldots S$, as a draw from the distribution of $\boldsymbol{\theta}$ and the known-distribution net benefit for this parameter vector as $\mathrm{NB}_t(\boldsymbol{\theta}_s)$.

2.2. Value of Information Measures

Under the currently available information about the parameters represented by $p(\boldsymbol{\theta})$, the optimal treatment option is the treatment that maximises the expected known-distribution net benefit. However, incomplete evidence for the model parameters may imply that the treatment that is optimal given current evidence is not truly optimal. Thus, additional information may change the decision and save financial resources by preventing the widespread implementation of an inefficient treatment. Thus, VoI is a formal method that combines the probability and financial consequences of making the incorrect decision to determine the explict value of additional information. Different VoI measures consider varying levels of addtional information with the following three VoI measures used most commonly.

Expected Value of Perfect Information

The Expected Value of Perfect Information (EVPI) assumes that it is possible to learn the *exact* value of every model parameter, known as "perfect" information. If we were able to learn that $\boldsymbol{\theta}$ is exactly equal to $\boldsymbol{\theta}'$ then the value of the optimal decision would be

$$\max_t \mathrm{NB}_t(\boldsymbol{\theta}').$$

In this setting, there is no remaining uncertainty in the model (individual level variability is already marginalised out) so there is no need to take expectations. Thus, it is relatively

simple to compute the value of learning $\boldsymbol{\theta} = \boldsymbol{\theta}'$. However, we do not know the "true" value of $\boldsymbol{\theta}$ and, thus, we summarise the value of obtaining perfect information across all possible values of $\boldsymbol{\theta}'$. The EVPI is computed by taking the expectation over all values of $\boldsymbol{\theta}'$;

$$\text{EVPI} = \text{E}_{\boldsymbol{\theta}} \left[\max_t \text{NB}_t(\boldsymbol{\theta}) \right] - \max_t \text{E}_{\boldsymbol{\theta}} \left[\text{NB}_t(\boldsymbol{\theta}) \right]. \tag{2}$$

The EVPI is the upper limit on the value that can be obtained from any study aimed at reducing uncertainty in the model parameters. If this value is very small, then we can conclude that there is little value in investigating any of the model parameters and therefore the optimal treatment can be selected using the current information without considering additional data collection. If, however, the EVPI shows that there is value in a future study, it is useful to determine where future research should be targeted.

Expected Value of Perfect Partial Information

Health economic models typically have a relatively large number of parameters as these models synthesize evidence about the costs and effectiveness of different treatments. Thus, a future trial will normally only target a subset of these models parameters $\boldsymbol{\phi}$, while the remaining model parameters $\boldsymbol{\psi}$ are not investigated. The Expected Value of Perfect Partial Information (EVPPI) computes the value of obtaining perfect information about $\boldsymbol{\phi}$. To define the EVPPI, assume that we have perfect information about the parameters of interest $\boldsymbol{\phi} = \boldsymbol{\phi}'$. Under this condition, the value of the optimal treatment is then equal to

$$\max_t \text{E}_{\boldsymbol{\psi}|\boldsymbol{\phi}'} \left[\text{NB}_t(\boldsymbol{\phi}', \boldsymbol{\psi}) \right], \tag{3}$$

where the expectation is taken over the remaining uncertainty for the parameters in $\boldsymbol{\psi}$.

The EVPPI is then calculated by taking the expectation of equation (3) across the support of $\boldsymbol{\phi}$ and subtracting the value of the current optimal decision:

$$\text{EVPPI} = \text{E}_{\boldsymbol{\phi}} \left[\max_t \text{E}_{\boldsymbol{\psi}|\boldsymbol{\phi}} \left[\text{NB}_t(\boldsymbol{\phi}, \boldsymbol{\psi}) \right] \right] - \max_t \text{E}_{\boldsymbol{\phi},\boldsymbol{\psi}} \left[\text{NB}_t(\boldsymbol{\phi}, \boldsymbol{\psi}) \right]. \tag{4}$$

The EVPPI is bounded below by 0 and above by the EVPI. The EVPPI is most useful when it demonstrates that there is little value in learning about a subset of parameters. This is because it is rarely possible to obtain perfect information about a model parameter. If the EVPPI for a set of parameters is high, then we are interested in how to reduce this parametric uncertainty.

Expected Value of Sample Information

The value of a specific study, aimed at reducing uncertainty in a subset of the model parameters, is known as the Expected Value of Sample Information (EVSI). It is defined in a similar way to both the EVPI and the EVPPI, but rather than learning the exact value of the parameters we consider that the study would give rise to data $\boldsymbol{X}$. These data would be combined with the current information to determine the posterior distribution for the net benefit across each treatment. The value of the optimal decision under this additional information is then

$$\max_t \text{E}_{\boldsymbol{\theta}|\boldsymbol{X}} \left[\text{NB}_t(\boldsymbol{\theta}) \right], \tag{5}$$

where $\mathrm{E}_{\boldsymbol{\theta}|\boldsymbol{X}}\left[\mathrm{NB}_t(\boldsymbol{\theta})\right]$ is the posterior mean of the known-distribution net benefit.

As it is not known what data will arise from the future study, we calculate the EVSI as the expectation of (5) over all the possible data sets from the future trial;

$$\mathrm{EVSI} = \mathrm{E}_{\boldsymbol{X}}\left[\max_t \mathrm{E}_{\boldsymbol{\theta}|\boldsymbol{X}}\left[\mathrm{NB}_t(\boldsymbol{\theta})\right]\right] - \max_t \mathrm{E}\left[\mathrm{NB}_t(\boldsymbol{\theta})\right], \tag{6}$$

where the distribution of the future data $\boldsymbol{X} \sim p(\boldsymbol{X})$ is the prior predictive distribution for the data. This distribution is defined through the sampling distribution for the future data conditional on the model parameters $p(\boldsymbol{X} \mid \boldsymbol{\theta})$. Parameter uncertainty is then integrated out to calculate;

$$p(\boldsymbol{X}) = \int_{\boldsymbol{\Theta}} p(\boldsymbol{X} \mid \boldsymbol{\theta}) p(\boldsymbol{\theta}) d\boldsymbol{\theta},$$

where $p(\boldsymbol{\theta})$ is the prior/PSA distribution for the model parameters $\boldsymbol{\theta}$.

The EVSI should be compared directly with the cost of the study to determine whether there is net value in undertaking the study. If the EVSI is greater than the cost of the study, then it should go ahead. If, on the other hand, the study cost exceeds the EVSI, then the current information is sufficient to make a decision. However, there are a number of additional considerations required to compare the EVSI with the study costs.

Expected Net Benefit of Sampling

Firstly, the net monetary benefit of each treatment is normally calculated per person who would receive the treatment. As the EVSI is calculated based on this individual level model, it is equal to the value of the information contained in the sample for each person that would receive the treatment. As improved decision making benefits all these people, the EVSI must be multiplied by the number of people who will benefit from the treatments under consideration, known as the incidence population (Thokala, Goodacre, Ward, Penn-Ashman, and Perkins 2015).

The size of the incidence population will depend on the number of years the treatment is available, known as the length of the treatment life-cycle. In standard economic analysis, discounting is used to imply that immediate benefits are more valuable than future benefits (National Institute of Health and Care Excellence 2013). Thus, we multiply the EVSI by the yearly incidence population and by the length of the treatment life-cycle, discounting for the fact that the information is worth less for patients who receive the treatment in the future, to determine the total value of the proposed research.

The Expected Net Benefit of Sampling (ENBS) is then defined as the difference between the population-level discounted EVSI and the cost of undertaking the study. If the ENBS is greater than 0, then the study has value to society and should be considered for funding. Within the **EVSI** package, we use continuous discounting to estimate the ENBS for appropriate incidence populations and lengths of the treatment life-cycle. Thus, the ENBS is calculated as

$$\mathrm{ENBS} = \frac{P}{d}\left(1 - e^{-dT}\right)\mathrm{EVSI} - C_{\mathrm{study}}$$

where P is the incidence population, d is the discount factor (normally, 3.5% (National Institute of Health and Care Excellence 2013)), T is the length of the treatment life-cycle and C_{study} is the cost of undertaking the study.

The ENBS can also be used to find the study design with the greatest net benefit for society. In theory, we could consider an infinite number of potential designs. For example, we could vary number of study participants, number of treatment arms, number of screening intervals, number of outcomes etc. However, within the **EVSI** package, we provide functions to automatically estimate the EVSI across sample size for a fixed study design.

Computational Challenges

In practice, it is rarely possible to find analytic solutions for VoI measures. This is because it is challenging to determine the expectation of a maximum. Additionally, the known-distribution net benefit is normally a complex function of $\boldsymbol{\theta}$ that is approximated through simulation. Thus, VoI measures are estimated through Monte Carlo (MC) simulation methods.

While the EVPI can be relatively simple to estimate using simulation, the EVPPI and EVSI are defined with nested expectations. These nested expectations create a significant computational burden, especially when coupled with realistically complex health economic models that cannot be computed instantaneously. Therefore, solutions were needed to allow for VoI calculations in practice. Recent methodological advancements have reduced this computational burden (Strong *et al.* 2014, 2015; Heath *et al.* 2016, 2017, 2018, 2019; Jalal *et al.* 2015; Jalal and Alarid-Escudero 2018; Menzies 2016), while the **BCEA** and **EVSI** packages will allow for the implementation of these methods in practice.

2.3. Example: A Novel Chemotherapy Treatment

To demonstrate VoI calculations within R, we use a health economic model developed in Heath and Baio (2018) to evaluate two chemotherapy interventions, i.e., the current standard of care, costing £110, and a novel treatment, costing £420, that reduces the number of adverse events. These two options have equal clinical effectiveness so the model focuses solely on the adverse events. The probability of adverse events for the standard of care is denoted π_0 and ρ denotes the proportional reduction in the probability of adverse events with the novel treatment. Patients without adverse events or those that have recovered have a quality of life (QoL) measure of q.

To model the health economic impact of adverse events, we assume that all patients are in one of the four mutually exclusive states, Home Care, Hospital Care, Recovery or Dead. Patients can transition between different states each day with a fixed probability of transition that depends solely on the state in which the patient currently resides. The permitted state transitions and their associated probabilities are depicted in Figure 1. This model structure is known as a Markov Model.

We assume that any patient that experiences side effects is initially treated at home. The parameters γ_1 and γ_2 denote the constant probability of requiring hospital care and dying, respectively, and λ_1 and λ_2 denote the constant probability of recovery given that an individual remains at home or enter hospital, respectively. We track all patient outcomes for 15 days after they experience the first adverse event. Recovered patients incur no further cost while patients who die have a one-time cost of terminal care. There are costs and QoL measures associated with home and hospital care. A Bayesian statistical model for these parameters written in the jags language is defined below. The data and hyperparameters required to define this model are given in Table 1 alongside their parameter name in our Bayesian model.

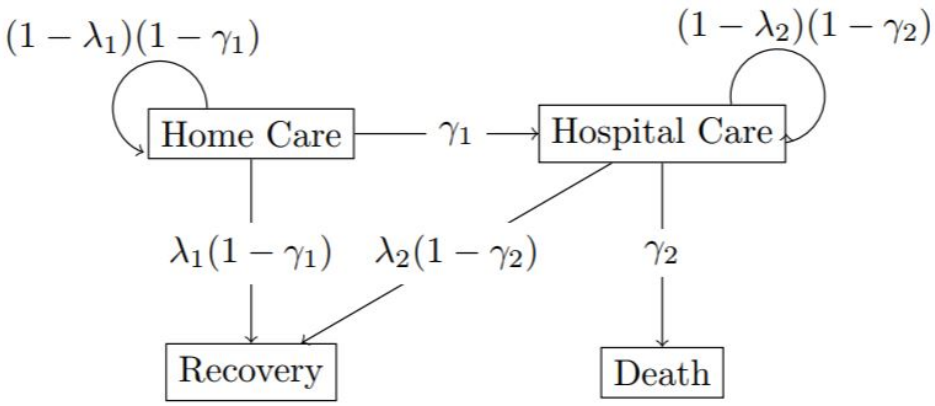

Figure 1: A four state Markov model used to model the health economic impact of adverse events from a chemotherapy treatment.

```
> model <- function(){
+   num.se ~ dbin(pi[1], num.pat)
+   pi[1] ~ dbeta(1, 1)
+
+   rho ~ dnorm(m.rho, tau.rho)
+   pi[2] <- rho * pi[1]
+
+   for (t in 1:2) {
+     SE[t] ~ dbin(pi[t], N)
+   }
+
+   num.hosp ~ dbin(gamma.hosp, num.se)
+   gamma.hosp ~ dbeta(1, 1)
+
+   num.dead ~ dbin(gamma.dead, num.se-num.hosp)
+   gamma.dead ~ dbeta(1, 4)
+
+   lambda.amb.rec.TH ~ dbeta(p1.amb.rec, p2.amb.rec)
+   lambda.hosp.rec.TH ~ dbeta(p1.hosp.rec, p2.hosp.rec)
+   lambda.amb.amb <- (1 - lambda.amb.rec.TH) * (1 - lambda.amb.hosp)
+   lambda.amb.rec <- (1 - lambda.amb.hosp) * lambda.amb.rec.TH
+   lambda.amb.hosp <- gamma.hosp / TH
+   lambda.hosp.hosp <- (1 - lambda.hosp.rec.TH) * (1 - lambda.hosp.dead)
+   lambda.hosp.rec <- (1 - lambda.hosp.dead) * lambda.hosp.rec.TH
+   lambda.hosp.dead <- gamma.dead / TH
+
+   c.amb ~ dlnorm(m.amb, tau.amb)
+   c.hosp ~ dlnorm(m.hosp, tau.hosp)
+   c.dead ~ dlnorm(m.dead, tau.dead)
+
+   e.chemo ~ dbeta(p1.chemo, p2.chemo)
```

```
+   e.amb ~ dbeta(p1.amb, p2.amb)
+   e.hosp ~ dbeta(p1.hosp, p2.hosp)
+ }
```

Model Input	Distribution	1^{st} Prior Parameter	2^{nd} Prior Parameter	Previous Data
π_0 (`pi[1]`)- Probability of adverse events	Beta	1	1	27 adverse events from 111 patients receiving standard of care
ρ (`rho`) - Reduction in adverse events with treatment	Normal	Mean: 0.65	Precision: 100	No
q (`e.chemo`) - QoL weight with no adverse events	Beta	18.23	0.372	No
Γ_1 (`gamma.hosp`) - Probability of hospitalization	Beta	1	1	17 hospitalisations from 27 adverse events
Γ_2 (`gamma.dead`) - Probability of death	Beta	1	1	1 death from 17 hospitalisations
γ_1 (`lambda.amb.hosp`) - Daily transition probability to hospital	$\frac{\Gamma_1}{15}$	-	-	-
γ_2 (`lambda.hosp.dead`) - Daily probability of death	$\frac{\Gamma_2}{15}$	-	-	-
λ_1 (`lambda.amb.rec.TH`) - Daily probability of recovery from home care	Beta	5.12	6.26	No
λ_2 (`lambda.hosp.rec.TH`) - Daily probability of recovery from hospital	Beta	3.63	6.74	No
Cost of death (`c.dead`)	LogNormal	8.33	0.13	No
Cost of home care (`c.amb`)	LogNormal	7.74	0.039	No
Cost of hospitalization (`c.hosp`)	LogNormal	8.77	0.15	No
QoL weight for home care (`e.amb`)	Beta	5.75	5.75	No
QoL weight for hospitalization (`e.hosp`)	Beta	0.87	3.47	No
Number of patients expected to receive treatment in the following year (`N`)	-	1000	-	No

Table 1: The prior specification for the parameters underlying the Chemotherapy example including the distributional assumption and its parameters. Unless specified, the parameters are specified in the order used in the jags language for Bayesian updating. We indicate whether the stated prior is combined with data.

The baseline PSA can be performed by running this Bayesian model using **R2jags** to obtain simulations from the posterior of the model parameters. In this paper, we use a PSA simulation size of 10000 estimated across three chains with a burn-in of 1000. We save all the model parameters that will be used to compute the costs and effectiveness for the two treatments in our health economic model. To run the jags model, we create a list `data` that contains all the data and hyperparameters specified in Table 1.

```
> library("R2jags")
> set.seed(1234)
> size.prior <- 10000
>
> n.chains <- 3
> n.burnin <- 1000
> n.iter <- ceiling(size.prior / n.chains) + n.burnin
>
```

```
> parameters.to.save <- c("pi", "rho", "gamma.hosp","gamma.dead", "SE",
+                         "lambda.amb.amb", "lambda.amb.hosp", "lambda.amb.rec",
+                         "lambda.hosp.hosp", "lambda.hosp.rec",
+                         "lambda.hosp.dead",
+                         "lambda.amb.rec.TH", "lambda.hosp.rec.TH",
+                         "c.amb", "c.hosp", "c.dead",
+                         "e.chemo", "e.amb", "e.hosp")
> prior.model <- jags(
+   data =  data,
+   parameters.to.save = parameters.to.save,
+   model.file = model,
+   n.chains = n.chains,
+   n.iter = n.iter,
+   n.thin = 1,
+   n.burnin = n.burnin,
+   progress.bar = "none"
+ )
```

Based on the parameter simulations from this model, we must estimate the costs and effectiveness for the two treatments under consideration. To achieve this, we calculate the average time each patient with adverse events spends in the health states of our Markov model, stored in the matrix `trace`. The function `markov.model` takes a row of the parameter simulations as inputs and then constructs a transition matrix that governs the transitions that can occur in our model. For example, patients in state 1 (Home Care) can transition to state 2 (Hospital Care) with probability `lambda.amb.hosp`, state 3 (Recovery) with probability `lambda.amb.rec` or remain in state 1 with probability `lambda.amb.amb`. Within the Bayesian model, we specify the predictive distribution of the number of patients in 1000 that would experience adverse events, with the variable name `SE`. The variable `SE` is a two-vector containing the number of adverse events for the standard of care and the novel treatment. Thus, we initially assume that `SE` patients are in the Home Care state at time 0. The `trace` matrix then calculates the number of patients in each state for each time point between 0 and 15 using matrix multiplication.

```
> markov.model <- function(SE,
+                          lambda.amb.amb, lambda.amb.hosp, lambda.amb.rec,
+                          lambda.hosp.hosp, lambda.hosp.rec, lambda.hosp.dead,
+                          TH)
+   {
+     MM.mat <- matrix(c(lambda.amb.amb, lambda.amb.hosp, lambda.amb.rec, 0,
+                        0, lambda.hosp.hosp, lambda.hosp.rec, lambda.hosp.dead,
+                        0, 0, 1, 0,
+                        0, 0, 0, 1),
+                      nrow = 4,
+                      ncol = 4,
+                      byrow = TRUE)
+     trace <- array(0, dim = c(4, TH + 1, length(SE)))
+   trace[1, 1, ] <- SE
```

```
+
+   for(i in 2:(TH + 1)){
+     trace[, i, 1] <- trace[, i - 1, 1] %*% MM.mat
+     trace[, i, 2] <- trace[, i - 1, 2] %*% MM.mat
+   }
+ return(trace)
+ }
```

Once we compute the number of patients in each state at each time point, the costs and effectiveness for the two treatments is calculated based on the costs or QoL measure for each health state. The costs or QoL measure is multiplied by the state occupancy and summed across time to give the cost and effectiveness for each treatment, respectively. We assume that patients who do not experience adverse events have a QoL measure of q (`e.chemo`) for 15 days. Finally, we compute a one-off cost of death for all patients who have died at the end of 15 days. The following functions `costs` and `effects` compute the costs and effectiveness respectively from the Bayesian model output.

```
> costs <- function(SE,
+                   lambda.amb.amb, lambda.amb.hosp, lambda.amb.rec,
+                   lambda.hosp.hosp, lambda.hosp.rec, lambda.hosp.dead,
+                   c.amb, c.hosp, c.dead,
+                   N=n.pred, TH=time.horz){
+     trace <- markov.model(SE,
+                           lambda.amb.amb, lambda.amb.hosp, lambda.amb.rec,
+                           lambda.hosp.hosp, lambda.hosp.rec, lambda.hosp.dead,
+                           TH)
+
+   c.states <- c(c.amb, c.hosp, 0, 0)
+
+   c.se <- array(NA, dim = 2)
+   c.se[1] <- (sum(c.states %*% trace[,,1]) + c.dead * trace[4, TH + 1, 1])/
+     (N * (TH + 1))
+   c.se[2] <- (sum(c.states %*% trace[,,2]) + c.dead * trace[4, TH + 1, 2])/
+     (N * (TH + 1))
+
+   # Treatment
+   c.drug <- c(110, 420)
+   cost <- c(c.drug + c.se)
+   return(cost)
+ }
>
> effects <- function(SE,
+                     lambda.amb.amb, lambda.amb.hosp, lambda.amb.rec,
+                     lambda.hosp.hosp, lambda.hosp.rec, lambda.hosp.dead,
+                     e.chemo, e.amb, e.hosp,
+                     N = n.pred ,TH = time.horz)
+   {
```

```
+   trace <- markov.model(SE,
+                         lambda.amb.amb, lambda.amb.hosp, lambda.amb.rec,
+                         lambda.hosp.hosp, lambda.hosp.rec, lambda.hosp.dead,
+                         TH)
+
+   e.states <- c(e.amb, e.hosp, e.chemo, 0)
+
+   q.se <- array(NA, dim = 2)
+   q.se[1] <- sum(e.states %*% trace[,,1])
+   q.se[2] <- sum(e.states %*% trace[,,2])
+
+   q.chemo <- (N - SE) * e.chemo * (TH + 1)
+   effs<-c(q.se + q.chemo)/
+     (N * (TH + 1))
+   return(effs)
+ }
```

The structure of these functions is required to estimate the EVSI within the **EVSI** package. Firstly, the **EVSI** package requires separate functions to compute the costs and effectiveness from the health economic model. This allows the **EVSI** package to estimate the EVSI across alternative willingness-to-pay thresholds k. Secondly, the arguments of these functions must have the same names as the variables stated in the Bayesian model. This is because the costs and effectiveness for the different treatments must be re-estimated conditional on the posterior distribution for the parameters $p(\boldsymbol{\theta} \mid \boldsymbol{X})$ to compute the EVSI. Thus, the **EVSI** package must match the function arguments and the variable names in the Bayesian model to recompute the costs and effectiveness. Finally, for each row of the Bayesian model output, these functions must output a vector that gives the costs or effectiveness across the alternative treatments, i.e., the objects `cost` and `effs` in the code above are vectors of length 2.

Using the PSA simulations stored in the `jags` object `prior.model` and the functions defined above, we can run the baseline cost-effectiveness analysis for the Chemotherapy example. The **BCEA** package can be used to generate standardized graphics to summarise this analysis. Figure 2 displays the cost-effectiveness plane to explore the baseline PSA results. Each point on this plane represents the incremental costs and effectiveness, i.e. the difference between the costs/effectiveness for the standard-of-care and the novel chemotherapy, estimated for a single row of the Bayesian model output. In general, the novel chemotherapy treatment is more costly and more effective than the standard of care. The shaded area in Figure 2 represent the simulations where the novel chemotherapy is considered cost-effective for a willingness-to-pay $k = 30,000$. The majority of the points fall outside of this shaded area, representing that the standard of care is cost-effective for $k = 30,000$.

3. Calculating the Value of Information

This section presents the algorithms used to estimate these three key VoI measures within the **BCEA** and **EVSI** packages. We also present the syntax required to produce these estimates within the two packages of interest.

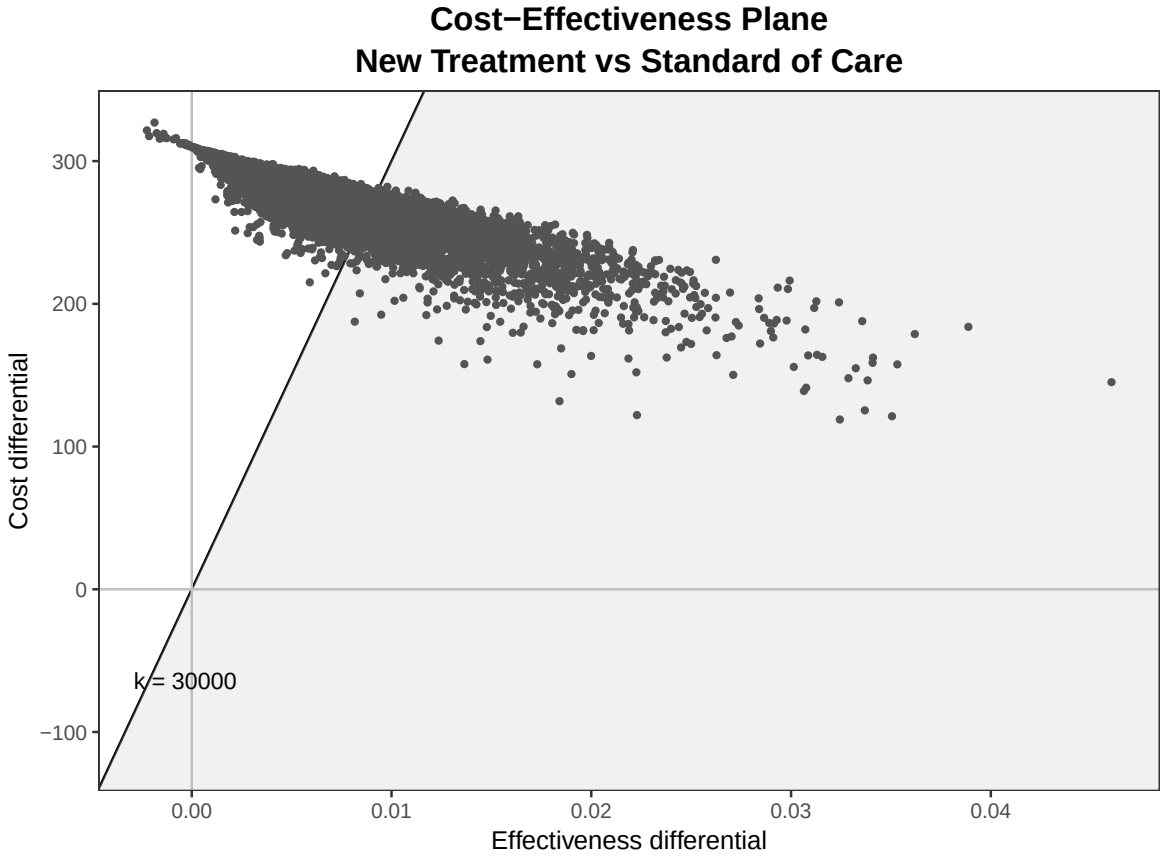

Figure 2: Baseline cost-effectiveness analysis for the Chemotherapy example.

3.1. Calculating the EVPI

The EVPI can be estimated by MC simulation from the baseline PSA simulations of the known-distribution net benefit values. From the definition of the EVPI in (2), the MC estimator of the EVPI is,

$$\widehat{\text{EVPI}} = \frac{1}{S}\sum_{s=1}^{S}\max_t \text{NB}_t(\boldsymbol{\theta}_s) - \max_t \frac{1}{S}\sum_{s=1}^{S}\text{NB}_t(\boldsymbol{\theta}_s).$$

As our baseline cost-effectiveness analysis simulates values of the known-distribution net benefit $\text{NB}_t(\boldsymbol{\theta}_s)$, the EVPI can be estimated as part of a standard PSA procedure. Thus, it is calculated as part of the standard `bcea` procedure. Within the **BCEA** package, the `bcea` function organises the output of the health economic model so it can be used within the standardised graphics and outputs provided by the package. Within this, the EVPI across different willingness-to-pay value is stored in the `bcea` object as `evi`. The following code extracts the EVPI for $k = 30,000$.

```
> library("BCEA")
> mod <- bcea(e, c, ref = 2,
```

```
+             interventions = c("Standard of Care", "New Treatment"))
>
> mod$evi[which(mod$k == 30000)]

[1] 43.74277
```

3.2. Calculating the EVPPI

Calculating the EVPPI based on naive MC simulation, i.e. where all expectations in (4) are replaced with MC integrals, is highly computationally intensive. This is because the inner conditional expectation $\mu_t^{\boldsymbol{\phi}} = \mathrm{E}_{\boldsymbol{\psi}|\boldsymbol{\phi}}[\mathrm{NB}_t(\boldsymbol{\theta})]$ in the first term in equation (4) would need to be estimated by simulation separately for each value of $\boldsymbol{\phi}$. This gives a nested simulation procedure where the health economic model must be re-run for each nested simulation.

Thus, Strong *et al.* (2014) developed a method to estimate $\mu_t^{\boldsymbol{\phi}}$ using regression methods and based directly on the PSA samples. They highlight that the net benefit can be decomposed into

$$\mathrm{NB}_t(\boldsymbol{\theta}_s) = \mu_t^{\boldsymbol{\phi}_s} + \varepsilon_s,$$

with $\varepsilon_s \sim \mathrm{Normal}(0, \sigma_\varepsilon^2)$. As $\mu_t^{\boldsymbol{\phi}}$ is a function of $\boldsymbol{\phi}$ only, we can estimate $\mu_t^{\boldsymbol{\phi}}$ using regression methods to estimate the functional relationship between the known-distribution net benefit and $\boldsymbol{\phi}$.

$$\mathrm{NB}_t(\boldsymbol{\theta}_s) = f(\boldsymbol{\phi}) + \varepsilon_s,$$

If $f(\cdot)$ adequately estimates the relationship between the known-distribution net benefit and $\boldsymbol{\phi}$, the $\mu_t^{\boldsymbol{\phi}}$ will be estimated by calculating the fitted values the EVPPI will be estimated correctly. As we have no knowledge about the functional form of the relationship between the known-distribution net benefit and $\boldsymbol{\phi}$, flexible regression methods should be used. These methods assume that the conditional expectation of the known-distribution net benefit is a smooth function of the important parameters $\boldsymbol{\phi}$ but make no other assumptions.

Strong *et al.* (2014) suggest two alternative non-parametric regression methods: Generalised Additive Models (GAMs) (Hastie and Tibshirani 1990) and Gaussian Processes (GPs) (Rasmussen and Williams 2006) which are both implemented in **BCEA**. The GP implementation is based on an efficient calculation method developed in Heath *et al.* (2016) while the GAM implementation is based on the **mgcv** package (Wood, Pya, Kneib, Hornik, Lonergan, Nilsson, Scheipl, and Ripley 2016). GAMs are fast and accurate when $\boldsymbol{\phi}$ is relatively small (fewer than 4) (Heath *et al.* 2017), in which case they are the default method in **BCEA**.

To explore the syntax for the `evppi` function, we calculate the EVPPI for the probability of experiencing adverse events for the two treatments, i.e. $\boldsymbol{\phi} = (\pi_1, \pi_2)$. In general, the key inputs for the `evppi` functions are as follows,

```
evppi(parameter, input, he)
```

where `parameter` is the column name or number of the parameters of interest, `input` is a matrix containing the PSA simulations for the model parameters and `he` is a `bcea` object. A `bcea` object is created based on two matrices `e` and `c` which contain the PSA simulations for the effectiveness and costs respectively for the two treatments. Based on these matrices, the code to compute the EVPPI for $\boldsymbol{\phi} = (\pi_1, \pi_2)$ is as follows:

```
> mod <- bcea(e, c, ref = 2,
+             interventions = c("Standard of Care", "New Treatment"))
>
> evppi.min <- evppi(c("pi[1]", "pi[2]"),
+                    prior.model$BUGSoutput$sims.matrix, mod)
```

The EVPPI for a specific willingness-to-pay can then be extracted using the following command:

```
> evppi.min$evppi[which(evppi.min$k == 30000)]

[1] 18.75631
```

The syntax for the `evppi` function is the same in situations where $\boldsymbol{\phi}$ contains more thans 4 elements. For example, the following code estimates the EVPPI for all effectiveness parameters, this includes the transition probabilities for patients who experience adverse events, i.e. $\boldsymbol{\phi} = (\pi_1, \pi_2, \gamma_1, \gamma_2, \lambda_1, \lambda_2)$.

```
> evppi.full <- evppi(c("gamma.hosp", "gamma.dead", "lambda.hosp.rec.TH",
+                       "lambda.amb.rec.TH", "pi[1]", "pi[2]"),
+                     prior.model$BUGSoutput$sims.matrix, mod)
```

The EVPPI for a willingness-to-pay of 30,000 can then be printed as follows:

```
> evppi.full$evppi[which(evppi.full$k == 30000)]

[1] 34.67565
```

Notice that the EVPPI for these 6 parameters is larger than the EVPPI for the probability of adverse events alone.

The **BCEA** package contains a function that performs residual checking to check the regression fit. If the regression fit is accurate, then the EVPPI is well-estimated. We provide plots of the residuals against fitted values and a qq-plot. The syntax required to achieve this residual checking is

```
diag.evppi(evppi, he, diag = c("residuals","qqplot"))
```

where `evppi` is the output from the `evppi` function, `he` is a `bcea` object and `diag` determines whether a plot of fitted values against residuals or a qq-plot to explore the normality of residuals is plotted.

3.3. Calculating the EVSI

The **EVSI** package calculates the EVSI using a method developed in Heath *et al.* (2018) and extended in Heath *et al.* (2019). Broadly speaking, this method combines the simulations μ_t^{ϕ}, used to estimate the EVPPI, and a nested MC sampling method to estimate the EVSI. Provided the sampling distribution of the data is only directly dependent on $\boldsymbol{\phi}$, the EVSI

can be estimated by re-scaling simulations of μ_t^{ϕ} to reduce their *variance*. Intuitively, the variance is reduced as the larger the sample size of $\boldsymbol{X}$, the more values the potential data could take. This implies that there is greater variance in the distribution of the potential means. As perfect information about $\boldsymbol{\phi}$ is equivalent to a dataset of infinite size, the variance of μ_t^{ϕ} should be reduced to estimate the EVSI.

The exact variance reduction factor is estimated using specific nested MC sampling that estimates the variance of the posterior distribution of the known-distribution net benefit based on Q alternative future samples, where Q is usually between 30 and 50 (Heath and Baio 2018). The approximation for this variance reduction factor improves as Q increases, provided sufficient simulations are taken from the posterior distribution of the known-distribution net benefit to adequately capture its uncertainty (Heath *et al.* 2019). Within the `EVSI` package, the posterior variance is estimated in the `mm.post.var` function.

This EVSI estimation method can compute the EVSI across different proposed sample sizes for the future trial (Heath *et al.* 2019). To achieve this, the variance of the posterior distribution of the known-distribution net benefit must be estimated based on Q future samples with a range of sample sizes. Once these posterior distributions have been estimated, the variance reduction factor required to estimate the EVSI for different sample sizes is calculated using Bayesian regression. Provided the future data sets have been generated correctly, the `evsi.calc` function in the **EVSI** package will fit the required Bayesian regression and estimate the EVSI. This method also allows us to estimate the uncertainty in our EVSI estimates, which is included in the `evsi.calc` function and can be displayed graphically.

Sampling from the prior-predictive distribution

The Q future datasets, which we denote $\boldsymbol{X}_q$, $q = 1, \ldots, Q$, should be generated using an algorithm developed in Heath *et al.* (2018). Specifically, the user must extract the quantiles of the PSA distributions for each element of $\boldsymbol{\phi}$. These quantiles should be combined into a matrix with each row of this matrix denoted $\boldsymbol{\phi}_q$. The future datasets should then be generated from the sampling distribution of the data $p(\boldsymbol{X} \mid \boldsymbol{\phi}_q)$ for $q = 1, \ldots, Q$. The **EVSI** package provides a function to create this "quantile" matrix so the data can be generated correctly. If you wish to estimate the EVSI across sample size, this function will also specify which future sample sizes should be considered.

Specifically, the `gen.quantiles` function is based on the following arguments:

1. The column names/number of the parameters of interest, i.e. the parameters in $\boldsymbol{\phi}$.
2. A matrix containing the PSA simulations for the parameters.
3. The number of future samples required Q.
4. The minimum and maximum sample sizes for which we would like to compute the EVSI. If this argument is left black then we assume that the user wishes to compute the EVSI for a single sample size.

For example, we will compute the EVSI for a trial that investigates the number of patients who experience adverse events with the standard of care and the novel chemotherapy. In this case, the sampling distribution of the data is two independant binomial distributions conditional on π_1 and π_2. We will estimate the EVSI for sample sizes between 5 and 1000.

Thus, the following code generates the "quantile" matrix that can be used to generate the future data.

```
> library("EVSI")
> Q <- 50
> quants <- gen.quantiles(c("pi[1]","pi[2]"),
+                         prior.model$BUGSoutput$sims.matrix,
+                         Q = Q, N = c(5, 1000))
```

Once this "quantile" matrix has been generated, the future data must be stored in a specific format to be used as input to the `mm.post.var` function. Specifically, we must generate a list of length Q where each element is a list of the data in a format suitable for use within **R2jags** or **R2OpenBUGS**. For our example, the data should be generated as follows:

```
> data.list.full <- list()
> for(i in 1:Q){
+   X.SE1 <- rbinom(1, quants[i,"N"], quants[i,"pi[1]"])
+   X.SE2 <- rbinom(1, quants[i,"N"], quants[i,"pi[2]"])
+   data.n <- list(X.SE1 = X.SE1, X.SE2 = X.SE2)
+   data.list.full[[i]] <- data.n
+ }
> data.list.full[[1]]


$X.SE1
[1] 1

$X.SE2
[1] 0
```

Note that each dataset is generated with a different sample size that is saved in the vector `quants[,"N"]`.

Calculating the Posterior Variance with Nested Sampling

Within the **EVSI** package, the EVSI is computed based on a Bayesian model that indicates the relationship between he parameters and the future data. By definition, this defines the sampling distribution for the data and through that it is possible to simulate from the prior-predictive distribution of $\boldsymbol{X}$. Thus, in certain situations, the **EVSI** package contains functions to generate the future datasets directly from this prior-predictive distribution and the `gen.quantiles` function is not required.

To compute the EVSI and generate the future data, the **EVSI** package requires a Bayesian model written in the jags or OpenBUGS languages. This model will be used to compute the posterior for the model parameters conditional on the future data and can also potentially specify the prior predictive distribution of the data. Thus, the following code defines a jags model for our proposed trial investigating the number of patients who experience adverage events with our two treatment options.

```
> model.data.min <- function(){
+     for(i in 1:n){
+   X.SE1[i] ~ dbin(pi[1], 1)
+   X.SE2[i] ~ dbin(pi[2], 1)
+     }
+
+   num.se ~ dbin(pi[1], num.pat)
+   pi[1] ~ dbeta(1, 1)
+
+   rho ~ dnorm(m.rho, tau.rho)
+   pi[2] <- rho * pi[1]
+
+   for (t in 1:2) {
+     SE[t] ~ dbin(pi[t], N)
+   }
+
+   num.hosp ~ dbin(gamma.hosp, num.se)
+   gamma.hosp ~ dbeta(1, 1)
+
+   num.dead ~ dbin(gamma.dead, num.se-num.hosp)
+   gamma.dead ~ dbeta(1, 4)
+
+   lambda.amb.rec.TH ~ dbeta(p1.amb.rec, p2.amb.rec)
+   lambda.hosp.rec.TH ~ dbeta(p1.hosp.rec, p2.hosp.rec)
+   lambda.amb.amb <-(1-lambda.amb.rec.TH)*(1-lambda.amb.hosp)
+   lambda.amb.rec<-(1-lambda.amb.hosp)*lambda.amb.rec.TH
+   lambda.amb.hosp<-gamma.hosp/TH
+   lambda.hosp.hosp<-(1-lambda.hosp.rec.TH)*(1-lambda.hosp.dead)
+   lambda.hosp.rec<-(1-lambda.hosp.dead)*lambda.hosp.rec.TH
+   lambda.hosp.dead<-gamma.dead/TH
+
+   c.amb ~ dlnorm(m.amb, tau.amb)
+   c.hosp ~ dlnorm(m.hosp, tau.hosp)
+   c.dead ~ dlnorm(m.dead, tau.dead)
+
+   e.chemo ~ dbeta(p1.chemo,p2.chemo)
+   e.amb ~ dbeta(p1.amb,p2.amb)
+   e.hosp ~ dbeta(p1.hosp,p2.hosp)
+ }
>
> R2OpenBUGS::write.model(model.data.min,"~/modelFile.txt")
```

This Bayesian model uses a non-standard specification for the future data. Each data point follows a Bernoulli distribution conditional on π_0 or π_1, rather than a binomial distribution. To generate Q suitable datasets from the prior-predictive distribution within the **EVSI** package, the data for each patient must be generated separately. This means that aggregate distributions, such as the binomial distribution, cannot be used.

This Bayesian model specifying the parameter distributions and sampling distribution for the data can now be used to estimate the posterior variance across multiple potential datasets using the `mm.post.var` function.

```
> mm.post.var(model.stats, data, data.stats = NULL,
+   N.name = NULL, N.size = NULL,
+   effects = NULL, costs = NULL,
+   he = NULL, evi = NULL, parameters = NULL,
+   Q = 30, update = c("bugs", "jags"),
+   n.burnin = 1000, n.thin = 1, n.iter = 5000)
```

This function takes the following arguments:

- `model.stats`: The file-path for a text file containing the model file. This can be written directly from the `model.data.min` function with the `write.model` function in the **R2OpenBUGS** package.
- `data`: This can be a character vector that contains the variable names for the future data in the Bayesian model. Alternatively, this can be a list as demonstrated in §3.3.1.
- `data.stats`: A list of the additional data that is required to run the Bayesian model, i.e. data used to define the priors or the hyperparameters.
- `N.name`: A character specifying the variable name of the sample size in the Bayesian model. If `NULL` then the EVSI is not estimated across sample size and the sample size of the future data must be specified either in the Bayesian model or the `data.stats` list.
- `N.size`: A numeric vector. If a single value is passed then the EVSI is computed for a single value. If a double is passed then the EVSI is estimated for the sample size between the two values. If a vector of length Q is passed then this should be the sample sizes for which the future data was generated (if generated externally).
- `effects`: A function that estimates the effectiveness measures based on the parameter simulations from the Bayesian model, see §2.3. If `NULL`, then the function searches for a variable named `effects` within the Bayesian model.
- `costs`: A function that estimates the cost measures based on the parameter simulations from the Bayesian model, see §2.3. If `NULL`, then the function searches for a variable named `costs` within the Bayesian model.
- `he`: A `bcea` object. If `NULL`, then the default `bcea` function is used internally to create `he`.
- `evi`: A `evppi` object. If `NULL`, then the default `evppi` function is used internally to create `evi`.
- `parameters`: If `evi` is `NULL`, then this argument must be provided as a character vector specifying the variable names for the parameters of interest ϕ.

- `Q`: A single numeric specifying the number of posterior updates used to estimate the EVSI.
- `update`: Either `jags` or `bugs` to specify whether Bayesian updating should be achieved with jags or OpenBUGS, respectively.
- `n.burnin`: A single numeric specifying the number of burn-in iterations used in the Bayesian updating procedure.
- `n.thin`: A single numeric specifying the thinning interval used in the Bayesian updating procedure.
- `n.iter`: A single numeric specifying the total number of simulations that should be saved in the Bayesian updating procedure.

Note that, based on the definition above the total computational cost of the `mm.post.var` function is proportional to `Q * (n.burnin + n.thin * n.iter)`.

For our example, the following code estimates the posterior variance across multiple potential datasets.

```
> EVSI.var.min <- mm.post.var("~/modelFile.txt", c("X.SE1", "X.SE2"),
+                          N.name = "n", N.size = 150,
+                    effects = effects, costs = costs,
+                    he = mod, evi = evppi.min,
+                    Q = 50, data.stats = data,
+                    update = "jags", n.iter = 3000)
```

Once this computationally intensive procedure has been completed, the EVSI is calculated using the `evsi.calc` function in the **EVSI** package. The advantage of decoupling these two functions is that the EVSI can be recomputed for different willingness-to-pay thresholds, using the argument `wtp`, without recomputing the variance. By default, the `evsi.calc` function estimates the EVSI for all willingness-to-pay thresholds contained in `he$k` from the initial `bcea` procedure. If the variance has been estimated across sample size, then the argument `N` can be used to estimate the EVSI across alternative sample sizes.

```
> EVSI.min <- evsi.calc(EVSI.var.min)
```

Calculating the EVSI with secondary outcomes

We now consider using the **EVSI** package for a two-arm randomized control trial whose primary outcome is the number of adverse events. As a secondary set of measures, the study monitors the treatment pathway for patients who experience adverse events. Thus, the trial directly informs six model parameters $\boldsymbol{\phi} = (\pi_0, \pi_1, \gamma_1, \gamma_2, \lambda_1, \lambda_2)$ by collecting six outcomes. The sampling distributions for π_0 and π_1 are binomial distributions, similar to the previous study;

$$X_{AE_0} \sim Bin(n, \pi_0) \text{ and } X_{AE_1} \sim Bin(n, \rho\pi_0).$$

The number of patients treated in hospital and the number of patients who die are modelled as

$$X_{Hosp} \sim Bin(X_{AE_0} + X_{AE_1}, \gamma_1) \text{ and } X_{Death} \sim Bin(X_{Hosp}, \gamma_2).$$

Finally, recovery time for patients who experience adverse events but recover is modelled with an exponential distribution conditional on the transition probabilities λ_1 and λ_2,

$$T_{HC}^{i} \sim Exponential(\eta_1)$$

with $\eta_1 = -\log(\lambda_1)$ and $i = 1, \ldots, X_{AE_0} + X_{AE_1} - X_{Hosp}$. The recovery time for every patient who recovers in hospital is modelled as

$$T_{H}^{j} \sim Exponential(\eta_2)$$

with $\eta_2 = -\log(\lambda_2)$ and $j = 1, \ldots, X_{Hosp} - X_{Death}$. The Bayesian model for this augmented study is specified below.

```
> model.data.full<-function(){
+   X.SE1 ~ dbin(pi[1], n)
+   X.SE2 ~ dbin(pi[2], n)
+   X.N.hosp ~ dbinom(gamma.hosp, X.SE1+X.SE2)
+   X.N.dead ~ dbin(gamma.dead, X.N.hosp)
+
+   recover.amb <- -log(1-lambda.amb.rec.TH)
+   recover.hosp <- -log(1-lambda.hosp.rec.TH)
+
+   for(i in 1:N.amb){
+     T.rec.amb[i] ~ dexp(recover.amb)
+     }
+
+   for(i in 1:N.hosp){
+     T.rec.hosp[i] ~ dexp(recover.hosp)
+     }
+
+   num.se ~ dbin(pi[1], num.pat)
+   pi[1] ~ dbeta(1, 1)
+
+   rho ~ dnorm(m.rho, tau.rho)
+   pi[2] <- rho * pi[1]
+
+   for (t in 1:2) {
+     SE[t] ~ dbin(pi[t], N)
+   }
+
+   num.hosp ~ dbin(gamma.hosp, num.se)
+   gamma.hosp ~ dbeta(1, 1)
+
+   num.dead ~ dbin(gamma.dead, num.se-num.hosp)
+   gamma.dead ~ dbeta(1, 4)
+
+   lambda.amb.rec.TH ~ dbeta(p1.amb.rec, p2.amb.rec)
+   lambda.hosp.rec.TH ~ dbeta(p1.hosp.rec, p2.hosp.rec)
```

```
+   lambda.amb.amb <-(1-lambda.amb.rec.TH)*(1-lambda.amb.hosp)
+   lambda.amb.rec<-(1-lambda.amb.hosp)*lambda.amb.rec.TH
+   lambda.amb.hosp<-gamma.hosp/TH
+   lambda.hosp.hosp<-(1-lambda.hosp.rec.TH)*(1-lambda.hosp.dead)
+   lambda.hosp.rec<-(1-lambda.hosp.dead)*lambda.hosp.rec.TH
+   lambda.hosp.dead<-gamma.dead/TH
+
+   c.amb ~ dlnorm(m.amb, tau.amb)
+   c.hosp ~ dlnorm(m.hosp, tau.hosp)
+   c.dead ~ dlnorm(m.dead, tau.dead)
+
+   e.chemo ~ dbeta(p1.chemo,p2.chemo)
+   e.amb ~ dbeta(p1.amb,p2.amb)
+   e.hosp ~ dbeta(p1.hosp,p2.hosp)
+ }
> R2OpenBUGS::write.model(model.data.full,"~/modelFilefull.txt")
```

In this setting, the `mm.post.var` cannot generate the data internally as the amount of data collected is dependent on other outcomes in the study[1]. Thus, we must use the `gen.quantiles` function to generate the data from the sampling distributions specified above. As we are estimating the EVSI across different sample sizes for the proposed study, we use the `N` argument in the `gen.quantiles` function.

```
> Q <- 50
> quants <- gen.quantiles(c("pi[1]","pi[2]",
+                           "gamma.hosp","gamma.dead",
+                           "lambda.amb.rec.TH", "lambda.hosp.rec.TH"),
+                         prior.model$BUGSoutput$sims.matrix, Q = Q,
+                         N = c(5, 1000))
>
> data.list.full <- list()
> for(i in 1:Q){
+   X.SE1 <- rbinom(1, quants[i,"N"], quants[i,"pi[1]"])
+   X.SE2 <- rbinom(1, quants[i,"N"], quants[i,"pi[2]"])
+
+   X.N.hosp <- rbinom(1, sum(X.SE1,X.SE2), quants[i,"gamma.hosp"])
+   X.N.dead <- rbinom(1, X.N.hosp, quants[i,"gamma.dead"])
+
+   N.amb <- sum(X.SE1,X.SE2) - X.N.hosp
+   recover.amb <- -log(1 - quants[i,"lambda.amb.rec.TH"])
+   T.rec.amb <- rexp(N.amb, recover.amb)
+   N.hosp <- X.N.hosp - X.N.dead
+   recover.hosp <- -log(1 - quants[i,"lambda.hosp.rec.TH"])
+   T.rec.hosp <- rexp(N.hosp, recover.hosp)
+
```

[1] As we are not generating the future data internally, we can use the binomial distribution to specify the sampling distribution for the data.

```
+   data.n <- list(X.SE1 = X.SE1, X.SE2 = X.SE2,
+                  X.N.hosp = X.N.hosp, X.N.dead = X.N.dead,
+                  N.amb = N.amb, T.rec.amb = T.rec.amb,
+                  N.hosp = N.hosp, T.rec.hosp = T.rec.hosp)
+
+   data.list.full[[i]] <- data.n
+ }
```

This example generates the future datasets with different sample sizes, again specified in the vector `quants[,"N"]`. As the future datasets are generated with sample size `quants[,"N"]`, this is passed directly to the `mm.post.var` function as the `N.size` vector. Compared to this previous example, this study informs a greater number of parameters and therefore the `evppi` object must be changed to `evppi.full`, calculated in §3.2.

```
> EVSI.var.full <- mm.post.var("~/modelFilefull.txt",data.list.full,
+                              "n",quants[,"N"],
+                              effects = effects, costs = costs,
+                              he = mod, evi = evppi.full,
+                              Q = 50, data.stats = data,
+                              update = "jags", n.iter = 200, n.burnin = 3000)
>
> EVSI.full <- evsi.calc(EVSI.var.full)
```

4. Visualising a Value of Information Analysis

VoI measures depend on the specified willingness-to-pay threshold k. This is because the value of the treatments are calculated using the net monetary benefit, which depends directly on k. To perform sensitivity analysis to this threshold, **BCEA** performs all analysis across a range of k values. By default the `bcea` function calculates the EVPI on a grid of 501 values between 0 and 50 000. To present these results coherently, the EVPI is plotted across the different values for the willingness-to-pay, as in Figure 3, using the following code:

```
> evi.plot(mod)
```

In general, graphical displays of VoI measures across willingness-to-pay exhibit break-points, seen at around 35600 in Figure 3. This is the willingness-to-pay threshold at which the optimal treatment switches and the uncertainty in the decision between the two treatments is maximised. In our example, the novel chemotherapy is more expensive and more effective than the standard-of-care. Thus, there is a threshold where the payer is then "willing-to-pay" for the additional level of effectiveness. At this point, the optimal decision switches from the standard of care to the novel treatment, creating the change point seen in Figure 3.

The same behaviour can be seen in Figure 4, which displays the EVPPI for the probability of adverse events in the top figure and for the six parameter subset considered in §3.2 in the bottom figure. To calculate the EVPPI across willingness-to-pay, we calculate two regression curves for each treatment option, one for costs and one for effectiveness. This allows us to compute the EVPPI across willingness-to-pay cheaply as we do not fit an additional regression curve for each value of k.

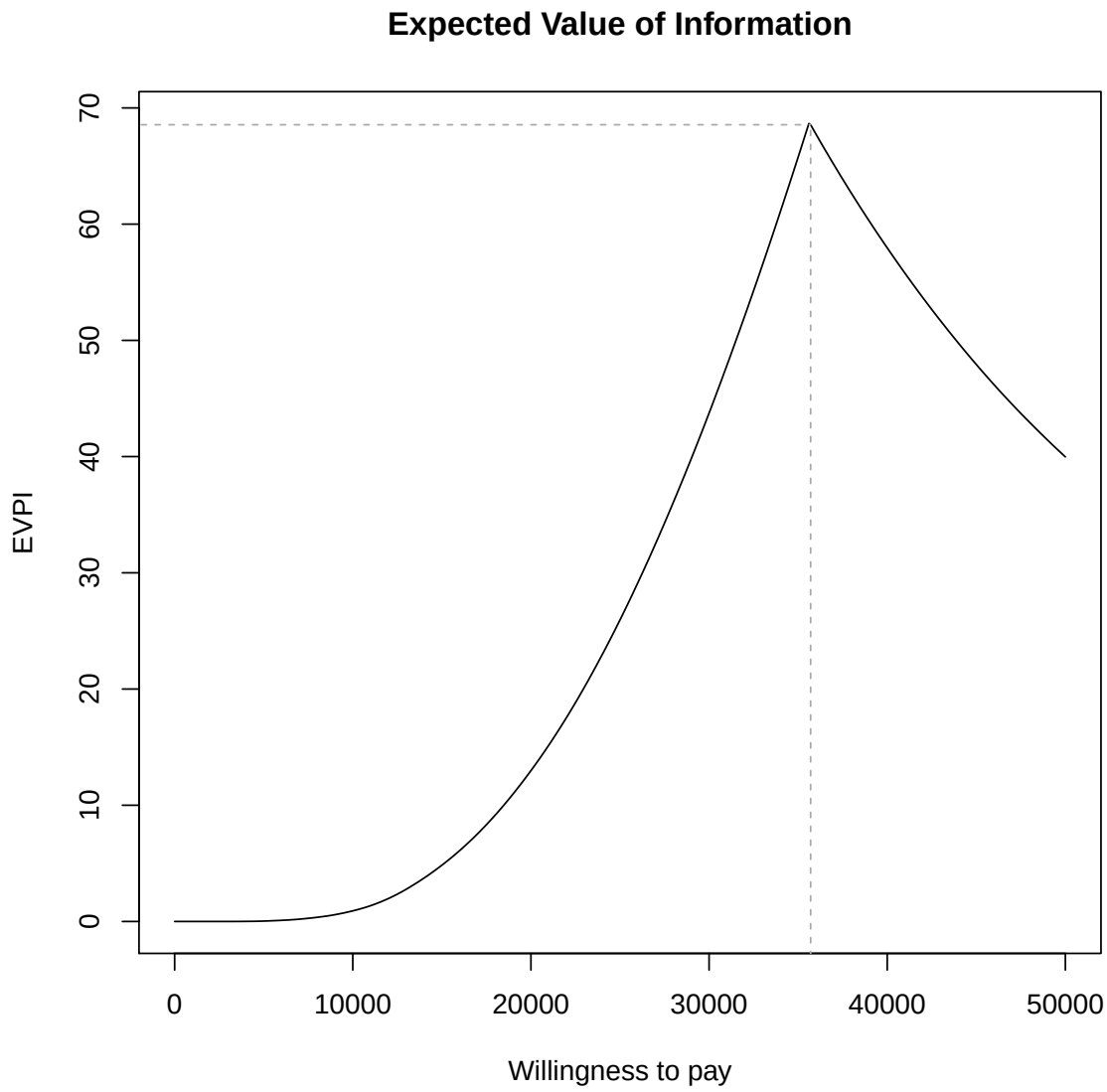

Figure 3: The plot of the EVPI against willingness-to-pay for the Chemotherapy example.

Figure 4 demonstrates that the EVPPI for the larger parameter subset is larger. At 20,000, the lower end of standard willingness-to-pay values National Institute of Health and Care Excellence (2013), investigating the probability of adverse events for the two treatments would have limited value but by adding the secondary outcomes, we could have a valuable trial.

4.1. Visualisations for the EVSI

Visualisations for the EVSI and the Expected Net Benefit of Sampling (ENBS) have a large number of variants including the willingness-to-pay, the sample size of the proposed trial, the incidence population, the time horizon and the cost of the trial. Thus, a suite of graphics

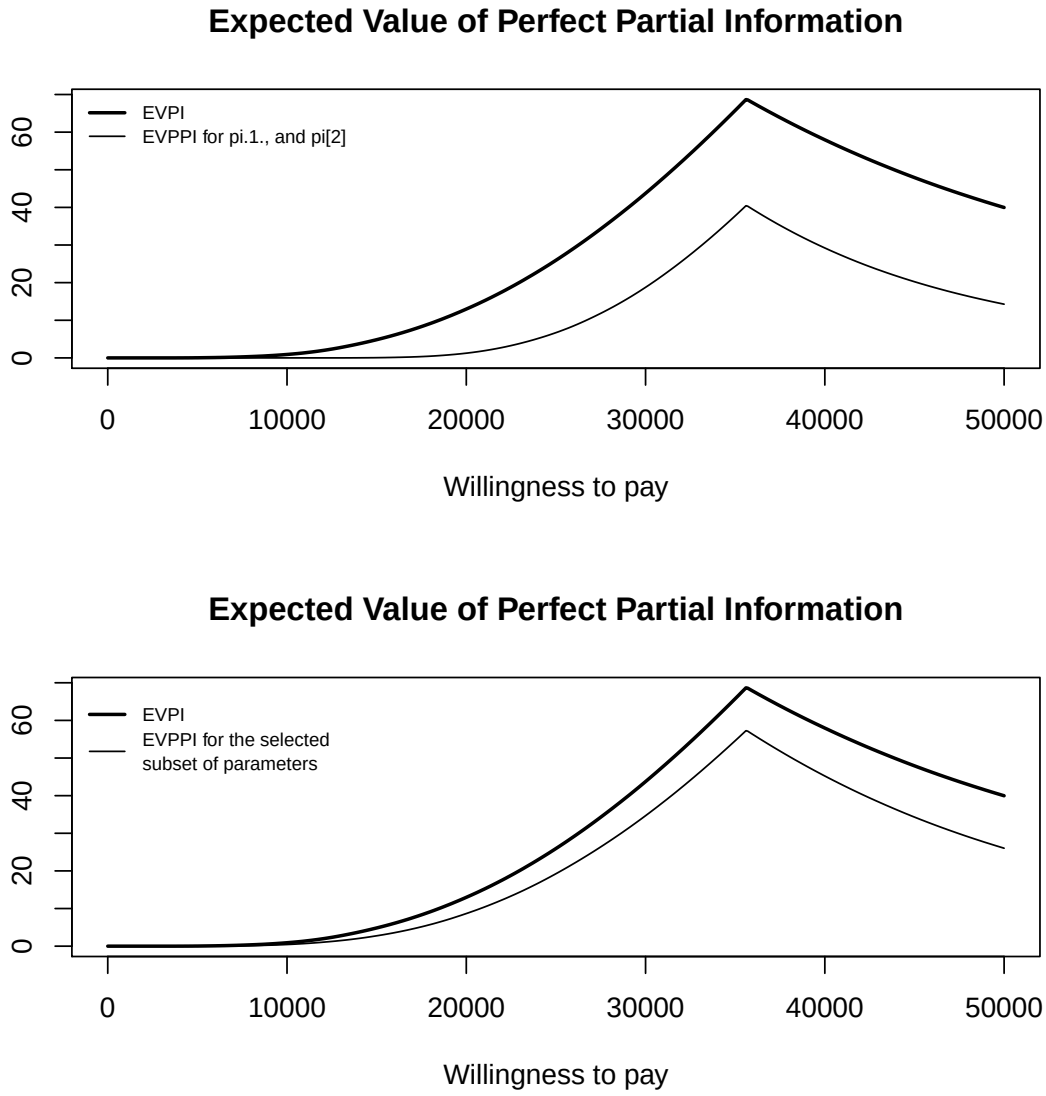

Figure 4: The EVPPI plotted against willingness-to-pay for the two subsets of parameters of interest considered in the paper for the Chemotherapy example.

has been included in the **EVSI** package to explore different aspects of the EVSI and ENBS analysis. These graphics have been incorporated into a **shiny** application (Chang *et al.* 2017) that can be launched directly from R with an `evsi` object from the `evsi.calc` function as the single argument.

```
> launch.App(EVSI.full)
```

This web interface allows researchers with no knowledge of R to explore the graphics presented below and is also available at https://egon.stats.ucl.ac.uk/projects/EVSI/.

In a similar manner to the EVPI and EVPPI, the `plot` command for an `evsi` object displays the EVSI across willingness-to-pay (Figure 5).

```
> plot(EVSI.min)
> plot(EVSI.full)
```

This compares the relative sizes of the EVSI, EVPPI and EVPI and demonstrates whether the sampling strategy efficiently updates information about the model parameters. Figure 5 (bottom) displays this graphic when the EVSI has been computed across different sample sizes. By presenting all the sample sizes, a user can ascertain how quickly the EVSI reaches its maximum. However, as this graphic can be difficult to read, we allow the sample size to be changed dynamically in the **shiny** web application so the researcher can efficiently explore the different possible sample sizes for the potential future study.

A `summary` function for `evsi` objects is also included to quickly summarise the key VoI results for a fixed willingness-to-pay and sample size. If the VoI results have not been computed for the given willingness-to-pay or sample size, then the closest available values are chosen with a warning.

```
> summary(EVSI.min, wtp = 30000)


Value of Information Summary

For willingness to pay parameter k = 30000

For sample size of proposed trial N = 150

EVPI: 43.7427726270863
EVPPI: 18.756314908665
EVSI: 9.24104591938057

> summary(EVSI.full, wtp = 30000, N = 246)


Value of Information Summary

For willingness to pay parameter k = 30000

For sample size of proposed trial N = 246

EVPI: 43.7427726270863
EVPPI: 34.6756523138328
EVSI: 20.2024464292563
```

Displaying the EVSI across sample size

If the EVSI has been estimated across sample size using Bayesian regression (Heath *et al.* 2019), then we can explore the EVSI across sample size for a fixed willingness-to-pay (Figure 6).

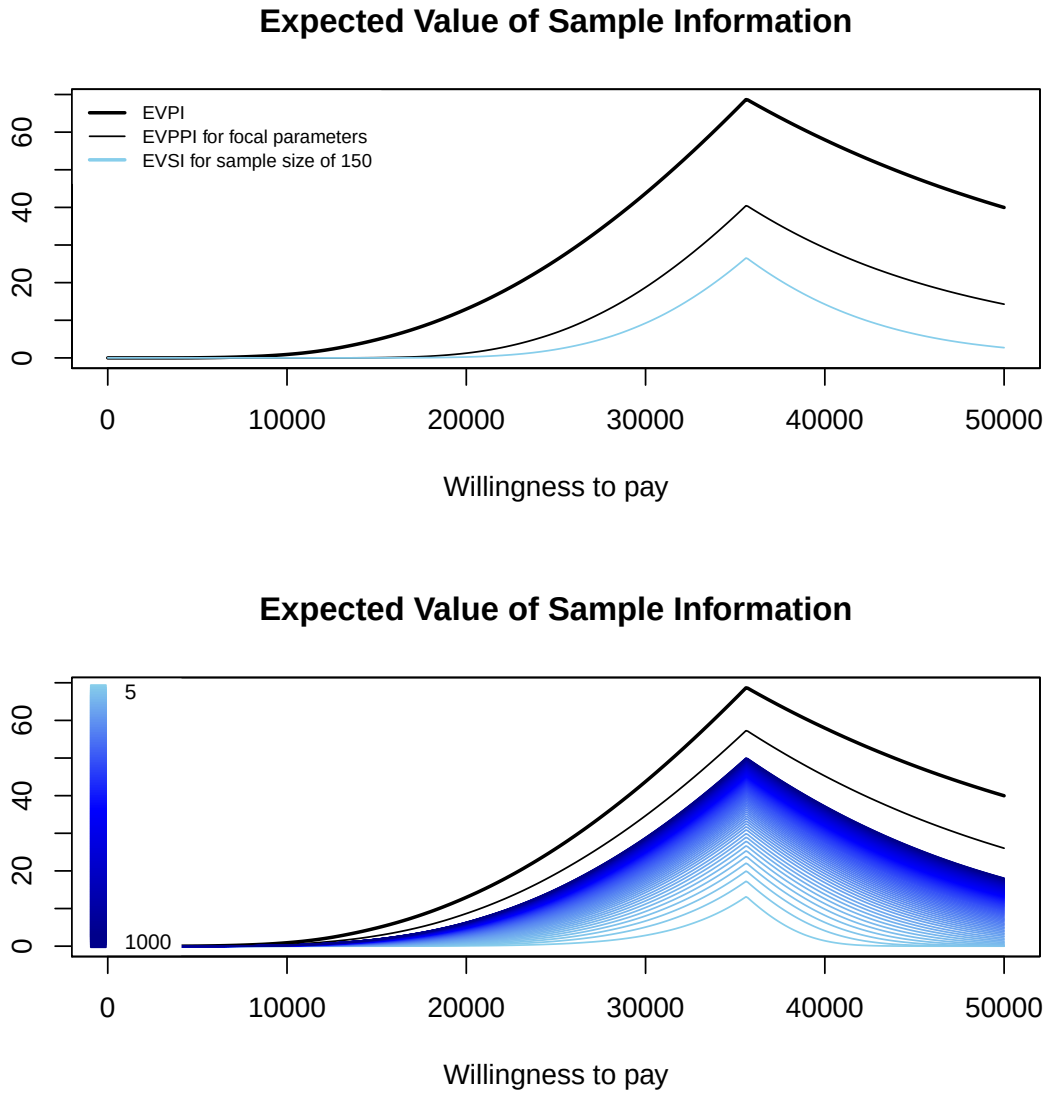

Figure 5: The EVSI across willingness-to-pay for the two examples. The top figure plots the EVSI for a single trial with 150 patients per arm, investigating the probability of adverse events for the standard of care and the novel chemotherapy. The bottom figure plots the EVSI for a number of trials with different sample sizes between 5 and 1000 investigating the probability of adverse event and 4 secondary outcomes to understand the treatment of adverse events.

```
> plot.samplesize(EVSI.full,wtp = 30000)
```

As discussed in §3.3, if the EVSI is estimated across different sample sizes using Bayesian regression, then we also obtain an estimate of the uncertainty in the EVSI estimate. Thus, by default, the `plot.samplesize` function displays the 75% and 95% confidence bands for

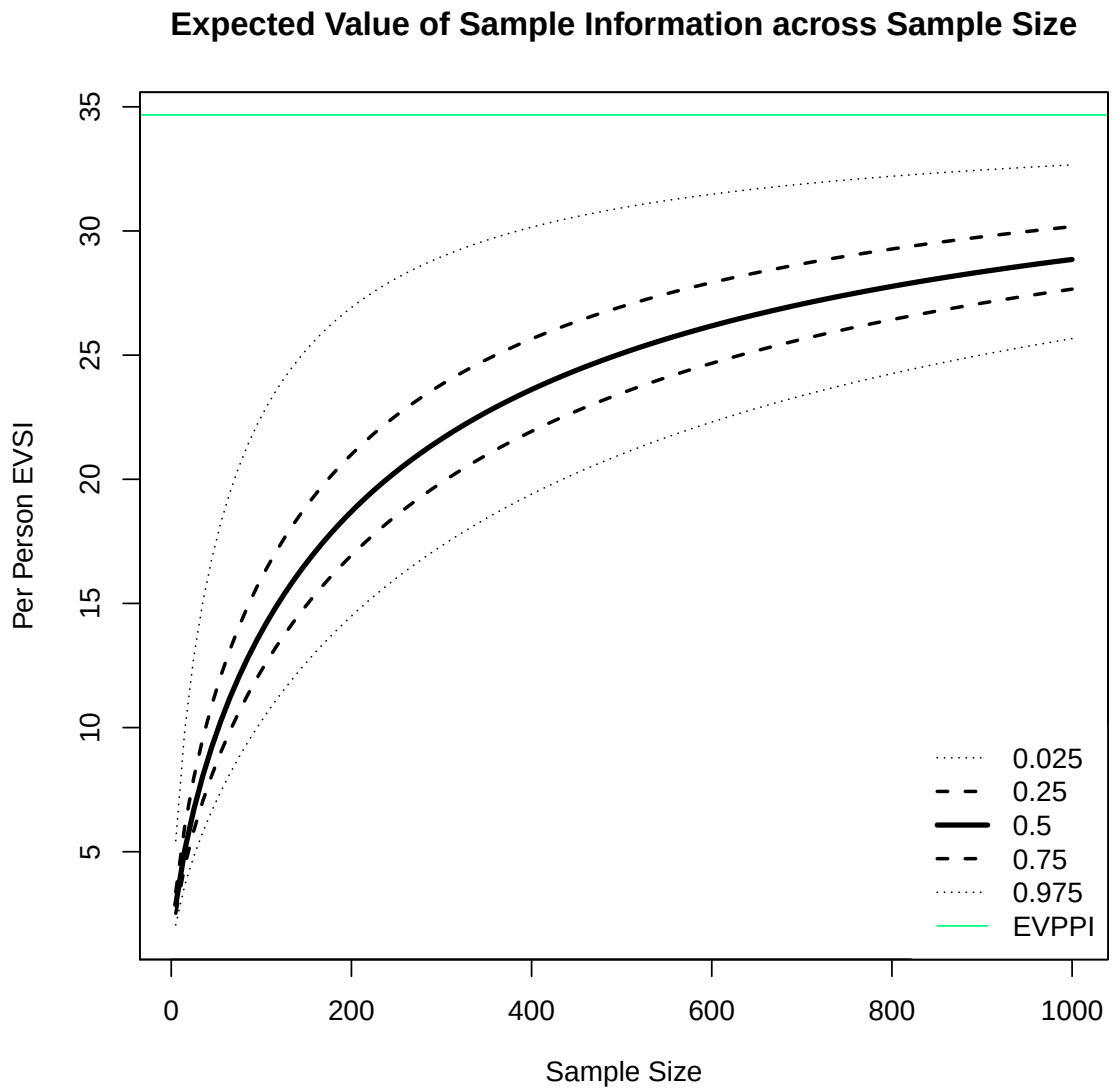

Figure 6: The EVSI plotted across sample size for a willingness-to-pay of 30,000. The solid central line is the median for the EVSI whilst the dashed and dotted lines are the 75% and 95% confidence bands respectively

the EVSI estimate.

The EVSI increases across sample size and should be bounded above by the EVPPI. A key feature of the Heath *et al.* (2019) method is that the EVSI becomes relatively more uncertain as the EVSI decreases. This can be explored using this graphic especially using the **shiny** web application which allows users to change the willingness-to-pay threshold dynamically.

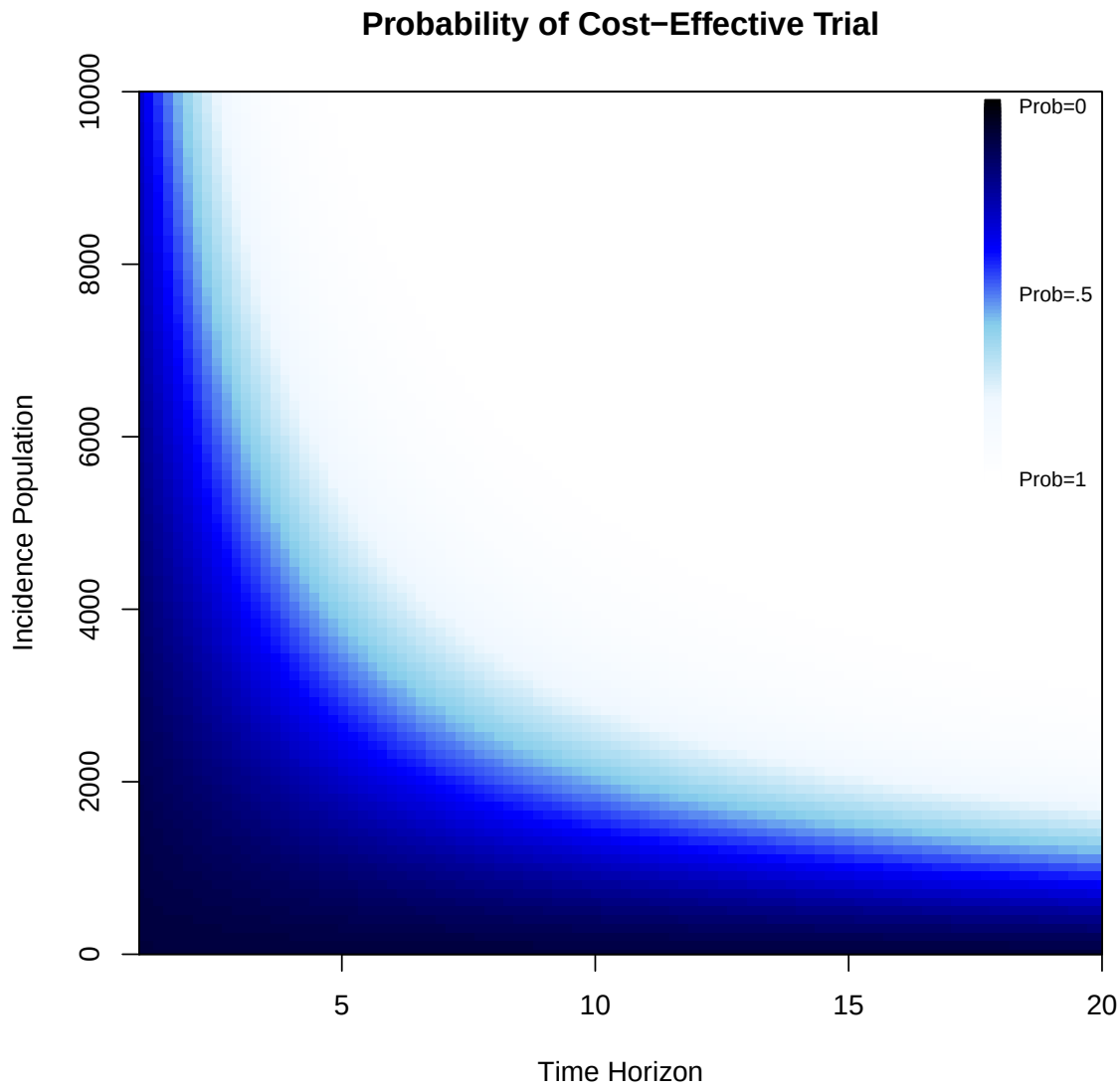

Figure 7: The probability of a cost-effective trial for the full trial with 6 primary and secondary outcomes for a willingness-to-pay of 30,000 and a sample size of 246.

Probability of a cost-effective trial

The ENBS §2.2.4 can determine whether a specific trial should go ahead. However, as the incidence population, time horizon and cost of the future trial are often unknown, we have developed graphics to explore these key elements of the ENBS definition. Firstly, we have developed a graphic that displays a heat-map for the probability of a cost-effective trial for different values of the incidence population and time horizon (Figure 7). For this graphic, uncertainty in the ENBS is due to uncertainty in both the EVSI and the study costs.

Practically, the user specifies maximum and minimum values for the trial costs. As these

must be included in funding applications, they are usually available. If the EVSI has been estimated across sample size, users specify the set up costs for the trial, typically sunk costs such as equipment or training that will be spent no matter the size of the trial, and per person costs, costs relating to recruitment and retention of each study participant. From this, the ENBS can be computed across the different sample sizes. Figure 7 displays the probability of a cost-effective trial for different combinations of incidence population and time horizon for the six outcome trial for a willingness-to-pay of 30,000, a sample size of 246, a setup cost between 100,000 and 200,000 and a per-person cost between 1,000 and 2,000.

```
> plot.prob.ce(EVSI.full, setup = c(1e5,2e5), pp = c(1e3,2e3),
+              wtp = 30000, N = 246)
```

Figure 7 demonstrates that this trial is likely to be cost-effective if the time horizon is greater than 5 and more than 40,000 people would receive this chemotherapy, for our fixed sample size and willingness-to-pay. Our **shiny** application allows users to explore the probability of a cost-effective trial dynamically across different sample sizes and the willingness-to-pay thresholds.

Optimal study design

The ENBS can also be used to find the optimal sample size of a proposed study. This analysis is based on a fixed willingness-to-pay `wtp`, incidence population `Pop` and time horizon `Time`. The `optim.samplesize` function can be used to perform this analysis.

```
> optim.samplesize(EVSI.full,setup = c(1e5,2e5), pp = c(1e3,2e3),
+                  wtp = 30000, Pop = 10000, Time = 10)

$SS.max
N.fit
  382

$ENBS
      1
1243297

$SS.I
[1] 246 558
```

The list object `SS.max` contains the sample size that maximises the ENBS, 382 patients in this example. The list object `ENBS` outputs the ENBS at the optimal sample size. Typically, there are a number of sample sizes where the ENBS is close to the maximum. This is where the additional value given by a patient is close to the cost of enrolling them in the trial. For this reason, the `optim.samplesize` function outputs an interval `SS.I` that highlights the sample sizes for which the ENBS remains within 5% of its maximum. In this example, therefore, any sample size between 246 and 558) would be approximately optimal.

The optimal sample size analysis can also be displayed graphically for a fixed willingness-to-pay, incidence population and time horizon.

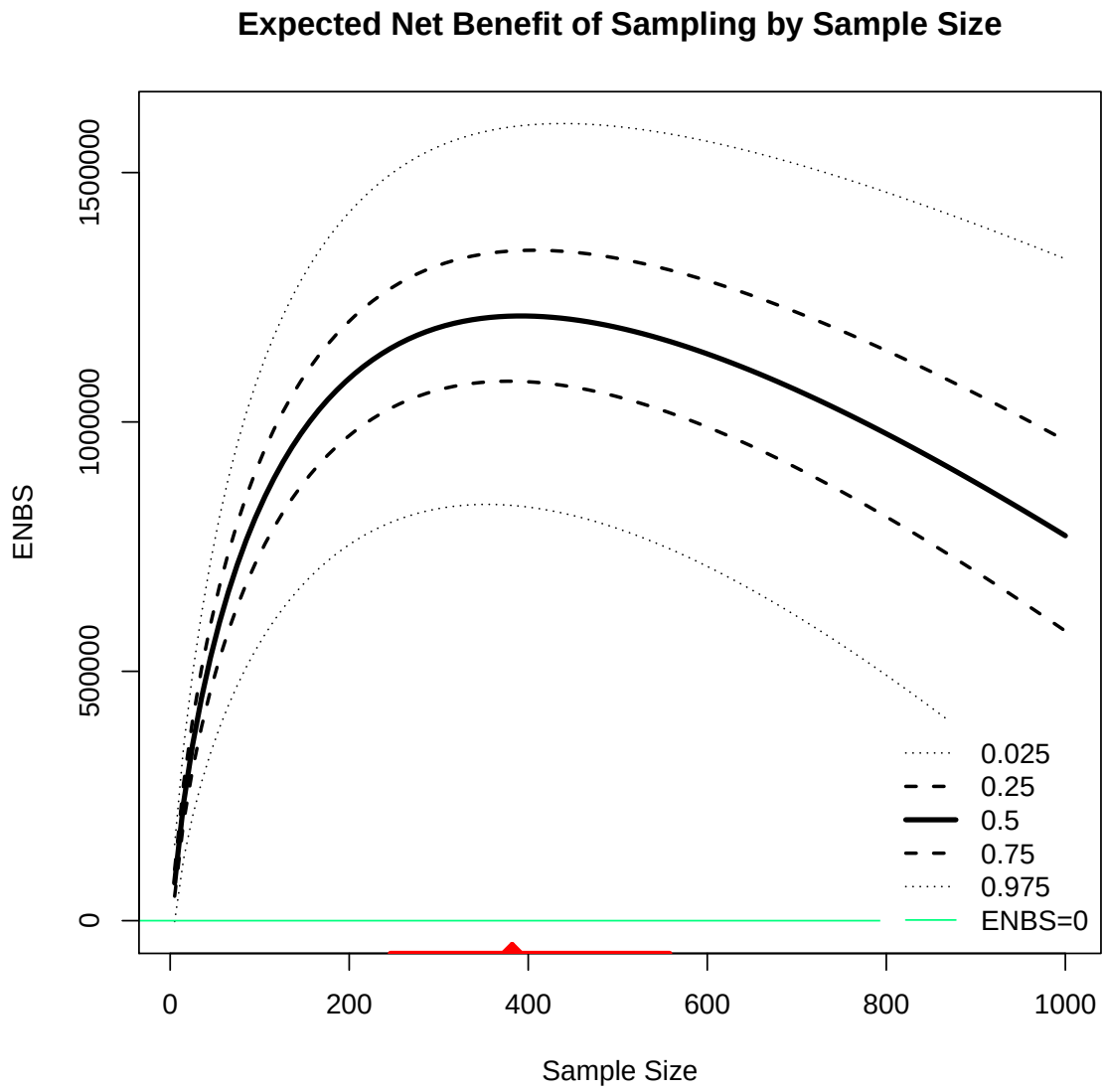

Figure 8: Graphic displaying the ENBS across sample size for a willingness-to-pay of 30000, an incidence population of 10000 and a time horizon of 10. The optimal sample size of 382 is given as a red diamond on the x-axis. The red line on the x-axis displays the interval within which the ENBS remains at 95% of the maximum. The solid central line gives the median ENBS, with the dashed and dotted lines giving the 75% and 95% confidence bands respectively. The green line highlights 0, the limit at which the trial is no longer cost-effective.

```
> plot.enbs(EVSI.full,setup = c(1e5,2e5), pp = c(1e3,2e3),
+           wtp = 30000, Pop = 10000, Time = 10)
```

Figure 8 displays the optimal sample size analysis for the six outcome trial with a willingness-to-pay of 30000, an incidence population of 10000 and a time horizon of 10. The ENBS

initially rises to an optimal value before descending from the optimal sample size. In Figure 8, the ENBS is always positive, so even though an optimal sample size exists, a trial of any of the considered sizes would give economic benefit. The red triangle on the x-axis marks the optimal sample size of 382 patients. The red line then highlights the sample sizes for which the ENBS is within 5% its maximum. Figure 8 also gives confidence bands for the ENBS taking into account uncertainty in the EVSI and the trial costs. The **shiny** application displays this graph dynamically for different combinations of willingness-to-pay values, incidence populations and time horizons. Thus, this graphical interface can be used to visually inspect both the probability of cost-effectiveness and the certainty surrounding this optimal sample size.

5. Summary and discussion

This paper presented R functions to undertake VoI analyses based on a Bayesian health economic decision model. These functions are contained within two packages, **BCEA** and **EVSI**. They implement recently developed VoI computation methods that significantly reduce the burden of these computations to allow practical VoI analysis. These packages significantly reduce the barrier to implementation for these methods. Thus, providing a Bayesian health economic model is developed, researchers can now use the EVPI and EVPPI to prioritise research streams and the EVSI to design cost-effective studies. In general, it is now possible to determine "optimal" trial designs from a health economic perspective.

In addition to the calculations, the **BCEA** and **EVSI** packages contain a suite of graphics to present the results of a VoI analysis to key stakeholders. These graphics also allow users to explore key assumptions that underpin VoI calculations. Thus, VoI analysis can now be explored, shared and interpreted using standardised graphical displays.

Computational details

The results in this paper were obtained using R 3.5.1 with the **BCEA** 2.2.6 package and the **EVSI** 0.0.0.9000 package. R itself and the majority of the packages used are available from the Comprehensive R Archive Network (CRAN) at `https://CRAN.R-project.org/`. The **INLA** package (Lindgren and Rue 2013) is available from `https://inla.r-inla-download.org/R/stable` and the **EVSI** package is available from GitHub `https://github.com/annaheath/EVSI`.

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References

Ades A, Lu G, Claxton K (2004). "Expected Value of Sample Information Calculations in Medical Decision Modeling." *Medical Decision Making*, **24**, 207–227.

Andronis L, Barton P, Bryan S (2009). "Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making."

Baio G (2012). *Bayesian methods in Health Economics*. CRC Press, Boca Raton, FL.

Baio G, Berardi A, Heath A (2017). *Bayesian Cost Effectiveness Analysis with the* `R` *package* `BCEA`. Springer.

Baio G, Dawid P (2011). "Probabilistic sensitivity analysis in health economics." *Statistical methods in medical research*, **24**(6), 615–634.

Canadian Agency for Drugs and Technologies in Health (2019). "Guidelines for the economic evaluation of health technologies: Canada [4th Edition]."

Chang W, Cheng J, Allaire J, Xie Y, McPherson J (2017). *shiny: Web Application Framework for R*. R package version 1.0.5, URL https://CRAN.R-project.org/package=shiny.

Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, Brazier J, O'Hagan A (2005). "Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra." *Health Economics*, **14**, 339–347.

Department of Health and Ageing (2008). "Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee: Version 4.3."

EUnetHTA (2014). "Methods for health economic evaluations: A guideline based on current practices in Europe - second draft."

Felli J, Hazen G (1998). "Sensitivity analysis and the expected value of perfect information." *Medical Decision Making*, **18**, 95–109.

Hastie T, Tibshirani R (1990). *Generalized additive models*, volume 43. CRC Press, Boca Raton, FL.

Heath A, Baio G (2018). "Calculating the Expected Value of Sample Information Using Efficient Nested Monte Carlo: A Tutorial." *Value in Health*, **21**(11), 1299–1304.

Heath A, Manolopoulou I, Baio G (2016). "Estimating the expected value of partial perfect information in health economic evaluations using integrated nested Laplace approximation." *Statistics in medicine*, **35**(23), 4264–4280.

Heath A, Manolopoulou I, Baio G (2017). "A Review of Methods for Analysis of the Expected Value of Information." *Medical Decision Making*, **37**(7), 747–758.

Heath A, Manolopoulou I, Baio G (2018). "Efficient Monte Carlo Estimation of the Expected Value of Sample Information Using Moment Matching." *Medical Decision Making*, **38**(2), 163–173.

Heath A, Manolopoulou I, Baio G (2019). "Estimating the Expected Value of Sample Information across Different Sample Sizes Using Moment Matching and Nonlinear Regression." *Medical Decision Making*, **39**(4), 346–358.

Jalal H, Alarid-Escudero F (2018). "A Gaussian Approximation Approach for Value of Information Analysis." *Medical Decision Making*, **38**(2), 174–188.

Jalal H, Goldhaber-Fiebert J, Kuntz K (2015). "Computing expected value of partial sample information from probabilistic sensitivity analysis using linear regression metamodeling." *Medical Decision Making*, **35**(5), 584–595.

Lindgren F, Rue H (2013). "Bayesian spatial and spatiotemporal modelling with R-INLA." *Journal of Statistical Software*.

Loomes G, McKenzie L (1989). "The use of QALYs in health care decision making." *Social Science and Medicine*, **28**, 299–308.

Menzies N (2016). "An efficient estimator for the expected value of sample information." *Medical Decision Making*, **36**(3), 308–320.

Minelli C, Baio G (2015). "Value of information: a tool to improve research prioritization and reduce waste."

National Institute of Health and Care Excellence (2013). "Guide to the methods of technology appraisal 2013."

O'Hagan A, Stevens J (2001). "A framework for cost-effectiveness analysis from clinical trial data." *Health Economics*, **10**, 303–315.

O'Hagan A, Stevens J, Montmartin J (2001). "Bayesian cost effectiveness analysis from clinical trial data." *Statistics in Medicine*, **20**, 733–753.

Raiffa H, Schlaifer H (1961). *Applied Statistical Decision Theory*. Harvard University Press, Boston, MA.

Rasmussen C, Williams C (2006). "Gaussian Processes for Machine Learning. ISBN: 026218253X."

Spiegelhalter D, Abrams K, Myles J (2004). *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. John Wiley and Sons, Chichester, UK.

Steuten L, van de Wetering G, Groothuis-Oudshoorn K, Retèl V (2013). "A Systematic and Critical Review of the Evolving Methods and Applications of Value of Information in Academia and Practice." *PharmacoEconomics*, **31**(1), 25–48. ISSN 1170-7690. doi:10.1007/s40273-012-0008-3. URL http://dx.doi.org/10.1007/s40273-012-0008-3.

Stinnett A, Mullahy J (1998). "Net health benefits a new framework for the analysis of uncertainty in cost-effectiveness analysis." *Medical Decision Making*, **18**(2), S68–S80.

Strong M, Oakley J, Brennan A (2014). "Estimating Multiparameter Partial Expected Value of Perfect Information from a Probabilistic Sensitivity Analysis Sample A Nonparametric Regression Approach." *Medical Decision Making*, **34**(3), 311–326.

Strong M, Oakley J, Brennan A, Breeze P (2015). "Estimating the Expected Value of Sample Information Using the Probabilistic Sensitivity Analysis Sample A Fast Nonparametric Regression-Based Method." *Medical Decision Making*, **35**(5), 570–583.

Thokala P, Goodacre S, Ward M, Penn-Ashman J, Perkins G (2015). "Cost-effectiveness of out-of-hospital continuous positive airway pressure for acute respiratory failure." *Annals of emergency medicine*, **65**(5), 556–563.

Willan A, Briggs A (2006). *The statistical analysis of cost-effectiveness data*. John Wiley and Sons, Chichester, UK.

Willan A, Pinto E (2005). "The value of information and optimal clinical trial design." *Statistics in medicine*, **24**(12), 1791–1806.

Wood S, Pya N, Kneib T, Hornik K, Lonergan M, Nilsson H, Scheipl F, Ripley B (2016). *mgcv: Mixed GAM Computation Vehicle with GCV/AIC/REML smoothness estimation and GAMMs by REML/PQL*.

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