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Value of Information Analysis for Research Decisions– An Introduction:

Report 1 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force

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Precis:

This report introduces VOI analysis, defines key concepts and terminology, and outlines VOI's role in decision-making, including the steps involved in undertaking and interpreting VOI analyses.

Highlights:

- Decision uncertainty, while not relevant to a risk-neutral decision-maker identifying the optimal choice in the current circumstances, is of interest for addressing the decision of whether to collect additional information to better inform future decisions. As such, probability distributions should be assigned to parameters to characterize uncertainty in the current evidence base, with probabilistic analysis used to assess the uncertainty. Parameters excluded from the PA will be excluded from the analysis of uncertainty.
- Value of Information (VOI) analysis provides a formal assessment of the value of research, based on the extent to which the information generated through research would improve the expected payoffs associated with a decision by reducing the uncertainty surrounding it. This value can then be compared to the cost of acquiring the information, to determine whether the research is potentially worthwhile and might be of value to undertake.
- This report was written to provide decision-makers, tasked with making decisions about the adoption of healthcare and/or the funding of healthcare research, with an introduction to the concept of VOI analysis and to the decisions that can be supported by this type of analysis, including: 1) research prioritization; 2) efficient research design; 3) reimbursement; and 4) efficient decision-making over the life cycle.
- The report describes the process of VOI analysis, providing a top-level description of the methods and steps involved in undertaking and interpreting the results of such an analysis, from conceptualizing the decision problem, through to development of the decision model, parameterizing the model, running the probabilistic analysis, calculating the value of information (perfect, partial perfect and sample) and determining the worth of research (expected net benefit of sampling).
- This report provides nine recommendations for good practice when planning, undertaking or reviewing the results of VOI analyses with the aim to improve accessibility of VOI analysis for all stakeholders.

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Abstract

(143 words)

Healthcare resource allocation decisions made under conditions of uncertainty may turn out to be suboptimal. In a resource constrained system in which there is a fixed budget, these suboptimal decisions will result in health loss. Consequently, there may be value in reducing uncertainty, through the collection of new evidence, to make better resource allocation decisions. This value can be quantified using Value of Information (VOI) analysis. This report, from the ISPOR VOI Task Force, introduces VOI analysis, defines key concepts and terminology, and outlines the role of VOI for supporting decision-making including the steps involved in undertaking and interpreting VOI analyses. The report is specifically aimed at those tasked with making decisions about the adoption of healthcare and/or the funding of healthcare research. The report provides a number of recommendations for good practice when planning, undertaking or reviewing the results of VOI analyses.

Keywords: value of information, value of research, decision-making, expected value of information, expected net benefit of sampling, expected value of perfect information.

Running Title: VOI: An introduction.

[Box 1 here]

Box 1: Background on the Task Force Process

The proposal to initiate an ISPOR Value of Information Good Practices Task Force was evaluated by the ISPOR Health Science Policy Council then recommended to the ISPOR Board of Directors for approval. The task force was comprised of international subject matter experts representing a diverse range of stakeholder perspectives (academia, research organizations, government, regulatory agencies and commercial entities). The task force met approximately every five weeks by teleconference and in person at ISPOR conferences. All task force members reviewed many drafts of the report and provided frequent feedback in both oral and written comments. To ensure that ISPOR Good Practices Task Force Reports are consensus reports, findings and recommendations are presented and discussed at ISPOR conferences. In addition, the first and final draft reports are circulated to the task force's review group for a formal review. All reviewer comments are considered. Comments are addressed as appropriate in subsequent versions of the report. Most are substantive and constructive improving the report.

1. Introduction

VOI in a nutshell

Healthcare decision-makers, tasked with selecting which technologies to adopt, need to determine the payoffs associated with each. These payoffs, usually represented in cost-effectiveness analysis by net benefits (NB) expressed in either health or monetary terms, are uncertain, reflecting imperfect and incomplete evidence. This means that there is inevitably some risk that decisions based on the available information will be incorrect, with consequences in terms of payoffs. This introduces the possibility of error into decision-making (decision uncertainty); there is a chance that the best decision made today is suboptimal, in the sense that better outcomes could have been achieved with a different decision had more information been available. Acquiring more information could reduce uncertainty in the evidence base, and the associated risk and consequences of making the wrong decision in the future, but can be costly. Before resources are invested in gathering additional information (e.g. through research), the associated costs and benefits should be considered. Value of information (VOI) analysis provides a framework to assess these costs

and benefits. Specifically, VOI analysis provides a formal assessment of the value of research, based on the extent to which the information improves the expected payoffs associated with a decision by reducing uncertainty. This value is compared to the cost of acquiring the information to determine whether it is worthwhile.

A Task Force for VOI

While VOI analyses are increasingly published in academic journals, uptake in real world decision-making remains limited (1). This is partially due to perceptions that it is complex to perform, difficult to interpret, requires substantial computational time, and does not reflect key relevant uncertainties (2), and partly due to lack of dissemination of methods and capacity to undertake this type of analysis (3). As such, ISPOR formed the VOI Task Force to improve accessibility of VOI analysis for all stakeholders, through development of good practice guidance for using VOI analysis to inform research prioritization (both private and public) and other decisions pertaining to the development and reimbursement of healthcare technologies.

VOI Task Force Reports

This first report from the ISPOR VOI Task Force is directed toward decision-makers; including funders of research tasked with determining which studies to support, stakeholder groups identifying research priorities, or healthcare payers using formal assessment processes to inform their decisions about funding healthcare technologies.

The report introduces the concept of VOI analysis, identifies the decisions that can be supported by VOI analysis, and describes the methods, details the steps and the interpretation of results. The report presents emerging good practice recommendations throughout the text, for planning, undertaking or reviewing VOI analysis. The report does not discuss the costing or grading of evidence from specific studies, or the responsibility for undertaking additional research when it is found to be valuable.

The second report from the ISPOR VOI Task Force (4), which is directed towards methodologists and/or analysts undertaking VOI analysis to inform decision-making, provides detailed guidance and emerging good practices on the principal methods required for assessing the value of information to inform a range of decisions.

Report 1 assumes an underlying CE framework where the objective is to maximize health from a limited budget; this is relaxed in Report 2 in which a more generic objective function is considered

(4). In both reports, technologies should be taken to refer to any healthcare, or public health, interventions, procedures, programs or policies.

2. How can VOI be used? Healthcare decisions supported by VOI analysis

VOI analysis can inform a variety of healthcare decisions including: (i) research prioritization; (ii) efficient research design; (iii) reimbursement; and (iv) efficient decision-making over the life cycle. Box 2 provides a brief summary of the application of VOI analysis to decision making in healthcare, with references.

Research prioritization decisions

Research funders have limited budgets, which necessitates prioritizing research investments. VOI analysis can support research prioritization and commissioning decisions, by quantifying the value of the additional information generated by each proposed study. The proposals can then be ranked according to expected return, assessed by subtracting the expected costs from this value, to determine priorities (5, 6,7). Pilot projects to assess the feasibility of using VOI analysis for research prioritization have been undertaken in both the UK (8,9) and US (10,11,12).

Efficient research design

VOI analysis can also inform research design to maximize the return on investment. This involves assessing the value of studies of different types (e.g. primary or secondary) and scopes (in terms of study size, length of follow-up etc.) based on their ability to reduce uncertainty. This value is compared to the cost of the research to identify the most efficient design, identified as that which maximizes the expected return (5).

Reimbursement and coverage with evidence development (CED) decisions

VOI analysis can be used to inform decisions about reimbursement of healthcare technologies when the evidence base to support their use is not mature, such as required in systems with early access arrangements. Use of a premature evidence base for decision-making carries substantial risk and uncertainty for patient outcomes, but also creates a disincentive to invest in further research that would reduce this uncertainty and risk. Reimbursing the technology could waste resources on cost-ineffective, or even harmful, practices which, once adopted, are difficult to eliminate (13). Conversely, delaying adoption until further research is conducted, could deny access to a clinically important and cost-effective technology. Decision-makers must balance the

value of delaying adoption until better information is available, against the value of providing patients with early access. Here, the gain from waiting for more evidence (in terms of reduced uncertainty) should be weighed against the losses associated with a delay in adopting the technology (in terms of payoffs forgone) to determine the expected net gain (14, 15, 16). Additionally, decision-makers must decide whether actively gathering further evidence to reduce uncertainty is worthwhile (14).

In situations where it is possible to go beyond conventional "yes/no" reimbursement decisions to consider options for coverage with evidence development (CED), decision-makers can also decide to provide conditional coverage while research is conducted (14,17,18). This is particularly important when reversing the adoption decision is difficult or costly, such as when there are significant sunk costs associated with adoption (e.g. investments in equipment or buildings) (14). For example, in the presence of sunk costs, it may be more appropriate for a cost-effective technology where more research is worthwhile, to be reimbursed only for those enrolled in research (Only In Research - OIR) rather than approved for general reimbursement while the research is conducted (Approval With Research - AWR). This avoids the commitment of irrecoverable costs until the results of research become known. The downside is that patients not involved in the research would not have access to the new technology during the research and, as such, would potentially miss out on the best technology. Claxton et al. (2012) present a framework, based on VOI, for selecting between coverage options from a cost-effectiveness perspective, in the presence of irrecoverable costs (14, 19). McKenna et al. (2015) present a checklist outlining the sequence of assessments required to inform the different conditional coverage options (e.g., OIR or AWR) together with an illustration of the application of the checklist to an example in Enhanced External Counterpulsation Therapy (EECP) (20).

Efficient decision-making over the life cycle

VOI analysis should be undertaken early in the development of a technology and reassessed when an element of the decision changes (e.g. research is published or a new comparator becomes available), to determine the impact on the reimbursement and/or research decisions (21-25). When incorporated with CED, this early and iterative approach ensures efficient reimbursement and research decisions (what and when) over the lifetime of the technology (21-23). This aligns with the aim of the Adaptive Pathways approach, initiated by the European Medicines Agency, to balance timely access to technologies with the evolving nature of the evidence base through (re)assessment of evidence at different stages in the product's life cycle (26,27). The approach

also provides the opportunity for "stop/go" development decisions. When a technology is not effective and/or cost-effective on the basis of current evidence, and VOI analysis suggests that research is not worthwhile, then development of the technology should stop (28).

[Box 2 here]

Box 2: Applications of VOI analysis in healthcare

VOI analysis originated from Bayesian decision theory (29-32) and the theory of the economics of information (33). Claxton (1999) and Meltzer (2001) formalized approaches for VOI analysis for research prioritization in healthcare (34,35). Since then, VOI analysis has also been used to address the following:

- Identification of efficient research design, conditional coverage and early development (9,36,37)
- Value of individualized care and precision medicine (38,39)
- Value of regulatory trials from the perspective of the pharmaceutical industry (40)
- Value of information analysis to inform decisions about public and mental health interventions (16,41)
- Value of a sequence of trial designs, optimizing the order and respective sample sizes (42,43)
- Value of promoting uptake of an evidence-based technology (44)
- Value of managed entry agreements (45,46)
- Value of biomarker collection in clinical practice (47)
- Value of subgroup information & value of identifying subgroups (38,39,48-50)
- Outcomes-based contracting for risk-averse manufacturers (51)
- Portfolio balance-risk over multiple projects (52,53)
- Prioritizing the update of systematic literature reviews (54)
- Alternative designs for research studies and program of studies e.g. Bayesian Clinical Trial Simulation of phase II and III programmes (55)

Thorn et al (2016) and Koffijberg et al (2018) present the results of systematic reviews of VOI applications in healthcare (56,57).

3. Decision-making under uncertainty and the role of VOI analysis: A framework

Decisions made without complete information are inherently uncertain; there is a possibility that the decision is incorrect, with consequences in terms of the payoffs associated with the decision. Bayesian decision theory indicates that the optimal choice, for a risk-neutral decision-maker, is to select the option with the maximum expected payoff irrespective of the uncertainty (34,35). However, decision uncertainty is of interest to ascertain the value of collecting additional information to better inform the decision in the future (34,35). This involves a formal assessment of the decision uncertainty, not only in terms of the probability of making an error but also the consequences associated with an error (i.e. the payoff foregone when decision uncertainty leads to the incorrect decision being taken). This provides an estimate of the expected costs of the uncertainty. VOI analysis establishes the value of research according to the extent to which it might reduce the expected costs of uncertainty by reducing uncertainty in the evidence base. Essentially this involves comparing the expected value of a decision made with and without additional information. Where payoffs are expressed in terms of monetary NB, VOI analysis provides an explicit monetary valuation of the expected value of research that can be directly compared to the expected cost of research to determine whether it is worthwhile.

The assessment of the value of information can be undertaken at different levels:

- *Expected value of perfect information* (EVPI) - quantifies the value of acquiring perfect information about all aspects of the decision (i.e. eliminating all uncertainty). This is equivalent to the expected costs of uncertainty associated with making the decision based on the current evidence.
- *Expected value of partial perfect information (EVPPI)* also sometimes called partial EVPI or expected value of perfect parameter information - quantifies the value of perfect information for a specific (group of) parameter(s) in the decision. It is the difference in the expected value of a decision made with perfect information for these parameter(s) and the expected value of the decision based on the current evidence.
- *Expected value of sample information* (EVSI) - quantifies the expected value associated with a given research study with a specific sample size and a particular design which results in a reduction (rather than elimination) of uncertainty. It is the difference in the expected value of a decision made with reduced uncertainty and the expected value of the decision based on the current evidence.

- *Expected net benefit of sampling* (ENBS) – quantifies the net payoff for a given research study with a specific sample size and particular design (i.e. the difference between the EVSI and the expected total cost of the study). Note that here, the cost of research not only includes the cost of performing the study, but also the opportunity cost for participating individuals who will not benefit from the study (58).

Box 3 provides an overview of the sources of uncertainty in both model- and trial-based evaluations that induce uncertainty in payoffs. Published VOI analyses have principally focused on parameter uncertainty, which is the focus for this report; Report 2 of the ISPOR VOI Task Force discusses sources of uncertainty in more detail (4).

[Box 3 here]

Box 3: Sources of uncertainty

There are different types and sources of uncertainty. For further details see Report 6 of the ISPOR-SMDM Modeling Good Research Practice Task Force (59).

- Parameter uncertainty is the uncertainty surrounding the "true" values of the parameters in a decision model due to imperfect knowledge and/or measurement (e.g. uncertainty surrounding the mean duration of effect associated with a treatment in the population of interest)
- Structural uncertainty is the uncertain error that results from using a model that is not a perfect representation of reality and therefore relates to the assumptions employed within the construction of a model (e.g. the health states used to describe the progression of disease in a model) (59-61)[*]
- Stochastic uncertainty reflects uncertainty in the payoffs for any specific individual due to chance (e.g. experience of an adverse event following treatment)
- Methodological "uncertainty" [¥] reflects uncertainty regarding analytic methods and choices (e.g. the perspective taken in a cost-effectiveness analysis) (62)
- Heterogeneity[±] reflects known differences in individual-level parameter values associated with identifiable differences in patient characteristics including demographics (e.g. age, gender, income), preferences (e.g. attitudes or beliefs) and/or clinical characteristics (e.g. disease severity, disease history, genetic profile) (63)

[*] Note that the distinction between parameter and structural uncertainty is somewhat artificial given that many structural choices could be parameterized.

[¥] As there is no single "correct" method of evaluation, differences in methodology do not strictly reflect uncertainty about the "truth" (59). As such, and also because it is not possible to reduce methodological uncertainty through further research, it is not considered a source of uncertainty in the ISPOR VOI Task Force Reports.

[±] As heterogeneity does not reflect uncertainty about the truth it is not considered a source of uncertainty in the ISPOR VOI Task Force Reports.

4. Overview of the steps for conducting and reporting a VOI analysis

The process of undertaking a VOI analysis is illustrated graphically in Figure 1.

[Figure 1 here]

Constructing the decision-analytic model

The initial step involves constructing a decision-analytic model to represent the problem. As detailed in Report 2 of the ISPOR-SMDM Modeling Good Research Practice Task Force, this should involve a two-stage conceptualization process which (i) converts knowledge into a representation of the problem and (ii) identifies a specific model type to meet the needs of the problem (64). The process requires a clear statement of the decision problem, the modeling objective and scope; including the disease area considered, the analytic perspective, the target population, the alternative technologies, health and other outcomes of interest, and the time horizon of the analysis.

Uncertainty in the current evidence base

The next step involves characterizing the uncertainty in the current evidence base. This involves assigning a (joint) probability distribution for the model parameters, accounting for any correlations between parameters. Expressing the uncertainty surrounding the "true" value of a parameter involves identifying the range of values that could be reasonably attributed to it and the likelihood that the parameter takes any specific value in this range. These should be informed by the best available evidence. Guidelines exist to aid the selection of distributions for parameters (5).

Probability distributions must be assigned to all uncertain parameters otherwise they will be excluded from the analysis of uncertainty and assessment of VOI. Excluding a parameter because there is little or no information with which to estimate it, is equivalent to assuming it is known with certainty. These are precisely the parameters that need to be *included*, with a wide distribution, to represent this uncertainty. Where evidence is limited, probability distributions for uncertain parameters can be derived using expert elicitation (65-67).

Good practice recommendation 1

Probability distributions should be assigned to all uncertain parameters to reflect the evidence base.

Probabilistic analysis

A complete assessment of the uncertainty in the existing evidence base requires assessment of the uncertainty in all parameters simultaneously (68). This is achieved through probabilistic analysis (PA). In addition, where there are non-linearities within a model structure (e.g. the relationship between payoffs and health state transition probabilities in a Markov model), only PA will correctly determine the expected payoffs. A deterministic analysis (evaluating the model at the mean parameter values) will result in error. Deterministic analysis can provide some information about the sensitivity of a decision to a parameter value but has the potential to mislead, especially in models with multiple correlated parameters. As such, and in line with the ISPOR-SMDM Modeling Task Force (Report 6) and the 2nd Panel on Cost-Effectiveness, this task force recommends the use of PA (5,68).

Good practice recommendation 2

Use probabilistic analysis (PA), which accounts for uncertainty in parameters simultaneously, for an appropriate quantitative assessment of payoffs and associated uncertainty.

Assessing Uncertainty

Within PA, Monte Carlo sampling is used to propagate the uncertainty in parameters through the decision model. This involves drawing parameter values from each of the joint parameter distributions and running the model, using the selected set of parameter values, to provide an estimate of the outcomes of interest for each option being evaluated. The process is repeated many times (e.g. 10,000), in order to generate a distribution for each outcome of interest. Each iteration, in the distribution, represents a possible realization of the truth as captured by the PA, while the average of the distribution provides the expected value of each outcome of interest.

In CEA, the individual iterations for the outcomes of interest (costs and QALYs) are plotted on a (incremental) cost-effectiveness plane, providing a graphical representation of the joint uncertainty in payoffs (Figure 2). The spread of the points in the horizontal plane illustrates the uncertainty surrounding the (incremental) QALYs, while the spread in the vertical plane illustrates the uncertainty surrounding the (incremental) costs.

Decision uncertainty

VOI analysis focuses on the quantification of, and consequences associated with, decision uncertainty. Uncertainty in outcomes does not necessarily translate into decision uncertainty. Assessment of decision uncertainty requires a decision with which to compare the payoffs associated with the different options. In CEA, the standard decision rule involves comparing the incremental cost-effectiveness ratio (ICER), with a pre-defined cost-effectiveness threshold value (λ) specified in terms of cost per additional unit of health outcome, e.g. QALY. Decision uncertainty may be minimal or even absent, even when costs and effects are highly uncertain. This would be the case where the entire joint distribution of expected incremental costs and incremental effects falls above/below the threshold (λ) (e.g. technology A in Figure 2).

[Figure 2 here]

Establishing whether more research is potentially worthwhile

In addition to identifying the decision uncertainty, the results of the PA may be used to calculate the expected cost of the uncertainty given current evidence. Given that the ideal research would resolve all uncertainty, this expression can also be interpreted as the expected value of perfect information (EVPI).

Once gathered, information would be of value every time a choice is made between the options represented by the decision, as such, the EVPI should be scaled up for the beneficiary population. This population represents those that could potentially benefit from the information. Determining this population involves assessing the current (prevalent) and future (incident) cohorts for the time frame over which the decision would be relevant. While estimating the future incidence and prevalence of the disease may be done with a reasonable degree of accuracy, determining the effective time horizon over which the decision is expected to be relevant - and thus over which the incidence and prevalence of the population should be calculated - is less straightforward (69). Factors that might be considered include time to patent expiry of the technology, time to launch of an in-class substitute therapy, availability of diagnostic and screening tests that could change the size of the beneficiary population, and any anticipated price changes of the technologies. Assessments of these could be based on past empirical evidence, or on priors elicited from experts. Published studies tend to present results for a population based on a time horizon of 1 year and then 10-20 years, however there is no clear justification for this. This is a concern, as VOI estimates can be highly sensitive to the effective time horizon of the decision (70).

Good practice recommendation 3

Justify the effective time horizon chosen and explore the impact of alternative time horizons on the VOI results in scenario analyses.

Note that the benefits of any study would not be realized until the study is completed. Therefore, the beneficiary population, as calculated based on prevalence and/or incidence, is usually adjusted to reflect the time it will take for a study to finish (71,72). However, those study participants enrolled in the optimal arm will also receive the benefits of the optimal technology while the study is conducted (58).The impact of this on the VOI depends on the size of the population, relative to the sample size of the study, and is thus much more pronounced in rare diseases.

Estimating the appropriate size of the beneficiary population, especially where information might be generalizable and hence valuable across multiple jurisdictions (6), and establishing methods to assess the global value of information, are key priority areas for methods research (69,73,74).

Good practice recommendation 4

The size of the beneficiary population should be calculated based on the prevalent and/or incident cohorts as appropriate given the decision problem. This should be adjusted for the number of patients to be enrolled in a future study if the reimbursement decision is delayed while more information is gathered, as these patients will generally not benefit from the information yielded.

As perfect information is not achievable through research with a finite sample size, EVPI cannot establish that research is worthwhile. EVPI can only provide a measure of the expected maximum payoff that could result from research, i.e. it is an explicit expected upper limit on the value of further research that would eliminate all decision uncertainty (75). This expected maximum value can be compared to the cost of gathering further information to determine whether further research is *potentially* worthwhile, providing a necessary, but not sufficient, condition for determining the value of further research (76). If the population EVPI is less than the estimated cost of research, this provides a sufficient condition for establishing that future research is *not* of value to the decision-maker. In this circumstance, the VOI process should stop. If the population EVPI is greater than the estimated cost of research, this provides a necessary, but not sufficient, condition to suggest that research is *potentially* worthwhile. In this circumstance, the VOI process continues to examine the value of more targeted information.

Good practice recommendation 5

Compare population EVPI to the expected costs of research to determine if further research is <u>potentially</u> worthwhile. Where the expected costs of research exceed the EVPI then research is <u>not worthwhile</u> and the VOI process should stop.

Box 4 presents a worked example illustrating how to calculate the EVPI and population EVPI directly from the results of the PA. The appendix contains an intuitive explanation of the value of information.

[Box 4 & Table 1 here]

Box 4: EVPI: A worked example

A mathematical definition of EVPI is presented in ISPOR VOI Task Force Report 2 (Rothery et al., 2020). EVPI can also be understood by showing how it is calculated from the results of the PA. Table 1 shows five iterations from a PA, each of which represents a possible realization of uncertainty relating to the choice between treatments X, Y and Z. These iterations show the uncertainty in net health benefit (NHB) relating to existing evidence (columns 2, 3 and 4). The cost-effective (optimal) treatment, based on current evidence, for a risk-neutral decision-maker is that which generates the highest expected (mean) NHB. This is treatment Y with 13 NHB. The error probability associated with the decision is 60% (iterations 1, 2 and 4 where either X or Z is actually the optimal choice).

Perfect information would remove all uncertainty, which is equivalent to the decision-maker being able to select the optimal treatment in each iteration. This is shown in column 5 for each of the possible realizations of the uncertainty. If the uncertainty resolves as represented by iterations 3 or 5, then Y turns out to be the optimal treatment. However, if the uncertainty resolves as represented by iterations 1, 2 or 4, the optimal treatment is either Z (iteration 1) or X (iterations 2 and 4).

Column 6 presents the NHB associated with the optimal treatment (as identified in column 5) for each iteration. This is equivalent to the maximum NHB for each iteration. Given the uncertainty is not yet resolved, but that each iteration is equally likely to occur, the expected value of the decision with perfect information is calculated as the mean of these maximum NHB (i.e. 15 NHB). The EVPI is given by the difference between the expected value of the decision with and without perfect information, i.e. by subtracting the mean of column 3 from the mean of column 6. In this example, the value of the decision with perfect information is 15 NHB. Without perfect information, it is 13, hence the EVPI = 2 NHB.

Alternatively, the EVPI can be determined by calculating the opportunity loss associated with making a decision based on the current evidence in each iteration (column 7) and then averaging over all iterations. In this example, based on the current evidence, treatment Y is chosen (by a risk-neutral decision-maker). Where uncertainty has <u>not</u> led to an incorrect decision, e.g. iterations 3 and 5, there is no opportunity loss associated with the current level of evidence. However, an incorrect decision was made based on the current evidence in

iterations 1, 2 and 4, and hence, there is some opportunity loss associated with these iterations. Averaging the opportunity loss over all iterations gives the expected value of perfect information, in this example the EVPI = 2 NHB (as above).

If the beneficiary population is estimated at 100 people per annum and the time horizon for the decision is estimated as 5 years, the population EVPI = 943 NHB[#]. Assuming a threshold of $50,000/QALY this equates to a population EVPI of $47 million. If the expected cost of research exceeds $47 million then further research will not be of value, but if the expected cost of research is less than $47 million then research is *potentially* valuable to the decision-maker.

[#] Note that due to discounting, this is not exactly equal to 100 people multiplied by 5 years multiplied by 2 NHB.

Identifying parameters where further research is most valuable

Where further research appears potentially worthwhile based on the population EVPI, the next step is to identify which particular aspects of a decision problem are potentially worth studying, to resolve the uncertainty surrounding them. This can be done by estimating the expected value of partial perfect information (EVPPI) for specific (groups of) parameters, and comparing the population EVPPI to the expected costs of research. Wherever new information is expected to be informative for a group of parameters, EVPPI should be calculated for the group, rather than calculated separately for the individual parameters within the group, since EVPPI is typically not additive.

Good practice recommendation 6

EVPPI should be undertaken for groups of parameters where it is likely that a new study (or studies) would be informative for the whole group, rather than for individual parameters.

Calculation of EVPPI has traditionally involved a nested double-loop Monte Carlo sampling scheme. First, a value is sampled for the (group of) parameter(s) of interest, i.e. those for which uncertainty is to be resolved (outer loop). Then, a PA is undertaken with these parameter(s) fixed at the sampled value(s) while all other parameters vary as before (inner loop). For each outer loop, given the sampled value(s) for the parameter(s) of interest, the optimal decision (i.e. the technology associated with the maximum expected NB) is identified. The process is repeated for different sample values for the parameter(s) of interest (outer loops), each time identifying the optimal decision and the maximum expected NB associated with the choice. Averaging the maximum expected NB over all of the outer loops provides the expected value of the decision with perfect information for the parameter(s) of interest. Subtracting the expected NB with current information (as calculated for EVPI) gives the EVPPI.

Further details of the calculation of EVPPI, including a range of methods to simplify the process, are described in Report 2 of the ISPOR VOI Task Force (4).

Note that the parameters with the highest EVPPI will not necessarily correspond to the parameters that are most uncertain. EVPPI will only be high for those parameters for which parameter uncertainty drives decision uncertainty. There will only be value associated with reducing uncertainty for parameter(s) where this may change the decision, and hence, the decision payoffs. Eliminating uncertainty in a very uncertain but unimportant parameter (i.e. one that does not impact the decision), will have *no* value to the decision-maker.

As with the EVPI, the population EVPPI provides an expected upper bound on the value of additional research for specific (groups of) parameters.

Good practice recommendation 7

Estimates of population EVPPI should be compared to the expected costs of research on specific (groups of) parameters to determine whether research is potentially valuable.

Estimating the value of specific research

If further research for specific (groups of) parameters appears potentially worthwhile based on the population EVPPI, the next step is to determine whether specific research is worthwhile. This involves establishing that the population expected value of sample information (EVSI) exceeds the expected cost of undertaking specific research.

Determining the EVSI involves determining the reduction in the expected costs of uncertainty associated with specific research. This will depend on the 'informativeness' of the research, i.e. the extent to which uncertainty and the associated consequences are reduced by the information provided by the research. This is a function of the design of the research study, including the sample size and allocation, length of follow-up, and the endpoints of interest. These factors will also impact the cost of research. For example, further research on relative treatment effects may require a randomized controlled trial, whereas observational studies might be suitable for other parameters (such as cost or health-related quality of life associated with particular clinical events).

The process of identifying the optimal research design requires the ability to appropriately estimate the costs associated with specific research designs (77-79). These expected costs include three components: 1) fixed costs, (e.g. set-up costs, salaries); 2) variable cost per study participant, and 3) opportunity cost for those participants who receive the technology that is expected to be inferior

while the study is underway (7,58). The total cost is commonly determined from a societal perspective. However, it may also be considered from the perspective of the sponsor of the study.

EVSI is traditionally calculated using a nested double-loop Monte Carlo process similar to that used for determining EVPPI. Detailed methods to calculate the EVSI are described in Report 2 of the ISPOR VOI Task Force (4) along with methods to simplify the process in order to reduce computational load.

Good practice recommendation 8

Compare population EVSI, for the proposed study design, to the expected costs of the study to determine if the specific study is worthwhile.

Identifying the appropriate research design

The difference between the population EVSI for a specific study and its expected total cost gives the net payoff or expected net benefit of sampling (ENBS) associated with the specific research design. A positive expected net benefit of sampling (ENBS) indicates that the benefits (population EVSI) associated with a specific research study are expected to outweigh the costs and the research is worthwhile. This provides a sufficient condition regarding the worth of a specific research study. A negative ENBS indicates that a research study of a specific size and design would not be worthwhile. In this circumstance, a redesigned study (fewer participants, shorter follow-up) might improve the ENBS and turn out to be worthwhile. EVSI and ENBS should be calculated for a range of study designs (in terms of sample size and allocation; length of follow-up; endpoints of interest etc.) to identify the most efficient design, i.e. the design that generates the maximum ENBS (68). When no design has a positive ENBS, the current available evidence should be considered sufficient for decision-making (80).

Good practice recommendation 9

Identify the most efficient study design as that with the greatest Expected Net Benefit of Sampling (ENBS).

Reporting and interpreting results

In CEA, the cost-effectiveness acceptability curve (CEAC) provides a graphical summary of the uncertainty in cost-effectiveness associated with each of the technologies being considered, while the cost-effectiveness acceptability frontier (CEAF) presents the decision uncertainty for a range

of values of the cost-effectiveness threshold (81). Similarly, the results of VOI analyses should be presented graphically for a range of values of the cost-effectiveness threshold. Where there are explicit thresholds of interest, results of VOI (individual and population level) that correspond to these thresholds should be emphasized in text, tables or figures. Where EVSI and ENBS calculations are undertaken, these results should be presented for the different research designs considered for a range of values of the cost-effectiveness threshold.

All assumptions made during the analysis regarding the policy options available to the decision-maker should be clearly stated (64,68).

Results of VOI analysis should be used to guide decision-making under uncertainty, with the understanding that a positive EVPI or EVPPI is a necessary, but not sufficient, prerequisite to decide that further research is potentially valuable.

5. Other considerations and potential challenges

Additional considerations for decision-makers

This ISPOR VOI Task Force Report has described how to generate and use the results of a VOI analysis for reimbursement and research prioritization decisions based on the premise of efficiency (i.e. the decision-maker wants to maximize health, through reimbursement and research, from a limited budget) and an assumption of risk-neutrality. The assumption of risk-neutrality has been challenged by some, even for a population-level decision-maker, and alternative decision criteria that account for the risk aversion of a decision-maker may be applied for adoption decisions in some circumstances (82,83).

In addition, Koffijberg et al. (2018) demonstrated that, where decision-makers have additional criteria of interest (e.g. public opinion, ethical issues and budget constraints), this can substantially impact the value of information (84). In these circumstances, the standard outputs from a VOI analysis may not accurately reflect the value of information to the decision maker and should serve as a valuable, but not sole, input to the overall decision-making process.

Other factors with potential relevance to decision-making include: (i) likelihood that research will be undertaken if the technology is widely reimbursed rather than being funded only in the context of research; (ii) the extent of irreversible costs incurred in delivering a new technology, (iii) whether other information of relevance is likely to emerge over time and (iv) the size of the beneficial population for rare diseases. These issues are dealt with in more detail in Report 2 of the ISPOR VOI Task Force (4) and in the 2nd Panel on Cost-Effectiveness (68, chapter 11).

Alternatives to VOI

Other approaches that have been used to assess the value of undertaking further research include: implicit approaches where experts express their opinions as to the importance of different evaluative research, utilizing an assessment of burden of disease to identify priority topics, focusing research on areas where there are large variations in practice, and methods that determine the prospective payback from research in terms of the improvements in payoffs that accrue from changes in clinical practice that are assumed to follow the results of that research.

The payback approach is similar to VOI in estimating the value of research in terms of improved payoffs however, with payback methods, it is not possible to identify the extent to which the payoffs are improved through the research per se, as opposed to the resulting change in implementation

(85-90). This is important, as research is not necessarily the most efficient or only way to change clinical practice.

Information vs. Implementation

One of the assumptions of VOI analysis is that clinical practice aligns perfectly with decision-making, i.e. all clinicians will implement an option when this is the optimal choice on the basis of expected payoffs, even in the absence of a statistically significant clinical effect size (91). In reality, implementation is often imperfect for a variety of reasons, including the existence of different perspectives or incentives or asymmetries of information. Imperfect implementation of cost-effective technologies reduces the efficiency of the healthcare system. As a result, there has been growing interest in implementation strategies to improve uptake and adherence among practitioners.

Fenwick et al. (2008) present a framework, similar to the VOI framework, to formally assess the value of strategies to improve implementation (15,44,92, 93). The value of implementation approach differs from the payback methods by providing a framework that allows the separate, but linked, decisions regarding investment in research and investment in implementation activities to be made simultaneously.

Limitations of VOI

The extent to which any VOI analysis is sufficient to address the question of further research, is conditional on the model and on the specification of parameter uncertainty. As such it is imperative that the uncertainty in the current evidence base is appropriately considered and included in the PA. However, it is impossible for any assessment, no matter how carefully undertaken, to assess and incorporate unknown unknowns. As such, there will always be occasions when new evidence, which may not have been identified as required, causes a paradigm shift. This should not prevent the use of VOI analysis, but rather encourage creativity when developing models and assessing uncertainty.

Potential challenges

This report has focused primarily on the processes for pharmaceuticals, where developing decision-analytic models is often required to comply with the process of reimbursement or price negotiation (e.g. United Kingdom, Netherlands, France). When a decision-analytic model is not available, or feasible, at the time of funding (e.g. non-pharmaceutical interventions, public health

programs), a ‘rapid VOI’ or minimal modeling approach may be considered. This allows rapid estimation of the value of further research, for further details see the second report from the ISPOR VOI Task Force (4).

In situations where payers and funders of possible additional research are not one and the same, close collaboration will be required in order to undertake, and implement the results of, VOI analysis.

6. Conclusions

This, first, report of the ISPOR VOI Task Force demonstrates the importance of VOI to decision-makers, introducing readers to the concepts of VOI analysis and outlining decisions that can be supported by VOI analysis. It also provides an overview of the steps required to conduct a VOI analysis; and shows how the results should be calculated, used and interpreted. Box 5 provides a summary of the good practice recommendations, for conducting and reviewing VOI analyses, presented throughout this report.

[Box 5 here]

1. Box 5: ISPOR Value of Information Analysis Task Force Report's Good Practice Recommendations for Conducting and Reporting a VOI analysis

1) Probability distributions should be assigned to all uncertain parameters to reflect the evidence base.
2) Use probabilistic analysis (PA), which accounts for uncertainty in parameters simultaneously, for an appropriate quantitative assessment of payoffs and associated uncertainty.
3) Justify the effective time horizon chosen and explore the impact of alternative time horizons on the VOI results in scenario analyses.
4) The size of the beneficiary population should be calculated based on the prevalent and/or incident cohorts as appropriate given the decision problem. This should be adjusted for the number of patients to be enrolled in a future study if the reimbursement decision is delayed while more information is gathered, as these patients will generally not benefit from the information yielded.
5) Compare population EVPI to the expected costs of research to determine if further research is *potentially* worthwhile. Where the expected costs of research exceed the EVPI then research is *not worthwhile* and the VOI process should stop.
6) EVPPI should be undertaken for groups of parameters where it is likely that a new study (or studies) would be informative for the whole group, rather than for individual parameters.
7) Estimates of population EVPPI should be compared to the expected costs of research on specific (groups of) parameters to determine whether research is potentially valuable.
8) Compare population EVSI, for the proposed study design, to the expected costs of the study to determine if the specific study is worthwhile.
9) Identify the most efficient study design as that with the greatest Expected Net Benefit of Sampling (ENBS).

Report 2 of the ISPOR VOI Task Force (4) provides guidance on implementation of VOI analysis, with step-by-step algorithms, information about efficient computational approaches and details of available software.

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Table 1 - Calculating the EVPI from the results of a probabilistic analysis

Possible realizations of the uncertainty (i.e. how things could turn out)	Net health benefits associated with treatment				NHB that would be achievable if perfect information were available to determine the best choice in each iteration	Opportunity loss from lack of perfect information
Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7
	Treatment X	Treatment Y	Treatment Z	Best choice in each iteration		
Iteration 1	7	12	15	Z	15	3
Iteration 2	16	11	9	X	16	5
Iteration 3	9	14	11	Y	14	0
Iteration 4	13	11	10	X	13	2
Iteration 5	10	17	15	Y	17	0

Mean over all iterations	11	13	12	-	15	2

1

Figure 1 – The VOI process

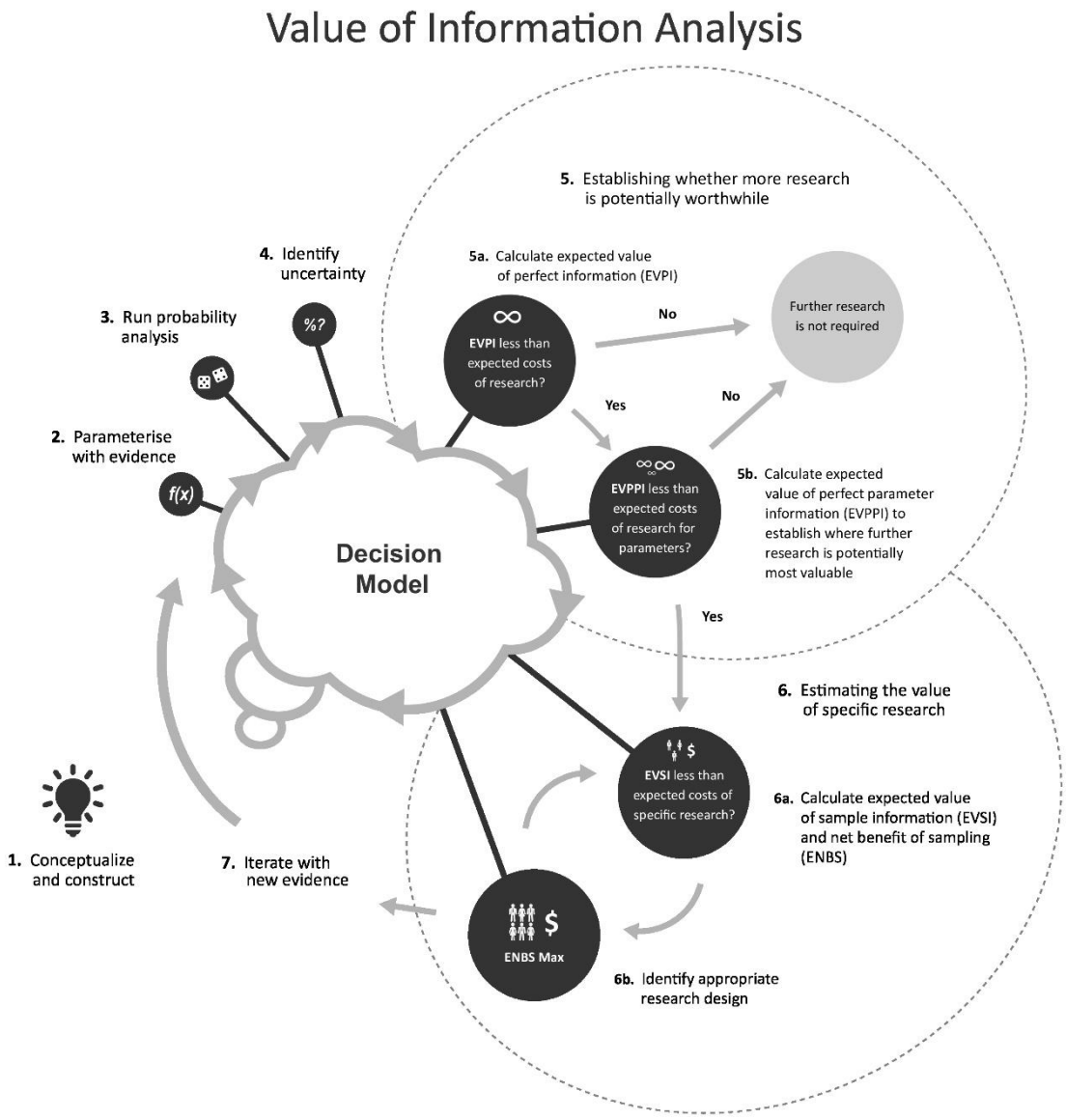
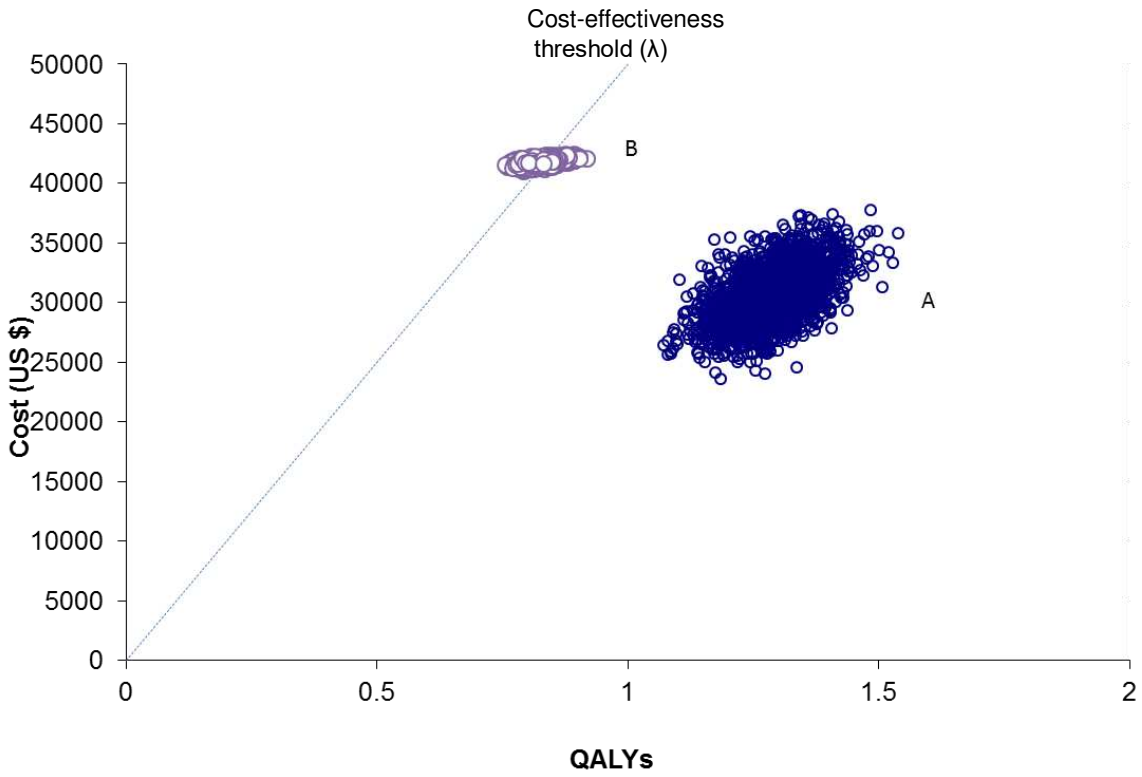


Figure 2 – Cost-effectiveness plane



Technology A involves considerable uncertainty in both the incremental costs (vertical plane) and incremental effects (horizontal plane) but there is no decision uncertainty at the cost-effectiveness threshold shown. Technology B involves decision uncertainty despite less uncertainty in payoffs (a more compact cloud of points) as the joint distribution crosses the cost-effectiveness threshold shown (λ).

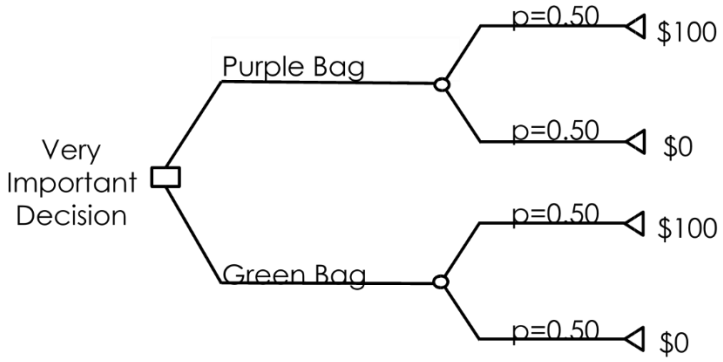
Appendix: An intuitive explanation of Value of Information

[This illustration has been adapted, and expanded on, from an EVPI teaching example created by Carrie Benette PhD, for the University of Washington, Seattle.]

Consider two bags:

One contains $100 while the other contains nothing of value. You can choose only one bag. How much would you pay to look inside one bag before making your decision?

This equates to a straightforward decision problem as depicted in the figure below:



Without looking inside either bag (i.e. with current information) there is a 50% chance of winning $100. Hence, the *expected value* of choosing a bag without peeking is: 0.5 * $100 = $50

After looking inside one of the bags (i.e. with *perfect* information) there is a 100% chance of winning $100. The *expected value* of choosing a bag after peeking in one bag is: 1.0 * $100 = $100

The added value associated with peeking in one bag (i.e. getting perfect information) is equal to the difference between the expected value *with and without information*. In numerical terms, the Expected Value of Perfect Information (EVPI) = $100 - $50 = $50

This is equivalent to the maximum you should be willing to spend to look in one of the bags.

Consider what happens to the EVPI when the consequences associated with making the wrong decision increase.

Again, consider two bags, one contains $1000 and the other nothing.

Now, the expected value without peeking in either bag (i.e. the expected value with current information) is 0.5 * $1000 = $500 while the expected value with peeking is $1000.

The EVPI is: $1000- $500 = $500. Thus, value of information is higher when the consequences of a (wrong) decision are larger.

Consider what happens to the EVPI if there is more uncertainty. What if there were five bags (instead of the previous two).

As before, one bag contains $100; all other bags are completely empty.

With five bags and no peeking in any bag, the probability of picking the bag with the money is only 0.2. Hence the *expected value* without peeking is now only $20 (0.2 * $100). The expected value associated with peeking in four bags (i.e. knowing which bag contains the money) is still $100.

The EVPI is: $100 - $20 = $80. Thus, value of information is higher when there is more uncertainty.

In reality, perfect information is unattainable.

Instead of obtaining perfect information (i.e. peeking in four bags), suppose we are restricted to peeking in only three bags. This mimics the situation of obtaining further information from a future trial with a limited sample size.

Again, without peeking the expected value is: 0.2 * $100 = $20. With peeking, there is a probability of 0.6 (3/5) that the $100 will be in one of the three bags that are picked and a probability of 0.4 (2/5) that the $100 will not be in one of these three bags. In this case, there is a 50:50 chance that each of the remaining bags contains the $100. Thus, the expected value of peeking in three bags is: (0.6 * $100) + (0.4 * 0.5 * $100) = $80. The Expected Value of Sample Information (EVSI) generated by peeking in three bags is: $80 - $20 = $60.

If there is a fee (fixed cost) of $10 for the opportunity to peek into any bag and an additional fee (variable cost) of $5 for each bag (up to three) that is peeked into, then the cost of peeking into three bags is: $10 + (3 * $5) = $25. In this case peeking into three bags will improve expected payoffs by: $60 - $25 = $35. This is equivalent to the expected net benefit of sampling (ENBS).

Glossary for VOI Task Force papers

Term	Definition
Bayesian analysis	Bayesian analysis is used to synthesize information known about a parameter prior to conducting a new study. The prior is then updated by synthesizing the new data (generated from the study) with the prior information to produce a posterior distribution for the parameter.
Bayesian decision theory	Refers to decision making under uncertainty which is informed by Bayesian analysis.
Incremental cost-effectiveness plane (ICE plane)	Visual representation of the incremental costs and incremental health outcomes associated with technologies compared to a comparator (often the least costly/effective). Plotted in four quadrants of a two-dimensional plane, with health outcomes usually plotted on the x-axis and costs on the y-axis. ICE planes are also used to present the uncertainty in outputs by representing the cloud of points on the plane corresponding to the iterations of incremental costs and incremental health outcomes generated from a probabilistic analysis.
Cost-effectiveness acceptability curve (CEAC)	A graph summarising the impact of uncertainty on the cost-effectiveness of technologies. It presents the probability that the technology is cost-effective, relative to the alternative options, plotted over different values of the cost-effectiveness threshold.
Cost-effectiveness acceptability frontier (CEAF)	A graph summarising the decision uncertainty. It presents the probability that the technology identified as cost-effective, based on expected value, is cost-effective, relative to the alternative options, plotted over different values of the cost-effectiveness threshold.
Cost-effectiveness threshold (λ)	A pre-defined value which reflects the monetary value attributed to an additional unit of health outcome. It represents the health opportunity costs, which is the improvement in health that would have been possible if the additional resources required to fund a decision option had, instead, been made available for other health care activities.
Decision-analytic model	An analytic framework that is used in decision analysis to bring together all relevant information on health outcomes and costs for each technology into a structured decision problem. This includes different judgments and beliefs and the degree of uncertainty and knowledge about a particular state of the world. The aim of the model is to explore the implications of alternative assumptions or judgments.
Expected value of perfect information (EVPI)	A summary measure of the expected maximum payoff from additional research. It is the difference between the expected gain in payoffs from eliminating all uncertainty surrounding a

	decision (perfect information) and the expected payoffs associated with a decision made on the basis of the currently available information (current information).
Expected value of perfect partial (or parameter) information (EVPPI)	A summary measure of the expected maximum payoff from additional research about a particular parameter, or group of parameters, in a decision model. It is the difference between the expected gain in payoffs associated with eliminating all uncertainty for a particular parameter (or group of parameters) of interest and the expected payoffs associated with a decision made on the basis of the currently available information.
Expected value of sample information (EVSI)	A summary measure of the expected payoff from additional research associated with a specific research design that will result in the reduction (rather than elimination) of uncertainty. It is the difference between the expected gain in payoffs associated with reducing uncertainty surrounding a parameter (or group of parameters) based on a specific research design and the expected payoffs associated with a decision made on the basis of the currently available information.
Expected net benefit of sampling (ENBS)	A summary measure of the expected net payoff from additional research associated with a specific research design that will result in the reduction of uncertainty. It is the difference between the expected payoff with sample information (EVSI) and the expected costs of collecting the additional sample information for the specific research design.
Health technology	According to the World Health Organization* "A health technology is the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives." * http://www.who.int/health-technology-assessment/about/healthtechnology/en/
Linear or multilinear model	A model is linear if it can be written as the sum of its parameters. In a linear model, the expectation of the model outputs is the same as the model evaluated at the expectation of the model input parameters. This is true whether or not the parameters are correlated. A model is multilinear if it can be written as a sum of products of parameters. In a multilinear model, the expectation of the model outputs is the same as the model evaluated at the expectation of the model input parameters, if and only if there are no correlations between parameters that act together multiplicatively.
Minimal modeling	A rapid approach for the estimation of the value of research without constructing a full decision-analytic model.
Monte Carlo simulation	A technique that involves repeatedly sampling from the (joint) probability distributions for the model input parameters.

Multiparameter evidence synthesis (MPES)	A method of generalization of meta-analysis in which multiple variables (e.g. efficacy parameters) are estimated jointly.
Net health benefit (NHB) and Net monetary benefit (NMB)	A summary statistic that represents the value of a decision option by comparing the benefits to the costs. It can be expressed in health or monetary terms. Net health benefit (NHB) is the difference between the expected health benefits of a decision option and the health expected to be forgone elsewhere by diverting resources to the decision option (expected costs divided by the maximum acceptable cost-effectiveness threshold value). Net monetary benefit (NMB) is the difference between the monetary value of the expected health benefits (expected benefits multiplied by the maximum acceptable cost-effectiveness threshold value) and the expected costs.
Non-linear model	A model is non-linear if it can not be written as a sum of its parameters. More loosely, a model is non-linear model if it is not linear or multilinear. In a non-linear model, the expectation of the model outputs is not the same as the model evaluated at the expectation of the model inputs.
Opportunity cost	Payoffs that the decision maker could have received if they had chosen another option rather than the one selected.
Parameter uncertainty	The uncertainty surrounding the "true" values of the parameters in a decision model due to imperfect knowledge and/or measurement. Parameter uncertainty is most usually represented by a probability distribution.
Probability	The degree of belief in a statement. The language of probability is used to describe uncertainty. Uncertainty can be defined using a probability distribution.
Probabilistic analysis (PA) (often called "Probabilistic Sensitivity Analysis (PSA)" in the health economics literature)	A technique that is used to quantify the level of confidence in the output of the analysis by taking account of the joint uncertainty in model inputs. This involves specifying a probability distribution for each uncertain input parameter (taking into account any correlations between input parameters). Then using Monte Carlo sampling to repeatedly sample from the joint distributions of the parameters. The model is re-analysed following every Monte Carlo draw using the sampled values and a distribution of outcomes is generated for each decision option.
Risk-neutral decision-maker	In decision theory, in a choice between alternative decision options, a risk-neutral decision-maker would select the option that maximizes the expected pay-off.
Structural uncertainty	A source of modeling uncertainty which reflects imperfect knowledge about the "true" real-world process that the model is trying to represent. If a model does not adequately reflect reality then, even if it is evaluated at the "true" values of its input parameters, there will be an error between the model outputs and

	the “true” real world values of those outputs. Uncertainty about this structural error is termed “structural uncertainty”.
Utility function	A generic term used to measure preferences over a set of decision options. In cost-effectiveness analysis, the utility function is often described in terms of net monetary or net health benefit, and the decision options represent alternative interventions within the set of available options.
Value of Information (VOI)	Evaluates the extent to which new information might reduce the occurrence, and expected consequences, of decision-making errors associated with uncertainty, by reducing the level of uncertainty in the current evidence-base.