Title:

Expected Net Present Value of Sample Information: From burden to investment

Authors:

Peter S Hall[1,3,4], Richard Edlin[1] , Samer Kharroubi[2], Walter Gregory[3] and

Christopher McCabe[1]

1. Academic Unit of Health Economics, Leeds institute of Health Sciences, University of Leeds.

2. Department of Mathematics, University of York.

3. Clinical Trials Research Unit, University of Leeds.

4. St James Institute of Oncology, Leeds Teaching Hospitals NHS Trust.

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CORRESPONDANCE:

Dr Peter Hall
Charles Thackrah Building
University of Leeds
101 Clarendon Road
Leeds, United Kingdom
LS2 9LJ
Tel. +441132164298
Email. p.s.hall@leeds.ac.uk

Abstract

The Expected Value of Information Framework has been proposed as a method for identifying when health care technologies should be immediately reimbursed and when any reimbursement should be withheld whilst awaiting more evidence. It assesses the value of obtaining additional evidence to inform a current reimbursement decision. This represents the burden of not having the additional evidence at the time of the decision. However, when deciding whether to reimburse now or await more evidence, decision makers need to know the value of investing in more research to inform a future decision. Assessing this value requires consideration of research costs, research time, and also what happens to patients whilst the research is undertaken and after completion. We describe here a development of the calculation of the expected value of sample information that assesses the value of investing in further research, including an only-in-research strategy and an only-with-research strategy.

Introduction

Institutions responsible for the financing of health care must decide whether or not to adopt a new therapy. Such a decision will rest on the expected costs and expected benefits of an adoption decision in light of current evidence and the size of the available budget. Value of Information Analysis has been proposed as a method for informing choices between providing coverage for new therapies and awaiting further information to reduce the risk of making the wrong decision.(1-2) However, conventional Expected Value of Sample Information (EVSI) is a measure of the burden of decision uncertainty at the point in time when the decision has to be made. It is not a measure of the value of investing in research to reduce that uncertainty.

The conduct of further research has consequences in terms of resources invested. It also results a delay to a final or revised adoption decision, the consequences of which may either be the denial of an effective therapy to patients or the suboptimal investment in an inappropriately adopted therapy. Three important determinants of the value of investing in research are therefore missing from the standard EVSI model; (i) time that it takes for the research to report, (ii) the uncertainty around the time it will take to report (e.g. uncertain recruitment rate into a study) and, (iii) the costs and outcomes of patients whilst the research is undertaken and once it has reported. Eckermann and Willan have considered some of these issues but not in the context of multi-parameter decision analytic modeling.(3-5) They take a parametric approach which relies on the availability of individual patient data which must be considered adequate to inform the decision problem in its entirety. McKenna and Claxton considered (i) and (iii) within a decision modeling framework, allowing the synthesis of all available sources of evidence, but there is a need to

incorporate (ii) into their approach and the consequent significant differences in the analytical method.(6) There is also a need to expand on the limited number of worked examples in the literature.

The standard formulation of EVSI is outlined below. In the methods section of this paper we describe a development of the expected value of sample information framework that incorporates all these missing factors. The enhanced framework is extended to show how it can be used to address questions such as the relative value of only-in-research versus only-with-research reimbursement decisions. Such conditional decisions are accepted as a variation on an emphatic decision whether or not to adopt a new therapy. In the absence of adequate evidence they provide an incentive for further research with an opportunity to revise a decision in light of future evidence development.(7)

To differentiate between the conventional EVSI calculation and our new specification of the value of investing in further research, we refer to the value of investment in further research as the Expected Net Present Value of Sample Information (ENPVSI).

Expected Value of Sample Information: Current method.
A decision to adopt a new intervention within a portfolio of interventions funded from a fixed healthcare budget will result in reallocation of resources from an alternative intervention (or standard care). Such a decision is optimal if the new intervention provides greater net benefit (in terms of cost or health gain), given a specified willingness-to-pay threshold, than that provided by a displaced intervention. Where this decision relies on uncertain evidence there will be a risk of making an incorrect allocation decision. By definition, an incorrect decision will

result in a lower overall net benefit and from this derives the value in reducing this decision uncertainty.

A decision relies on a number of uncertain parameters θ, for which the current evidence $p(\theta)$ defines a multivariate probability distribution. The expected value of sample information (EVSI) represents the expected payoff from conducting further research into a subset of parameters (or single parameter) of interest θ_I. The conceptual framework within which an EVSI calculation lies applied to the healthcare lies is introduced in detail by Claxton.(1)

The calculation of EVSI relies on the Bayesian updating of the uncertain distribution of θ_I on the basis of an increasing notional sample size for research, further informing θ_I. The value attributable to the reduction in decision uncertainty is calculated by subtracting the expected net benefit with current information from the expected net benefit with the information from the notional sample. This is typically calculated as the EVSI per patient. For a technical guide to the calculation of EVSI see Ades et al.(5)

In order to calculate the total EVSI for a population served by a healthcare budget, the accepted method is to multiply the per patient EVSI by the number of patients for whom the intervention is indicated. This should take into account the expected time over which the intervention is useful and the reimbursement decision is pertinent; a suitable discount rate should also be applied. As further research takes place there will be a number of patients who are directly affected as participants in the research sample. A portion of these may be treated with the current standard of care while a proportion will be treated with the intervention(s) under investigation. All others will be treated with the treatment or strategy believed optimal at the time the patient presents to the healthcare provider.

If there are j alternative interventions with uncertain parameters θ (current evidence), the optimal treatment strategy that maximises net benefit (NB) for the expected mean of θ achieves:

$$\text{Expected Net Benefit|Current Information} = \max_j E_\theta NB(j, \theta)$$

where $E_z[f(z)] = \int f(z)p(z)\mathrm{d}z$, is the expectation of function f averaged over values taken by random variable z.

Now, consider a particular research study that might provide new data relating to a subset of parameters of interest θ_I. The data $X_{\theta I}$ obtained from a proposed study will update our knowledge concerning the parameters of interest θ_I. It is this process of updating the probability distributions $p(\theta)$ given new data $X_{\theta I}$ that makes EVSI inherently Bayesian. If parameters are correlated, the additional information about θ_I may additionally tell us something about the complementary set of parameters $\theta_I{}^c$, i.e. $\theta = (\theta_I, \theta_I{}^c)$.

If we imagine we have obtained data X_{θ_I}, then it is reasonable to make a revised decision based on our updated prior information. This will lead us to choose the treatment with the highest expected net benefit now given the data. This expectation is taken over the joint posterior density of $\theta_I | X_{\theta_I}$ and can be written as, $\max_j E_{\theta_I{}^c, \theta_I | X_{\theta_I}} NB(j; \theta_I, \theta_I{}^c)$. If θ_I and $\theta_I{}^c$ are independent, then this expectation is taken over the prior density of $\theta_I{}^c$, and the posterior density of θ_I given X_{θ_I}.

As yet we do not know what the result of the proposed collection of data X_{θ_I} will be. Thus, to calculate the expected value of a decision made after data have been collected, we must take an expectation over the density of of X_{θ_I}, giving

$$E_{X_{\theta_I}}\left[\max_j E_{\theta_I{}^c,\theta_I|X_{\theta_I}} NB(j;\ \theta_I,\theta_I{}^c)\right].$$

Finally, the standard form for the expected value of sample information is the difference between the expected value of a decision made after data X_{θ_I} have been collected and expected value of a decision made now, with only current information. That is:

$$\text{EVSI} = E_{X_{\theta_I}}\left[\max_j E_{\theta_I{}^c,\theta_I|X_{\theta_I}} NB(j;\ \theta_I,\theta_I{}^c)\right] - \max_j E_\theta NB(j,\theta)$$

(1)

This provides the EVSI for a single patient at a given point in time. It also makes the assumption that the additional information to be obtained from the sample is available instantaneously. The accepted calculation for extrapolating to the EVSI for the population for whom the decision is pertinent is given by:

$$popEVSI|N = EVSI.\sum_{t=1}^{T}\frac{I_t - N}{(1+r)^t}$$

(2)

where N is the number of people taking part in research when obtaining further information, T is the time over which the decision is pertinent, I_t is the disease

incidence over time interval t, and r is the discount rate. When calculating the population EVSI, the benefit is only assessed over those whose treatment could be affected by the additional information $(I_t - N)$.

Methods

Expected Net Present Value of Sample Information

In order to inform the decision of whether to invest in research to reduce the decision uncertainty, it suffices to assess whether the costs of investing in the research over time are justified by the expected present value of the information becoming available at an uncertain future point in time, τ. As before, the research would provide data X_{θ_I} and update parameter values from the prior θ to the posterior $\theta|X_{\theta_I}$.

The purpose of a study is to obtain more information about the impact of alternative treatments and incurs costs in both a financial and a health sense. The health impact can be assessed according to the therapies received between the time of the decision to invest in the research and the time when the research reports. By the nature of any comparative research, at least some individuals must receive treatment(s) determined to be less efficient once the research has reported. This holds irrespective of whether or not those individuals were actively involved in the research. The value of the research consists of the reduction in the expected cost of making the wrong decision based upon current evidence compared to the expected cost of making the wrong decision based upon the updated evidence which will be available once the research has reported.

Both the costs of the research and the value of the research need to be discounted to reflect that the new information and any change in the reimbursement decision will occur at an uncertain point in the future. Therefore to accurately capture the expected net present value of sample information it is necessary to model:

1. The costs and outcomes of patients involved in the study up to the point of the research reporting;

2. The costs and outcomes of all patients not involved in the research study up to the point of the research reporting ;

3. The costs and outcomes of all patients, both those involved in the study and those outside the study after the research has reported and the reimbursement decision been made; and

4. The uncertain timing of the reporting of the research.

To do this, it is necessary to incorporate a trial simulation model into the standard expected value of sample information to represent the uncertain estimate for the time for research to take place (τ). This is likely to depend on a number of uncertain factors including the expected effectiveness of each strategy (comparator) and the baseline rate of the event of interest where clinical outcomes are time-dependent, the uncertain time to set up research and an uncertain recruitment rate. It may also incorporate a risk that research will not complete at all.

If we consider a research design comparing standard care with a single intervention in a two-arm randomized controlled trial, the assessment of net benefit over time needs to consider the per-patient NB in each of four groups of patients, multiplied by the number of patients over the relevant time period for each group. The ENPVSI

will be the combination of the expected net benefits of these groups of patients (Figure 1):

5. Within research:

    a. Treated with standard care ($popNB_{trial.1}$)

    b. Treated with intervention ($popNB_{trial.2}$)

6. Out-with research ($popEVSI_{out}$)

    a. Treated with standard care

    b. Treated with intervention

Constraints are placed on those patients for whom the disease is incident prior to the time research reports, such that the choice of treatment may be constrained by inclusion in one arm of the trial. The expected net benefit for the patients in the trial may be read-out from the simulated trial result on the basis of the notional sample size.

Given that the health impacts of inefficient treatment may only be evident after the research has concluded, the expected net benefit for patients out-with the research remains uncertain until the research reports. However, these patients have their treatment allocated according to the information available before the trial reports – that is, subject to the specific decision rules employed by the decision maker at time zero. At time zero, the decision maker is not constrained to require that patients out-with the trial receive the treatment that is currently deemed cost-effective. Instead, the decision maker can consider cases in which approval for new interventions are given either only in research (OIR) or the intervention is adopted

conditional on research taking place (only with research - OWR); the ENVPSI framework incorporates both options, alongside the standard assumption that patients treated out-with the trial are treated with the option currently considered most cost-effective.

The expected net present value of sample information when comparing J treatments is given by:

$$\mathbf{ENPVSI} = \sum_{j=1}^{J} popNB_{trial.j} \ + \ popNB_{out} - popNB_{current}$$

(3)

where, assuming that θ_I and $\theta_I{}^c$ are independent:

$$popNB_{trial.j} \ = \ E_\tau \left\{ E_{X_{\theta_I}} \left[E_{\theta_I{}^c, \theta_I | X_{\theta_I}{}^c} NB(j; \theta_I, \theta_I{}^c) \right] . \sum_{t=1}^{\tau} \frac{n_{jt}}{(1+r)^t} \right\}$$

$$popNB_{out} = E_\tau \left\{ E_{X_{\theta_I}} \left[max_j E_{\theta_I{}^c, \theta_I | X_{\theta_I}} NB(j, \theta_I, \theta_I{}^c) \right] . \left[\sum_{t=1,}^{\tau} \frac{I_t - n_t}{(1+r)^t} + \sum_{t=\tau+1,}^{T} \frac{I_t}{(1+r)^t} \right] \right\}$$

$$popNB_{current} \ = \ max_j \ E_\theta NB(j, \theta). \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

n_t = number of patients in trial during time interval t,

j = trial arm or intervention j,

τ = time for further sampling (time for research to report)

T = time over which decision is pertinent

The Monte Carlo sampling algorithm for implementation as a two-level simulation is outlined in the appendix.

 [Figure 1]

Results

Exemplar model: A New Treatment for Early Breast Cancer

We consider the cost effectiveness of a new targeted antibody treatment called bevacizumab for triple negative early breast cancer (TNBC). This is a hypothetical decision context which looks at a reimbursement decision to be made at a hypothetical time point prior to a phase III trial reporting. TNBC is a subtype of breast cancer where the tumor cells are negative for over-expression of three cell-surface proteins – estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2. Treatment takes place over one year, starting immediately after surgical resection of a primary breast cancer, concurrently with chemotherapy. There is a short (3 month) window after surgery during which treatment is indicated and the condition can be considered temporarily prevalent. After this window there is no further opportunity to treat. The comparator is standard care.

A time-dependent state transition cohort model is used to estimate incremental costs and effects between standard care and the addition of the new drug. Parameter uncertainty is examined using probabilistic sensitivity analysis via Monte Carlo simulation. The rationale for model structure, underlying assumptions, parameterization and parameter distributions have been discussed elsewhere in a similar model assessing trastuzumab for eary breast cancer.(8) The model used here is a simplified version adapted to the decision context for

illustration only. In particular, as there is not randomised comparison to provide an estimate of efficacy of bevacizumab in this context, this (the log-hazard ratio for disease free survival) has been derived from discussion with clinical experts. In a formal economic evaluation, a structured elicitation exercise would be desirable to populate this parameter.

The model is used as the basis to determine the ENPVSI of a proposed randomized controlled trial comparing standard care with bevacizumab. In this hypothetical trial design 2000 patients are randomized between two arms. The primary outcome measure (specified in classical terms) is disease free survival whereby 388 events are required by the pre-specified power calculation. The proposed trial will only inform the hazard ratio for disease free survival and therefore this is the parameter of interest θ_I with all other parameters in Table 1 comprising $\theta_I{}^c$.

This example has been chosen because the time to trial report is particularly important due to the high cost of clinical trials in early breast cancer and the particular unmet therapeutic need in TNBC. As the final analysis of the primary outcome is dependent on reaching a pre-defined number of events, its timing is not only uncertain but is also dependent on the hazard ratio θ_I and the underlying event rate (within $\theta_I{}^c$). It is in fact possible that the trial will not report at all within the useful lifetime of the drug; in this case the expected net benefit for all patients would default to the case where no research was planned and the ENPVSI would be negative.

Model summary

The model consists of five states: 'disease free', 'local recurrence', 'disease free after local recurrence', 'distant recurrence' and 'death' (see Figure 2). We calculate mean costs and QALYs for a hypothetical cohort of women with triple negative breast cancer of average age 50 (n=2000). The model has an annual cycle and a fifty year time horizon, by which point all patients have died. The analysis is undertaken from the perspective of the UK National Health Service.

[Figure 2]

The model parameters are transition probabilities, costs and utilities. The specification and evidence base for each parameter is reported in Table 1.

[Table 1]

Trial simulation model to estimate the time for research to report (τ)

A clinical trial testing a new adjuvant breast cancer therapy will typically rely on a time-dependent primary outcome measure such as progression free survival. In this example τ represents the time between the opening of the trial and the reporting of the final event required for analysis. This time interval is calculated using a trial simulation model with time-dependency - here a simple time-dependent state-transition model is used with a cycle length of one month. The model structure is shown in Figure 3.

There are five states in the model: State A contains patients recruited from the incident population at monthly intervals. These patients can then transit, by randomization to either state B (Control Intervention arm) or State C

(Investigational Intervention arm). A certain proportion of patients in both arms will be lost to follow-up (State D) and therefore will not provide event data to the study, and a certain proportion of patients in both arms will experience outcome events (State E).

[Figure 3]

Monte Carlo simulation is used to sample from uncertain input trial parameters, producing as an output the distribution for τ, where τ is defined as the time from commencement of the trial until the trial reports. Uncertain parameters include: the monthly probability of a progression event (p) the hazard ratio for progression free survival between a control arm and an intervention arm (HR), a sample size (N), a vector of monthly recruitment (x_t) and a monthly rate of loss to follow-up (f). The distribution of τ from this model is shown in figure 4.

[Table 2]

[Figure 4]

The Expected Time to Trial Report parameter τ is incorporated into the ENPVSI calculation for a proposed trial of 2000 patients randomized between two treatments (n=1000 in each arm) to generate additional evidence only on the effectiveness (hazard ratio) of a new treatment for TNBC, in three frameworks:

1. The ENPVSI when the new treatment is available to patients outside the trial only if it represents the most cost-effective treatment strategy prior to the trial commencing;

2. The ENPVSI when the new treatment is only available within the trial (only-in-research); and

3. The ENPVSI, when the new treatment is adopted for all patients outside of the trial regardless of baseline estimates of cost-effectiveness (only-with-research).

For comparison the conventional population Expected Value of Sample Information is also reported.

These analyses will allow the exploration of (a) the potential impact of using the expected net present value of sample information rather than the expected value of sample information to assess the value of further research; and (b) the ability of the ENPVSI framework to compare the value of only-in-research vs. only-with-research approaches to addressing decision uncertainty in the reimbursement setting.

Model outputs – EVSI vs. ENPVSI

The expected incremental cost effectiveness ratio at baseline (i.e. based on current information) is reported in Table 3. The ICER is around £90,000 and therefore beyond the level at which a therapy would normally be approved for funding by NICE. However, as a breast cancer therapy likely to be associated with a strong patient lobby, it is credible that there would be significant pressure for the treatment to be made available, at least within research.

[Table 3]

Figure 5 plots the conventional measurement of the expected value of sample information, the EVSI; and the ENPVSI. Note that it is the population value of information that is reported, as the concept of individual ENPVSI cannot be captured in a single number – whether the individual is involved in the research determines how their health is assessed. We can see that for some willingness-to-pay (WTP) thresholds, the ENPVSI is negative whilst the EVSI does not fall below zero. This reflects the fact that research that would not change the decision and so has resource implications but no value.

When the ENPVSI is positive, the EVSI is higher indicating that the burden of limited information overstates the return on investment in obtaining that information. This would be the case even if the cost of the research was zero, as the ENPVSI includes the discounted value of information becoming available in the future.

Only in research vs. Only with Research

Figure 6 shows the ENPVSI for the trial when the treatment is only available to patients involved in the research (Only in Research) and the ENPVSI when the treatment is available to all patients outside of the trial whilst the research is completed (Only with Research). It shows clearly that an OWR approach produces negative health benefits until the WTP threshold is around £60,000, whilst the OIR produces positive health benefits for WTP thresholds above £45,000. As the WTP

threshold increases beyond the expected ICER, the value of OIR falls rapidly, reflecting the greater value attached to the health foregone whilst waiting for the research to report; whilst the value of OWR reduces much more slowly.

[Figure 5]

[Figure 6]

Discussion

The Expected Value of Information Framework has been proposed to identify when health care technologies should be immediately reimbursed and when reimbursement should be withheld whilst awaiting more evidence. The standard expected value of information framework assesses the value of having additional evidence available to inform a current decision. This can be thought of as the burden of not having the additional evidence available at the time of the decision. However, the information that decision makers need to decide whether to reimburse now or await more evidence is the value of investing in the creation of the new evidence to inform a future decision. Assessing this value requires the analysis to incorporate the costs of the research, the time it will take for the research to report, what has happened to patients whilst the research is undertaken, and what will happen once it has reported.

In this paper we have shown how the standard approach to estimating expected value of sample information can be extended to incorporate these factors. This suggests that the standard expected value of sample information calculations will

overestimate the value of additional research because the EVSI does not fully incorporate opportunity costs incurred for those allocated to a sub-optimal treatment strategy within the research.

Eckermann and Willan have described a closed form model for estimating expected value of information analysis which takes account of how long it takes the research to report. Our framework develops these insights for incorporation in a decision analytic modeling framework.(5, 9)

We have shown how this framework can be used to examine the relative value of OIR and OWR approaches to generate more evidence. Importantly, the analyses will allow the explicit quantification of the health gain foregone by patients denied access to a therapy until the research is completed (OIR) and health gain foregone by other patients when a therapy is reimbursed that is subsequently found to be insufficiently effective (OWR).

Our framework incorporates conventional clinical trial simulation modeling into the decision analytic cost effectiveness framework; bridging two complementary but historically independent approaches to research optimization. Given the increasing importance of reimbursement decisions to regulatory trial design considerations,(10) this is a potentially important demonstration of the intellectual link between these two endeavors. Predicting the time for research to report has always been a high priority and particularly so in the case of expensive Phase III

drug trials,. In the public arena this is a consequence of a desire to minimize the delay for patients in accessing new treatments. In an industry setting, prolonging research often means lost revenue. It therefore seems essential that an estimate of the duration of research is incorporated into value of information analysis if it is to find real-world applications. This will be particularly important where the proposed research is either large or time consuming, as will often be the case in the context of early cancer, where absolute gains may be small and occur over a long time-horizon.

There are many uncertainties in the evidence base for any decision and the value of research to reduce these uncertainties can differ substantially.(11) Our framework suggests that conventional assessments of value of information that do not take account of the time it takes for research to report and the costs and outcomes of patients whilst the research is completed produce incorrect estimates of the relative value of different research studies. In addition, incorporating the differential time for different types of research to report will impact on the assessment of the value of sequential research designs. Discounting implies that quicker research has a higher value, which will also impact upon the residual value of further research on other parameters in the decision problem. We hypothesize that efficient sequential research designs would incorporate stopping rules for later studies based upon the results of earlier studies in the research process; and the optimal ordering of studies within sequential designs will depend heavily upon the time it takes for the research to report and the (as yet unmodelled) delays whilst studies are analysed.(12)

The constituent parts of formula (3) rely on the expected net benefit for the patients in each group. The choice of which expectation should be used for each deserves some consideration. Patients allocated to participate in proposed research are synonymous with the notional sample size used for Bayesian updating and simulation of a likelihood ("data" or X_{θ_I}) and consequent posterior distribution $p(\theta)$ over the outer loop of the Monte Carlo algorithm. It is therefore internally consistent to use this data, which can be considered known or observed, as the basis for our expected net benefit for within-trial patients ($popNB_{trial,j}$). The posterior distribution for θ, $p(\theta|X_{\theta_I})$ should be used for the expected net benefit of all other patients ($popNB_{out}$). This is true even for those patients who will be treated prior to the research reporting ($t < \tau$) because as soon as we make a decision to conduct research, our best estimate of the net benefits for any future patient includes the information provided by the research and therefore the posterior distribution of θ.

A major analytical difference between our approach and that taken by McKenna and Claxton is the necessity to move the extrapolation from individual patient EVSI to population EVSI for each group of patients into the outer loop of the Monte Carlo simulation (outlined in the appendix).(6) Without taking this step, which is a central characteristic of ENPVSI as we have defined it, uncertainty around the time taken for proposed research would be ignored. Meaningful differences in value of information would result where time for research is partially dependent on prior estimates for the effectiveness of an intervention.

The framework for implementation of ENPVSI outlined here is generalizable to instances in which the likelihood for the proposed data is conjugate with their independent prior distributions, such that it is possible to specify posterior distributions in closed form.   Additional nested simulations would be one way in which this requirement could be relaxed but would lead to further substantial computational burden.

In this paper we only consider the gold standard method for EVSI calculation as specified by Ades et al. whereby an inner Monte Carlo simulation is nested within an outer loop.(5)   In doing so, implementation required considerable computer processing time.   Our exemplar calculations could only be completed within a sensible time-frame by using a high performance parallel processing cluster (ARC1, Leeds Node of the White Rose High Performance Computing Grid) implemented using the R statistical programming language.(13)   For simple models the requirement for an inner loop, with resultant high computational burden, may by side-stepped by assumptions of model linearity or multi-linearity.(14)

Our example illustrates the methodological advances proposed by this paper. We have attempted to keep this example simple in order to illustrate our message clearly. For practical application there would undoubtedly be a requirement to expand on the work presented here. For example, our calculation of τ, the time for research to report, does not currently take into account the time for trial set-up and analysis. We also do not take the next essential step which would be to calculate the Expected Net Benefit of Sampling, which takes account of the costs of

research, which will invariably be related to τ, and subtracts these from the EVSI. The methods for doing this are clearly described by others.(1, 9) Equally, we do not take account of the expected value of perfect implementation, which considers that not all research evidence is implemented into clinical practice.(15)

In conclusion, expected value of information and Bayesian decision theory offers an explicit framework for rational reimbursement decision making and efficient research design. When applied to specific research designs, consideration of treatment allocation to different groups of patients and the time taken for information to be obtained will meaningfully influence the calculation of EVSI. The updated framework presented here will require further development to consider complex or multi-parameter research design proposals and issues such as forecasted prices and the introduction of alternative technologies over the lifetime of a new intervention.

Acknowledgements

Tables

Table 1. Model parameters

Parameter	Mean	Distribution	Notes	Source
TRANSITION PROBABILITIES				

Recurrence rate:
  Log-scale parameter
  Shape parameter
	$\begin{pmatrix} -2.08 \\ -0.27 \end{pmatrix}$	$\begin{pmatrix} 0.33 & -0.007 \\ -0.007 & 0.003 \end{pmatrix}$	Gompertz survival distribution. Shape and scale parameters are drawn from a bivariate normal distribution (mean and var-covar matrix shown here)	(16)

Proportion local recurrence	0.13	Beta(4.4,29.5)	Proportion of recurrences that are local to the original breast cancer primary	(16)
Death after distant recurrence	0.6	Beta(37,23)	Annual probability of death after a distant recurrence	(16)
Background mortality	Age - specific	fixed	Life tables	(17)

Effect size
  Log-hazard ratio
  Duration of benefit
	-0.36
	5 yrs
		N(-0.36,0.37)*
		LN(1.6,1.03)*
			Hazard ratio for distant recurrence	Expert opinion

On-treatment toxicity
  gut perforation
  haemorrhage
  arterial thrombosis
  febrile neutropaenia
  proteinuria
  allergic reaction
  nausea
  hypertension
  heart failure
	
	0.005
	0.005
	0.019
	0.008
	0.035
	0.004
	0.021
	0.148
	0.013
		
		Beta(1.8,363)
		Beta(1.8,363)
		Beta(6.9,358)
		Beta(2.92,362)
		Beta(12.8,775)
		Beta(1.46,364)
		Beta(7.67,357)
		Beta(54,311)
		Beta(3,220)
			Additional toxicity incurred by bevacizumab	From E2100 trial (18)

COSTS**				
Local recurrence (first year)	£14,409	LN(9.57,0.255)		(19)
Distant recurrence	£11,522	LN(9.35,0.072)		(19)
Cost of terminal six months	£8,127	LN(9.00,0.112)		(19)

Follow-up (Disease free)
  Clinic
  Mammogram
	
	£296
	£40
		
		LN(5.52,0.025)
		LN(3.70,0.192)
			
			Annual medical oncology clinic
			Annual mammogram for 5 years
				
				(20)
				(20)

Treatment Costs
  Drug cost
  Delivery cost
  MUGA scan (3 monthly)
	
	£46,382
	£154
	£164
		
		fixed
		LN(4.89,0.401)
		LN(5.01,0.206)
			1 year, 3-weekly at 15mg/kg (avg. 73kg) (assumes 100% relative dose intensity)
			cardiac multi-gated acquisition scan
				
				BNF 2008
				(20)
				(20)

Toxicity
  gut perforation
  haemorrhage
  arterial thrombosis
  febrile neutropaenia
	
	£3,912
	£1,633
	£2,744
	£3,024
		
		LN(8.27,0.463)
		LN(1.83,363)
		LN(6.94,358)
		LN(8.01,0.477)
				
				(20)
				(20)
				(20)
				(20)

proteinuria	£4.45	LN(1.49,0.400)	(20)
allergic reaction	£293	LN(5.68,0.411)	(20)
nausea	£910	LN(6.810.523)	(20)
hypertension	£31.68	LN(3.46,0.25)	(20)
heart failure	£2,339	LN(7.76,0.25)	(21)

UTILITIES

Disease free	0.779	Beta(463,131)	(22)
Local recurrence	0.779	Beta(83,24)	(22)
Distant recurrence	0.685	Beta(135,62)	(22)

| **Discount rate for costs** | 3.5% |
| **Discount rate for benefits** | 3.5% |

Table 2. Transition matrix

	$\rightarrow$ A	$\rightarrow$ B	$\rightarrow$ C	$\rightarrow$ D	$\rightarrow$ E
A $\rightarrow$	$1 - x_t$	$x_t/2$	$x_t/2$	0	0
B $\rightarrow$	0	$1 - p - f$	0	f	p
C $\rightarrow$	0	0	$1 - p.HR - f$	f	$p.HR$
D $\rightarrow$	0	0	0	1	0
E $\rightarrow$	0	0	0	0	1

Table 3. Cost-effectiveness output from the exemplar model.

	Costs (£)	QALYs	Cost/QALY (ICER)
Standard care	7,693	10.77	
Intervention	56,311	11.31	
Incremental change	48,619	0.54	89,659

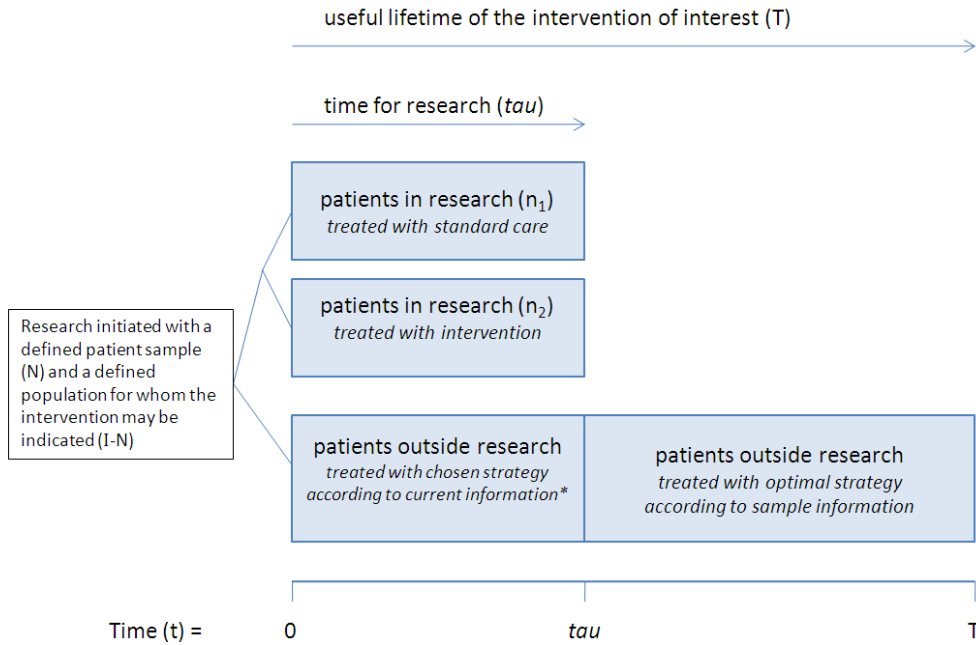| **Probability cost-effective**	
WTP* = £20k/QALY	0.06
WTP* = £30k/QALY	0.19
WTP* = £60k/QALY	0.42

*WTP = willingness-to-pay threshold

Figure Legend

Figure 1:   Diagrammatic presentation of calculation of net benefit from sample information.

Figure 2:   Schematic of TNBC cost effectiveness model

Figure 3:   Schematic of trial simulation model

Figure 4:   Expected time to trial report based upon 10,000 simulations. For each simulation in the value of information analysis a time to research reporting is sampled from the distribution τ ($\bar{\tau}$ = 40.6 months).

Figure 5:   Expected Value of Sample Information and Expected Net Present Value of Sample Information for a trial of the effectiveness of a new adjuvant treatment in TNBC. (Note: patients outside the clinical trial are treated with the strategy offering the highest NB. For WTP < £90,000 per QALY this is standard care, and otherwise the intervention.)

Figure 6:   ENPVSI of only with research vs. only in research for a trial of the effectiveness of a new adjuvant treatment in TNBC. It is clear that when the new treatment is cost effective (i.e. ICER < WTP) OIR is the preferred approach. When ICER > WTP, OWR is preferred. For ICER $\approx$ WTP the difference is small.

Figures

Figure 1:

useful lifetime of the intervention of interest (T)

time for research (*tau*)

patients in research (n_1)
treated with standard care

patients in research (n_2)
treated with intervention

Research initiated with a defined patient sample (N) and a defined population for whom the intervention may be indicated (I-N)

patients outside research
treated with chosen strategy according to current information*

patients outside research
treated with optimal strategy according to sample information

Time (t) =   0   *tau*   T

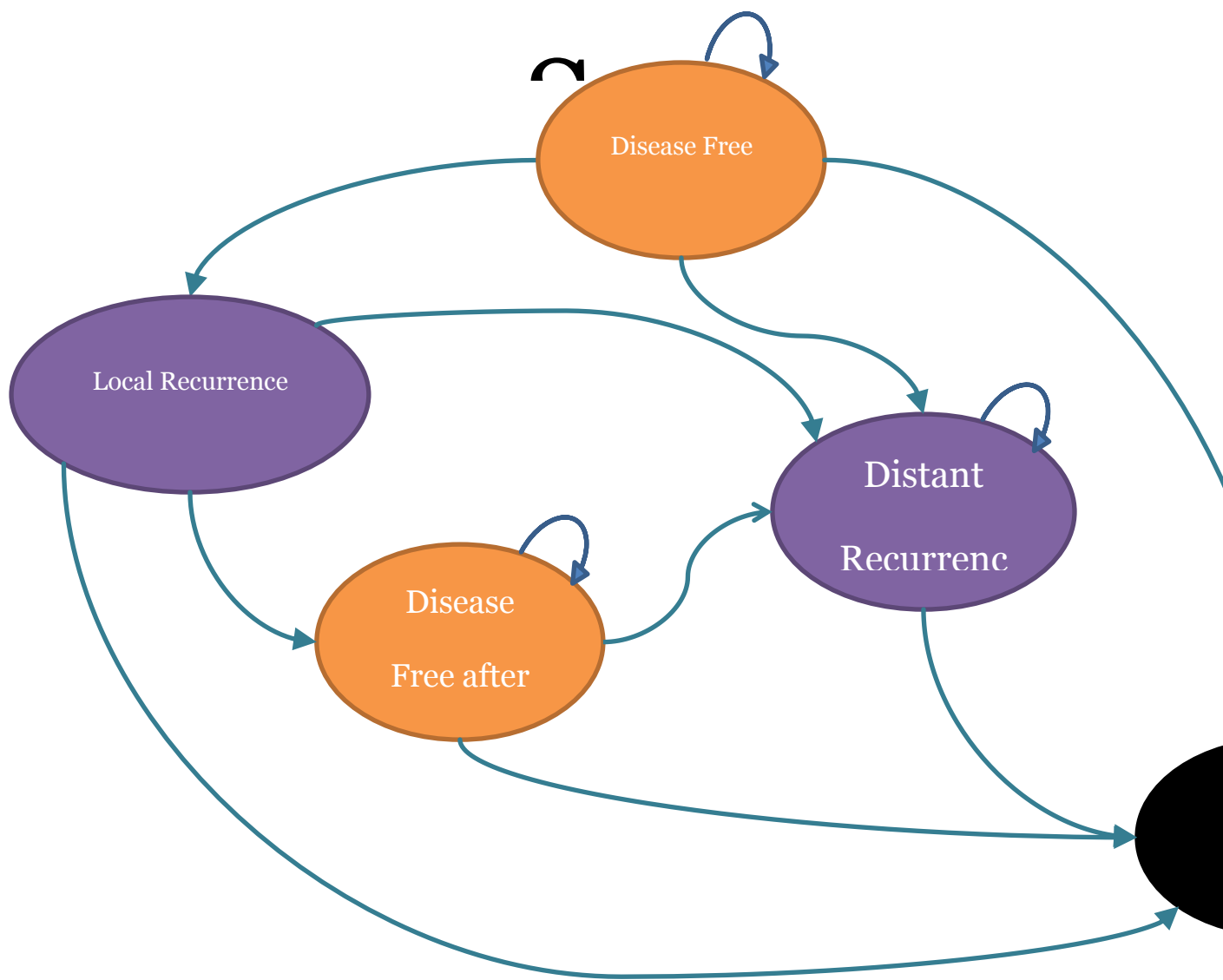* this will depend on whether the strategy with the highest net benefit is used or whether this is constrained by an only-in-research or only-with-research arrangement.
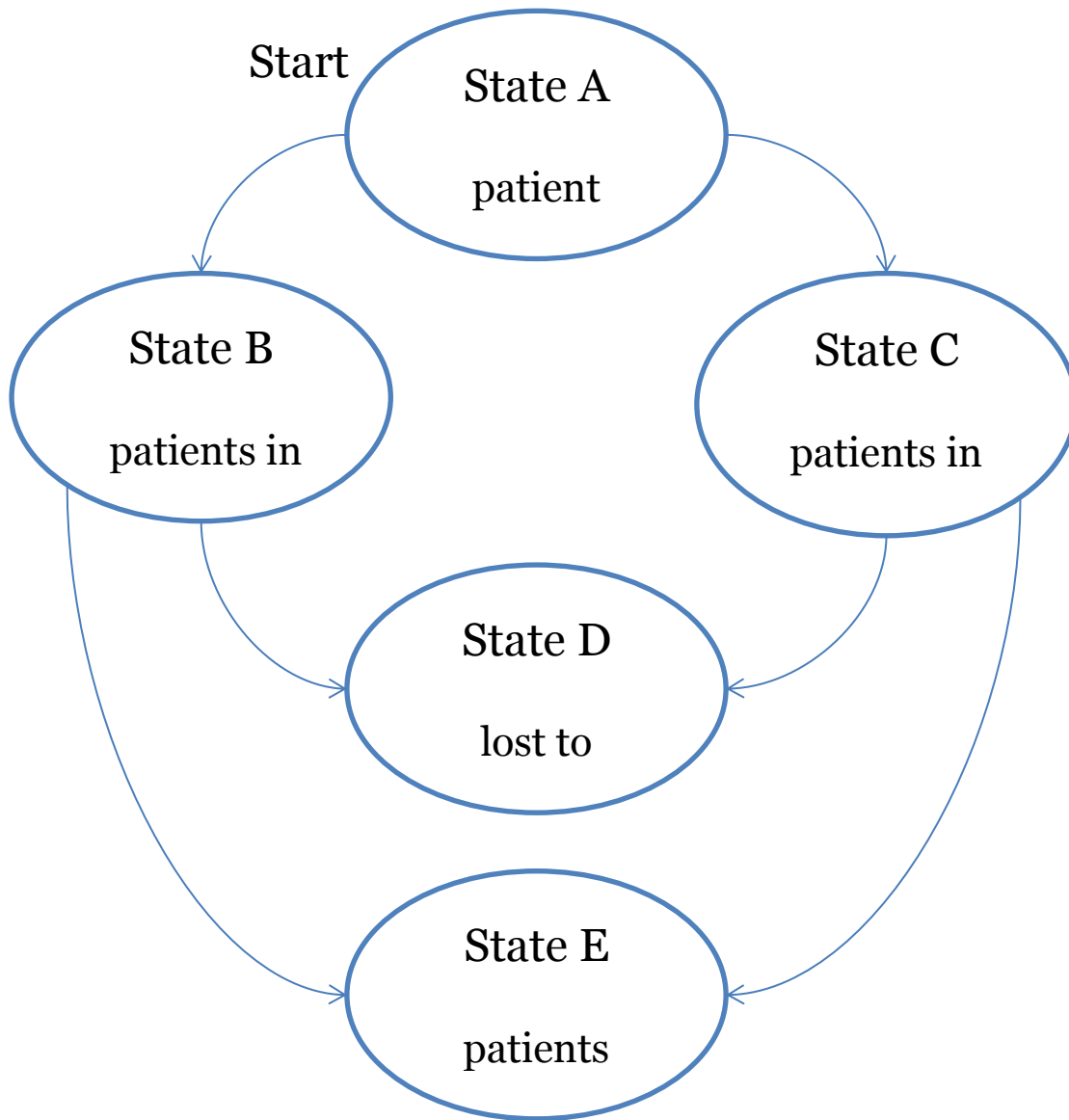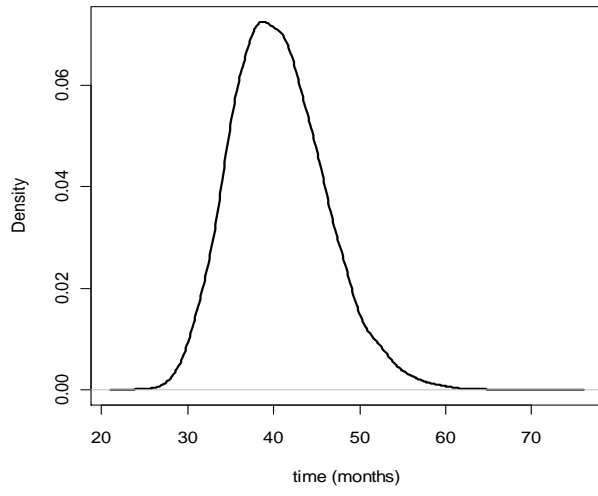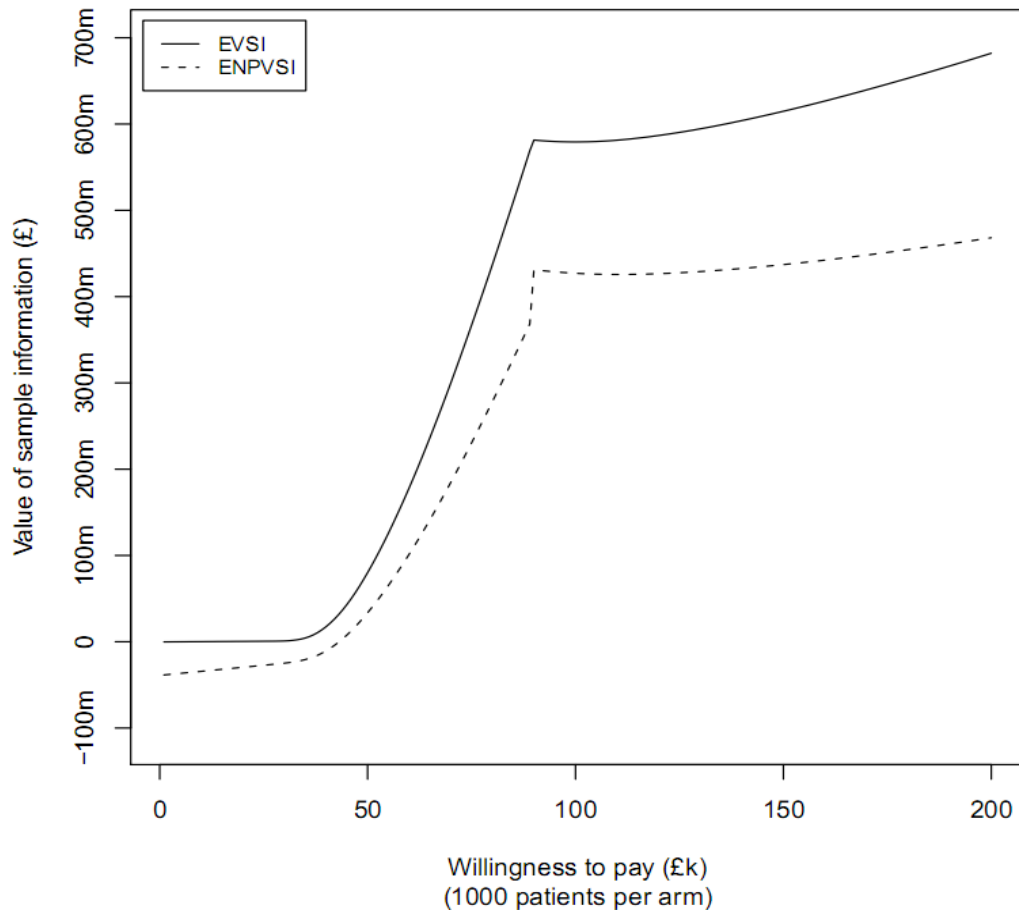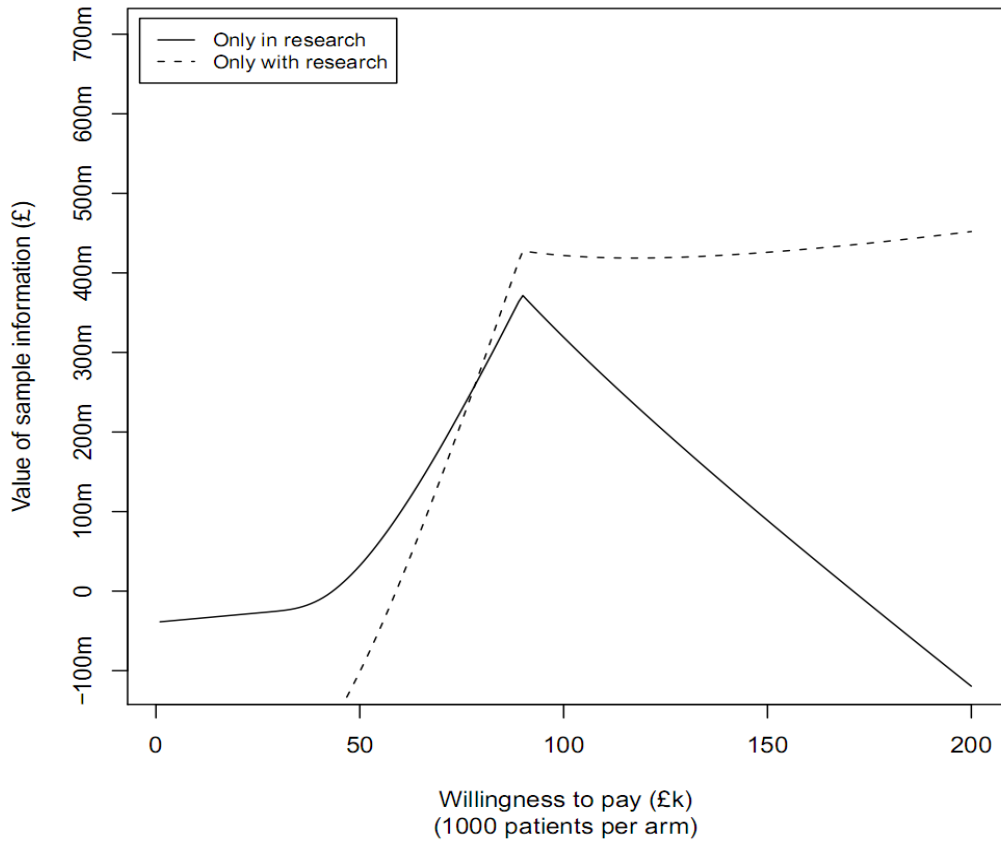
Figure 2:

Figure 3:

Figure 4:

Figure 5:

Figure 6:

Appendix 1: [suitable for publication as supplemental online material]

General Monte Carlo sampling algorithm for calculation of population ENPVSI

Adapted from Ades et al. Medical Decision Making 2004 24;207

θ_I = parameters of interest (here assumed independent of $\theta_I{}^c$)

First record the net benefit of an optimal decision based on current information. Then define a proposed piece of research from which data $X_{\theta I}$ will be collected to inform θ_I.

A1. For i =1,2... N simulations

    B1. Draw a sample $\theta_I{}^{(i)}$ from the prior (baseline) distribution of θ_I.

    B2. Draw a sample $X_{\theta I}{}^{(i)}$ from the distribution of the sufficient statistic $X_{\theta I} \mid \theta_I{}^{(i)}$ arising from a new study of defined size.

    B3. Calculate posterior (updated) expected net benefits for each strategy j, using an inner Monte Carlo simulation loop using the posterior distribution $\theta_I{}^{(i)} \mid X_{\theta I}{}^{(i)}$

    B4. Calculate expected net benefits for each strategy j given the likelihood $X_{\theta I}{}^{(i)}$, evaluated at its mean, using an inner Monte Carlo simulation loop.

    B5. Find the strategy *j* maximizing expected net benefit for simulation *i* based on B3.

    B6. Draw a sample from the distribution of time to trial reporting (τ) using $X_{\theta I}{}^{(i)}$.

    B7. Using the expected net benefit given the mean of the likelihood $X_{\theta I}{}^{(i)}$ (B4.) allocate net benefit to patients allocated to trial arms for each strategy *j* for each time interval up to τ, discounted.

    B8. Using the posterior expected net benefits (B3.) record the population net benefit for patients not in trial for time intervals prior to time τ who receive the optimal strategy *j* given a decision based on the prior expected net benefits up to time τ, discounted.

    B9. Record the population net benefit for the optimal strategy *j* given a decision based on the posterior expected net benefits using the discounted population for each time interval after the trial has reported.

    B10. Record the sum of the expected net benefits over all groups in B7, B8 and B9.

A2. Find the average of the population expected net benefits (B10), over the N simulations. This is the population expected value of a decision based on sample information.

A3. Subtract from this the population expected value of a decision based on current information to give the ENPVSI.

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