A PILOT STUDY OF VALUE OF INFORMATION ANALYSIS TO SUPPORT RESEARCH RECOMMENDATIONS FOR THE NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

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Abstract

Purpose: To demonstrate the benefits and feasibility of value of information analysis to support research recommendations made by the National Institute for Clinical Excellence (NICE)

Methods: A series of six case studies was selected from recent technology appraisals conducted by NICE. The case studies included: clopidogrel and dipyridamole in secondary prevention (CD); glycoprotein antagonists (GPAs); screening for age related macular degeneration (AMD); neuroaminidase inhibitors (NIs) for influenza; liquid based cytology (LBC); and beta interferons for multiple sclerosis (BIs). The case studies were broadly consistent with the recent NICE guidance on reference case analysis and included a probabilistic decision analytic model. In each case a re-analysis using value of information analysis was conducted.

Results: The reanalysis of each case study was completed within 4 weeks. 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. In other cases it indicated that additional research should be commissioned. The analysis also indicated which comparators should be included and which patient sub-groups should be enrolled in future trials. The case studies highlighted a number of general methodological issues including: consideration of all comparators, synthesis of direct and indirect evidence, and considering structural as well as parameter uncertainty.

Conclusions: Value of information analysis can be conducted in a timely way, which can inform the research recommendations made by NICE.

1. Introduction

Decisions to adopt, reimburse or issue guidance on the use of health technologies are increasingly being informed by an explicit cost-effectiveness analysis of the alternative interventions.[1] This requires an analytic framework which can represent these decision problems explicitly, combine evidence from a range of sources and facilitate the extrapolation of costs and effects over time and between patient groups and clinical settings.[2] Such an analytic framework must be able to inform both the decision to adopt or reject a technology and whether additional research is required to support this decision in the future.

Policy background

Decision analytic modelling provides such a framework and has become central to the assessment of health technologies by the National Institute of Clinical Excellence (NICE). The importance of decision analytic modelling for informing decisions about the use of health technologies is reflected in the recently updated NICE guide on the methods of technology appraisal.[3] The updated guidance details what the Institute considers to be appropriate methods for estimating the cost-effectiveness of technologies, and for characterising the uncertainty surrounding these estimates. One feature of the guidance is the development of 'reference case' requirements for analysis which includes among other things a characterisation of decision uncertainty through probabilistic sensitivity analysis (PSA)[4].

The guidance states that it is important for the Appraisal Committee to know about the uncertainty associated with clinical and cost effectiveness information.[3] Although, there are strong arguments for basing decisions about resource allocation on *expected* cost-effectiveness rather than the traditional and arbitrary rules of inference,[5] expected value decision making in no way implies that decision uncertainty is unimportant. Indeed, an assessment of the implications of decision uncertainty is an essential part of a decision making process that is consistent with objectives and constraints of any health care system.

An honest and transparent characterisation of uncertainty is needed for a number of reasons. Firstly, NICE does make recommendations about further research, and can

issue guidance which is conditional on additional evidence being provided,[5] on the conduct of pilot studies before wider adoption[6] or on a technology only being used within a clinical trial.[7] Secondly the date when the guidance will be reconsidered must be specified which may well be informed by the uncertainty surrounding the decision and the anticipation of further evidence being available in the future,

" It is important for the Appraisal committee to know about the uncertainty associated with clinical and cost-effectiveness information. This quantification of decision uncertainty may then feed into subsequent decisions about the need for future research." (5.2.4.1)[3].

In principle, many of these issues could be formally addressed using value of information analysis[5, 8] and real options pricing.[9] However, these formal approaches were not specified as part of the reference case although value of information analysis was recommended,

" Candidate topics for future research can be identified on the basis of evidence gaps identified by the systematic review and cost-effectiveness analysis. These may be best prioritised by considering the value of additional information in reducing the degree of decision uncertainty." (5.9.6.1)[3].

Value of information analysis was also recommended to identify those parameters of groups of parameters which contributed most to decision uncertainty and where additional information would be most valuable,

"It is also helpful to present the contribution of the uncertainty in each parameter to overall decision uncertainty. This can be achieved using expected value of information methods." (5.9.3.2)[3]

Some assessment of whether existing evidence is sufficient to support the use of a technology, the appropriate length of time until the reconsideration of the guidance and the needs for further research must be made as part of any decision making process. The issue is one of who should be responsible for such an assessment, i.e., should these assessments be made informally by the Appraisal Committee and the Research and Development committee supported by NICE, or should these assessments be informed by a more formal and transparent analysis of the value of information.

This study pilots 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.

Methodological background

A number of methods for setting priorities in research and development of health care technologies have been proposed, and some have been used to identify priority areas for research. These include measures of the burden of disease, or the technology[10, 11] measures of the expected "payback" from research,[12-14] and estimates of the welfare losses due to variations in clinical practice.[15] However each of these proposed methods has serious methodological problems. Firstly, all of the approaches currently proposed view research simply as a means of changing clinical practice rather than considering research as providing additional information, which will reduce the uncertainty about what is appropriate clinical practice. Indeed, measures of "payback" or welfare losses due to variations in clinical practice require the analysis to identify "appropriate utilisation" or which technology should be adopted a priori. Therefore, these methods implicitly assume that there is no uncertainty surrounding the decision that the proposed research is supposed to inform.

Secondly these approaches, particularly measures of burden, attempt to identify research priorities using aggregate measures across broad clinical areas. However, the information generated by evaluative research is only valuable if it informs specific clinical decisions for specific groups of patients. The measures of burden methods assume that the value of research in a clinical area is simply made up of the value of research about each of the constituent clinical decision problems faced within that area. Therefore, simply because aggregate measures such as burden of disease may suggest a clinical area is a "high" priority, it does not mean that specific evaluative research relating to any one clinical decision problem will be valuable. Similarly, proposed research to inform a particular decision in a "low" priority disease area may be very valuable.

In this sense, attempts to identify research priorities across broad clinical areas using aggregate indicators may be mistaken. What is required is a measure of the societal value of particular research, which can inform specific clinical decisions for defined groups of patients. An appropriate methodological framework should consider the

uncertainty surrounding the adoption of a health technology in terms of the likelihood of making a wrong decision if it is it adopted. It should also view the value of research as the extent to which further information will reduce this *decision* uncertainty. An appropriate framework should value the additional information generated by research in a way which is consistent with the objectives and the resource constraints of health care provision.

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 [16, 17] and have been successfully used in other areas of research such as engineering and environmental risk analysis.[18, 19, 20] 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.[2]

2. Methods

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 consisted of a series of case studies based on recent technology assessment reports completed by the York and Sheffield group for NICE. 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 came as close to the new reference case analysis as possible. Any shortcomings with respect to the new reference case were identified and discussed and an overall assessment was made of the new reference case as a suitable basis of 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)
- 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 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.[21] Since the case studies were selected on the basis that the existing TAR comes as close to the new reference case analysis as possible each had a developed probabilistic decision model. Each case study was intended to be a supplement to the original TAR on which the decision analytic model and probabilistic analysis is based. The details of the analysis for each can be found in the full report [22] which can be read in conjunction with the associated TAR. Each case study followed 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.

3. 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, the specific shortcomings are highlighted in in each case. 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 [23]. 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 [21]

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

Implications for research prioritisation

The value of research differed substantially across the 6 technology appraisals and ranged from £2.8m (LBCs scenario 2) to £865m (ClO scenario 2). The results for selected scenarios for each of the case studies are reported in table 8.1.

Table 8.1: Summary of EVPI results

Case Study	Patient Group	Population EVPI	EVPI for parameters
AMD Screening	Visual acuity 20/40 Visual acuity 20/80	£6.2m £15.3m	Quality of life with and without PDT (£3,370,000 for 20/40)
Glycoprotein IIb/IIIa	Acute treatment following non-ST-elevation acute coronary syndrome (scenario 2)	£171m	Relative risk of death for non acute PCI for GPA as medical management and for Clopidogrel (£85,041,000, and £68,137,000 respectively)
Clopidogrel and dipyridamole for secondary prevention	Stroke Transient Ischaemic Attack Myocardial Infarction Peripheral Arterial Disease (scenario 2)	£865m £250m £710m £240m	Relative risks of vascular and non vascular death (£780m for ASA-MR-dipridamole compared to clopidogrel in the stroke subgroup)
Neurominidase inhibitors	Otherwise healthy adults not at elevated risk of complications	£66.7m	Quality of life with influenza, the effect of oselatimivir and amantadine (£44.3m, £0.43m and £0.23m respectively)
Liquid Based Cytology	Women aged 18 to 64 years (scenario 3)	£20m	Specificity (£3.6m)
Disease modifying therapies for multiple sclerosis	Relapsing remitting and primary progressive multiple sclerosis (scenario 2)	£86.2m	Relative risk of progression for copaxone, Betaferon and rebif (22mg) (£14m, £13.6m and £7m respectively) Also the cost of care, costs of relapse and quality of life (£10m, £7m and £6m respectively)

In some cases the analysis indicated that further research should not be regarded as a priority, e.g., the EVPI surrounding LBC following the evidence from the pilot study was low (£2.8m scenario 2). In other cases it indicated that additional research should be regarded as a priority, e.g., the EVPI surrounding CLO for stroke patients was high (£865). In other cases the analysis re-focuses the original research recommendations, e.g., in the AMD case study, although further research appears to be potentially worthwhile, it is additional evidence about quality of life with and without photo dynamic therapy rather than the performance of self screening itself which is valuable.

The analysis indicated which comparators should be included in future research and also suggested other parameters that could be excluded, For example, the value of information for NIs was significant (£66.7m) but it is further evidence about quality of life with influenza which is most important (£44.3) rather than additional evidence about the effect on symptoms. Although there is some value in further RCTs of the effect of oselativir and amantadine on symptoms (0.43m and 0.23m respectively) there is no value in further trials of Zanamivir. Similarly in the MS case study, although there is value in additional RCT evidence of the effect on progression of the disease, it is the effect of copaxone and betaferon which should be regarded as a priority (£14m and £13.6m respectively). However, in this case evidence about cost of care and relapse, and quality of life are also valuable. In these cases further research will not require experimental design and may be less costly to acquire (£10m and £6m respectively) so maybe regarded as priorities.

Estimates of value of information for the decision problem and for groups of parameters were also presented for relevant patient sub groups, e.g., for example the value of information different across the patient groups considered in the CLO case study (from £856m to £240m). This suggests that further research on the stroke and MI subgroups should be regarded as a priority although research on the TIA and PAD subgroups may also be worth while. Similarly the value of additional evidence for AMD differs by visual acuity (from £6.2m to £15.3m), and suggests that additional research should include those subgroups with lower starting visual acuity.

The analysis also indicates which endpoints should be included in further research. For example, in the GPA case study further research is valuable and should be regarded as a priority. It also indicated that it is RCT evidence of the effect of GPA as medical management and Clopidogrel which is most valuable. However, it also indicates that it is the mortality endpoint for patients with non-acute PCI which should be the primary endpoint in any future trial.

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.

A more detailed discussion of the implications for research prioritisation including the implications 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 in each of the areas, can be found in full report [22]

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. It is important that in identifying and recommending methods the full characterisation of decision uncertainty should be a primary concern.

Although each case study was selected to be as close as possible to the new reference case there were a number of departures where the existing TAR model fell short of the new requirements. These are detailed in each case study.[22] However, in general the most common and significant departures surrounded the quality of the evidence on quality of life available in the original TAR analysis. In addition and unsurprisingly the difference in discount rate between the original and new methods guidance was common to all case studies. It should be noted that even when the differences in discounting have a modest effect on estimated of cost-effectiveness then can have a substantial impact on value of information, e.g., in LBC case study changing the discount rate had a significant impact on the value of information.

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 it should be recognised that the key constraint is the capacity to conduct adequate probabilistic decision analytic modelling.

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

i) 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.

ii) 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.

Non of the case studies included patient level simulation. However the MS and LBC case studies included computational expensive models and both used different techniques to overcome the computational problems. For example LBC attempted to estimate a linear relationship between model inputs and output, MS case study evaluated a number of approaches including a Gaussian process which does not impose linearity. Linear approximations maybe adequate for estimating costs and effect but my perform less will when estimating the value of information. The use of Gaussian process performs better than linear regression particularly when estimating value of information but the number of parameters, which can be included is limited. Again further works is required to pilot the use of techniques to evaluate computationally expensive models.

4. Critical issues and methodological challenges

It should be recognised that the key challenges for this type of analysis are not primarily 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:

Structuring decision problems

- 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. For example, excluding clopidogrel as an alternative in the GPA case study would have lead to an underestimate of the EVPI. The full range of clinical policies must also be included. For example, the CLO case study was restricted to evaluating 2 year treatment policies. However, if other policies such as life time treatment was evaluated then although the cost-effective strategy may not change the

value of information may be higher and may focus on the longer term effect of secondary prevention

- Exploring and reflecting the additional uncertainty surrounding alternative but credible structural assumptions. For example, in the AMD case study three scenarios of alternative structural assumptions about how the information from self screening would change the chance of self referral to an ophthalmologist were modelled. Although the alternative assumptions had limited impact on estimates of cost-effectiveness (the overall cost-effectiveness of the strategies were unchanged) they did have a more substantial impact on the value of information (from £6.3m to £30.5m for visual acuity 20/40). This suggests that uncertainty and therefore evidence about the structural relationship may be as valuable as evidence about the value of the model parameters. In this pilot these types of uncertainty have been modelled as scenarios. However it is possible to assign probabilities (priors) to alternative assumptions and generate a value of information for this uncertainty. This would require elicitation of probabilities from experts and decision makers within an iterative process of analysis. Another example of these issues are found in the NI case study, e.g., whilst the base case value of information is driven by the uncertainty in quality of life, when this is modelled solely as a function of length of influenza illness, the value of information is reduced substantially.
- Model complexity and characterising uncertainty. The MS and LBC case studies included computational expensive models and both used different techniques to overcome the computational problems. For example, the LBC case study attempted to estimate a linear relationship between model inputs and output, the MS case study evaluated a number of approaches including a Gaussian process which does not impose linearity. Linear approximations maybe adequate for estimating costs and effect but my perform less will when estimating the value of information. The use of Gaussian process performs better than linear regression, particularly when estimating value of information, but the number of parameters which can be included is limited. Again further work is required to pilot the use of techniques to evaluate computationally expensive models.

Evidence synthesis and characterising uncertainty

- The synthesis of both direct and indirect evidence for measures of effect but also for other model parameters. This is a key issue for all the case studies. The GPA case study demonstrates that only considering the 6 month trial evidence (scenario 1) would overestimate the uncertainty and value of information. The more appropriate analysis (scenario 2), which included all the trial evidence, required more sophisticated methods of evidence synthesis. The CLO case study employed an indirect comparison of the two main treatments of interest, clopidogrel and modified-release dipyridamole, because no direct trial data were available. Such indirect comparisons are necessary for a full comparison of all treatment options, but are always subject to an increased level of uncertainty. It is not surprising then that the relative treatment effect of clopidogrel compared to modified-release dipyridamole on mortality was associated with significant value of information.
- Dealing simultaneously with heterogeneity (variability by observed patient characteristics), variability (variability by unobserved characteristic) and uncertainty. In the GPA case study, if higher and lower risk patients could have been identified then sub group analysis could have been conducted. However, this was not possible and the analysis was conducted for average risk patients. It should be recognised that the current analysis is for patients with the average risk not the group of patients with variability in risk which make up the average. The latter is more policy relevant but requires both variability and uncertainty to be modelled.
- 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. The AMD case study used alternative structural assumptions to explore the substantial uncertainty and potential bias is estimates of self referral rates. This type of scenario analysis indicated that value of information was sensitive to these issues.
- Modelling the exchangeability of the evidence with the parameters required in the model and reflecting any additional uncertainty. For example, a meta regression was conducted to establish whether relative risk was related to base

line risk in the GPA case study. This enabled the evidence from US trial (where baseline risks differed from the UK) to be used in the UK context. However the additional uncertainty introduced by using the US evidence was not explicitly modelled.

- The inclusion or exclusion of unrelated events from the evidence and the potential role of prior elicitation from "experts". The CLO case study illustrated that the cost-effective treatment strategy and value of information can be significantly affected by the inclusion (exclusion) of unrelated (related) events. Where there is considerable uncertainty about how to include effects on events which may not be connected to the treatments under consideration, as with non-vascular mortality in the antiplatelets, trial. In such instances expert opinion on the validity of excluding the event from the model, or prior beliefs on the magnitude and extent of any potential treatment effects may have an important role in augmenting trial data.
- The potential role of using priors elicited from "experts" within the NICE process and appropriate methods of elicitation of priors. In the AMD case study expert judgements for the probabilities of self referral conditional on loses in visual acuity were used. The distributions assigned to these estimates were diffuse to represent the substantial uncertainty in the value of the parameters. However, more formal methods of elicitation for the whole prior distribution are available and would be more appropriate for future reference case analysis.
- Establishing efficient methods of searching for evidence on all model parameters not simply those associated with measures of effect. Each case study was based on a TAR which included a systematic review of the evidence on effect. However, the models and the probabilistic analysis rely on estimates of many parameters other than measures of effect. Clearly methods of systematic and efficient searching for all model parameters must be considered if all evidence is to be used to estimate costs and effects and fully characterise uncertainty.

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. 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.

Issues specific to VOI

Although the key challenges are more general and relevant to estimating cost, effect and decision uncertainty there are a number of issues which are specific to VOI which need to be addressed

- Estimating the effective population that may benefit from additional evidence, including estimating time horizons for different technologies and incorporating this uncertainty in the estimates of value of information.
  For example, the CLO case study considered only modified-release dipyridamole, as it is now considered superior to the standard release formulation. Following the technological advance which allowed an extended release formulation, standard release dipyridamole, will likely fall out of use. In contrast, aspirin has been in use for more than the 15 years considered in the current EVPI calculations, and is still recommended for use in the guidance from the CLO appraisal despite the arrival of newer, competing technologies (clopidogrel and dipyridamole). Thus there is uncertainty around the effective future lifetime of these technologies and there is likely to be different effective life times for different technologies relevant to the same decision problem. In the NI case study the size of the population are based on the numbers of people currently presenting to the GP classified as influenza like illness. But the drugs need to be used within 48 hrs of symptom onset and are likely present similarly to a common cold. Therefore true "population" could be much greater than estimated once the technologies are available.
- Estimating the value of information for correlated parameters.
  The methods of evidence synthesis required to make comparisons between technologies generates correlation between estimates of effect. For example, in the CLO case study the relative risks were correlated and it should be recognised that the EVPI for these relative risks individually did not account for the correlation and could either under or over estimate EVPI. Similarly in the MS case study two scenarios were used to explore the impact of regarding

each of the treatments as independent or as perfectly correlated (the same drug) and showed the effect on the estimates of value of information. Work is ongoing into accounting for correlations when calculating EVPI for parameters.

- Estimating the overall value of information based on estimates of the value of information for patient subgroups
  The AMD, GPA and CLO case studies included a number of patients sub groups. The EVPI for each patient group is useful in identifying were research will be most valuable. However it must be recognised that further evidence about one sub groups may inform other patient groups. Therefore the subgroup EVPI is likely to be a lower bound on the value of conducting research on that sub group alone. Similarly the summation across subgroups will overestimate the value of research for all patient groups together. What is required is to model the exchangeability between subgroups and indeed to other decision problems.
- Develop methods to assess the stability of estimates and required iterations.
  The number of iterations required to provide stable estimates of the EVPI and the EVPI for particular parameters depends on the nature of the model (non linearity) the number of parameters and their distributions. No clear general "rule" is available. Further work on measures of stability would be useful
- Presenting the value of information and the value of full implementation of guidance on use with in the same framework of analysis.
  The value of information conducted in this pilot focuses on the value of evidence about what is a cost-effective intervention. There is clearly a separate issue of the value of ensuring that clinical practice is consistent with the current evidence of cost-effectiveness and indeed that if additional research is commissioned that clinical practice will respond to the results.

5. Discussion

In each case study the existing TAR came close to the new reference case although a number of specific shortcomings where highlighted. The more general issue of whether the existing references case is a sufficient basis for value of information analysis 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. 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 limited and even less than required within this pilot study which was based on pre reference case assessment reports.

Implementation to inform research recommendations

There are a range of possible options to implement DA-VOI within the NICE process, to inform research recommendations. 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 need to be more fully developed. 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.

Challenges in context

Of course there are many challenges to adopting more explicit and transparent approaches to informing decision about the adoption of health technologies and decision about the need for additional evidence to support these decision in the future. However, the challenges, which have been detailed above, are not, with a few exceptions, specific to value of information analysis or indeed to decision modelling generally. The issues of interpretation of evidence, synthesis, potential bias, exchangeability etc, have always been present in any informal and partial review of evidence. In fact until quite recently these challenging issues could be conveniently ignored by both policy makers, clinicians and analysts while decision making was opaque and based on implicit criteria and unspecified "weighing" of the evidence. These challenges must be faced as more to explicit and transparent approaches to decision making are being taken. Indeed one of the many advantages of taking more transparent and explicit approach to decision making is that it exposes many important methodological issues which have previously been ignored or avoided by presenting partial analysis which do not directly address the decisions which must be made.

References

1. Hjelmgren J, Berggren F, Andersson F. Health economic guidelines - similarities, differences and some implications. Value in Health 2001;4(3):225-250.

2. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence. Lancet 2002;360:711-715.

3. National Institute for Clinical Excellence (NICE). Guide to the Methods of Technology Appraisal. London: NICE, 2004.

4. Claxton K, Sculpher S, McCabe C, Briggs A, Buxton M, J Brazier J. and O'Hagan A. Probabilistic Sensitivity Analysis for NICE Technology Assessment:

Not an Optional Extra. Health Economics, forthcoming.
5. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. Journal of Health Economics 1999;18:342-64.
6. National Institute for Clinical Excellence. Health Technology Assessment Report on Liquid Based Cytology (www.nice.org.uk). London: National Institute for Clinical Excellence, 2000.
7. National Institute of Clinical Excellence (NICE). Guidance on the Use of Laparoscopic Surgery for Colorectal Cancer (www.nice.org.uk). London: National Institute for Clinical Excellence, 2000.
8. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. Health Economics 1996;5:513-524.
9. Palmer S, Smith PC. Incorporating option values into the economic evaluation of health care technologies. Journal of Health Economics 2000;19:755-766.
10. Gross CP, Anderson GF, NR P. The relation between funding by the National Institutes of Health and the burden of disease. *New England Journal of Medicine* 1999;340:1881-7.
11. Michaud CM, Murray CJ, BR. B. Burden of disease--implications for future research. *Journal of the American Medical Association* 2001; 285.
12. Townsend J, Buxton M. Cost-effectiveness scenario analysis for a proposed trial of hormone replacement therapy. *Health Policy* 1997;39:181-94.
13. Davies L, Drummond MF, Papanikolaou P. Prioritizing investments in health technology assessment. *International Journal of Technology Assessment in Health Care* 2000;16:73-91.
14. Buxton M, Hanney S. Assessing payback from Department of Health Research and Development: Second report. HERG Research Report 24. Uxbridge: Brunel University, 1997.
15. Phelps CE, ST P. Priority setting in medical technology and medical practice assessment. *Medical Care* 1990;28.
16. Raiffa H, Schlaifer R. *Probability and Statistics for Business Decisions*, 1959.
17. Pratt J, Raiffa H, Schlaifer R. *Statistical decision theory*. Cambridge MA, 1995.
18. Thompson KM, Evans JS. The value of improved national exposure information for perchloroethylene (perc): a case study for dry cleaners. *Risk Analysis* 1997;17:253-271.
19. Howard RA. Information value theory. IEEE Transactions on Systems Science and Cybernetics SSC2, 1966:122-26.
20. Hammitt JK, Cave JAK. Research planning for food safety: a value of information approach.: RAND publication series, 1991.
21 Ades AE, Lu G, Claxton K, Expected value of sample information in medical decision modelling. Medical Decision Making, 2004 (24); 2: 702-228
22 K Claxton, S Eggington, L Ginnelly, S Griffin , C McCabe, Z Philips, P Tappenden, and A Wailoo. A pilot study of using value of information analysis to support research recommendations for the National Institute for Clinical Excellence. Centre for Health EconomicsHE TP 2004
23 Fenwick, E., Claxton, K., and Sculpher, M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 2001; 10: 779-89.