BIJLAGE 3

Onzekerheid en Value of information (VOI)

Inhoud

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1 Uncertainty and Value of Information Analysis

Mathematical models are often used to assess the cost-effectiveness of a new health technology. Since the true value of the input parameters of the model is usually unknown, the outcomes of a cost-effectiveness analysis are surrounded by uncertainty. This text aims to support structured and consistent use of the appropriate type of analysis (sensitivity and/or value-of-information (VOI) analyses) in decisions informed by model based cost-effectiveness analysis. Such analyses may determine the robustness of the model results, the value of additional research to reduce the uncertainty about the model's outcomes, support the choice of endpoints (characterized as input parameters of the model) for which additional research might be worthwhile and determine the most efficient research design, including duration of the research (and data collection).

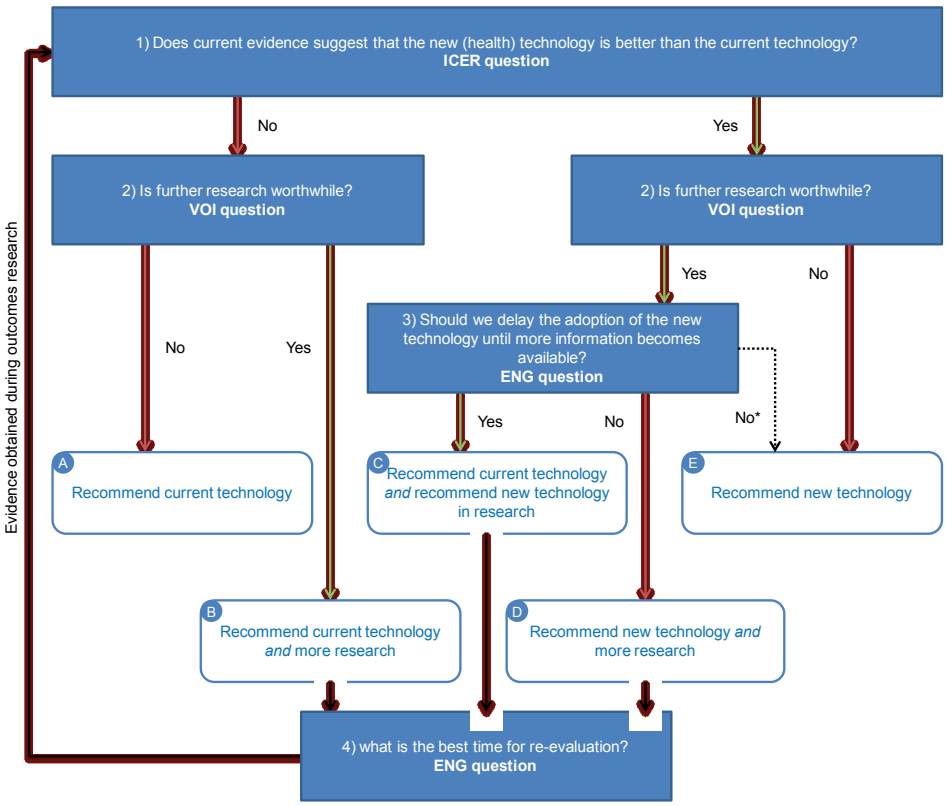
Figure 1 illustrates an adapted version of the framework developed by Chalkidou et al.[1] that can be used to formally integrate VOI analyses in Dutch decision making concerning health care policy and to choose the optimal decision out of the following options: (A) recommend the current health technology without further research, (B) recommend the current health technology and more research, (C) recommend the current health technology and recommend the new health technology only in research, (D) recommend the new health technology and more research (access with evidence development) and (E) recommend the new health technology without further research. To choose between these options using evidence based decision making, four distinct but connected questions need to be informed:

- Does current evidence suggest that the new health technology is better than the current health technology?
- Is further research worthwhile?
- Should we delay the adoption of the new technology until more information becomes available?
- What is the best time for re-evaluation?

The first two questions above can be informed by performing economic evaluations, in particular using the incremental cost-effectiveness ratio (question 1) and VOI analyses (question 2). The third question can be informed by performing real option analysis (ROA).[2] Note that this third question only becomes relevant if the second question can be answered by 'Yes' based on the economic analysis. Moreover, when more research is recommended, a fourth question arises: what is the best time for re-evaluation.

In the remainder of this text we will stepwise summarize the methods that are recommended to properly inform these four questions. References to more elaborate explanations are provided in Technical appendices 1-3. It should be noted that in principle, VOI analyses could be performed solely from an effectiveness perspective (e.g. using varying thresholds for the required minimum clinical difference).[3] Moreover, in some cases decision analytic models are not built because cost-effectiveness or VOI analyses are based on clinical data only. In such situations non-parametric bootstrap methods are often used to perform uncertainty and VOI analyses. However, more complex partial VOI analysis, which will be described below, are not possible in absence of decision analytic models. The generally used model-based cost-effectiveness perspective will be adopted in this text for sensitivity and VOI analyses.

Figure 1: Adapted version of the framework by Chalkidou et al.[1]



*ICER = Incremental Cost-Effectiveness Ratio, VOI = Value of Information, ENG = Expected Net Gains. * As it will be explained below, it is possible to go from question 3 to option E if the real option analysis indicates (in contrast with VOI analysis) that further research is not worthwhile (which happens when the expected net gains are negative).*

1.1 Does current evidence suggest that the new health technology is more cost-effective than current practice?

The incremental cost-effectiveness ratio (ICER) is used to determine which health technology provides most value for money (i.e. which one is cost-effective) based on current evidence. The ICER can be calculated by dividing the incremental costs by the incremental effects. The ICER can subsequently be compared with the threshold that society is willing to pay per additional QALY to examine which health technology is cost-effective. Alternatively, provided that a willingness-to-pay threshold is available, the incremental net monetary benefit (INMB) can also be used to determine which health technology is cost-effective. The INMB can be calculated by multiplying the incremental effects by the willingness-to-pay threshold and subtracting the incremental costs. When the INMB is positive the new health technology is cost-effective. Thus, the ICER and the INMB can both be used to inform the first question of the framework, i.e. whether current evidence suggest that the new health technology is better than current practice. Note that several of these measures as well as measures mentioned below can only be computed using an explicit threshold value.

1.2 Is further research worthwhile?

The first question in Figure 1 is answered based on the current evidence. The next step is to further study the uncertainty associated to the decision and whether it is worthwhile to invest in reducing this uncertainty. This can be done by exploring the value of collecting additional information in order to eliminate

or to reduce decision uncertainty. Making the wrong decision comes at a cost that is equal to the benefits forgone due to the wrong decision. Hence, the value of reducing decision uncertainty through collecting additional information can be quantified by combining the probability that a certain decision is wrong with the value of its consequences in the so-called VOI analysis.[4] In order to perform a full VOI analysis the following steps will be followed:

1. Determine how uncertain we are about our decision (i.e. what is the probability that the decision based on current evidence (e.g. ICER) is wrong?).
2. Quantify the impact of making the wrong decision (i.e. what are the consequences if the wrong decision is made?).
3. Study to what extent additional research will reduce the current decision uncertainty.
4. Establish how much the additional research is likely to cost and what the likely benefits are in terms of improved decision certainty.

A VOI analysis usually starts with the estimation of the expected value of perfect information (EVPI). To calculate the EVPI, the uncertainty about the decision is determined from a probabilistic sensitivity analysis (step 1 above) together with the monetary consequences of a wrong decision (step 2 above). The EVPI is the maximum amount the decision-maker should be willing to pay to eliminate all uncertainty in the decision. Further detail can be provided by the expected value of partial perfect information (EVPPI). This is the EVPI associated to one model parameter or subset of model parameters. The EVPI and EVPPI set an upper limit on the value of conducting further research, i.e. further investigation will only be potentially worthwhile if the EVPI exceeds the costs of further research. When the EVPI turns out to be lower than the costs of further research, this confirms that current decision uncertainty is small enough that further research to reduce it is not worthwhile and thus the decision is to be based on the currently available evidence (for an example we refer to the cost-effectiveness analysis to support guideline for irritable bowel syndrome[5]). However, the EVPI and EVPPI assume complete elimination of decision uncertainty. This can only be achieved by an infinitely large sample. Thus, the practical task is to calculate the expected value of sampling information (EVSI), which estimates the value of reducing current decision uncertainty through obtaining additional data (step 3 above). Weighing the EVSI against the costs of obtaining the sample (step 4 above) results in the expected net gain (ENG). When the EVSI exceeds the cost of the additional research (i.e. when the ENG is positive), the research is worth funding. Calculating the ENG for different types of research supports careful study design, and this includes considering the best period of follow-up.[5,6,7] EVPPI and EVSI procedures can be computationally burdensome. However, EVPPI analyses may not always be necessary; a more extensive (partial probabilistic) sensitivity analysis (plus an EVPI analysis) could be used to prioritize additional research.[8] To accurately estimate the ENG of additional research it is a prerequisite that all uncertainty affecting the policy decision is parameterized in the model to enable its inclusion in a VOI analysis.[9] To assess whether a model based health economic evaluation is applicable to the policy decision a checklist has been developed.[10]

In Technical appendices 1-3 we present a more detailed explanation of the concepts introduced above and a practical guide on how to compute them.

1.3 Should the recommendation of the new health technology be delayed until more information becomes available?

If further research is indeed worthwhile, the next question that would arise is whether the recommendation decision must be delayed until more information becomes available. In order to answer this question, decision makers should weigh gains of waiting for more evidence against losses of a delay in the decision. For this purpose, potential costs of delaying a definite decision to conduct further research (including opportunity losses) are compared to the benefits of delaying a final decision and waiting for more information. This is the value of having delayed a definite decision and being able to decide after additional evidence has been gathered. This is especially valuable if a recommendation decision is difficult, costly or even impossible to reverse.

If the new technology seems better, but a delay is worthwhile ("yes" to question 3 in Figure 1), the new technology could be made available only in the context of research. In this case, patients outside the study population will not have access to what seems the optimal health technology, resulting in opportunity health losses, which can be valued in monetary terms. On the other hand, the final decision is made later with more information available, preventing high (potentially irreversible) costs of making a wrong decision.

If the new technology is immediately implemented ("no" to question 3 in Figure 1), it may be recommended while additional research is being conducted (access with evidence development), most often observational research. In this case, expected opportunity losses are zero, but costs of reversal are quite relevant. Costs of reversal refer to the costs to the healthcare providers regarding the change in the recommendation decision, as well as the sunk costs of training and capital for a health technology which later turns out to be the non-optimal option. Thus for both choices: "recommend the new health technology only in research" and "recommend the new health technology with more research" (options 3 and 4 in Figure 1), the expected net gain (ENG) can be calculated as the difference between gains of waiting for more evidence (EVSI) and losses of a delayed decision (costs of research, opportunity losses and reversal costs).

The choice with the highest ENG is most optimal. How this is assessed quantitatively is explained in Technical appendix 3.

The main challenge in the ENG calculation is the estimation of the INMB distribution. A decision must be made between delaying the recommendation decision ("yes" or "no" to question 3) when no additional trial information would be available. Hence, a hypothetical future INMB distribution must be assigned. This can be done using Bayesian methods,[11] maximum likelihood[12] or other relevant statistical approaches. However, it is not usually possible to come to an estimate without making certain assumptions. The validity of the assumptions regarding how the INMB distribution will change in the future must be examined before any decision is made. In order to minimize the effect of the uncertainty in the calculation of the EVSI, it is best to simulate the future INMB based on a range of possibilities in many iterations, and then compute the expected EVSI over all iterations. Eckermann and Willan[6] also suggest calculating an optimum trial sample size before identifying the optimal strategy (hence optimizing the EVSI with respect to a certain n, and using the optimal ENG in the decision).[6] However, it might not always be possible to run future studies with the exact optimal patient numbers. Especially when data is gathered in the form of a registry (which is quite often the case in an access with evidence development decision) the number of patients is a function of the accrual rate and it is hard to fix at an optimal pre-calculated n.

1.4 What is the best time for re-evaluation

While the above refers to a delayed definite decision point, it does not discuss when this decision point is to be. This timing could be based on an explicit trade off between costs and benefits. To find a suitable time point for reconsidering the decision, time is divided into some stages (say i=0, 1, … , T) of fixed duration*. The duration of each stage may not be the same for different health technologies and conditions. The end point of each stage is a potential time for re-evaluation. At the end of each stage the ENG is evaluated and by calculating how the ENG increases with an additional stage, an optimal number of stages may be found. Two different approaches to find this optimal number exist, either ex ante, or "on the go". In the first case, the optimal time for re-evaluation is determined based on the information available at baseline (ex ante, i.e. at i=0). The basic idea is that the distribution of the INMB will be simulated for (future) consecutive re-evaluation points. Subsequently, the ENG will be calculated for a number of stages. At stage i, ENG_i is calculated as the gains between stage i-1 and i. The sum of consecutive ENG_i values up to any stage is the cumulative ENG. When the ENG_i values are positive, the cumulative ENG increases and when the ENG_i becomes negative, the cumulative ENG decreases. The maximum

** Note that for reasons of practical feasibility, a maximum time T must be set to the period of research. This avoids the reconsideration to be delayed to a time point so late that yet newer technologies are already introduced and a decision does not make sense anymore.*

cumulative ENG determines the optimal stage to stop research and to make a final decision. A model representing the calculations for this method has been programmed before, and a graphical user interface is openly available for users to test the outcomes.

In the latter case, the optimal time for re-valuation is based on the new information that is retrieved from the additional research (on the go).Therefore, the parameters that will determine the consecutive distributions of the INMB can be directly observed using the study information up to the end of the ith stage. Such an update will still be uncertain since the observed data sample is just one from the range of possible samples, but it is more precise than the ex-ante approach. However, in this case the decision maker has to wait for data collection before being able to estimate a decision time. Besides that, a stopping criterion for the research period must be established in the beginning.[5] This method implies specific designs like a sequential trial, or an observational study with flexible follow-up time. It will also require a heuristic to determine when ENG is at its maximum, since it is in general not possible to find this maximum analytically.[6,13]

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2 Technical appendix 1: Probabilistic sensitivity analysis

2.1 What is it?

In a probabilistic sensitivity analysis (PSA) the uncertainty around the input parameters of a decision analytic model is quantified through probability distributions. The purpose of the PSA is to estimate the impact of all these sources of uncertainty on the model outcomes. This is done by varying all input parameters at the same time for a large number of iterations. In each iteration a random value from each of the probability distributions is drawn and these drawn values are used as input parameters for the decision model to calculate the model outcomes. Thus, a new estimate of the incremental costs and incremental effects, and therefore the incremental cost-effectiveness ratio (ICER), is obtained per iteration.

2.2 How to perform it?

For a detailed explanation on how to perform a PSA we refer to the handbook by Briggs et al.[1] Points of attention when performing a PSA should include:

- Parameterization of all uncertainty relevant to the policy decision, the use of proper probability distributions for the parameters at hand, and the inclusion of relevant correlations between parameters.
- Perform a sufficiently large number of iterations.[2]
- Use a well working random number generator and define a random seed in order to be able to reproduce the model outcomes.[3]
- In case of micro simulation models be careful not to mix variability/heterogeneity and uncertainty.[4,5]

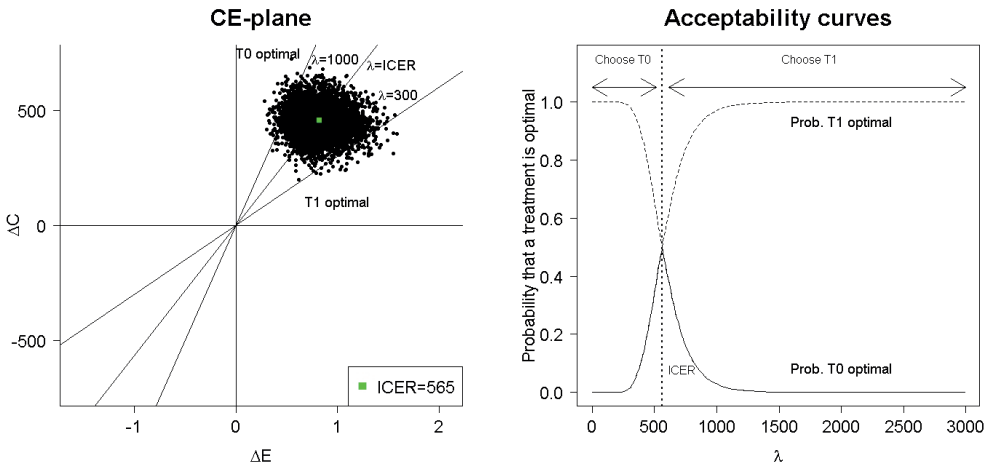
With regard to the first point, it is important to bear in mind that the PSA will only reflect the uncertainties that are quantified by the use of the chosen distributions (and correlations) for parameters. As VOI and expected net gains analyses draw on the results of the PSA, for these analyses the same prerequisite applies. Therefore, in order for these analyses to be meaningful, it is particularly important that the structure of and the parameter distributions in the decision analytical model reflect the actual decision problem as well as possible.[6] A checklist has been developed to systematically assess whether a health technology assessment reflects the decision problem.[7] This checklist can be a helpful tool to increase the applicability of the results of the model-based economic evaluation to the decision problem at hand. The checklist consists of 11 questions, of which the following are particularly relevant for reimbursement/adoption decisions:

- What is the patient population relevant for the decision problem? (e.g., age, health status, sex, other characteristics)
- What are relevant comparators for the decision problem? (e.g., care as usual, alternative technologies)
- How are the technologies embedded in clinical practice? (e.g., diagnostics, clinical instead of research protocol)
- Which time horizon is relevant for the decision problem? (e.g., lifetime, one year)
- Which consequences are relevant for the decision problem? (e.g., final versus intermediate outcomes, indirect and/or rare consequences)
- What is the patient use that is relevant for the decision problem? (e.g., uptake, compliance, adherence)
- What is the use of the technology by health care professionals that is relevant for the decision problem? (e.g., skills, experience, beliefs)
- What price level and resource use are relevant for the decision problem? (e.g., personnel providing the intervention)

2.3 How to report its results?

PSA results are usually presented as a scatter plot of incremental effects and incremental costs on the cost-effectiveness (CE) plane. An example of this can be seen in Figure 1, where two hypothetical health technologies (denoted by T0 and T1) are being compared. Furthermore, the cost-effectiveness acceptability curve (CEAC) describes for a range of values of the threshold ICER the probability that a technology is cost-effective.[8] The CEACs corresponding to the PSA described in Figure 1 can be observed in Figure 2. For the situation where the scatter plot covers several quadrants, and for CEACs in case of multiple treatments being compared, we refer to Fenwick et al. 2004.[9]

Figure 1. CE plane with PSA outcomes (left) and CEACs (right).



2.4 Templates

The online assignments in the handbook by Briggs et al.1 can be used as template for modellers using Excel. The R package 'BCEA' developed by Baio and Berardi can be used to perform cost-effectiveness analyses including PSA.[10]

References

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3 Technical appendix 2: Value of information analysis

3.1 Expected value of perfect information

The first step in a value-of-information (VOI) analysis is the estimation of the expected value of perfect information (EVPI), which is the maximum amount the decision-maker should be willing to pay to eliminate all uncertainty in the decision to adopt a new health technology. The decision is based on the expected net benefit given current information. Thus, the health technology with the highest expected net monetary benefit (NMB) is chosen as optimal. Given the results of a probabilistic sensitivity analysis (PSA), the EVPI can be calculated in three equivalent ways:

1. As the average of the maximum net benefits across all PSA outcomes (expected net benefit of perfect information) minus the maximum average net benefit for the different health technologies (expected net benefit given current information). With the notation in Briggs et al.[1], the EVPI can be expressed as mean (Max(NMB)) - Max(mean(NMB)).
2. As the average of the opportunity losses of all PSA outcomes, where opportunity loss is defined as the difference in net monetary benefit between the optimal health technology and the technology chosen based on current information.
3. As the probability of making a wrong decision (error probability) times the average of the nonzero opportunity losses.

We would like to emphasize that all the elements needed to compute the EVPI can be estimated from a PSA. An example of EVPI calculation for two health technologies, denoted by A and B, is shown in Table 1.

Table 1. EVPI calculation using PSA results

PSA iterations (1=yes)	NMB(A)	NMB(B)	Max(NMB)	Opp. Loss (L)	Wrong decision?
1	€ 13,564	€ 20,355	€ 20,355	€ 0	0
2	€ 20,891	€ 16,809	€ 20,891	€ 4081	1
3	€ 15,202	€ 16,093	€ 16,093	€ 0	0
4	€ 18,670	€ 21,451	€ 21,451	€ 0	0
5	€ 14,641	€ 10,313	€ 14,641	€ 4327	1
…	…	…	…	…	…
10,000	…	…	…	…	…
mean	€ 17,779	€ 18,084	€ 19,809	€ 1724=EVPI	0.3 = error probability

*EVPI = mean(Max(NMB)) - Max(mean(NMB)) = mean(L) = mean(L|L>0) * error probability*

With the estimates of the incremental costs and incremental effects obtained in a PSA we can estimate the mean net monetary benefit associated to each health technology, the opportunity loss and the error probability. The results in Table 1 show that technology B should be chosen as optimal since it has the highest mean net monetary benefit. However, the probability of making the wrong decision is 0.3 and the estimated EVPI is equal to € 1724.

It is important to stress that the EVPI estimated above is per patient. In order to reflect the actual value of information that is relevant to the decision about additional research the EVPI has to be scaled up to a population level. Following Ades et al. definition if Ni denotes the number of patients that is relevant for the decision problem in year i[2], T denotes the effective lifetime (in years) for the new health technology and α is a discount rate, then the population EVPI (PEVPI) can be defined as follows:

$$PEVPI = EVPI * \sum_{i=1}^{T} \frac{N_i}{(1+a)^i}$$

Note that both N_i and T may also be unknown parameters on which additional information could also be sought. Additional research might be justified, at least in theory, when the PEVPI exceeds the expected costs of additional research. When this occurs, decision-makers should identify the input parameters for which extra data collection is needed. This is assessed by the expected value of partial perfect information (EVPPI).

3.2 Expected value of partial perfect information

The contribution of individual parameters or groups of parameters to the overall decision uncertainty and its consequences can be examined through expected value of partial perfect information (EVPPI) analyses. An EVPPI requires a two-level sampling algorithm in which multiple simulations are performed for different values of the parameter of interest (denoted by Θ_i). The two-level sampling algorithm uses two nested levels of Monte Carlo sampling over the plausible ranges for both the parameter(s) of interest, and the remaining uncertain parameters (denoted by Θ_c). There are different algorithms (which are mathematically equivalent) to compute the EVPPI[3] but in this technical appendix we use the approach by Claxton1. It consists of an inner loop and an outer loop. In the inner loop, a value is drawn for the parameter of interest Θ_i, and with that fixed value, a simulation is done where all other parameters are drawn once in each iteration, similar to the normal PSA. As for the EVPI, the $\text{Mean}_{\Theta_c}(\text{NMB}(\cdot|\Theta_i))$ is recorded, as illustrated in Table 2. This procedure is repeated many times in an outer loop, each time with a new fixed value of the parameter of interest. Now all data that are needed to calculate the EVPPI for the parameter of interest are available, as shown in Table 3. The EVPPI for the parameter of interest can be calculated by subtracting $\text{Mean}^{\Theta i}(\text{Max}_T\{\text{Mean}_{\Theta c}(\text{NMB}(\cdot|\Theta_i))\})$ from $\text{Max}_T\{\text{Mean}_{\Theta i}(\text{Mean}_{\Theta c}(\text{NMB}(\cdot|\Theta_i)))\}$.

Table 2. EVPPI calculation part I – Inner loop.

Inner loop		
iterations	$\text{NMB}(A\|\Theta_i)$	$\text{NMB}(B\|\Theta_i)$
1	€ 15,654	€ 21,552
2	€ 22,810	€ 16,090
3	€ 14,020	€ 13,903
4	€ 17,706	€ 19,514
5	€ 23,461	€ 20,103
…	…	…
1,000	…	…
$\text{Mean}_{\Theta c}(\cdot)$*	€ 19,798	€ 19,845

** $\text{Mean}_{\Theta c}(\text{NMB}(\cdot|\Theta_i))$ is recorded after the inner loop is completely run (with Θ_i at a fixed value) and it is used as input for one iteration in the outer loop (see e.g. Table 3 – the input for iteration 1 is the output from Table 2).*

Table 3. EVPPI calculation part II – Outer loop.

Outer loop			
Iterations	$\text{Mean}_{\Theta c}(\text{NMB}(A\|\Theta_i))$	$\text{Mean}_{\Theta c}(\text{NMB}(B\|\Theta_i))$	$\text{Max}_T\{\text{Mean}_{\Theta c}(\text{NMB}(\cdot\|\Theta_i))\}$
1*	€ 19,798	€ 19,845	€ 19,845
2	€ 25,684	€ 23,528	€ 25,684
3	€ 18,799	€ 19,587	€ 19,587
4	€ 22,365	€ 20,634	€ 22,365
5	€ 21,951	€ 22,032	€ 22,032
…	…	…	…
5,000	…	…	…
$\text{Mean}_{\Theta i}(\cdot)$	€ 22,450	€ 21,895	€ 23,978

EVPPI = $\text{Mean}_{\Theta i}(\text{Max}_T\{\text{Mean}_{\Theta c}(\text{NMB}(\cdot|\Theta^i))\})$ - $\text{Max}_T\{\text{Mean}_{\Theta i}(\text{Mean}_{\Theta c}(\text{NMB}(\cdot|\Theta_i)))\}$ = € 23,978 - € 22,450 = € 1,528

** The input for every iteration in the outer loop is the result of a complete run in the inner loop (see Table 2). Note that the fixed values of Θ_i differ between different inner loops.*

It is important to stress that the number of inner- and outer-loops must be chosen carefully. The approach described above may require a large number of runs to obtain accurate partial EVPI estimates, which can be a practical limitation. Moreover, if a small number of inner samples is used the EVPPI estimates can be biased. The algorithm presented in Oakley et al.[4] can be used to determine how many outer and inner loops are needed for a desired level of accuracy. A practical application of this approach can be found in Mohseninejad et al.[5]

A new approach for computing EVPPI has been recently proposed.[6] It is a regression-based approach that requires only the PSA sample. The method is implemented in R and the code is made available in the paper. Moreover, an online application of this R code is available at: http://savi.shef.ac.uk/SAVI .

3.3 Expected value of sample information and expected net gain

The expected value of sample information (EVSI) represents the reduction in the expected loss due to obtaining sample information. The EVP(P)I establishes an upper limit on the societal returns to further research. However, perfect information cannot be achieved in practice (an infinitely large sample would be needed). Therefore, an optimum sample size for a future study must be found and the relevant comparison weighs the potential benefits of this study (i.e. the EVSI) against the expected costs of obtaining the sample. The difference between the EVSI and the cost of sampling is the expected net gain (ENG) and represents the societal return to proposed research. Thus, the sample size that maximizes the ENG represents also the optimum size for future research.

The computation of the EVSI involves simulating a "new" hypothetical study result which will be used to update our prior knowledge about the parameters of interest (Θ_i). This method is known in statistics as Bayesian update. The new study result (with sample size n) is simulated according to a certain likelihood function from where we obtain additional information about the parameters of interest. With these "new" data (denoted by X) we update our prior beliefs about the parameters of interest by computing their posterior distribution ($\Theta_i|X$). The difference with the prior distribution is that the parameters of the posterior distribution have been changed ("updated") based on the "new" observed data of the hypothetical study. The choice of an appropriate likelihood function for the "new" study requires scientific expertise on both process and probabilistic modelling. As suggested by Ades et al.[2] the likelihood function of the 'new' data can be chosen such that it is conjugate with the prior distributions. This means that the posterior distribution is in the same family of distributions as the prior distribution that was used in the initial model and the parameters of the posterior distribution can be calculated as a function of the parameters of the prior distribution and the simulated data. Examples of a Bayesian update for different prior and likelihood functions can be found in many text books (see e.g. Lee[7]).

The EVSI is defined as the difference between the expected value of a decision made after data X have been collected and the expected value of a decision made given current information. Its computation consists of an inner loop and an outer loop as in the EVPPI. In the inner loop, first a value is drawn for the "new" observed data X and then the parameters of interest are updated $\Theta_i|X$. With that fixed (posterior) value, a simulation is done where all other parameters are drawn once in each iteration, similar to the normal PSA. Furthermore, as for the EVPI, the $Mean_{\Theta}c(NMB(\Theta_i|X)$ is recorded, but now conditional on the fixed updated parameter of interest, as shown in Table 4. This procedure is repeated many times in an outer loop, each time with a new value of the "new" observed data. Now all data that are needed to calculate the EVSI for the parameter of interest are available, as can be seen in Table 5. The EVSI for the parameter of interest can be calculated by subtracting the $Max_T\{Mean_{\Theta}NB(\Theta)\}$, which was obtained from the EVPI calculation (see Table 1), from the $Mean_X(Max_T\{Mean_{\Theta c}NB(\Theta_i|X)\})$.

Table 4. EVSI calculation part I – Inner loop.

Inner loop		
iterations	$NMB_A(\Theta_i\|X)$	$NMB_B(\Theta_i\|X)$
1	€ 24,565	€ 21,562
2	€ 25,051	€ 26,909
3	€ 24,262	€ 23,390
4	€ 27,600	€ 29,451
5	€ 23,419	€ 20,310
…	…	…
1,000	…	…
$Mean_{\theta c}(\cdot)$*	€ 24,996	€ 25,005

** $Mean_{\theta c}(NMB(\Theta_i|X))$ is recorded after the inner loop is completely run and it is used as input for one iteration in the outer loop (see e.g. Table 5 – the input for iteration 1 is the output from Table 4).*

Table 5. EVSI calculation part II – Outer loop.

Outer loop			
Iterations	$Mean_{\theta c}(NMB_A(\Theta_i\|X))$	$Mean_{\theta c}(NMB_B(\Theta_i\|X))$	$Max_T\{Mean_{\theta c}(NMB(\Theta_i\|X))\}$
1*	€ 24,996	€ 25,005	€ 25,005
2	€ 25,846	€ 23,852	€ 25,846
3	€ 28,979	€ 29,758	€ 29,758
4	€ 22,536	€ 20,463	€ 22,536
5	€ 21,195	€ 22,203	€ 22,203
…	…	…	…
5,000	…	…	…
$Mean_x(\cdot)$			€ 25,109

*$EVSI = Mean_x(Max_T\{Mean_{\theta c}(NMB(\Theta_i|X))\}) - Max_T\{Mean_\theta(NMB(\Theta))\}$ = € 25,109 - € 18,084** = € 788*

** The input for every iteration in the outer loop is the result of a complete run in the inner loop (see Table 4). ** This is the mean net monetary benefit of alternative B in Table 1.*

An approach similar to the one used for computing the EVPPI based on a PSA sample[6], has also been proposed, although it is not published yet (www.shef.ac.uk/polopoly_fs/1.327190!/file/EVSI_Discussion_paper_Strong_Oakley_Brennan.pdf). The method is also implemented in R and the code is made available online (www.shef.ac.uk/polopoly_fs/1.378931!/file/SMDM_VoI_course.zip).

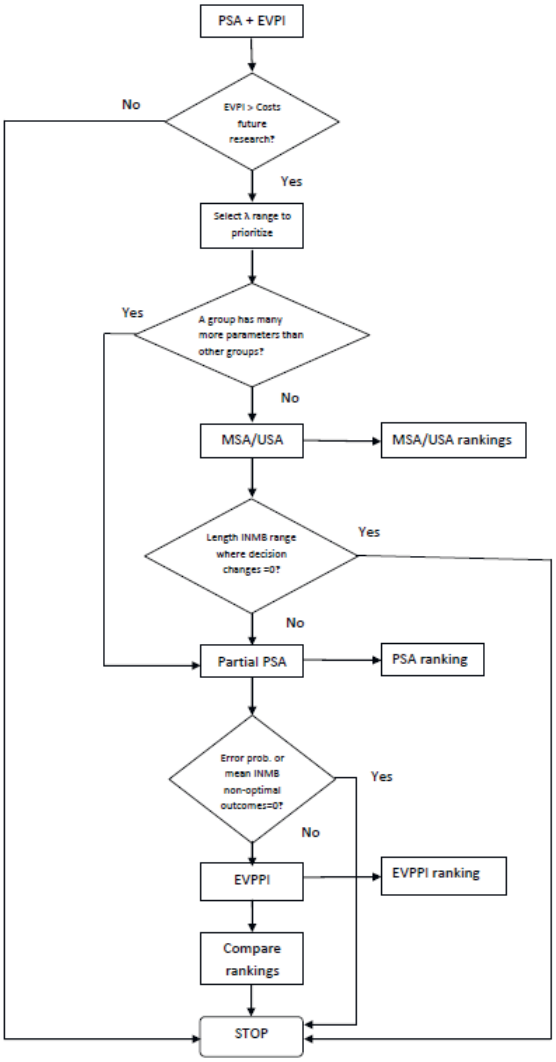
In the papers by Eckermann (see for example 8) the EVSI is operationalized in a different way (see technical appendix 3 for details). There the EVSI is defined as the difference between the EVPI given current information and the EVPI after data X have been collected. The need for and prioritization of further research is then informed using the ENG. However, prioritization as defined above represents a different problem than in Eckermann et al. papers where different HTAs are prioritized, according to the ENG until certain available budget is consumed. Prioritization is defined above within a particular HTA, where the focus is on (a group of) input parameters, and requires partial methods. This issue is not addressed in Eckermann et al. papers as they state that their methodology does not allow partial analyses, for which they refer to Ades et al.[2]

3.4 When to perform a full EVPPI analysis

EVPPI procedures can be computationally burdensome. For complex decision-analytic models the number of iterations needed to obtain accurate EVPPI estimates may be a practical limitation. However, EVPPI analyses may not always be necessary; a more extensive (partial probabilistic) sensitivity analysis (plus an EVPI analysis) could be used to prioritize research in the period of conditional reimbursement.[9] We propose the following recommendations (see Figure 1). The analysis should start with a PSA/EVPI calculation to determine whether further research might be worthwhile and on which range of values of λ (if any) we should prioritize. Assuming we want to start with the computationally least expensive method

and only use more complex methods when strictly necessary, we come to the following sequence. If all the groups of parameters have (approximately) the same number of individual parameters, we may start with a multivariate sensitivity analysis, from where we compute the length (or the proportion with respect to the largest INMB range) of the INMB range that can change the choice of the optimal health technology. When this is zero for a group, there is no added value in performing an univariate sensitivity analysis, a partial PSA or a VOI analysis. Otherwise, we can proceed with the univariate sensitivity analysis, if we want to identify the most important parameters within the group, or with the partial PSA per group. From the partial PSA we compute the error probability and the mean INMB (in absolute value) of the non-optimal outcomes. Note that when one of these (or both) is zero for a group, there is no added value in computing the univariate partial PSA (or the EVPPI for this group). Otherwise, if we want to identify the most important parameters within the group, we can proceed with the univariate partial PSA. When the purpose of the study at hand is the prioritization of additional research only the analysis can be stopped here. If we really want to know the value of doing additional research, the computation of the EVPPI is always required.

Figure 1. Flowchart with guidelines to establish the need for EVPPI.



3.5 How to report its results?

EVPI and EVPPI results are usually depicted graphically for a range of values of the threshold ICER, similarly to cost-effectiveness acceptability curves. An example of these curves (Corro Ramos et al.[10]) can be seen in Figure 2. EVSI and ENG curves are similar to EVPI curves but at each value of the threshold ICER λ, the curves are depicted for different values of the simulated sample size n. An example of these curves can be seen in Figure 3.

Figure 2. Examples of EVPI and EVPPI curves.

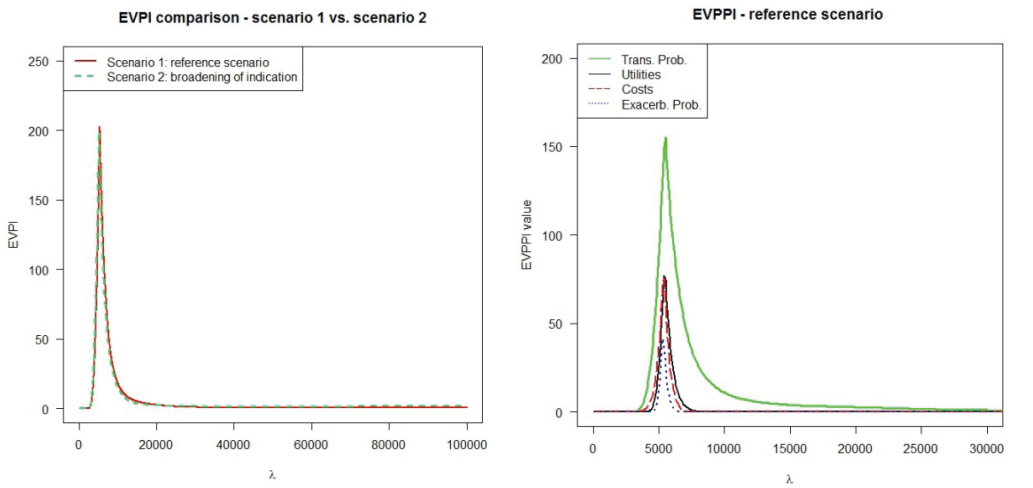
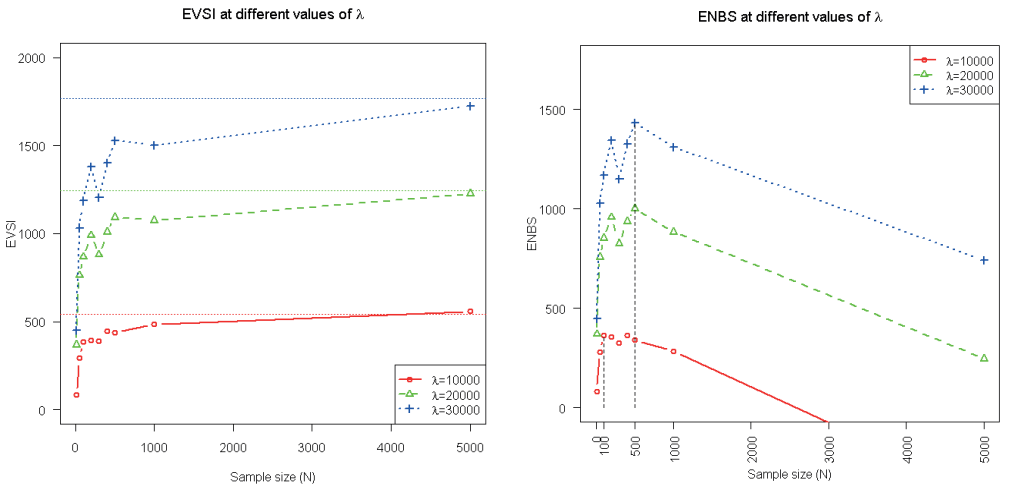


Figure 3. Examples of EVSI and ENG curves.



3.6 Templates

Different templates can be used to help modellers with the implementation of the VOI concepts discussed above. The online assignments in the handbook by Briggs et al.1 can be used as template for modellers using Excel. The R package 'BCEA' developed by Baio and Berardi can be used to perform economic evaluations including VOI analyses (cran.r-project.org/web/packages/BCEA/BCEA.pdf). The non-parametric regression-based approaches to EVPPI (www.shef.ac.uk/polopoly_fs/1.305039!/file/R_functions.txt) and EVSI can also be downloaded from Strong website (www.shef.ac.uk/polopoly_fs/1.378931!/file/SMDM_VoI_course.zip).

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4 Technical appendix 3: Quantitative assessment of the ENG question

In order to address question 3 in a quantitative way, we use the framework introduced by Eckermann and Willan (2007).[1] Although this framework is only considering trials as a method of data gathering, it can be easily adjusted to address other types of research like registries and observational studies. The key parameters to add to the methods described in Technical appendix 2 – Value of information analysis are the opportunity losses and reversal costs. Opportunity losses are the health benefits forgone due to delaying the decision, since more patients could have benefited from the optimal health technology if the definite decision was made earlier. Costs of reversal refer to the costs to the healthcare providers regarding the change in the adoption decision, as well as the sunk costs of training and capital for a health technology which later turns out to be the non-optimal option. If ENG^D denotes the expected net gain of the decision "adopt the new health technology only in research (delay decision)" (i.e. the value of sample information assuming delay minus the costs of the trial), and ENG^A denotes the expected net gain of the decision "adopt new health technology with more research" (i.e. the difference between the value of sample information assuming adoption and the cost of the research), the following decision rules can be defined:

Decision rule 1: $ENG_D < 0$ and $ENG_A < 0$ => Recommend the new technology:
Decision rule 2: $ENG_A < ENG_D$ and $ENG_D > 0$ => Recommend the current technology and more research
Decision rule 3: $ENG_D < ENG_A$ and $ENG_A > 0$ => Recommend the new technology and more research

Decision rule 1 indicates that when the expected net gains of both types of additional research are negative (i.e. the additional research is not worthwhile), the new technology must be adopted with no further trials (this corresponds to option E in Figure 1 in the main text). We would like to emphasize that the calculations here are different from those in Technical appendix 2 – Value of information analysis, since now opportunity losses are considered. Hence, although additional research may be worthwhile when considering costs of research (i.e. "yes" to question 2), adding opportunity losses may change the recommendation to adoption with no further trials (option E in Figure 1 in the main text). Decision rule 2 indicates that when expected net gains of adopt and trial are smaller than delay and trial, the decision must be delayed while additional data are being gathered (only-in-research; hence "yes" to question 3). Finally, decision rule 3 states that when the expected net gains of adopt and trial exceed the expected net gains of delay and trial, the decision is to adopt the new technology and also conduct further research (access with evidence development; hence "no" to question 3). Next we explain the calculations of ENG_D and ENG_A in detail.

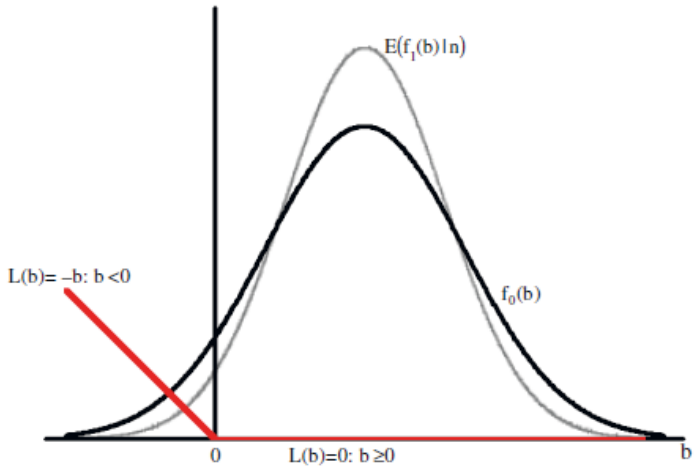
4.1 Expected net gains for only in research

This decision path involves continuing the current health technology (B), while doing research on the new health technology (A). It keeps the option of a (randomized) study design in the jurisdiction ("yes" to question 3 in Figure 1 in the main text).
From now on it is assumed that the type of additional research indeed is an RCT because it is most common, although this framework is also applicable to other study types like single-arm trials.[2] Thus, for any sample of patients (e.g. for the patients in a trial) the Incremental Net Monetary Benefits (INMB) of the new health technology (A) versus the current technology (B) can be estimated as $\lambda(EA-EB)-(CA-CB)$, where λ represents the willingness-to-pay threshold, EA and EB the mean effects of the new and current health technology, and CA and CB are the mean costs of the new and current health technology, respectively.
Let b be the estimate of the INMB. As in the framework developed by Eckermann and Willan[1] we assume that the INMB follows a Normal distribution. To calculate the expected value of sample information for delaying the decision until time t, the opportunity loss function must be first calculated. For this purpose, suppose the situation depicted in Figure 1. The black curve represents the (prior) distribution

of the INMB at time o with a positive expected value (which corresponds to the peak of the curve).The gray line represents the (posterior) distribution of the INMB after observing the trial data. As shown in Figure 5, after observing trial data, the posterior expected INMB is still positive, meaning that the decision would be to adopt the new technology. However, if it turns out that the current technology was actually more cost-effective (which occurs when b<o), patients would have not been using the optimal health technology, which leads to opportunity losses, denoted by L(b) and illustrated by the red line in Figure 1. The opportunity loss is zero when b is positive (because the new technology is the optimal one) and starts to increase with negative values of b. The opportunity loss function as depicted in Figure 1 is hence defined as follows:

$L(b) = o$ $\quad if\ b \geq o$
$L(b) = -b$ $\quad if\ b < o$

Figure 1. The opportunity loss function and INMB distributions in only-in-research case



For each value of b where b<o, the opportunity loss for the prior and the posterior INMB can be found by multiplying the loss function (red line) by the probability of making a wrong decision (black and gray lines, respectively). By taking the integral between minus infinite and zero we obtain the expected opportunity loss for the prior and posterior INMB. The difference between these two opportunity losses are the opportunity losses avoided by waiting for more information. This is the monetary value of the gain obtained by going from the prior INMB to the posterior INMB. The expected value of sample information at time t for the only-in-research decision is then calculated by multiplying these per patient gains by the size of the population that would benefit from the decision, i.e.:

$$EVSI_D = N_t \left[\int_{-\infty}^{U} -b\{(f_o(b)\}db - \int_{-\infty}^{U} -b\{(f_1(b)\}db \right]$$

where Nt is the number of patients that can benefit from the new health care health technology at time t, and fi() is the probability density function from the Normal distribution (i=o: time o, that is the prior INMB and i=1: after a delay of t, that is, the posterior INMB).

To calculate the study costs, let k represent the incidence rate of the condition in question, n the number of patients per arm recruited to the trial, t the length of the delay period, Cf the fixed cost of doing the trial and Cv the additional variable cost per patient of being on trial relative to the same health technology outside of trial (assumed to be the same by treatment arm). Since the new technology is not yet adopted, patients who are outside of the trial are still missing the opportunity of using the new technology (for duration of t). Hence, a loss equal to the initial estimation of the INMB (bo) is borne by tk-n patients. Counting for costs of the trial, we have:

$$TC_D = C_f + 2nC_v + (tk - n)b_o$$

And therefore:

$$ENG_D = EVSI_D - TC_D$$

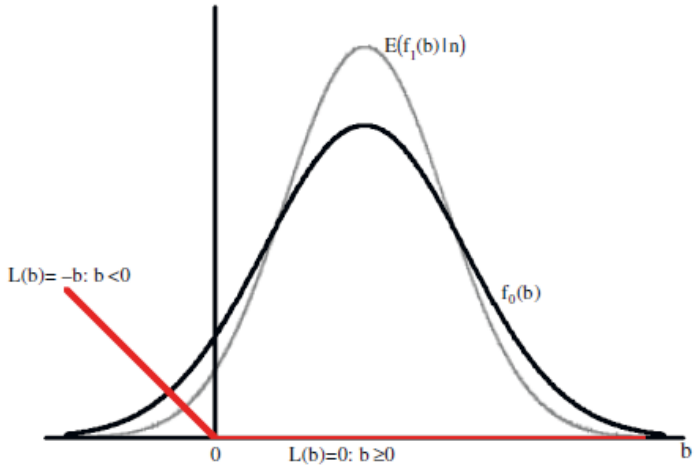
4.2 Expected net gains for access with evidence development

When considering the expected value of further research for the case in which the new innovation is adopted, the first issue to address is the costs of reversal. Assuming Cr are the expected costs of reversing the adoption decision, the opportunity loss function for adopting the new health technology conditional on costs of reversal can be defined as follows:

$L(b) = o$ *if* $b \geq - Cr/Nt$
$L(b) = - (b+Cr/Nt)$ *if* $b < - Cr/Nt$

Since reversing the decision is costly, the loss function shifts in a way that the opportunity loss for some negative INMB values is still considered zero. The reason is that for these negative values the reversal costs would actually prevent changing the decision and hence the original decision would still be the best one, implying no opportunity costs. This is illustrated in Figure 2.

Figure 2. The opportunity loss function and INMB distributions in access with evidence development case



The calculation of the EVSI is similar to the only-in-research case, only with a different opportunity loss function. Thus the expected value of sample information for the access with evidence development case is given by:

$$EVSI_A = N_t \left[\int_{-\infty}^{-C_r/N_t} -(b + C_r/N_t)\{f_o(b)\}db - \int_{-\infty}^{-C_r/N_t} -(b + C_r/N_t)\{f_1(b)\}db - \right]$$

Here studies are commonly registries. Adjust next sentence. For this case of adoption, the only patients using the non-optimal choice are the patients in one arm of the trial, and the total costs are defined as:

$$TC_A = C_f + 2nC_v + nb_o$$

And finally:

$$ENG_A = EVSI_A - TC_A$$

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