# A Pilot Study of Value of Information Analysis to Support Research Recommendations for the National Institute for Clinical Excellence

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# Contents

# Executive summary

## Background

This project developed as a result of the activities of the Research Teams at the Centre for Health Economics, University of York, and ScHARR at the University of Sheffield in the methods and application of decision analysis and value of information analysis as a means of informing the research recommendations made by NICE as part of its Guidance to the NHS in England and Wales and informing the deliberations of the NICE Research and Development Committee.

Bayesian decision analysis and value of information analysis (DA-VOI) provides a methodological framework which explicitly considers the uncertainty surrounding the decision of a health care system to adopt a health technology. Specifically, using existing evidence, these methods focus on the likelihood of making a wrong decision if the technology is adopted. The value of additional research is based on the extent to which further information will reduce this decision uncertainty. This framework values the additional information, which may be generated by further research, in a way which is consistent with the objectives and the resource constraints of heath care provision (the cost-effectiveness threshold). This allows a comparison of the potential benefits of further research with the costs of further investigation, a comparison and prioritisation of alternative research recommendations, both within and between Technology Assessments, as well as an assessment of the value of investing resources in research or other activities, such as the provision of health service. In this sense it provides a unified and coherent framework for prioritisation of research and the use of heath care technologies.

## Objectives

The specific objectives of the pilot study were to:

- Demonstrate the benefits of using appropriate decision analytic methods and value of information analysis to inform research recommendations.
- Establish the feasibility and resource implications of applying these methods in a timely way, to inform NICE.

- Identify critical issues and methodological challenges to the use of value of information methods for research recommendations (with particular regard to the new reference case as a suitable basis for this type of analysis).

The project consists of a series of case studies based on recent technology assessment reports completed by the York and Sheffield group for NICE. These included:

- Screening for age related macular degeneration (AMD)
- Glycoprotein IIb/IIIa antagonists for acute coronary syndrome (GPAs)
- Clopidogrel and dipyridamole in the secondary prevention of occlusive vascular events (CLO)
- Neurominidase inhibitors for the treatment of influenza (NIs)
- Liquid based cytology screening for cervical cancer (LBC)
- Beta interferon and glatiramer acetate in the management of MS (MS)

The purpose was to establish the feasibility and requirements of value of information analysis once submissions and Technology Assessment Reports (TARs) are conducted within the reference case specified in the recent methods guidance. Therefore case studies were selected on the basis that the existing TAR comes as close to the new reference case analysis as possible

**Results**

With the exception of screening for AMD all the other case studies met the original selection criteria for inclusion. Screening for AMD was not included in the original TAR for AMD. However, it was a recommendation for further research and the analysis for this case study is based on a screening model for AMD which was developed for the NCCHTA. The other five associated TARs included an appropriate decision analytic model probabilistic analysis. In each case the existing TAR came close to the new reference case. However, any specific shortcomings are highlighted in each case study chapter. The more general issue of whether the existing references case is a sufficient basis for DA-VOI is discussed in chapter 8 and suggests that with the ongoing development of more detailed methods guidance on modelling, probabilistic analysis and evidence synthesis, a well conducted reference case analysis will provide a sufficient basis for value of information analysis. The core tasks and initial reanalysis of the case studies were completed in a timely way and within the

proposed timeframe (4 weeks). It is anticipated that the additional resources required to move from a well conducted reference case analysis to full value of information analysis will be less than required within this pilot study which was based on pre reference case assessment reports.

The decision uncertainty surrounding the choice between strategies was characterised in the form of cost-effectiveness acceptability curves and frontiers. In each case the decision model was reanalysed and value of information analysis conducted. The Expected Value of Perfect Information (EVPI) surrounding each decision problem for the population of England and Wales, and the EVPI associated with particular model inputs was established using appropriate non-parametric methods

The value of research differed substantially across the 6 technology appraisals (EVPI ranged from £2.8m to £865m). In some cases the analysis indicated that the original research recommendations should not be regarded as a priority, e.g., the EVPI surrounding LBC for was low (£2.8m). In other cases it indicated that additional research should be commissioned, e.g., the EVPI surrounding CLO for stroke patients was high (£865).

The analysis indicated which comparators should be included in future research and also suggested other parameters that could be excluded. Estimates of value of information for the decision problem and for groups of parameters were also presented for relevant patient sub groups, e.g., the value of information different across the patient groups considered in the CLO and AMD case study. A number of case studies presented scenarios to explore alternative views of the relevant evidence e.g., inclusion of related and "unrelated events" in the assessment of CLO and impact of restricting consideration of evidence at 6 months in GPAs ; different structural assumptions regard mechanism of action, e.g., additive nature of information gains during screening for AMD; as well as the impact on value of information when relevant alternative may have been excluded from the original scope of the appraisal, e.g., the including the potential role of clopidigrel in the GPA case study.

The implications for the value of research in each of the areas were presented at a general level, as well as for the design of any future research in terms of features such

as the relevant patient groups and comparators, and whether experimental design was likely to be required. The full reporting of the analysis conducted, and a discussion of the results for each of the case studies, can be found in Chapters 2 to 7. The case studies also highlighted a number of more general methodological issues including: consideration of all comparators, synthesising direct and indirect evidence, and considering structural as well as parameter uncertainty which are more fully discussed in chapter 8.

## Conclusions and Recommendations

*Demonstration of benefits*

The framework proved by DA-VOI was successfully implemented for each of the 6 case studies and provides the value of additional information, which may be generated by further research. This is consistent with the objectives of the heath care system (maximise the health gains of the population of England and Wales) and is based on the same resource constraints (the cost-effectiveness threshold which is used to develop guidance on use of the technology).

- For a particular assessment, this allows comparison of the potential benefits of further research (EVPI) with the costs of further investigation. If the potential benefits exceed the additional costs (including opportunity costs to patients) then further investigation maybe required to support guidance on use. The EVPI associated with the groups of parameters indicates the type of evidence that will be most valuable and therefore the type of studies that should be recommended.
- It also allows comparisons to be made across different technology assessments and prioritisation between alternative research recommendations, as well as a comparison between the value of investing resources in research or other activities such as the provision of health service. In this sense it provides a unified and coherent framework for prioritisation of both research and the use of heath care technologies

*The reference case as a sufficient basis for VOI*

The results of any analyses are conditional on the use of appropriate model structure, appropriate synthesis of evidence and characterisation of other uncertainties. This is important for estimates of expected cost-effectiveness but even more important for estimates of value of information which are particularly sensitive to these issues. The existing reference case and methodological guidance requires supplementary guidance on the detailed use of methods to ensure that the adequacy of reference case submission can be assessed and that an adequate reference case analysis will provide sufficient basis for value of information analysis. This process of developing detailed methodological guidance is underway, coordinated by the National Decision Support Unit. It is important that in identifying and recommending methods the full characterisation of decision uncertainty should be a primary concern.

*Critical issues and methodological challenges*

It should be recognised that the key challenges for this type of analysis are not the VOI methods themselves but structuring decision problems, synthesis of evidence and the characterisation of uncertainty (required for estimating costs and effects as well as VOI). The development of methods in these areas is ongoing and will require continued support from a variety of sources. Particular issues, many of which have been highlighted in the case studies, include:

- Ensuring a sufficiently wide scope for the assessment to include all the relevant alternative strategies. This includes other technologies as well as different clinical policies (start and stop criteria) for a single technology. The exclusion of alternative strategies may not change the overall guidance on use of a technology but in some cases it may have a substantial impact on the value of information and on research recommendations.
- Dealing simultaneously with heterogeneity (variability by observed patient characteristics), variability (variability by unobserved characteristic) and uncertainty.
- Reflecting the additional uncertainty due to potential biases in the evidence, which may come from different types of study and/or suffer from publication bias.
- Modelling the exchangeability of the evidence with the parameters required in the model and reflecting any additional uncertainty.

- The inclusion or exclusion of unrelated events from the evidence and the potential role of prior elicitation from "experts".
- The potential role of using priors elicited from "experts" within the NICE process and appropriate methods of elicitation of priors.
- Exploring and reflecting the additional uncertainty surrounding alternative but credible structural assumptions.
- Establishing efficient methods of searching for evidence on all model parameters not simply those associated with measures of effect.
- The synthesis of both direct and indirect evidence for measures of effect but also for other model parameters.

Many of these issues are being addressed though various programmes of research around the UK. However these areas of research require further development and continued support. In additional it should be recognised that these issues require multidisciplinary working with collaboration across many different centres. Infrastructure support to facilitate full collaboration across these areas of work should be sort from a variety of sources. As all these methods evolve, it should be recognised that the detail of what is required within an adequate reference case analysis will also develop over time.

*Other issues specific to VOI include:*

- Estimating the effective population that may benefits from additional evidence, including estimating time horizons for different technologies and incorporating this uncertainty in the estimates of value of information
- Estimating the value of information for correlated parameters
- Estimating the overall value of information based on estimates of the value of information for patient subgroups
- Presenting the value of information and the value of full implementation of guidance on use with in the same framework of analysis

Again work is currently ongoing on all of these issues but continued support from a number of sources for this methods work as well as support for an infrastructure of collaboration is needed.

*Feasibility and resource implications*

The pilot demonstrates that VOI is feasible within reasonable time lines, even based on pre reference case analysis. The use of VOI as part of the reference case (taking account of the recommendations made above) is for most types of models limited, not by time and resource requirements, but by the capacity to conduct this type of analysis and the dissemination of these methods. Therefore training in VOI methods should be considered as a cost-effective means of easing these capacity constraints.

However, complex and computationally expensive models (patient level simulations) make probabilistic analysis and therefore VOI potential very time and resource intensive. There are therefore 2 issues that should be addressed:

- It should be recognised that using patient level simulation is very costly in the sense that it may prevent reliable estimates of cost-and effect, and decision uncertainty as well as VOI being presented. In these circumstances it should be avoided if possible (by use of alternative structures and programming techniques). More work is required to establish those circumstances were the use of patient level simulation unavoidable.
- Where patient level simulation is required then there are techniques available to solve computationally expensive models, characterise uncertainty and estimate VOI. Indeed these have been used in NICE submissions. Further work is required to pilot their feasibility when patient level simulation is unavoidable and dissemination of appropriate methods.

*Implementation to inform research recommendations*

There are a range of possible options to implement DA-VOI within the NICE process, to inform research recommendations. These are more fully discussed in chapter 9. In this chapter we avoid making recommendations for implementation but outline possible options with some assessment of their strengths and weaknesses for NICE to consider. In general there a two levels at which DA-VOI could be implemented:

- DA-VOI could be implemented at the TAR stage of the process, either selectively or ultimately becoming part of the reference case for the Assessment Report. This would mean that the analysis would be available to inform the research recommendations made by the Appraisals Committee which generally to date have not been based on any formal analytic framework

or evidence. The advantage of this would be that the decisions about the use of a technology and the evidence required to support the guidance could be appropriately considered at the same time.

- Alternatively DA-VOI could be implemented in a similar way to the case studies presented here: as a supplementary analysis to and existing TAR once guidance on use and research recommendations have been made. This would then provide an analysis that could inform the deliberations of the NICE Research and Development Committee in considering which of the research recommendations made should be regarded as a priority. Potential ways of identifying which of the research recommendations should be considered for DA-VOI and are outlined in chapter 9. Although this approach may reduce the resource requirements (it may not if DA-VOI is in addition to the TAR) and in the short run avoid the current capacity problems in conducting this type of analysis there will always be a danger that some very valuable research requirements will be missed and other less valuable evidence requirements will be prioritised.
- However, these two alternatives need not be viewed as substitutes. The latter maybe regarded as the most feasible way of progressing in the short run. But, as capacity and methods develop, a move towards making DA-VOI a routine part of the TAR and the research recommendations in the guidance more firmly grounded on evidence and an explicit analysis may be achievable in the medium term.

# Chapter 1: Introduction and overview of methods

## Introduction

This project developed as a result of the activities of the Research Teams at the Centre for Health Economics, University of York, and ScHARR at the University of Sheffield in the methods and application of decision analysis and value of information analysis (DA-VOI) as a means of informing the research recommendations made by NICE as part of its Guidance to the NHS in England and Wales and informing the deliberations of the NICE Research and Development Committee.

The specific project proposal was developed following a presentation of the potential role of DA-VOI in identifying those circumstances were additional evidence will be required to support guidance on the use of particular technologies and prioritise research recommendations made by the Appraisals Committee. In addition the framework of analysis allows decision makers to identify what type of evidence would be most valuable and the type of studies which should be conducted to better inform guidance decisions in the future.

## Objectives

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- Identify critical issues and methodological challenges to the use of value of information methods for research recommendations (with particular regard to the new reference case as a suitable basis for this type of analysis).

The project consists of a series of case studies based on recent technology assessment reports completed by the York and Sheffield group for NICE. The purpose is to establish the feasibility and requirements of value of information analysis once submissions and Technology Assessment Reports (TARs) are conducted within the reference case specified in the recent methods guidance. Therefore case studies were selected and reported on the following basis:

- The existing TAR comes as close to the new reference case analysis as possible.
- The VOI analysis will be conducted using the case studies as they were developed and reported in the respective TARs.
- Any shortcomings with respect to the new reference case will be discussed, particularly if these have implications for the feasibility and reliability of value of information analysis.
- In each case, an assessment will be made of the suitability of the new reference case as a suitable basis of value of information analysis.
- Issues required for value of information analysis, which are not currently part of the reference case, will be highlighted.
- Selection of case studies will be made to highlight particular issues and challenges for value of information analysis.

A series of six case studies were selected based on recent technology assessment reports completed by York and Sheffield for NICE. These included:

- Screening for age related macular degeneration (AMD)
- Glycoprotein IIb/IIIa antagonists for acute coronary syndrome (GPAs)
- Clopidogrel and dipyridamole in the secondary prevention of occlusive vascular events (CLO)
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A brief and non-technical overview of DA-VOI methods is presented below followed by brief reports on each of the case studies in chapters 2-7. Each case study chapter is intended to be a supplement to the original TAR on which the decision analytic model and probabilistic analysis is based. For full details of the analysis each chapter should be read in conjunction with the associated TAR. However, each case study chapter is intended to stand-alone and can be read independently of the rest of this report. Each case study chapter follows a common format including: the background to the original Appraisal and Guidance; a brief description of methods referencing the original TAR, a reporting of results for the adoption decision (estimates of cost-effectiveness and decision uncertainty) and for research recommendations (the value of information for the decision problem and for groups of model parameters), and a discussion of implications for research reconditions as well as some of the methodological issues raised specific to the case study.

Chapter 8 provides a general discussion of the results and the methodological issues and challenges raised during the pilot. It also includes an assessment of whether the new reference case will provide a good basis for value of information analysis and identifies some key issues in modelling such as, evidence synthesis, computation, bias, and structural uncertainty, which need to be addressed for the future application of DA-VOI. Chapter 9 provides a brief discussion of the feasibility of using DA-VOI to inform research recommendations, resource requirements and outlines possible strategies for the implementation of value of information methods to inform research recommendations within the NICE process. A summary of the key findings and conclusions are provided in chapter 10.

**An overview of methods**

Bayesian decision theory and value of information analysis provides an analytic framework which can be used to establish the value of acquiring additional information to inform a decision problem. These methods have firm foundations in statistical decision theory[7 8] and have been successfully used in other areas of research such as engineering and environmental risk analysis.[9 10 26] More recently these methods have been extended to setting priorities in the evaluation of health care technologies.[11-16] In addition they have been usefully applied to a number of different

health technologies,[17-22] including a series of case studies taken from guidance issued by NICE.[23]

The application of these methods requires three core tasks to be completed: (i) the construction of a decision analytic model to represent the decision problem; (ii) a probabilistic analysis of this model to characterise the current decision uncertainty; and (iii) establishing the value of additional information.[19]

## Decision analysis

Evaluative research is useful insofar as it informs the choice between alternative strategies for patient management. Decision analysis presents these decision problems and the key inputs to these decisions explicitly.[27 28] Decision modelling requires all of the relevant inputs to the decision to be explicitly identified, and facilitates the synthesis of data from a variety of sources.[16] Randomised trials are a crucial source of parameter estimates for decision models, particularly estimates of the magnitude of treatment effects. Other sources of data – for example, the baseline risk and resource implications of particular clinical events – may be taken from non-trial sources such as observational studies and administrative datasets. In some circumstances, where no evidence exists for particular inputs, clinical judgement may also be incorporated.

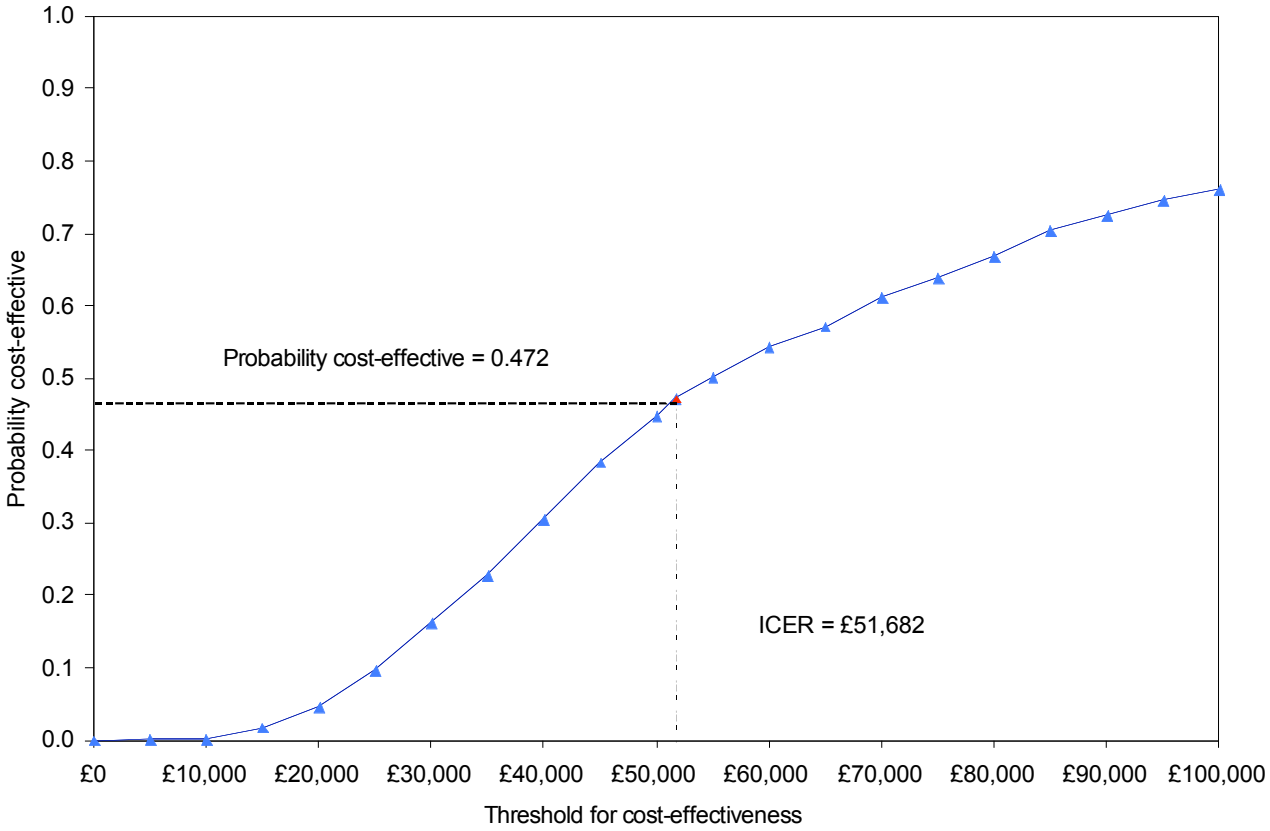
## Probabilistic analysis

All decisions about the cost-effectiveness of interventions are based on uncertain information about variables such as clinical effects, health-related quality of life and resource use. Decision analytic models and methods of evidence synthesis can be used to combine evidence on each parameter to assess the extent of uncertainty in the decision.[28] The extent and the quality of the evidence available, for each of the inputs, can be reflected in probability distributions assigned to these estimates, where more uncertainty about an input (less information or information of poorer quality) is represented by assigning a more diffuse distribution. Without access to patient level data, these distributions are assigned based on secondary sources (e.g. published literature, meta- analysis and evidence synthesis). The choice of the type of distribution and its parameters for a particular model input is not arbitrary, but should

be based on the existing evidence and what the type of distribution would be most appropriate. For example, probabilities should be represented by Beta distributions, which are bounded by zero and one, and their parameters can be based on either the number of observations or on mean and variance. [3 28-30]

The uncertainty surrounding the decision problem can be characterised by 'propagating' these distributions through the model using Monte Carlo simulation methods, where values for the input parameters are drawn at a random from the probability distributions which have been assigned.[3 28-30] This random sampling is repeated a large number of times. The output of these simulations provides a distribution of expected costs and outcomes for each strategy being compared. The uncertainty surrounding the cost-effectiveness of a technology, for a range of thresholds for cost-effectiveness, can be represented as a cost-effectiveness acceptability curve (CEAC).[11] Figure 1 illustrates an example of a CEAC where the probability that the intervention is cost effective increases as the willingness to pay for additional heath (QALY) or the threshold for cost-effectiveness increases.

**Figure 1: Cost-effectiveness acceptability curve example**




If the objective underlying health technology assessment is to make decisions that are consistent with maximising health gains from available resources, then decisions should be based on expected cost-effectiveness given the existing information (i.e. using the mean differential costs and outcomes between the scenarios being compared). This does not necessarily mean that the intervention which has the highest probability of being cost-effective should be adopted. For example, in figure 1 if the threshold for cost-effectiveness was just greater than £51,682 (the ICER) then the intervention should be adopted even though the probability that it is cost-effective is less than 0.5 (0.472). This is because the distribution of the additional net benefits (where health outcomes are re-scaled in monetary terms using the cost-effectiveness threshold)[31 32]is positively skewed, with a mean greater than its median value. The adoption decision can be represented with a CEAC by including a cost-effectiveness frontier, which indicates which of the alternatives will be cost-effective.[11]

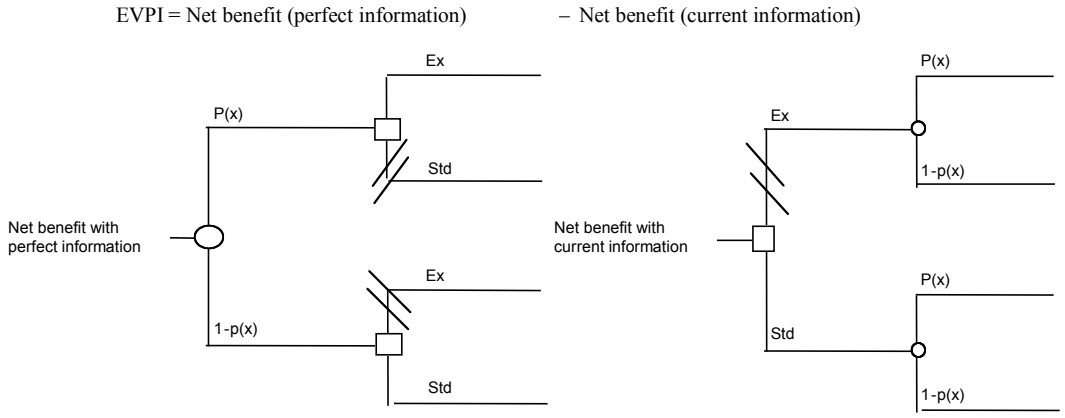
Although decisions should be based on expected cost-effectiveness given the existing information, this does not mean that adoption decisions can simply be based on little, or poor quality, evidence, as long as the decision to conduct further research to support adoption (or rejection) is made simultaneously.[12 19]

## The value of information

Decisions based on existing information will be uncertain, and there will always be a chance that the wrong decision will be made. If the wrong decision is made, there will be costs in terms of health benefit and resources forgone. Therefore, the expected cost of uncertainty is determined jointly by the probability that a decision based on existing information will be wrong and the consequences of a wrong decision. The expected costs of uncertainty can be interpreted as the expected value of perfect information (EVPI), since perfect information can eliminate the possibility of making the wrong decision. If the objective of the health care system is to maximise gains in health outcome subject to a budget constraint then this is also the maximum that the health care system should be willing to pay for additional evidence to inform this decision in the future, and it places an upper bound on the value of conducting further research.[12 13 17 19 33] However, there may be other objectives of health care provision such as equity. If these other objectives can be identified and valued then these can be incorporated into the analysis and the societal value of information.[12]

This general idea is illustrated in Figure 2. With current information, decisions must be made before we know how the uncertainties (p(x)) will be resolved - i.e. we must make a decision now based on the expected values of the all of the model inputs (choose "std" in Figure 2). However, with perfect information we can make our decisions once we know how these uncertainties (p(x)) are resolved - i.e., we can make different decisions for different resolutions of the uncertainties (choose "std" if 1-p(x) but choose "Ex" if p(x)). The EVPI is simply the difference between the payoff (expected net benefit) with perfect and current information.[21 33]

**Figure 2: Calculating EVPI example**




We can work out EVPI directly from the simulated output from our model as it relates to the individual patient.[9 21 33 34] For example, if there are two alternative interventions (t = 1,2) interventions, with unknown parameters θ. Then given the existing evidence, the optimal decision is the intervention that generates the maximum expected net benefit:

$$\max_t E_\theta B(t, \theta),$$

i.e., the maximum net benefits over all the iterations from the simulation because each iteration represents a possible future realisation of the existing uncertainty (a possible value of θ).

With perfect information, the decision-maker would know how the uncertainties would resolve (which value θ will take) before making a decision and could select the intervention that maximises the net benefit given a particular value of theta:

$$\max_t B(t, \theta).$$

However, the true values of θ are unknown (we don't know which value θ will take), Therefore, the expected value of a decision taken with perfect information is the found by averaging the maximum net benefit over the joint distribution of θ:

$$E_\theta \max_t B(t, \theta),$$

i.e., first calculate the maximum net benefit for each iteration from the simulation (for a particular value of θ), then take the average over these maximum net benefits (over the possible values of θ).

The expected value of perfect information for an individual patient is simply the difference between the expected value of the decision made with perfect information about the uncertain parameters θ, and the decision made on the basis of existing evidence:

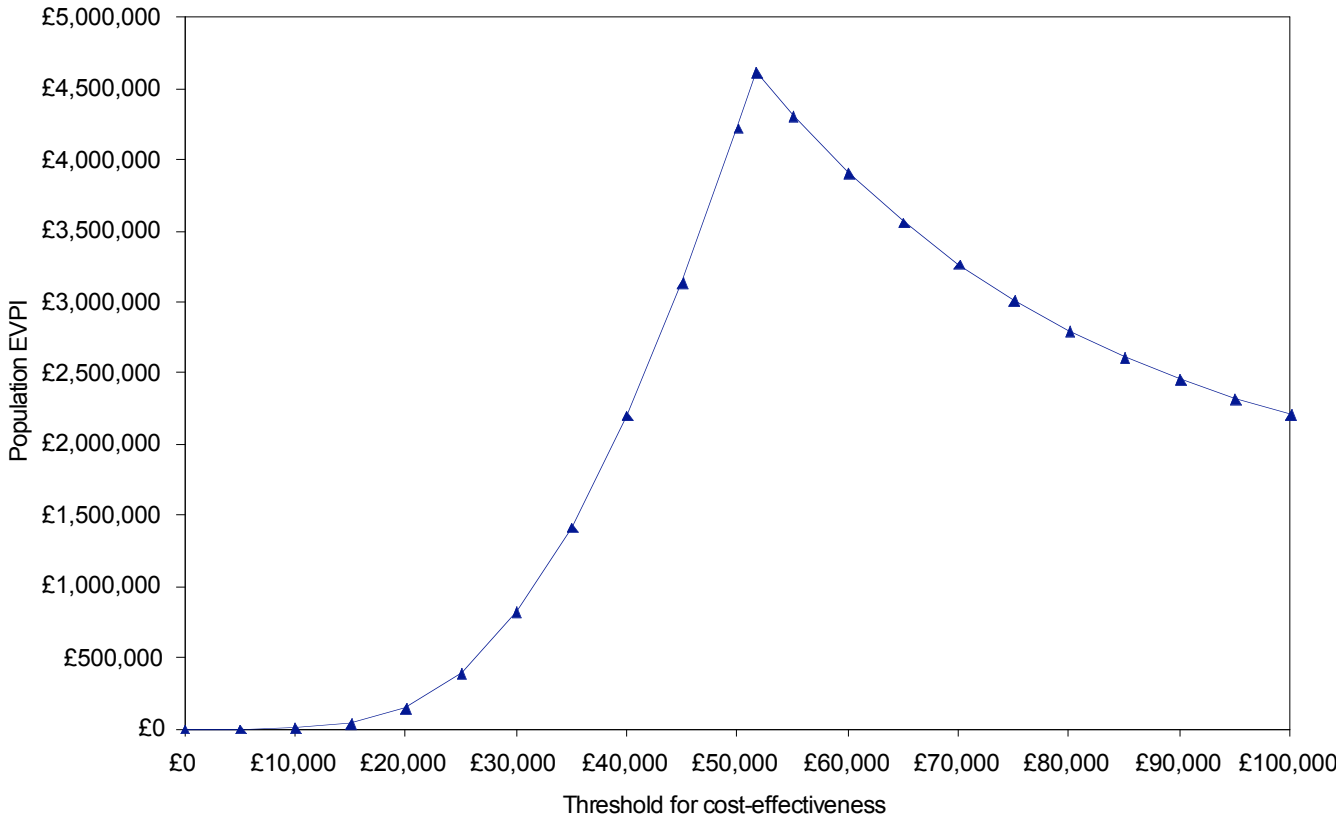
$$E_\theta \max_t B(t, \theta) - \max_t E_\theta B(t, \theta).$$

This provides the EVPI surrounding the decision as a whole for each time this decision is made (for an individual patient or individual episode). However, once information is generated to inform the decision for an individual patient or patient episode then it is available to inform the management of all other current and future patients as well. Therefore, for research prioritisation it is important that EVPI is expressed for the total population of patients who stand to benefit from additional information over the expected lifetime of the technology. This requires some assessment of the effective lifetime of the technology (the period over which information about the decision will be useful), estimates of incidence over this period and prevalence in the first year. The EVPI associated with future patients is discounted to provide the total EVPI for the population of current and future patients. If this population EVPI exceeds the expected costs of additional research, then it is potentially cost-effective to conduct further research.[12 13]

Figure 3 illustrates the population EVPI for the example used in Figure 1. When the threshold for cost-effectiveness (maximum value of health outcome) is low, the technology is not expected to be cost-effective and additional information is unlikely to change that decision (EVPI is low). In these circumstances the EVPI increases with the threshold because both the decision uncertainty increases (tendig to increase the EVPI) and the consequences of information changing the decision are valued more highly. Conversly, when the threshold is higher than the ICER, the intervention is expected to be cost-effective and this decision is less likely to be changed by further research as the threshold is increased. In these circumstances the decision uncertainty falls as the threshold increases (tending to reduce the EVPI), but the consequences of information changing the decision are valued more highly (tending to increase the EVPI). For higher values of the threshold the EVPI falls because in this case the reduction in decision uncertainty off sets the increased value of information changing decision. However, the EVPI will ultimately increase with very high values of the threshold because decision uncertainty will fall at a declining

rate with the threshold increasing at a constant rate i.e., the effect of the value of changes in decision will ultimately off set the reduction in decision uncertainty. In this particular case, the population EVPI reaches maximum when the threshold is equal to the expected incremental cost-effectiveness ratio of this technology. In other words, the EVPI reaches a maximum when we are most uncertain about whether to adopt or reject the technology based on existing evidence.[12 13 17]

**Figure 3: EVPI curve example**




However, most decision problems involve more than two alternatives. The principles of calculating EVPI remain the same but the EVPI curve can take a variety of shapes depending on whether the alternatives being considered are cost-effective at some value of the threshold (there will be a number of peaks or a discontinuities in the EVPI curve at threshold values equal to the ICER of each of the alternatives) or if some of the alternatives are dominated or extendedly dominated (the peak or discontinuity will be in negative threshold space i.e., we would only wish to adopt the alternative if your willing to pay to reduce heath outcome).

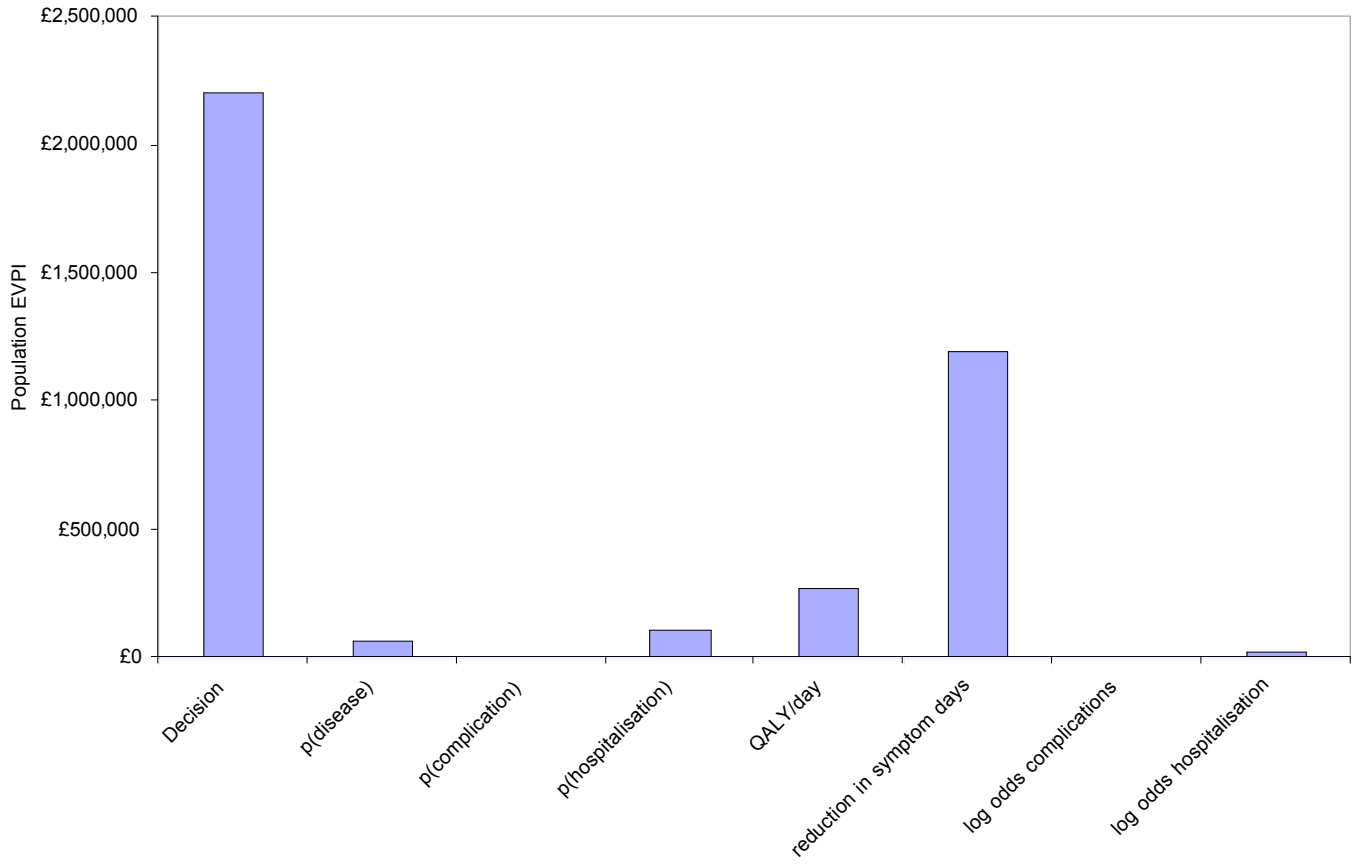
It should be clear from this discussion of EVPI suggests that the value of further research will depend on both the uncertainty surrounding estimates of cost and effect but also on how cost-effective or cost ineffective a technology is expected to be given existing evidence, and the size of the patient population that could benefit from additional research. One implication is that it is perfectly possible that the value of further research about a new technology, which is substantially cost-effective based

on existing evidence, will be very low even if there is uncertainty surrounding the parameters, i.e., there may be uncertainty in cost and outcomes but the decision uncertainty and therefore the EVPI may still be low. In these circumstances the technology should be adopted and no further research is required to support this decision.

The value of reducing the uncertainty surrounding particular input parameters in the decision model can also be established (partial EVPI). This type of analysis can be used to focus further research by identifying those inputs for which more precise estimates would be most valuable. In some circumstances, this will indicate which endpoints should be included in further experimental research. In other circumstances, it may focus research into getting more precise estimates of particular inputs which may not necessarily require experimental design and can be provided relatively quickly. The analysis of the value of information associated with each of the model inputs (partial EVPI) is, in principle, conducted in a very similar way to the EVPI for the decision as a whole.[9 17 21 33 34] In this case the expected value with perfect information is found by taking the maximum expected net benefit given perfect information only about the parameter of interest (calculating expected net benefits over all the other uncertain parameters the model) and then averaging over all the possible value of the parameter of interest. The EVPI for the parameter is again simply the difference between the expected net benefit with perfect information and the expected value with current information (the same as for decision EVPI). However, this does require substantial additional computation for models where the relationship between the inputs and expected cost and outcomes is not linear, for example in Markov models.[21 33]

Figure 4 illustrates the partial EVPIs associated with the decision EVPI in Figure 3 at a threshold of £40,000 per QALY. In this example, the EVPI associated with reduction in symptom days is relatively high and suggests that further experimental research may be worthwhile. However, other inputs with lower partial EVPI, such as the baseline probability of hospitalisation, may not require experimental research but may also be important if the costs of further investigation (resources and delay) are low. It should be noted that the partial EVPIs will not sum to the overall EVPI due to the interactions within the model structure.

**Figure 4: Partial EVPI example**




# Prioritising Research Recommendations

The EVPI places an upper bound on the societal returns to further investigation. The EVPI for the decision problem can be used as a first hurdle for proposed research.[12 13 17 19 21] If the costs of investigation exceed the EVPI, then the proposed research will not be cost-effective, i.e., the population EVPI can be used to rule out research recommendations which will not be worth while for a societal perspective

For those decision problems where the EVPI exceeds the costs of research it is possible to compare EVPIs across patient groups and different technologies to prioritise research recommendations. In general, additional research will be more valuable for a patient groups or technology where the EVPI is higher. However, it should be noted that this direct comparison requires some assessment of the cost of proposed research. For example, even where the EVPI is lower research in that area

may not be a lower priority if the costs of further investigation are expected to be substantially lower. In principle it would be useful to explicitly compare the marginal benefits and costs of research proposals in prioritising research. The same framework of DA-VOI can be extended to establish the expected value of sample information for particular research designs and to compare these marginal benefits of research to the marginal costs. However, this type of analysis is beyond the scope of the current pilot.[12 14 18 33]

The EVPI associated with groups of model parameters can be used to focus potentially cost-effective research on those inputs for which more precise estimates would be most valuable. This may indicate which endpoints should be included in further experimental research, or it may focus research on getting more precise estimates of particular inputs, which may not necessarily require experimental design and can be provided relatively quickly.[17 21 33]

**Conclusion**

Bayesian decision analysis and value of information analysis provides a methodological framework which explicitly considers the uncertainty surrounding the decision of a health care system to adopt a health technology. Specifically, using existing evidence, these methods focus on the likelihood of making a wrong decision if the technology is adopted. The value of additional research is based on the extent to which further information will reduce this decision uncertainty. This framework values the additional information, which may be generated by further research, in a way which is consistent with the objectives and the resource constraints of heath care provision (the cost-effectiveness threshold). This allows a comparison of the potential benefits of further research with the costs of further investigation, a comparison and prioritisation of alternative research recommendations, both within and between Technology Assessments, as well as an assessment of the value of investing resources in research or other activities, such as the provision of health service. In this sense it provides a unified and coherent framework for prioritisation of research and the use of heath care technologies.

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Chapter 2: The cost-effectiveness and value of information associated with repeat screening for age related macular degeneration

# 2.1 Background

***Condition and Technology***

Age-related macular degeneration (AMD) is a degenerative condition of the macula. It is one of the most common causes of vision loss in people over 50. The disease varies in severity, from a slight loss in vision to near blindness. AMD is classified as either wet (neovascular) or dry (non-neovascular), it is neovascular AMD that progresses most rapidly and causes the more severe vision loss. About 10% of patients who suffer from macular degeneration have wet AMD. If one eye develops neovascular membrane, the other eye is at moderate risk of having the same problem. Neovascular AMD is further defined by its location in the choroidal neovascular vessels (subfoveal, justafoveal or extra-foveal) and by its pattern of leakage (classic, occult, mixed or recurrent).(1)

Treatments for certain types of AMD have developed over the last few years and include confluent argon laser photocoagulation, verteporfin photodynamic therapy (PDT), radiotherapy and transpupillary thermotherapy.(1)

***Technology Assessment Review***

Photodynamic therapy for age related macular degeneration has recently been appraised by the National Institute for Clinical Excellence (NICE).(2) The evidence from the Assessment Report, and the provisional guidance issued by NICE, indicated that PDT will only be potentially cost-effective for the treatment of AMD in the better seeing eye (after 1$^{st}$ eye involvement) and only for certain types of AMD (neovascular, predominantly classic, subfoveal) AMD can progress rapidly (declining visual acuity) and is a significant cause of blindness. Early PDT can halt or slow the decline in visual acuity. Earlier treatment with PDT at better starting visual acuities is more cost-effective, and treatment is not recommended for starting visual acuities lower than 20/100.

## *NICE guidance*

In September 2003, NICE issued guidance on the use of PDT for age-related macular degeneration. The guidance recommended the following(3):

1. Photodynamic therapy (PDT) is recommended for the treatment of wet age-related macular degeneration for individuals who have a confirmed diagnosis of **classic with no occult** subfoveal choroidal neovascularisation (CNV) and best-corrected visual acuity 6/60 or better. PDT should be carried out only by retinal specialists with expertise in the use of this technology.

2. PDT is not recommended for the treatment of people with **predominantly classic** subfoveal CNV associated with wet age-related macular degeneration, except as part of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including data on optimum treatment regimens, long-term outcomes, quality of life and costs.

3. The use of PDT in **occult** CNV associated with wet age-related macular degeneration was not considered because the photosensitising agent (verteporfin) was not licensed for this indication when this appraisal began. No recommendation is made with regard to the use of this technology in people with this form of the condition.

4. Patients currently receiving treatment with PDT could experience loss of well being if their treatment is discontinued at a time they did not anticipate. Because of this, all NHS patients who have begun a course of treatment with PDT at the date of publication of this guidance should have the option of continuing to receive treatment until their clinical condition indicates that it is appropriate to stop.

## *Research recommendations*

The recommendations for further research, issued as part of the NICE guidance were that:

- Several randomised controlled trials of PDT are ongoing, including two placebo-controlled trials of verteporfin PDT, one in patients with minimally classic CNV using standard or reduced laser settings, and one in patients with occult CNV.

- The Committee recommended that further research is needed on the use of PDT for individuals with predominantly classic subfoveal CNV related to ARMD. The primary objectives of this research should be to determine the optimum treatment regimen and long-term benefit of PDT, and to add to the current evidence on quality of life for this group of individuals.

- At present it is not known whether population screening for ARMD would be practical or cost effective. Research on screening for ARMD is being commissioned by the UK HTA programme.

## 2.2 Methods

Given that treatment with PDT is more effective the earlier it is initiated in the course of the disease, there is a *prima facie* case that screening would be cost-effective by identifying patients with AMD before their visual acuity declines. A self-screening test of central vision distortion called the Amsler grid(4) is available and it has been suggested that this could be used as a basis of screening.(2)

Following the conclusions of the Assessment Report undertaken for NICE(2) and the provisional guidance regarding the use of PDT, we have focused on the use of weekly self-screening following 1$^{st}$ eye involvement with neovascular AMD. This self-screening strategy is compared to two alternatives: no screen but diagnosis and treatment of eligible AMD following self-referral (due to declining visual acuity) to an ophthalmologist (this strategy is consistent with provisional NICE guidance); and a strategy of no screening and no PDT. The analysis reported here has assessed the cost-effectiveness of, and potential value of future research for, these alternative strategies. Full detail of this model can be seen in a forthcoming HTA report.(5)

Although the structure of the model developed was consistent with published evidence regarding the natural history of the disease, a number of structural assumptions were questioned after consultation with clinical experts. Alternative structural assumptions, consistent with these alternative clinical opinions, were therefore explored

***Model Structure***

The structure of the decision model is illustrated in Figure 1. A Markov process(6) is used to model the incidence of 2nd eye neovascular AMD over 10-years and the associated decline in visual acuity following undiagnosed 2nd eye involvement.

Patients enter the model with neovascular AMD previously diagnosed in the 1st eye. Two alternative starting visual acuities are modelled, 20/40 or 20/80. The implication of this is that the worse seeing individuals would generally receive PDT or no PDT at a lower visual acuity. Each week patients can decide to self-screen (comply) using the Amsler grid, which is an A4 sheet of paper containing a series of lines, which appear distorted if a change in vision has occurred.

Patients with positive screen results (self diagnosed) will refer for a full eye exam by an ophthalmologist. Patients may also self-refer due to declining visual acuity, measured as a loss of 1 or more lines. In the base case model at a loss of 4 or more lines, all patients will have self-referred to the ophthalmologist (in the absence of data expert judgement was used to specify the probability that patients self refer on loss of visual acuity). The full eye examination will identify patients with neovascular AMD in the 2nd eye (i.e. false positives are identified). Angiography is then undertaken in those with confirmed neovascular AMD to identify the type of neovascular disease that is present, and thus determine if the patient is eligible for PDT. Since angiography is used to identify and monitor AMD in the clinical trials of PDT it is taken to be the gold standard test in this model**.**

Patients with diagnosed AMD that is eligible for PDT will then either have PDT (screen + PDT and no screen + PDT strategy), or not have PDT (no screen + no PDT strategy). Costs and QALYs associated with the use or non-use of PDT are then assigned. The expected quality of life with PDT depends on the visual acuity at

diagnosis, where patients with better visual acuities will experience better quality of life. The costs of PDT are constant throughout the visual acuity groups.(7)

***Alternative structural assumptions***

Currently the effect of the Amsler grid, in terms of identifying patients with AMD, can occur before AMD develops and at each stage of visual acuity loss. However it may be that there is no additional benefit from the Amsler grid after a patient has developed a visual acuity problem (after a loss of one or more lines). Also patients only refer to see an ophthalmologist once they have a decline in visual acuity, when there are noticeable changes in their eyesight. However given that patients in the model have already had first eye involvement and may therefore be expected to be more vigilant in recognising changes in their vision, patients may refer when there is no loss in visual acuity (AMD state). This may be because they are using other stationary objects to imitate the Amsler grid. These alternative structural assumptions were modelled.