

Systematizing the Use of Value of Information Analysis in Prioritizing Systematic Reviews



Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Systematizing the Use of Value of Information Analysis in Prioritizing Systematic Reviews

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10058

Prepared by:

University of Chicago Medical Center through the Blue Cross and Blue Shield Association
Technology Evaluation Center Evidence-based Practice Center

Investigators:

Ties Hoomans, Ph.D.
Justine Seidenfeld, B.A.
Anirban Basu, Ph.D.
David Meltzer, M.D., Ph.D.

This report is based on research conducted by the University of Chicago Medical Center through the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10058). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Financial support for this work was provided by the Agency for Health Care Policy and Research through the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center with funds through the American Recovery and Reinvestment Act (290-2007-10058-I) (Huang/Meltzer PI), a Midcareer Career Development Award from the National Institute of Aging (1 K24 AG031326-01, Meltzer, PI) and the Agency for Healthcare Quality and Research through the Hospital Medicine and Economics Center for Education and Research in Therapeutics (CERT) (U18 HS016967-01, Meltzer, PI).

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted for which further reproduction is prohibited without the specific permission of copyright holders.

Persons using assistive technology may not be able to fully access information in this report. For assistance, contact EffectiveHealthCare@ahrq.gov.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Hoomans T, Seidenfeld J, Basu A, Meltzer, D. Systematizing the Use of Value of Information Analysis in Prioritizing Systematic Reviews. (Prepared by the University of Chicago Medical Center through the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058.) AHRQ Publication No. 12-EHC109-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Joanna Siegel, Sc.D., R.N.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Investigator Affiliations

Ties Hoomans, Ph.D.¹

Justine Seidenfeld, B.A.¹

Anirban Basu, Ph.D.²

David Meltzer, M.D., Ph.D.^{1,3,4}

Institutions

¹ Section of Hospital Medicine, Department of Medicine, The University of Chicago

² Department of Health Services, School of Public Health, University of Washington

³ Department of Economics, The University of Chicago

⁴ Harris Graduate School of Public Policy Studies, The University of Chicago

Systematizing the Use of Value of Information Analysis in Prioritizing Systematic Reviews

Structured Abstract

Background: As a means to inform clinical and health policy decisions, systematic reviews are inexpensive relative to clinical trials and other (observational) studies but are costly enough that not all possible systematic reviews can be performed. Value of information (VOI) analysis has been considered as a tool to help prioritize topics for systematic review. Since VOI analysis typically involves constructing a complex decision-analytic model of the disease and its treatment to fully characterize the uncertainty in the health outcomes and costs of the treatments or other health interventions being studied, the standard approach to VOI may be prohibitively costly for use in prioritizing systematic reviews. As alternatives to typical full modeling VOI, three newer approaches to analyzing the value of information can be identified that are less burdensome: (1) In a conceptual approach to VOI, information is used about multiplicative elements of VOI, which include comprehensive outcome measures and the implementation and durability of review findings, to provide informative bounds on value of research without formally quantifying this through modeling. (2) In a minimal modeling approach to VOI, which is possible when data on comprehensive outcome measures, such as quality-adjusted life-years or net benefit, are readily available from existing research, VOI can be estimated without constructing a complex model. (3) In a maximal modeling approach to VOI, a single comprehensive model may be constructed to simultaneously inform priorities concerning multiple clinical questions. The presence of these lower cost VOI methods creates the possibility for VOI analysis to be practically applied in priority-setting process for systematic reviews, and raises questions about how the use of VOI can be systematized.

Methods: This study (1) reviews VOI methods and the approaches currently used to inform priorities for systematic reviews in the literature and in practice; (2) describes an algorithm for selecting an effective and efficient approach to VOI for a given clinical question; and (3) applies this algorithm to assess its potential utility in prioritizing topics nominated to the Agency for Healthcare Research and Quality (AHRQ) and Quality Evidence-based Practice Centers (EPCs) for systematic review.

Results: Our review of past research identified a substantial number of VOI studies but found that VOI had not been used to set priorities for systematic reviews. We did find that many of the elements that are used to estimate VOI are often considered in prioritizing systematic reviews, but they are rarely quantified or combined in an explicit manner that would be consistent with VOI principles. We propose an algorithm that describes a multistage process for identifying an effective and efficient approach to VOI for a given clinical question. This process begins with conceptual VOI to provide informative bounds on VOI, followed by the clustering of review topics and consideration of the use of maximal modeling VOI, and then minimal modeling using comprehensive outcome measures of the benefits of the alternative treatments or health interventions under study. In applying our algorithm to topics nominated to AHRQ's EPCs for systematic review, we found the algorithm useful in selecting the appropriate VOI methods to inform priorities for systematic reviews and found examples in which each of the lower cost VOI

approaches might be valuable. Although full modeling VOI may aid in the planning and design of research, we find limited conditions for its use in prioritizing systematic reviews.

Conclusion: We conclude that consideration of VOI principles and methods may have a useful role in informing priorities for systematic reviews. VOI can help decision makers and others involved in priority-setting for systematic reviews to explicate criteria and quantify measures of expected value that can be used to prioritize reviews. Systematic application of VOI using an algorithm that guides the choice among conceptual VOI, maximal modeling, minimal and full modeling may aid in minimizing the costs and burden to the practical application of VOI. We propose future work that would (1) incorporate VOI into the process by which systematic review topics proposed to AHRQ's EPCs are prioritized, and (2) assess whether that process is found to be useful by decision makers and others.

Contents

Introduction	1
Review	4
Part 1: Review of the Theoretical Approaches to Research Prioritization and VOI	
Analysis	4
Approaches to Research Prioritization.....	4
Principles of VOI and its Conceptual Elements	5
Approaches to Calculating VOI.....	7
Use of VOI Estimates To Inform Research Decisions	15
Part 2: Review of VOI Studies in the Literature	16
Methods.....	16
Results.....	16
Part 3: Review of the Priority-Setting Processes for Systematic Reviews in Practice..	24
Methods.....	24
Results.....	24
Conclusion	32
Theory	33
Introduction	33
Conditions of Value of VOI Analysis in Systematic Reviews.....	33
Algorithm for Selecting the VOI Approach To Prioritize Systematic Reviews.....	34
Stage 1: Use of Conceptual VOI to Bound Value in Systematic Reviews and	
Formal Quantification of VOI	37
Stage 2: Consideration of Maximal Modeling VOI When Topics Cluster Within	
or Across Clinical Domains.....	37
Stage 3: Use of Minimal Modeling VOI When Data on Comprehensive	
Outcomes Measures Are Available	38
Stages 4 and 5: Use of Full Modeling VOI When Additional Collection of	
Primary Data Is Expected To Be Both Valuable and Costly	39
Other Issues in the Use of VOI Estimates To Prioritize Systematic Reviews	39
Conclusion.....	40
Application	41
Methods	41
Results	42
Identification of Topics Nominated for Systematic Review.....	42
Approaches to VOI in Prioritizing Systematic Reviews.....	42
Applications of Conceptual VOI	45
Application of a Maximal Modeling Approach to VOI: Multiple Topics	
Clustering in Diabetes Care	47
Application of a Minimal Modeling Approach to VOI	48
Conclusion.....	53
Discussion	54
General Findings.....	54

Information Requirements of Application of Algorithm to VOI	54
Applicability of Algorithm to Select VOI Approaches	55
Applicability of Approaches to Calculating VOI	55
Limitations of VOI Approach to Research Prioritization.....	56
Future Directions of Research	57
Incorporation of VOI in Priority-Setting Processes.....	57
Standardization of VOI Calculations	58
Evaluation of the Use of VOI for Prioritizing Health Research	58
Conclusion	59
Abbreviations and Variables	62
References	64
Tables	
Table 1. Approaches for Calculating Value of Information in Research Topics in Health Care	9
Table 2. Checklist for Collecting Evidence for Conceptual VOI to Prioritizing Health Research.....	14
Table 3. Summary of the Extracted Data on the Clinically Related Applications (N=72) in Value of Information Studies (M=77)	19
Table 4. Summary of Extracted Data on the Consideration of Conceptual Elements of VOI and Comparison With Other Studies in Clinically Related Empirical Applications (N = 72) in Value of Information Studies (M = 77)	23
Table 5. Selected Health Care Decisionmaking Bodies and Research Funding Agencies.....	33
Table 6. Summary of the Reported Use and Operationalization of Conceptual Elements of VOI for Systematic Review Topics in Priority-Setting Processes of the Different Organizations Under Review (K=13)	30
Table 7. Details of Application for Minimal Modeling Approach to VOI in Acute Respiratory Failure.....	51
Figures	
Figure 1. Flowchart of the Review of VOI studies.....	17
Figure 2. Flowchart of the Review of Priority-Setting Processes in Health Care Organizations That Perform and/or Fund Systematic Reviews	25
Figure 3. Algorithm for Identifying the Effective and Efficient Approach to Calculating VOI in Informing Priorities for Systematic Reviews	36
Figure 4. Application of Algorithm for Identifying the Effective and Efficient Approaches to VOI To Inform Priorities for Topics Nominated to the AHRQ EPCs for Systematic Review in 2009	44
Figure 5. Acceptability Curve (A) and Population Expected Value of Information (B) for Comparing Noninvasive Positive Pressure Ventilation with Standard Therapy ..	54

Appendixes

Appendix A. Search Criteria from Previous VOI and Priority-Setting Reports

Appendix B. Data Extraction Form for VOI Studies

Appendix C. Extracted Data on Clinically Related VOI Applications (N=72) in Value of Information Studies (M=77)

Appendix D. Potentially Relevant Health Care Decisionmaking Bodies and Research Funding Agencies

Appendix E. Data Extraction Form for Priority-Setting Processes in Health Care Decisionmaking Bodies and Research Funding Agencies

Appendix F. Extracted Data from Priority-Setting Processes in Different Organizations (K=13)

Appendix G. Application of Multistage Algorithm to VOI for Prioritizing Topics for Systematic Reviews

Appendix H. Minimal Modeling VOI in Acute Respiratory Failure in WinBUGS

Introduction

Systematic reviews are an important and relatively inexpensive type of research to inform clinical decisionmaking and the development of clinical guidelines, coverage or payment policies, and investments in implementation.¹⁻³ Through the rigorous review and synthesis or meta-analysis of existing evidence, these studies may also reveal heterogeneity in patients and treatment effects, and suggest further research that can fill gaps in evidence. Indeed, systematic reviews have been found to be highly valuable to decisionmaking bodies and research funding agencies such as the Agency for Healthcare Research and Quality's (AHRQ's) Evidence-based Practice Centers (EPCs) because of their potential to promptly address diverse clinical questions or research topics, such as the comparative effectiveness of particular treatments and approaches to healthcare delivery.⁴ Systematic reviews are generally less expensive than trials or other (observational) studies in which primary data on health interventions are collected, i.e., less than \$300,000 for a review compared with multimillions for large-scale randomized controlled clinical trials. However, systematic reviews consume research capacity and are costly enough that not all possible systematic reviews can be performed. With limited funds available to perform systematic reviews, it is essential to have an approach to set priorities among possible reviews so that the benefits from research funding are maximized (e.g., in terms of population health).

Value of information (VOI) analysis has been proposed as a strategy to inform priorities that can improve the effectiveness of spending on health research, including systematic reviews.^{5,6} In contrast with subjective methods and more objective approaches to research prioritization like the burden of disease, clinical variation and "payback from research", VOI explicitly quantifies the improvement in population-level benefits that is expected from research about the outcomes of alternative health interventions. This involves both predicting which of the interventions under consideration is preferred for all possible research outcomes and determining the expected value of that preferred option compared with the alternatives. An estimate of the VOI for a given trial, observational study, systematic review, or a combination or series of studies, can be calculated at the population-level and be compared with the costs of research, and the potential value of other research activities. In effect, the value expected from spending on a particular research project can be directly compared with the value expected from other ways to use those resources to improve health care in order to inform research decisions.

VOI calculations typically involve the construction of a decision-analytic model of the disease and its treatment to fully characterize the uncertainty in the benefits of particular treatments or health interventions being studied. As such, these "full-modeling VOI" analyses can aid in prioritizing studies that address research topics that may only be partial determinants of specific clinical or health policy decisions, and in prospectively estimating the efficiency in the design of new research studies. However, executing these exercises is often complex, demanding large degrees of analytic effort and data. In effect, a full modeling approach to VOI is likely to have substantial costs, which include not only resources invested in constructing the model and generating data as input for the analysis, but also the opportunity costs associated with the time it takes to report the results of VOI and decide upon research. The costs of VOI may sometimes exceed those of the studies under consideration, particularly when these studies are lower cost research efforts such as systematic reviews.

As alternatives to typical full-modeling VOI, newer approaches to analyzing the VOI can be identified that are less burdensome. We refer to these approaches as "minimal modeling," "maximal modeling", and "conceptual" VOI. A "minimal modeling" approach to VOI can

sometimes be applied when evidence is available on the uncertainty in comprehensive measures of outcomes (e.g., both quality-adjusted life-years [QALYs] and costs) that readily address the clinical or policy decision in question.⁷ With this approach, the direct replication or bootstrapping of these outcomes can provide population-level estimates of VOI. Maximal modeling VOI requires a single comprehensive model to simultaneously establish the value of studying multiple research topics or clinical questions clustering within or across clinical domains. This approach is more demanding than full modeling VOI but can be advantageous if multiple topics can be addressed because the costs of VOI per individual topic are minimized. A third option to minimize the burden of VOI is to use a conceptual approach to VOI before formally quantifying the value of information through modeling. “Conceptual VOI” is based on the observation that VOI is calculated as a function of multiplicative elements, which include the potential difference in benefits between the topics or interventions under study, the effect on uncertainty about these benefits through further research, the probability that new evidence is durable and gets implemented into practice, and the size of the affected patient population. If any of these conceptual elements of VOI are relatively small, it is unlikely that the overall value of research, including VOI modeling, will be large. These less complex, lower cost approaches to VOI suggest the potential for practical application in informing research priorities for systematic reviews and other studies that are too inexpensive to justify a costly prioritization exercise.

Because the resources needed to support VOI often come out of budgets that might otherwise be used to fund new research, investments in VOI analyses should be made only if they improve the overall effectiveness of spending on health research. This is a special concern when VOI methods are applied to prioritize lower cost studies like systematic reviews. The question raised by the funder of this study, AHRQ, concerned whether and how VOI could be valuably applied to prioritize systematic reviews. In considering how VOI might be applied, we sought to assess whether an algorithmic approach could be developed to systematize how to identify the conditions under which the efforts invested in performing a VOI analysis to inform research priorities are likely to be well spent, and what type of VOI analysis to perform. As part of this, such an algorithm would help to determine when a less complex and lower cost VOI approach could be a feasible alternative to a full modeling approach so as to increase the practical application of VOI in developing meaningful estimates of the value of research.

The purpose of this study is to explore whether and how VOI analysis might be effectively and efficiently used to inform priorities for systematic reviews. Specifically, we (1) review VOI methods and the approaches currently described in the literature and used in practice to inform priorities for systematic reviews; (2) describe an algorithm for selecting the most appropriate approach to VOI for a given clinical question; and (3) apply this algorithm to assess its potential utility in prioritizing topics nominated to AHRQ’s EPCs for systematic review.

The outline of this report is as follows. In the next section, we report our review of VOI methods in which we outline the principles of VOI and the information on conceptual VOI elements necessary to provide a full estimate of the population value of information that would result from conducting further research. In addition, that section defines and discusses in detail the full, minimal, and maximal modeling and conceptual approaches to performing VOI, and describes whether and how these VOI methods have been used to date to inform priorities for clinical research studies, with a focus on their use in prioritizing systematic reviews. Based on insights from the review of VOI methodology, we then present the theory section of the report in which we describe an algorithmic approach for systematizing the use of VOI in informing research priorities. In the following section, we describe the results of our efforts to use this

algorithm to identify the most effective and efficient VOI methods in prioritizing systematic reviews topics nominated to AHRQ's EPCs. This section also illustrates how conceptual VOI, maximal modeling and minimal modeling may be feasibly applied as alternatives to full modeling VOI using a series of clinically related applications. Finally, in the last section, the discussion section, we discuss the main findings of our study and its practical implications for the use of VOI analysis to set priorities for systematic reviews.

Our results confirm that the consideration of VOI principles and methods may have a useful role in the process of informing priorities for systematic reviews, and that the practical application of value of information analysis can be systematized by following an algorithm that guides the process of identifying effective and efficient approaches to performing VOI. As such, VOI complements other subjective and more objective approaches to prioritizing research activities because it can motivate decisionmaking bodies or research funding agencies such as AHRQ to explicate the criteria relevant for priority-setting. In particular, VOI may provide useful quantitative measures of the potential value of research spending, or be a useful framework to help decisionmakers organize information about the value of research, including that about the durability of research findings, which we found had often been neglected in prior work. In effect, the results of our study suggest the implementation of a two-stage process by which VOI can be used in current triage or prioritization of systematic review topics, in which (1) conceptual VOI is applied to identify systematic reviews with no or limited expected value without formally quantifying this through complex modeling exercises, and (2) practical applications of minimal modeling, maximal modeling and full modeling VOI are selected to calculate the relative population-level value in the other systematic reviews topics on the basis of which these can be ranked and prioritized. A future direction of research would be to evaluate whether VOI analysis and a possible two-stage process to its practical application would be perceived as useful by those involved in research prioritization, and to formally test whether adding VOI to the standard priority-setting process would change decisions about performing systematic reviews and whether the outcomes of reviews in which decisions changed are in fact more valuable according to the different stakeholders in health care and improve the outcomes of research spending.

Review

In this section, we review various formal approaches to prioritizing health research, including both methods discussed in the literature and methods applied in practice, with a focus on the use of VOI to prioritize systematic reviews. Part 1 first briefly discusses theoretical approaches to research prioritization with a focus on the principles of VOI and its conceptual elements. This part then defines and discusses alternative approaches to calculating VOI, and discusses how VOI estimates can inform decisions about research spending. Part 2 reviews the literature that has applied VOI to assess the value of clinical research studies, focusing on the methods applied in those studies. Part 3 reviews the processes that decisionmaking bodies and research funding agencies that perform and/or fund systematic reviews have used to set priorities among systematic reviews. We conclude that there is the potential, at least in theory, to systematically use VOI to inform priorities for systematic reviews.

Part 1: Review of the Theoretical Approaches to Research Prioritization and VOI Analysis

Approaches to Research Prioritization

Approaches to research prioritization, including the use of VOI analysis, differ in how they reflect objective and subjective elements in the priority-setting process, and how they measure or explicitly value health research. In general, opinions, judgments, and consensus among decision makers, experts and other stakeholders in health services provision and research form the basis for the subjective assessment and ranking of research. These qualitative assessments may be, and probably often are, informed by objective measures of the value of research. Objective measures include: (a) the burden of disease or costs of illness, (b) the “payback” from conducting and implementing research, (c) the welfare losses due to variations in clinical practice, and d) VOI.^{8,9} “Burden of disease,” “payback,” and “clinical variation” approaches view research as a means of improving practice by providing information for clinicians, policymakers and patients to help them make decisions about the implementation of particular treatments and interventions. These approaches, particularly measures of disease burden or costs of illness, use aggregate indicators across broad clinical domains rather than the incremental returns from addressing specific clinical questions when identifying priorities for health research. These approaches often consider whether there is some decision maker who might change their decision as the result of the information that could be generated. However, they often do not consider the uncertainty in the magnitude of the potential benefits of a change in decision, the likelihood that information would be generated that would suggest a change in decision would be desirable, or the likelihood that a decision would change even if the information obtained suggested that a change would be desirable (implementation). VOI analysis addresses these limitations by providing a formal framework for analyzing the value of additional information resulting from research to inform clinical or health policy decisions.^{5,6} By measuring the value of research in terms of health outcomes and resources forgone, VOI methods analyze research decisions using a common framework of health benefits and costs that are relevant to decisionmaking concerning health care.

Principles of VOI and its Conceptual Elements

VOI analysis can provide estimates for the population expected value of information ($pEVI$) from health research. The $pEVI$ in a particular research topic can be represented as a function of several multiplicative conceptual elements (Equation 1). These elements include the difference in benefits expected from alternative treatments or interventions on a per patient basis and the reduction in uncertainty therein, the implementation and durability of relevant information, and the size of the affected population of patients.

Equation 1:

$$pEVI = \sum_t \beta^t \cdot Dur_t \cdot Pop_j \cdot \left(\sum_j \text{Im } p_{j|I} \cdot E_{\theta|I} NB(j, \theta) - \sum_j \text{Im } p_{j\theta} \cdot E_{\theta} NB(j, \theta) \right)$$

The specific conceptual elements of VOI are delineated in further detail below.

Difference in Benefits and Reduction in Uncertainty

For research to have value in informing decisionmaking in health care, individual studies or systematic reviews must infer that the benefits between treatments or other health interventions differ and the research must change uncertainty in these benefits. Accordingly, VOI quantifies the expected value of information from research on a per patient basis (EVI) as the improvement in net benefit that is expected from a particular set of information (I) on uncertain parameters θ with which to decide among $j \in [1, 2, \dots, J]$ mutually exclusive interventions (Equation 2).

Equation 2:

$$EVI = E_I \max_j E_{\theta|I} NB(j, \theta) - \max_j E_{\theta} NB(j, \theta)$$

Even though the analysis of net benefit may be limited to the differences expected in terms of health outcomes ($E_{\theta} O(j, \theta)$) (e.g., life expectancy or QALYs), this is done perhaps most meaningfully on the basis of net monetary benefits in which costs ($E_{\theta} C(j, \theta)$) are also considered in the choice for particular treatments and health interventions¹. To do so, the health outcomes of the interventions under comparison are expressed in monetary terms by using some threshold value or willingness-to-pay for a unit of health outcome. The value of information at the population level, that is expected to come from research projects can be directly compared across different diseases, clinical conditions, other uses of resources, and with the costs of research, to inform research decisions.²

¹ The expected net monetary benefit of treatment or intervention j with uncertain parameters θ equals the expected health outcomes, multiplied by some threshold value or willingness-to-pay for a unit of health outcome (λ), less the costs that are expected to be associated with this particular intervention, i.e., $E_{\theta} NB(j, \theta) = \lambda \cdot E_{\theta} O(j, \theta) - C_{\theta}(j, \theta)$. Alternatively, the expected net health benefit can be calculated as the expected outcomes in health less the health outcomes that could be obtained by applying the costs of treatment or intervention j in a health intervention or program that is at the cost-effectiveness threshold [10].

² Notably, net monetary benefits measures, or its equivalent net health benefits, assume that diverse health outcomes and costs can be meaningfully analyzed in a utilitarian framework.

Probability of Implementation

Research only produces value when it leads to the implementation of more beneficial treatments or interventions than those provided on the basis of existing information. However, the provision of new evidence by itself may not ensure that the results of research are fully implemented into clinical practice. The extent to which this takes place is influenced by the knowledge and behaviors of health professionals, uptake or compliance by patients, and other contextual factors, such as the capacity to provide health services, and coverage or payment policies. Because of the dynamic and contingent nature of the implementation process, the probability of implementation is expected to vary over time ($Im p_{jt(t)} \in [0,1]$). Imperfect or delayed implementation of relevant information decreases the net benefit expected from research at a population level.¹¹⁻¹³

Durability of Information

Another conceptual element that impacts the population value of research is the probability that relevant information on a particular treatment or intervention is durable over time ($Dur_i \in [0,1]$). This durability of information generally is associated with the rate at which new clinical evidence and/or better alternatives for patient management emerge. For example, future research, and systematic reviews in particular, may have less value in the presence of numerous trials or other research studies that are expected to produce valuable insights into the research topic being addressed within the near future. Another example in which durability is more likely to be limited is when there is a rapid followup of modifications to procedures and techniques. This commonly occurs in clinical domains such as device development. Conversely, information on elements of fundamental human biology, such as the natural history of a clinical condition, may have more durable effects.

Size of Patient Population

In establishing a population-level statistic to inform research decisions, VOI should account for the size of the population of patients expected to benefit from research ($Pop_j \in [0,\infty]$). Along with the prevalence and incidence of a particular disease or clinical condition, the value of particular studies or systematic reviews varies with the scale of the at-risk population in whom it could be applied. Although research may have value on a global scale, the population VOI is most often calculated for the population of patients within the specific jurisdiction or health system within which the research is being considered. In calculating the value of research, some consideration may also be paid to the practical effects of research activities across interventions and populations. In practice, if VOI estimates are to be compared across potential research topics, it is essential that the estimates being compared refer to the same population of potential beneficiaries of research (e.g., patients in the relevant jurisdiction(s)). Time preference is also typically reflected in population-level value of research by discounting the future benefits from research with rate $\beta' \in [0,1]$ over the time period t for which a clinical or health policy decision is deemed relevant.

In the absence of information on these conceptual elements of VOI, it may be difficult to fully implement VOI. For example, this is the case when it is unclear as to what extent a particular study or systematic review is likely to produce information on set of outcomes and their associated probabilities that could affect the uncertainty in the expected benefits of

alternative health interventions. Similarly, it may be difficult to predict the durability of new evidence or predict how the results of research will impact clinical practice. Performing VOI with incomplete information typically requires making assumptions about the missing information or limiting the objective of the analysis. In effect, VOI analysis may be limited to calculating the value expected from perfect information. The expected value of perfect information ($EVPI$) and expected value of partial perfect information ($EVPPPI$) can provide upper bounds on the value of research through calculating the improvement in net benefit expected from eliminating all uncertainty in all parameters θ or a subset of these $\varphi(\in \theta)$, respectively.³ In contrast to full EVI calculations, more limited analysis such as that of the expected value perfect information requires information only about the distribution of (net) benefits of the interventions under consideration. Population level estimates for the value of perfect information are typically useful in identifying research priorities across disease areas or clinical domains and in quantifying the gaps in evidence on particular treatments or health interventions. However, because such measures provide only upper bounds, they can only establish necessary conditions for research spending and not sufficient conditions. In other words, bounding techniques can suggest that the expected value of a given type of research is small so that the research is unlikely to be worth performing. However, suggesting the research is worth performing requires the ability to actually estimate VOI.

Approaches to Calculating VOI

A variety of approaches can be used to calculate the value of information expected from health research, including “full modeling,” “minimal modeling,” “maximal modeling,” and “conceptual VOI.” These approaches typically vary in the extent to which modeling is complex and costly. The complexity of modeling is determined by the analytic efforts and data required to apply the approach. Even though more complex models may provide more accurate estimates of the VOI for particular research topics, it is often difficult to present these models and their assumptions transparently. Besides cost differences in terms of staff time, data input and other resources necessary for model implementation, the approaches to calculating VOI may also differ in terms of their potential for application in a given context, and the speed with which the analysis can be completed. Table 1 summarizes the full modeling, minimal modeling, maximal modeling and conceptual approaches to VOI, their requirements and potential scope for application, and their advantages and disadvantages.

Full Modeling

VOI calculations commonly involve full modeling of a particular disease or clinical condition, its treatment and the different health states to characterize the uncertainty in the benefits of treatment or health interventions under consideration. This may be performed using decision trees, Markov models, or discrete event simulation. In such modeling exercises, patient characteristics, risk attributes and transition probabilities are structured such that predictions of

³ $EVPI$ is calculated as the difference in maximum net benefit expected from making a clinical or health policy decision from among $j \in [1, 2, \dots, J]$ mutually exclusive treatments or interventions with perfect information and that with uncertain parameters θ , with $EVPI = E_{\theta} \max_j NB(j, \theta) - \max_j E_{\theta} NB(j, \theta)$.

The quantification of $EVPPPI$ for a particular parameter or subset of parameters $\varphi \in \theta$, with ψ the remaining set of parameters, can be described as follows: $EVPPPI_{\varphi} = E_{\varphi} \max_j NB_{\varphi|\psi}(j, \varphi, \psi) - \max_j E_{\theta} NB(j, \theta)$

disease progression and patient survival can be provided. This produces estimates for the probability of specific health states that can be combined with quality of life or utility estimates and costs in those health states which can be used to generate a wide set of comprehensive outcomes measures, including life expectancy, QALYs and costs or net benefits, that address clinical decisionmaking or health policy decisions.

Table 1. Approaches for calculating value of information in research topics in health care

Approach	Definition	Requirements	Clinical Application(s)	Advantages (+) and Disadvantages (-)
Full Modeling [§]	Full characterization of disease/treatment using a decision model or other simulation model of relevant health states	- Structuring of model, data input for each model parameter	- Individual research topics, within single disease area or clinical domain - Chronic conditions, complex diseases	- High costs of performing VOI in individual research topics - Complex and time-consuming modeling exercises + Accurate uncertainty analysis and VOI estimates, including calculation of EVPPI
Minimal Modeling, Subtype 'No modeling' [§]	Direct replication or direct computation of (incremental) effects on comprehensive health outcomes (e.g., life expectancy or QALYs), costs and/or net benefits	- Distributions of comprehensive health outcomes or QALYs, costs and/or net benefits	- Individual research topics, within single disease area or clinical domain - Acute conditions, end of life treatments - Direct measurement of final health outcomes and resource use	+ Low costs of performing VOI in individual research topics + Does not involve complex and time-consuming modeling + Complementary to adaptive research design - Requires clinical trial or data set that can provide comprehensive measure of net benefit - No comprehensive uncertainty analysis and VOI estimates (EVPPI)
Minimal Modeling, Subtype 'Limited Modeling' [§]	Any modeling necessary (e.g., modeling of patient survival, mapping of treatment effect to utilities or approximation of costs) without using a decision model or other simulation model of relevant health states	- Intermediate measures for health outcomes or QALYs, costs, and/ or net benefits; life expectancy or survival data	- Individual research topics, within single disease area or clinical domain - Acute conditions, end of life treatments	+ Reduced costs of performing VOI in individual research topics + Reduced need for complex and time-consuming modeling + Complementary to adaptive research design - Requires clinical trial or data set that can require only modeling of survival or other limited modeling to generate comprehensive measure of net benefit - No comprehensive uncertainty analysis and VOI estimates (EVPPI)
Maximal modeling [§]	Comprehensive modeling organized around clusters of individual but related topics (e.g., disease, meta- or multi-purpose models)	- Clustering of research topics and description of clinical relation, correlation in information about net benefit in/across different interventions/topics - Structuring of model, data input for each model parameter	- Multiple research topics, within or across disease areas or clinical domains - Chronic conditions, complex diseases, disease management or integrated care	+ Potential for minimal costs of performing VOI in individual research topics + Accurate uncertainty analysis and VOI estimates, including calculation of EVPPI + Potential for building an infrastructure for value of research calculations that would facilitate rapid and low-cost VOI estimates to aid future prioritization and planning of research - Highly complex and time-consuming modeling exercises - Requires evidence that captures correlation in information between individual research topics

Table 1. Approaches for calculating value of information in research topics in health care (continued)

Approach	Definition	Requirements	Clinical Applications	Advantages (+) and Disadvantages (-)
Conceptual VOI	Bounding exercise using information on the conceptual elements of VOI [†]	- Quantitative evidence of zero or low value in potential difference in net benefit, reduction expected in uncertainty, probability of implementation, durability of information, or size of patient population	- Individual or multiple research topics, within or across disease areas or clinical domains - Any application, e.g., rare diseases, controversial treatment, active R&D	+ No costs of performing VOI in individual or multiple research topics + Rapid indication of informative bounds on value of research - Requires evidence that any of the conceptual elements of VOI equals zero or low values - Potential for inaccurate uncertainty analysis and VOI estimates

EVPPI: expected value of partial perfect information; QALYs: quality-adjusted life-years; R&D: research and development; VOI: value of information

[§] In all modeling approaches, VOI calculations can be based on simulation / bootstrapping (parametric and/or non-parametric) or equation-based computations (parametric).

[†]The results of existing VOI studies may also provide information bounds on VOI in particular research topics, depending on the applicability of these studies to the specific context or setting in which decisions about the priority of the research topics are made.

Rich characterization in full decisions models, within which all potential sources of uncertainty are promulgated, allows for detailed assessment of VOI that can identify how information about specific parameters might have value in addressing the clinical question, and establish efficient research designs. However, the complexity of constructing such models makes full modeling VOI sufficiently time-consuming and costly that they may be impractical for many purposes, including that for prioritizing low-cost studies, such as systematic reviews.

Minimal Modeling

Minimal modeling approaches to VOI can be defined as those approaches that allow the calculation of VOI for individual research topics without constructing a full decision model of the disease and treatment process.⁷ Two subtypes of minimal modeling can be distinguished: “no modeling” and “limited modeling.”

“No modeling” VOI can be applied when existing research provides data on comprehensive outcome measures that are sufficient to address the clinical or health policy decision in question from the decisionmaking perspective adopted. Such comprehensive outcome measures may include health outcomes (e.g., life expectancy or QALYs), costs, and/or net benefits. For example, in a trial of treatment alternatives in which QALY differences were measured in patients until death, and the preference for treatment is based on QALYs, those QALY differences would be considered a comprehensive outcome measure. In such a case, direct replication of these raw data through bootstrapping or simulation would allow for calculating the value in further research studies, including systematic reviews. Alternatively, VOI can be based on equation-based computations for which parametric distributions on the comprehensive outcomes are to be specified. Aside from its practical application in end of life treatment, “no modeling VOI” may also be particularly feasible in acute diseases and short-symptom conditions.

In “limited modeling” VOI, a particular treatment or intervention affects morbidity but not mortality, and quality of life measures are directly available so that the quality of life measure can be easily combined with survival data to calculate the value of research. Modeling can then be limited to predicting patient survival or life expectancy and combining it with the quality of life data. A recent analysis of the value of research on atypical antipsychotics is an example of such a limited modeling VOI study.¹⁴ Depending on the evidence available from existing research and the clinical or policy decision in question, modeling to provide VOI estimates may also be limited to mapping treatment effects to utilities or approximating cost differences in treatments or health intervention under consideration.

In comparison with full modeling approaches, “limited” and “no” modeling VOI have less ability to accurately analyze the value of studying specific parameters that may partially determine the benefits of the intervention alternatives being considered. That is, the value of partial information ($EVPI$ and/or $pEVPI$) can only be assessed in the data on the comprehensive outcome measures that are used as input for the minimal modeling exercise. Moreover, “minimal” models cannot be tailored to different clinical setting or decisions contexts by manipulating the parameters of a model. On the other hand, VOI analysis with only minimal modeling significantly reduces the burden of VOI application, particularly in terms of the costs of staff time needed to construct and analyze a complex model. This makes it possible to consider its potential use to inform priorities for studies that are not very costly, such as systematic reviews.

Maximal Modeling

Instead of constructing separate models for the analysis of the value of research in individual topics, a maximal modeling approach to VOI uses a single comprehensive model to simultaneously inform priorities in multiple research topics that can be clustered within or across clinical domains. Such a “maximal model” is often organized around a particular disease or condition or health care program, in which the clustering of separate but related topics most commonly follows from the pathogenesis or pathophysiology of a disease or conditions, its natural progression, and treatment patterns or clinical pathways. The Coronary Heart Disease Policy Model is an example of a comprehensive model that simulates demographics and risk-factor-epidemiology, which includes disease history, to project the incidence, morbidity, mortality and costs of coronary heart disease (CHD) in the U.S. population. This model could be used to address many questions about the value of research in a broad range of CHD interventions, including control of hypertension, hypercholesterolemia, and acute treatment of myocardial infarction.¹⁵ The complexity and data demands of maximal modeling approaches to VOI are as great as or greater than those of full modeling approaches. Accordingly, maximal modeling approaches can provide estimates of VOI for specific parameters in much the way that full modeling approaches can provide such estimates.

Maximal modeling VOI is typically useful in chronic or complex diseases in which a patient’s health is affected by multiple related clinical conditions and interventions. In effect, the use of maximal models will perhaps be of greatest practical value in identifying priorities for research in disease-areas for which there are multiple interventions that could be pursued simultaneously. When modeling the value of research in topics that cluster with other research topics, it is important to account for potential correlation in information across these topics so as to establish the benefits of different types of research, especially in the context of other types of research.⁴ In some cases, information to address a particular research topic or clinical question may come from a combination or a series of complementary studies. For example, as opposed to relying on a single study, combining the results from a trial reporting the effect of a particular treatment on relevant outcomes along with observational data on prevalence and natural history of a disease and cost studies may be used to address issues of comparative effectiveness of alternative ways for patient management. Accounting for correlation and future prospects in research may be of particular relevance in valuing systematic reviews or other evidence synthesis studies, as these may often also be performed to identify relevant evidence gaps and to inform future research decisions related to sequential trials or adaptive research designs.¹⁶ Because of the potential computational burden, more complete modeling approaches may have to rely on meta-modeling concepts or network analyses.^{17,18} The main advantage of maximal modeling approach to VOI in this is that the costs of VOI calculations can be defrayed over multiple research topics. This may justify establishing infrastructure, perhaps building on existing decision models, to perform value of research calculations in a domain that can facilitate rapid and low-cost assessment of VOI for future topics.

⁴ The value that can be expected from research in multiple separate but related topics can never be larger than the value that could come from research in this domain that would otherwise be found from completely resolving a target disease or condition in a particular patient population.⁶

Conceptual VOI

In a conceptual approach to VOI, information is used about each of the multiplicative elements of VOI to assess the value of research studies without formally quantifying the value of information through modeling exercises. As described in Equation 1, the elements that go into conceptual VOI include the differences in benefits expected from different treatment or intervention options at patient level, the expected change in uncertainty about these benefits from obtaining more evidence, the implementation and durability of relevant information, and the size of the population of patients affected from research. Evidence collection on these different elements can be performed through various means, including the use of expert elicitation, as shown in Table 2. If information indicates that any of the conceptual elements of VOI has a value that is zero or close to zero, the product of these terms, and hence the VOI, will likely approximate zero. Unless the value of some other element is exceptionally large, this indicates that further research, including VOI modeling, is unlikely to be valuable.

Examples in which conceptual VOI may indicate a limited value of research include rare diseases where the population of patients affected from research is too small to justify research spending on performing VOI. In such cases, the conceptual VOI approach may also be applied to multiple topics simultaneously. The idea that a disease is too rare to justify research based on expected population benefit should not be construed as evidence that research is never justified. Instead, it argues that priorities in research topics with low conceptual VOI may have to be justified on the basis of measures other than VOI.

Table 2. Checklist for collecting evidence for conceptual VOI to prioritizing health research

Element of Conceptual VOI	Operationalization of Elements	Representative Variables	Potential Sources for Evidence
Difference in Benefits	<ul style="list-style-type: none"> - Potential for improvement in health outcomes, reduction of costs and perhaps improvement in net benefits? 	Expected differences in health outcomes, including measures for mortality, morbidity and quality of life, resources, prices or costs, net benefits	Previous studies, MEDLINE®/PubMed, expert elicitation
Reduction in Uncertainty	<ul style="list-style-type: none"> - Relevant studies with comparative information available? - Significant uncertainty in decisionmaking? - Potential for ambiguity in evidence? 	Standard deviation or error, confidence interval, probability or likelihood in health outcomes, costs and perhaps net benefits	Previous studies, MEDLINE®/PubMed, expert elicitation
Probability of Implementation	<ul style="list-style-type: none"> - Potential for improvement in implementation by health professionals and/or patients? - Potential for overcoming financial or organizational barriers? - Potential for controversy in making decisions about best practice? - Variability in diffusion of health technologies and significant variation in clinical practice? 	Technology diffusion, uptake implementation, (appropriate) use, adherence, compliance, variation in practice, patterns of care	MarketScan data, MEDLINE®/PubMed, postmarketing surveillance, expert elicitation
Durability of Information	<ul style="list-style-type: none"> - Forecasts of emergence of valuable new health technologies? - Potential for new evidence to become available? - Represents valid outcomes for clinical practice? 	Time frame for decisionmaking, rates of technology development, validity of evidence	Expert elicitation
Size of Patient Population	<ul style="list-style-type: none"> - Significant disease burden or large proportion of patients within a specific jurisdiction? 	Prevalence and incidence of disease, size of patient population	National Statistic Bureaus, National Health Institutes, expert elicitation

VOI: value of information

Use of VOI Estimates To Inform Research Decisions

By comparing the population-level expected value of information ($pEVI$) with the expected costs of research, the returns from particular research studies and systematic reviews can be assessed. Equation 3 describes the population-level returns expected from a set of information I produced by new research (Π_I). These returns depend on the benefits and costs of particular research projects (C_{It})⁵ and on the costs of performing VOI to identify research priorities (C_{VOI})⁶.

Equation 3:

$$\Pi_I = pEVI - \sum_t \beta_t \cdot C_{It} - C_{VOI}$$

In settings in which resources or budgets are fungible between research and other uses, it is possible that all studies for which the returns are expected to be positive are potentially worthwhile performing. However, when the resources for research are limited, only those (combinations of) primary studies or systematic reviews should be performed that maximize the expected returns of research across all potential research topics. In choosing between mutually exclusive studies in individual topics of research, efficient research designs can be established through choosing type of studies (e.g., trial versus systematic review), sample size, relevant outcomes, and the length of follow up for which the returns to research in terms of population health are maximized.¹⁹ In comparing estimates for VOI to prioritize among research projects, it is important that these estimates are standardized for key assumptions, including those related to the conceptual elements of VOI (e.g., relevant population) and discounting.⁷

⁵ Aside from the costs of setting up and conducting research studies, research may also incur costs for using up patients in (randomized) research and delaying decisionmaking until research reports. In effect, the likely short duration of performing and reporting systematic reviews may in part explain why this type of research is inexpensive relative to trials and other (observational) studies, and increasingly used to inform clinical and health policy decisions.

⁶ The approach to VOI affects costs in terms of its modeling requirements (e.g., staff and data input) as well as the opportunity costs compared with other approaches to research prioritization due to any delay in decisionmaking about research spending as a result of the time it takes to analyze VOI before particular research studies can commence.

Part 2: Review of VOI Studies in the Literature

We conducted a comprehensive review of the literature to identify clinical research studies with some empirical application of VOI and to describe the methodology applied to estimate the value of research within those studies. Where possible, we focus on potential implications for the use of VOI in prioritizing systematic reviews.

Methods

For our comprehensive review of the literature, we merged the results of a search for VOI studies in an earlier AHRQ report by the University of Chicago (UC) on Minimal Modeling Approaches to Value of Information Analysis for Health Research with the search results from the Duke Evidence-based Practice Center's (DEPC) report on Evaluating the Potential Use of Modeling and Value-of-Information Analysis for Future Research Prioritization Within the Evidence-based Practice Program. Both searches yielded publications on VOI in health services/health care settings, in English, between 1990 and 2010 (Appendix A). We reviewed only those studies with some clinically related empirical application of VOI analysis, and excluded all hypothetical applications as well as studies with theory/methods only. More details on the inclusion criteria for potential relevant VOI studies and the process of screening the ones initially identified can be found in the above-mentioned reports.^{20,21}

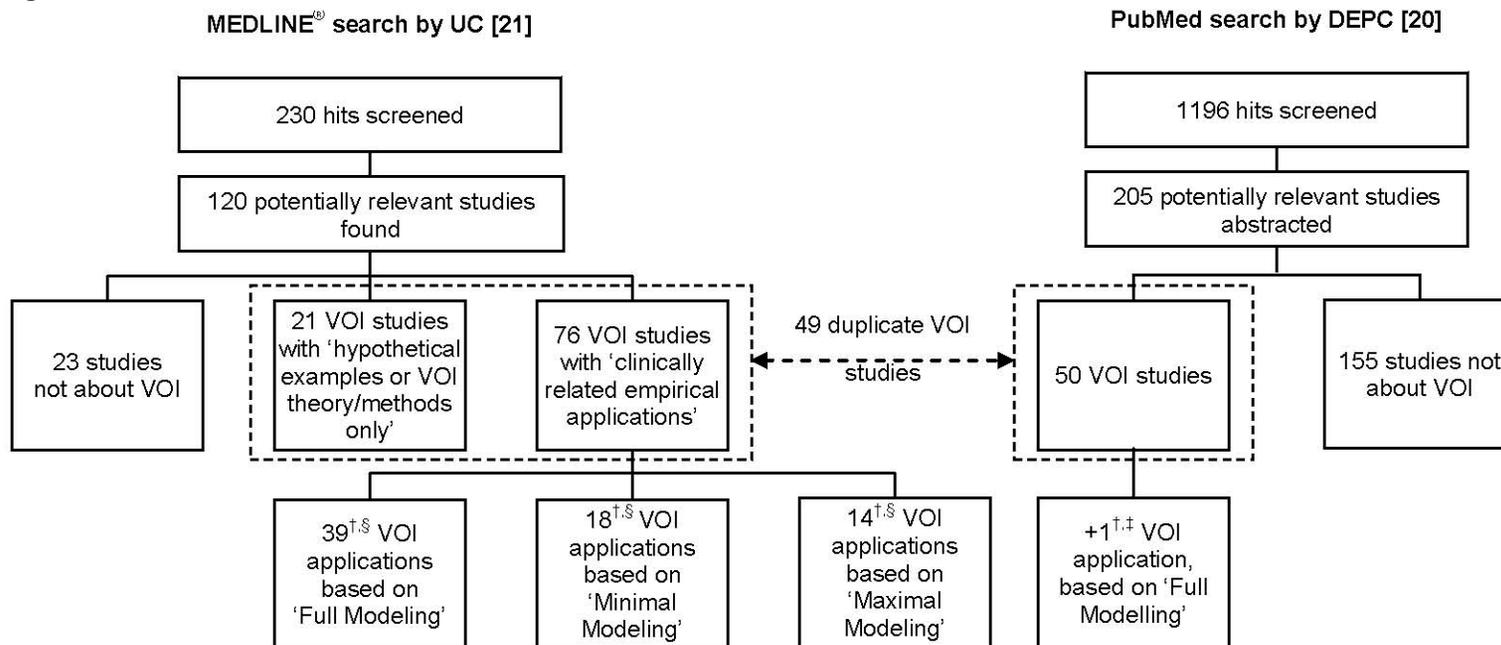
We developed a form to standardize data extraction for the review of VOI applications (Appendix B). For each application in the VOI publications, we extracted data on the approach to modeling and consideration of information on the conceptual elements of VOI, the results of VOI analysis and the comparison with other VOI studies and other approaches to research prioritization. Data were extracted by one investigator [TH], whereas the other investigators performed a check for accuracy and completeness of the extracted data, with disagreements resolved by consensus. Through a descriptive analysis of the review results, we outline whether and how methods for VOI are currently applied for prioritizing systematic reviews.

Results

Identification of VOI Studies

Figure 1 summarizes the process and results of our search for VOI applications in the literature. The MEDLINE[®]/PubMed database searches in the UC report and the DEPC report produced 230 hits and 1196 hits, respectively. After screening the abstracts and titles of these hits, 120 studies were identified as potentially relevant VOI studies from the UC search, and 205 from the DEPC report. Based on the full-text reading of all these studies, the UC search revealed 21 VOI studies with hypothetical examples or theory/methods only, and 76 studies with some clinically related empirical application of VOI.^{9,11-14,17,22-91} The DEPC report revealed one VOI application complementary to the UC report.⁹² Appendix C provides all the data extracted from the 72 VOI applications from in total 77 VOI studies included in our literature review.

Figure 1. Flowchart of the review of VOI studies



DEPC: Duke Evidence-based Practice Center; UC: University of Chicago; VOI: value of information

† 13 of 72 VOI applications were reported in multiple VOI studies

§ In 3 additional VOI applications, insufficient information was available to review the methods applied

‡ In 1 additional VOI application, insufficient information was available to review the methods applied

Applications of VOI and the Approaches to Modeling

Table 3 summarizes details of the 72 clinically related empirical applications in the published VOI studies being reviewed. In 55 percent of the applications, a full model was constructed for performing VOI calculations. Minimal modeling or maximal modeling approaches were applied less frequently, 26 percent and 19 percent, respectively. The value of research was analyzed across diverse clinical domains with heart disease, cancers, infectious diseases, and mental disorders as the most common ones. The interventions under evaluation ranged from screening strategies for breast cancer and diagnostics in minor head injuries to antipsychotics and changes in health services provision for patients with hearing impairment.^{14,73,78,86} More than half of the studies were conducted in the U.K., 19 percent in the U.S., 10 percent in Canada, and 7 percent in The Netherlands. Eighty-one percent of the VOI applications were undertaken from a societal or health care system perspective, as one might expect given the public characteristics of evidence collection.

The purpose of applying VOI varied across the VOI studies. Most applications (85%) sought to quantify the uncertainty in benefits associated with intervening in health care and/or the value of performing further research on particular treatments or interventions, with the results of the analyses mostly reported in terms of population measures for expected value of perfect information (EVPI). In fewer studies, VOI was also applied to analyze the value of studying individual or a subset of parameters with which to inform clinical or policy decisions (i.e., *EVPI* and/or *pEVPI*). Only 18 percent of the applications were set up to establish the expected value of particular types of studies and research designs, despite the potential relevance of such costs in decisions to fund specific clinical studies. Most published applications of VOI studies in health services/health care settings appear to be focused on demonstrating VOI methods rather than directly informing research priorities.

Although the value of research calculations often relied on evidence from systematic reviews (60%), VOI application studies occasionally recommended performing new systematic reviews as an implication of the analyses. In fact, recommendations to perform systematic review were stated only in 3 instances. Garside et al. identified areas of uncertainty related to patient management of Barrett's esophagus for which further research synthesis might be focused.⁸⁵ Fox et al. recommended reviews of evidence for predicting non-response to cardiac resynchronization therapy devices for patients with heart failure.⁶¹ The VOI analysis by Bojke et al. sought to address the appropriateness of the review and modeling of screening for age-related macular degeneration treatment in the U.K.⁸⁰ Even though these studies suggested systematic reviews as the next step, we should note that they were not undertaken in order to motivate a systematic review but to inform priorities for other, more costly studies. This suggests that, even if a VOI is not performed in order to inform priorities for systematic review related to a topic, once a VOI is performed on a topic for some other reason (e.g., to develop a design for a clinical trial), the results of such a VOI might also provide information on the potential value of a systematic review. As a result, funders of systematic reviews, such as AHRQ, may wish to regularly monitor the literature of VOI to look for applications in clinical areas where topics may arise. If a VOI study is found in areas where a systematic review is being considered, it might then be used to inform the priority for that systematic review, either through a conceptual VOI approach or a more quantitative approach, including by being adapted to assess VOI for a systematic review.

Table 3. Summary of the extracted data on the clinically related applications (N=72) in value of information studies (M=77)

		n (n / N%)
Approach to Calculating VOI	Full Modeling	40 (55%)
	Minimal Modeling, Subtype 'No Modeling'	9 (13%)
	Minimal Modeling, Subtype 'Limited Modeling'	9 (13%)
	Maximal Modeling	14 (19%)
Application	Heart Disease / Cardiovascular Disorders	17 (24%)
	Cancer	14 (19%)
	Infections	7 (10%)
	Mental Disorders	5 (7%)
	Asthma / COPD	4 (6%)
	Trauma-related Disorders	3 (4%)
	Diabetes / Obesity	2 (3%)
	Other	20 (28%)
Setting	U.S.	14 (19%)
	U.K.	38 (53%)
	Canada	7 (10%)
	The Netherlands	5 (7%)
	Other	8 (11%)
Perspective	Societal	20 (28%)
	NHS / NIH / Health care system	38 (53%)
	Third party payer	6 (8%)
	Other	2 (2%)
	Not Stated	6 (8%)
Purpose of VOI	Quantification of Decision Uncertainty and/or Overall Value of Further Research	
	At Patient Level Only (i.e., EVPI)	6 (8%)
	At Population Level Only (i.e., pEVPI)	31 (43%)
	Both at Patient and Population Level	24 (33%)
	Not Done	11 (15%)
	Analysis of Uncertainty in Element(s) of Decision and/or Particular Research Priorities	
	At Patient Level Only (i.e., EVPPI)	15 (21%)
	At Population Level Only (i.e., pEVPPI)	24 (33%)
	Both at Patient and Population Level	3 (4%)
	Not Done	30 (42%)
	Assessment of Value in Specific Research and/or Design of Particular Studies	
	At Patient Level Only (i.e., EVI, EVSI, ENG, or ENBS)	1 (1%)
	At Population Level Only (i.e., pEVI, pEVSI, pENG, or pENBS)	6 (8%)
	Both at Patient and Population Level	2 (3%)
	ICER _{trial}	4 (6%)
Not Done	58 (82%)	

Table 3. Summary of the extracted data on the clinically related applications (N=72) in value of information studies (M=77) (continued)

		n (n / N%)
Demonstration of Application of Method(s)		24 (33%)
VOI Calculations with Evidence from Systematic Review(s)	Done	43 (60%)
	Not Done / Not Stated	29 (40%)
Application of VOI to Prioritize New Evidence Synthesis Research, including Systematic Review(s)		3 (4%)
	Done	67 (93%)
	Not Done / Not Stated	2 (3%)
	Not Applicable	

COPD: chronic obstructive pulmonary disease; ENBS: expected net gain from sampling; ENG: expected net gain from trialing; EVPI: expected value of perfect information; EVPPI: expected value of perfect information for particular parameters; EVSI: expected value of sample information; ICER_{trial}: incremental cost-effectiveness ratio of a particular trial; NHS: National Health Services; NIH: National Institutes of Health; pENBS: population expected net gain from sampling; pENG: population expected net gain from trialing; pEVPPI: population expected value of perfect information for particular parameters; pEVSI: population expected value of sample information; VOI: value of information.

In the review, the VOI methodology was found to vary across the applications. In all 58 applications of full or minimal modeling VOI, the analyses addressed single clinical research questions. Minimal modeling approaches were applied in those situations where VOI estimates could be provided from direct replication of comprehensive outcome measures through bootstrapping, or from limiting modeling to the approximation of patient survival or life expectancy, for example, using (declining) exponential distributions.⁷ The models in maximal modeling VOI applications typically described the process of screening, diagnosis and treatment of patients in particular disease areas, including bacterial infections,^{69,70} and coronary heart disease.⁷¹ However, all of these analyses restricted their VOI calculations to single research topics rather than simultaneously assessing the value of studying the different topics clustering within the maximal model. Maximal modeling or full modeling is often applied to provide overall measures of uncertainty and value of research in treatments of health interventions (e.g., EVPI or EVPPI), even though more limited modeling approaches could perhaps have been of use in these instances.

Use of Conceptual VOI and Comparison of Results

We did find evidence of the use of a conceptual approach to VOI prior to performing more complex VOI analyses. Indeed, VOI applications commonly cited uncertainty in differences in health outcomes and costs between the treatments or health interventions being studied (Table 4) as a prerequisite to justifying further analysis. In addition, the population of patients that was expected to benefit from further research was also frequently referenced. However, the implementation and durability of relevant information was almost never considered in advance of performing VOI. Because such information could have bounded the value of information that could come from both new research and further VOI modeling, the explicit consideration of information on these additional conceptual elements that determine the population-level value of information might have led to decisions not to pursue VOI in some cases, increasing the efficiency of investments in VOI.

Another important finding of the review related to comparability across VOI studies. Indeed, we observed that it was often difficult to compare VOI estimates across all clinically related empirical applications of VOI. For example, the *EVPI* results varied from \$0–\$2.48 at the lower end^{49,11[c],35,92[a]} to \$17,326 at maximum per patient,⁵² while the population values for *EVPI* ranged between \$0–\$37.54046,^{56[b],68[b]} up to \$308 billion.^{14,7} Aside from the fact that the models and their assumptions were not always reported transparently, a meaningful comparison was often difficult because of the variation in the perspective and time horizon of the analyses, the methods for measuring health outcomes, costs as well as VOI (e.g., *pEVPI* versus sample size calculations), and the threshold value for cost-effectiveness used in the applications for which the VOI analysis was performed. With exception of population size and discounting, VOI elements were not consistently considered as a standard for bounding population-level estimates of the value of research (Table 4). Specifically, VOI calculations were adjusted for the probability that research findings are implemented in only 14 percent of clinical applications, as measured by screening rates or medication compliance. The durability of new information was generally simply assumed that to vary between 5 and 20 years. The lack of comparability in existing VOI studies may explain why the results of VOI applications were seldom compared with those of

⁷ All values are standardized on historical currency exchange rates (<http://www.oanda.com/currency/historical-rates> [Accessed: 2012 Feb 10]) and consumer price index (http://www.bls.gov/data/inflation_calculator.htm [Accessed: 2012 Feb 10]) but not on population size, time horizon of analysis, and cost-effectiveness threshold.

other studies (7%).^{11[b],35,45,50,66} Standardization would make value of research calculations more comparable, and increase the ability of VOI to inform research priorities.

Table 4. Summary of extracted data on the consideration of conceptual elements of VOI and comparison with other studies in clinically related empirical applications (n = 72) in value of information studies (m = 77)

		Stated, referring to source(s)	Stated, based on assumption(s)	Stated, without any reference	Not Stated	Not Applicable
		n (n/N%)	n (n/N%)	n (n/N%)	n (n/N%)	n (n/N%)
Consideration of Information on Conceptual Elements when Calculating VOI	Difference in Benefits	37 (51%)	4 (6%)	4 (6%)	26 (36%)	1 (1%)
	Reduction in Uncertainty	31 (43%)	4 (6%)	8 (11%)	28 (40%)	0 (0%)
	Probability of Implementation	0 (0%)	10 (14%)	0 (0%)	58 (81%)	4 (6%)
	Durability of Information	5 (7%)	41 (57%)	13 (18%)	11 (15%)	2 (3%)
	Size of Patient Population	43 (60%)	13 (18%)	7 (10%)	5 (7%)	4 (6%)
	Discounting	NA	NA	42 (58%)	28 (39%)	2 (3%)
Existing VOI Studies		2 (2%)	0 (0%)	0 (0%)	64 (90%)	5 (7%)
		n (n/N%)	n (n/N%)	n (n/N%)	n (n/N%)	n (n/N%)
Comparison of VOI Results with Those of Other VOI Studies		NA	NA	5 (7%)	62 (86%)	5 (7%)
Comparison of VOI Results with Those of Other Approaches to Research Prioritization		NA	NA	9 (13%) [†]	62 (86%)	1 (2%)

NA: Not applicable; VOI: value of information.

[†] Only 1 study was found in which the results of performing VOI was compared with other quantified measures for informing research priorities, i.e., research payback. ⁴⁷

Part 3: Review of the Priority-Setting Processes for Systematic Reviews in Practice

We reviewed the processes used to set priorities for among systematic reviews by major U.S. and international health care decisionmaking bodies and research funding agencies that are engaged in systematic review activities. This was done to understand how prioritization of systematic reviews proceeds in practice, and to examine whether VOI currently plays any role in this process.

Methods

For our review of the practice of priority-setting, we assembled an initial list of potentially relevant organizations from (1) the recent AHRQ-commissioned reports by Meltzer et al.²¹ and Myers et al.,²⁰ (2) an earlier review of practical approaches to health technology assessment priority setting,⁹³ and (3) consultation with a Technical Expert Panel convened to serve an advisory role on this project (Appendix D). This list was screened to identify those organizations that perform and/or fund systematic reviews as part of their research and/or decisionmaking activities. We reviewed only the processes of organizations that provided information in English and through Internet sources that was sufficiently detailed to allow their priority-setting processes to be meaningfully reviewed.

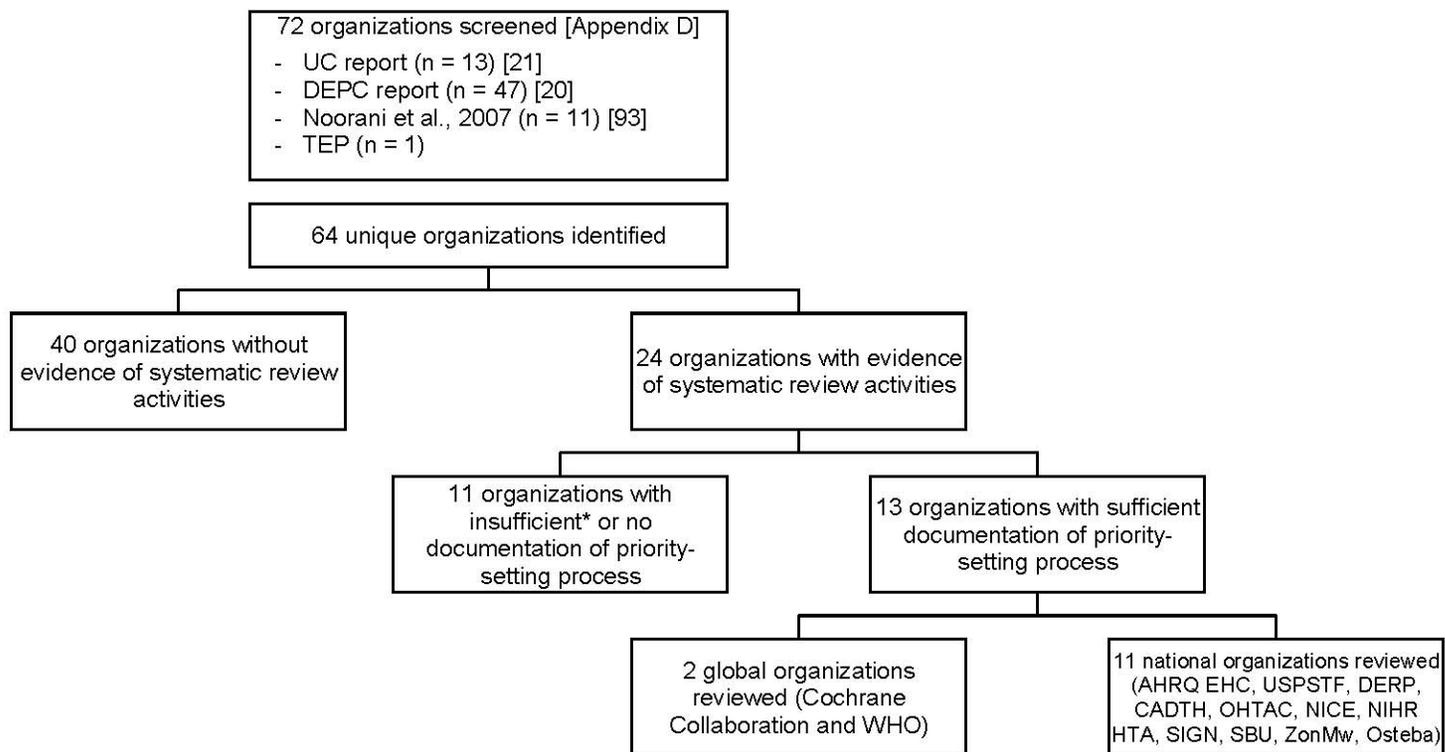
We developed a standardized form to extract data on the prioritization processes in the selected organizations (Appendix E). For each process, we extracted data related to the procedures and methods for research prioritization, including whether VOI was used, the stakeholders involved in the process, and the approach used for generating topics for systematic reviews. Data were extracted by one investigator [JS], whereas the other investigators performed a check for accuracy and completeness of the extracted data, with disagreements resolved by consensus (Appendix F). We limited our search for data to any reports that were publicly available from the Internet. Descriptive synthesis of the review results was performed to describe the priority-setting processes, focusing on any uses of VOI for prioritizing topics for systematic reviews.

Results

Identification of the Priority-Setting Processes for Systematic Reviews

Figure 2 summarizes the process and results of identifying the priority-setting processes in health care organizations that perform and/or fund systematic reviews. Of the 72 organizations that were initially listed and screened for inclusion in our review, 64 were identified as unique. Only 24 of these organizations reported any information on systematic review activities, and 11 of these were eliminated because either insufficient or no documentation of their priority-setting processes was available online. In total, we reviewed the processes for setting priorities for systematic reviews for 13 different organizations, including organizations whose activities are directed towards national, regional and global populations (Table 5).

Figure 2. Flowchart of the review of priority-setting processes in health care organizations that perform and/or fund systematic reviews



AHRQ EHC: Agency for Healthcare Research and Quality Effective Health Care program; CADTH: Canadian Agency for Drugs and Technologies in Health; DEPC: Duke Evidence-based Practice Center; DERP: Drug Effectiveness Review Project; NICE: National Institute for Health and Clinical Excellence; NIHR HTA: National Institute for Health Research Health Technology Assessment program; OHTAC: Ontario Health Technology Advisory Committee; Osteba: Basque Office for Health Technology Assessment; SBU: Swedish Council on Technology Assessment in Health Care; SIGN: Scottish Intercollegiate Guidelines Network; TEP: Technical Expert Panel; UC: University of Chicago; USPSTF: U.S. Preventive Services Task Force; WHO: World Health Organization; ZonMw: Netherlands Organisation for Health Research and Development.

* Note: 'Insufficient' documentation is defined as missing over 50% of information or categories included in the data extraction form.

Table 5. Selected health care decisionmaking bodies and research funding agencies

Organization (Jurisdiction)	Primary Purpose and Audience of Systematic Reviews	Annual Budget for Systematic Reviews¹(2011 U.S. Dollars)
Agency for Healthcare Research Quality Effective Health Care Program [AHRQ EHC] [§] (U.S.) [4,95]	Production of evidence on outcomes, comparative clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to inform health care decisions by practitioners, policymakers, and patients	\$25 million [\$0.08 per capita ²
Canadian Agency for Drugs and Technologies in Health Technology Assessments [CADTH HTA] [§] (Canada) [96,97]	Provision of information about effectiveness of drugs and other health technologies to decision makers on health policy and purchasing, service management, and clinical practice	\$5.16 million [HTA-program] [\$0.15 per capita ²]
National Institute for Health and Clinical Excellence [NICE] [§] (U.K.) [98]	Provision of guidance on public health, health technologies, and clinical practice to health professionals, National Health Services bodies and general public	~\$70 million [\$1.12 per capita ²]
National Institute for Health Research Health Technology Assessment programme [NIHR HTA] [§] (U.K.) [99]	Production of research information on healthcare treatments and tests to practitioners, policymakers, and patients care as part of National Health Services.	\$88 million [\$1.14 per capita] [HTA-program] [94]
U.S. Preventive Services Task Force [USPSTF] [§] (U.S.) [100]	Provision of recommendations on primary or secondary preventive services in primary care settings to primary care clinicians, policymakers, managed care organizations, public and private payers, quality improvement organizations, research institutions, and patients	~\$7.34 million [\$0.02 per capita]
World Health Organization [WHO] [†] (NA) [101,102]	Provision of clinical information and development of practice guidelines to countries	NA
Cochrane Collaboration [†] (NA) [103]	Provision of evidence to inform decisions about human health care by healthcare providers, policymakers, patients, their advocates and carers	NA
Netherlands Organisation for Health Research and Development [ZonMw] [§] (The Netherlands) [104]	Provision of information for evidence-based policymaking on the governmental level and promotion of evidence-based use of health technologies at practice level	~\$13.5 million [\$0.81 per capita][94]
Scottish Intercollegiate Guidelines Network [SIGN] [§] (Scotland) [105]	Provision of clinical Information to practitioners and development of practice guidelines	\$0.5 million [\$0.10 per capita] [94]
Swedish Council on Technology Assessment in Health Care [SBU] [§] (Sweden) [106]	Provision of information to inform healthcare decisions by professional caregivers, healthcare administrators, planners, health policymakers, patients and their families	\$9.5 million [\$1.00 per capita] [HTA-program] [94]
Ontario Health Technology Advisory Committee [OHTAC] [§] (Ontario, Canada) [107]	Provision of recommendations about adoption and coverage of health technologies by OHTAC	\$2 million [\$0.06 per capita] [HTA-program] [94]
Basque Office for Health Technology Assessment [Osteba] [§] (Basque, Spain) [108]	Provision of information on safety, efficacy, effectiveness, accessibility, and equity about different technologies to inform policymaking by Health Department, and to improve medical practice and organization of healthcare delivery by hospitals, clinicians and private care providers	\$2.3 million [\$1.24 per capita] [HTA-program] [94]

Table 5. Selected health care decisionmaking bodies and research funding agencies (continued)

Organization (Jurisdiction)	Primary Purpose and Audience of Systematic Reviews	Annual Budget for Systematic Reviews ¹ (2011 U.S. Dollars)
Drug Effectiveness Review Project [DERP] [§] (U.S.) [109,110]	Synthesis and judgment on clinical evidence for drug-class reviews for membership organizations.	\$4.2 million [NA]

HTA : health technology assessment; NA : not applicable; U.S.:United States.

[§] Serving national or regional populations

[‡] Serving global populations

¹ All budgets are standardized on historical currency exchange rates (<http://www.oanda.com/currency/historical-rates> [Accessed: 2012 Feb 10]) and consumer price index (http://www.bls.gov/data/inflation_calculator.htm [Accessed: 2012 Feb 10])

² Based on population estimates from: http://en.wikipedia.org/wiki/List_of_countries_by_population; <http://www.scotland.org/facts/population/>; http://en.wikipedia.org/wiki/Basque_people (All, Accessed: 2012 Feb 10).

Prioritization of Systematic Review Topics in Practice

Across all the health care organizations we reviewed, systematic reviews are performed and/or funded to provide information on the expected benefits of diverse treatments and health interventions, and to inform clinical and health policy decisions. The results of systematic reviews are commonly made publicly available. None of the organizations responsible for priority setting among potential review topics directly serve as the main authorities or bodies responsible for clinical policy or coverage decisionmaking for their respective populations. As a result, recommendations about clinical guidance or coverage following systematic reviews are typically not tied directly to reimbursement decisions or policies.

The budgets for systematic review programs vary considerably, and these budgets generally come from public funds. Most commonly, these funds are used to directly employ researchers so that the reviews and synthesis of evidence are performed by the priority-setting organizations themselves. By standardizing on population size (in 2011 U.S. dollars), we found that the review budgets ranged from around \$0.02 to \$1.24 per capita across the different populations served. These estimates are difficult to compare because the reported budgets for systematic review often pertain to the overall budget allocated for health technology assessment and the actual number of systematic reviews, or spending on systematic reviews, is not generally reported⁸. Nonetheless, the different decisionmaking bodies and research funding agencies may have divergent economic and political considerations regarding the use of systematic reviews as a means to inform decisionmaking in health care in their respective jurisdictions. In most organizations, budget spending on systematic reviews requires some prioritization alongside other (research) activities, including the development of clinical practice guidelines and provision of consumer-oriented materials on health care, and clinical/health services research.

The different processes for priority setting among systematic reviews generally comprise some form of criteria-based assessment and ranking of review topics. As one might expect, prioritization criteria commonly relate to burden of disease, the benefits expected from the treatments or health interventions under study and the feasibility, including costs, of performing systematic reviews. Although stakeholders are often reported to be engaged in the priority-setting processes, e.g., by inclusion in prioritization committees or panels, how their input is directly reflected in establishing priorities is generally not well-described. Regardless, prioritization decisions are often made with some consideration of ethical, legal, and social implications as well as public interest. Perhaps to this end, the prioritization of topics for systematic review is often reported to be done through some form of qualitative assessment or subjective judgment, using processes that can include informal discussions, voting, or iterative ranking exercises.

Use of VOI in Prioritizing Systematic Reviews

In the prioritization processes undertaken by the different organizations with systematic review activities, most of the criteria relating to the conceptual elements of population-level VOI are reported as being taken into consideration (Table 6). Only the durability of review findings is less often (23%) reported as a criterion for prioritization decisions, although the timeliness or relevance of reviews and the future availability of treatment alternatives are considered in some instances (i.e., CADTH, NICE, and Osteba). The measures of VOI are operationalized in

⁸ The number of ongoing research projects, which may include systematic reviews, is reported to vary between 9 projects [OHTAC] and 180 projects [ZonMw].⁹⁴

different ways, and very limited discussion is provided as to what types of information or data are developed on these measures and how this evidence is used to make prioritization decisions. AHRQ and CADTH both discuss the production of initial briefing reports on each potential topic that include information relevant to VOI-related criteria, but specific indicators for these criteria these are not described. None of the 13 organizations we reviewed provided guidance for using some type of analysis in which the elements of VOI are quantified and combined to prioritize potential systematic review topics, and none reported performing VOI to formally quantify the value of systematic reviews. This may perhaps not be surprising given that VOI analyses are often complex and often focus on demonstrating methods, as discussed in our review of the literature.

Topics for systematic review are usually generated through passive means such as through web nominations and/or consultations with experts. Even though some organizations report the use of environmental scans or literature searches, these methods typically serve to eliminate those topics for which systematic reviews have already been performed rather than to identify new review topics. Within the AHRQ Effective Health Care Program, recent initiatives have been undertaken to enhance the process of generation topic through scans of information sources and the engagement with relevant stakeholders.^{4,111} More systematic approaches to topic generation would reveal more topics with potential for systematic review, and make prioritizing among these using formal methods like VOI even more important.

Table 6. Summary of the reported use and operationalization of conceptual elements of VOI for systematic review topics in priority-setting processes of the different organizations under review (K=13)

Conceptual Elements of VOI	Difference in Benefits	Reduction in Uncertainty	Probability of Implementation	Durability of Information	Size of Patient Population
Reported Use, k (k/K%)	11 (92%)	6 (46%)	8 (62%)	3 (23%)	6 (46%)
Operationalization					
AHRQ EHC [4,95]	"Represents a significant disease burden"	"Represents important uncertainty for decision makers"	"Exists within a clinical, consumer, or policymaking context that is amenable to evidence-based change"	Not stated	"...affects health care decisionmaking... for a large proportion [or priority] of the U.S. population"
CADTH HTA [96,97]	"Prevalence, incidence, DALE, HYS of LE, economic burden or other relevant measurement of disease burden) of the population affected by changes to policy"	Not stated	Potential for assessment to inform decisions given rate of change in clinical practice and receptor capacity by policymakers"	"Alternatives currently or soon to be available for the conditions that this technology addresses"	"prevalence, incidence...of the population"
NICE [98]	"Does the proposed guidance address a condition which is associated with significant morbidity or mortality in the population as a whole or in particular subgroups?"	"Would guidance promote the best possible improvement in public health and wellbeing and/or patient care, and the reduction of inequalities in health, given available resources?"	"Would publication of formal guidance make a significant difference to improving the effectiveness of public health programmes or interventions?"	"Would guidance still be relevant and timely at the expected date of publication ...?"	Not stated
NIHR HTA [99]	Not stated	"What are the benefits in terms of reduced uncertainty? This could concern: outcomes for patients"	"How long before benefits could be realised, bearing in mind time taken to perform the assessment and affect a change in practice?"	Not stated	"Other factors including... prevalence of the condition "
USPSTF [100]	"whether the topic address a disease with a substantial health burden"	"New evidence (e.g., new studies or new analyses of previous data) that has the potential to change prior recommendations."	"Potential for a recommendation to affect clinical practice (based on existing controversy or the belief that a gap exists between evidence and practice."	Not stated	Not stated
WHO [101,102]	"Problems associated with a high burden of illness in low and middle-income countries, or new and emerging diseases."	"No existing guidelines or recommendations of good quality"	"Implementation is feasible, will not exhaustively use available resources, and barriers to change are not likely to be so high that they cannot be overcome"	Not stated	Not stated

Table 6. Summary of the reported use and operationalization of conceptual elements of VOI for systematic review topics in priority-setting processes of the different organizations under review (K=13) (continued)

Conceptual Elements of VOI	Difference in Benefits	Reduction in Uncertainty	Probability of Implementation	Durability of Information	Size of Patient Population
Cochrane Collaboration[103]	"Burden of disease, magnitude of problem and urgency'	Not stated	"Achievability and resources required", "opportunity for action"	"Timeliness'	'Large scale impact on population'
ZonMW [104]	"Actual burden of disease given current treatment strategies"	Not stated	Not stated	Not stated	"Number of patients"
SIGN [105]	Not stated	"Areas of clinical uncertainty as evidenced by wide variation in practice and outcomes"	Not stated	Not stated	Not stated
SBU [106]	"The subject should have a significant impact on mortality and health"	Not stated	Not stated	Not stated	Not stated
OHTAC [107]	"Technology must improve the net health outcome and/or safety "	Not stated	Not stated	Not stated	Not stated
Osteba [108]	"The difference in QALE between a patient who has the condition and receives conventional treatment and that of a person of same age who does not have the condition""	Not stated	"The expected effect of the results of the assessment on the outcome of illness for patients with the illness"	Not stated	"The number of people with the condition per 1,000 people in the general population"
DERP [109,110]	Not stated	Not stated	Not stated	Not stated	Not stated

AHRQ EHC: Agency for Healthcare Research and Quality Effective Health Care program; CADTH: Canadian Agency for Drugs and Technologies in Health; DALE: disease-adjusted life expectancy; DERP: Drug Effectiveness Review Project; HYS: health years; NICE: National Institute for Health and Clinical Excellence; NIHR HTA: National Institute for Health Research Health Technology Assessment program; LE: life expectancy; OHTAC: Ontario Health Technology Advisory Committee; Osteba: Basque Office for Health Technology Assessment; QALE: quality-adjusted life expectancy; SBU: Swedish Council on Technology Assessment in Health Care; SIGN: Scottish Intercollegiate Guidelines Network; USPSTF: U.S. Preventive Services Task Force; VOI: value of information; WHO: World Health Organization; ZonMw: Netherlands Organisation for Health Research and Development.

Conclusion

Though VOI methods have received extensive attention, VOI measures have not been used explicitly to inform priority setting in systematic reviews. The 77 VOI studies in the literature focus heavily on the demonstration of methods rather than the use of VOI in research prioritization. Full modeling is the dominant approach in VOI studies, even though minimal modeling using comprehensive outcome measures or constructing a maximal model could be used as practical approach in many cases. When such analyses are presented, there is no evidence that conceptual approaches to VOI were applied before deciding to invest resources in performing a more expensive full modeling VOI study. In publicly available descriptions of the priority-setting processes of 13 major U.S. and international organizations engaged in systematic review activities, we found that VOI was not used to inform priorities for systematic reviews. However, with the exception of durability of benefits, we did find that prioritization discussions often implicitly considered elements that affect VOI (i.e., differences in benefits and expected reduction in uncertainty, probability of implementation, durability of review findings, and the size of the affected patient population). Also, even when elements of VOI were considered, we found very little discussion of how elements were quantified or integrated into a framework that is consistent with VOI principles. Decisions about the focus of health research are typically made by qualitative assessment and subjective judgment processes in which a broad perspective is adopted so as to reflect the different values and preferences of stakeholders in the prioritization process. Thus, there has been little attention to whether the use of VOI can improve processes for prioritizing systematic reviews and how VOI might be most efficiently applied to do so. However, if efforts, such as that of the AHRQ's Effective Health Care (EHC) Program, to generate more potential topics for systematic review continue, resources to perform systematic reviews will likely not keep pace with the topics generated, and tools such as VOI that might help prioritize among topics may be of increasing importance.

Theory

Introduction

In this section, we describe an algorithm intended to guide the process of identifying the effective and efficient use of VOI in prioritizing systematic reviews. To develop this algorithm, we first identify the conditions under which VOI is likely to be valuable as an overall strategy to prioritize systematic reviews. We then seek to outline a logical sequence of stages in which full modeling, minimal modeling, maximal modeling, and conceptual VOI are considered in order to minimize the costs and burden of analyzing the value of systematic reviews. Following this, we detail a multistage algorithm for deciding about when to invest in VOI and what specific approach to VOI to use in different contexts. Finally, we discuss how prioritization decisions can be made on the basis of estimates of the value of information from performing systematic reviews. The algorithm we develop is intended to systematize the use of VOI analysis in prioritizing systematic reviews.

Conditions of Value of VOI Analysis in Systematic Reviews

Following the general principles of VOI (Part 1, Principles, above), we can identify several conditions under which it may be worthwhile to invest in performing a VOI analysis to inform priorities for systematic reviews. A first condition is that existing research indicates that none of the conceptual VOI elements for a particular topic have a zero or very low value, as described under Conceptual VOI (in Part 2) of this report. This implies that some difference is anticipated in the (net) benefits of the treatment or health interventions being compared, and that the synthesis of evidence from multiple studies might change the degree of uncertainty about the benefits of those options compared with relying on a single research study. In addition, the findings from a systematic review must be considered likely to be durable for at least some period of time, the information obtained must be considered likely to be implemented into practice, and the population of affected patients must not be very small. As a second condition, prioritization exercises with VOI are only valuable when the costs of VOI are less than the value expected from performing a systematic review net of its costs. An implicit assumption is that either the resources for systematic reviews are limited relative to the set of reviews that could be performed or that the resources for systematic reviews have alternative uses so that some prioritization among systematic review topics is necessary. A third condition that is necessary for investment in VOI to be worthwhile is that the research for which a decision to proceed might be affected by the systematic review is expected to be costly; if studying the question was very inexpensive, one would just do the study without either VOI or systematic review. More commonly, if a clinical study to address a particular question is expected to be very costly, then costly full-modeling or maximal modeling VOI studies may be rational. These VOI applications would not only inform whether an additional primary research study should be performed but also to identify an efficient study design.

These conditions make it possible to define a practical and efficient process for the use of VOI to inform priorities for systematic reviews by outlining a logical sequence of stages to select the VOI approach that will minimize cost and burden of analyzing VOI for systematic reviews. This process begins by applying the lowest cost VOI method and proceeds to higher cost methods for a given clinical question. Thus, the sequence we propose is: (1) conceptual VOI; (2) consideration of maximal modeling VOI in which costs are covered among multiple topics for

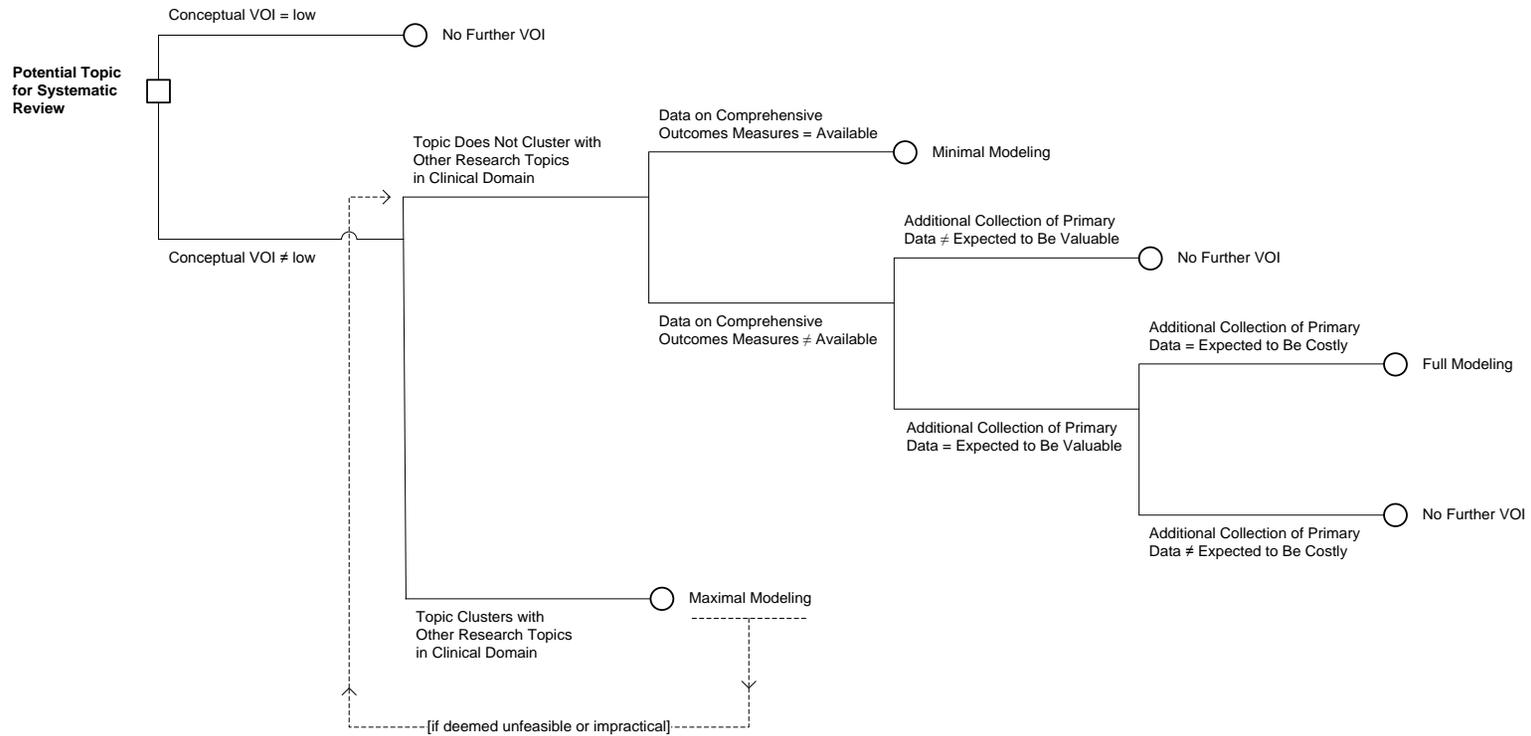
systematic review simultaneously; (3) consideration of a minimal modeling approach to VOI in individual review topics; and (4) consideration of full modeling VOI. When minimal modeling or conceptual VOI is selected, there may be a tradeoff between reducing the complexity and cost of modeling compared with the full characterization of the uncertainty in the benefits of particular health interventions and more accurate estimates of the value of information from applying full modeling or maximal modeling approaches to VOI. How this tradeoff is best navigated is likely to depend on the conditions, including timing and budget restrictions, under which decisions about research spending are to be made, and the extent to which it is important to address additional questions such as the value of information on specific parameters that may affect specific clinical or health policy decisions.

Before describing our approach to VOI of systematic reviews in more detail, we should note that we do not devote much attention to the possibility that a VOI analysis has already been developed for a specific decision problem. This is mainly because there are still relatively few problems for which VOI analysis has been performed and those for which it has been performed would need to be adapted to the specific question for which a systematic review is being considered. Nevertheless, as a first step, it would surely make sense to review the literature in a topic area to assess whether a VOI has been performed and consider adapting that VOI if less costly VOI approaches do not adequately address the VOI of the potential systematic review being considered.

Algorithm for Selecting the VOI Approach To Prioritize Systematic Reviews

As shown in Figure 3, we propose an algorithm that describes a multistage process for identifying the effective and efficient approach to VOI in prioritizing the performance of a systematic review to address a particular clinical question or research topic. This algorithm starts with the use of a conceptual approach to VOI, in which the expected change in uncertainty of the benefits of the treatment or interventions under consideration, the implementation and durability of review findings, and the size of the affected patient population are considered to assess whether there is likely to be any meaningful value of synthesizing existing evidence on individual topics nominated for systematic review (i.e., none of the elements of conceptual VOI approach zero). If this approach does not suggest a low conceptual VOI for a particular topic, the algorithm suggests clustering topics being considered for review for the potential use of “maximal” models that can simultaneously assess the potential value of multiple systematic reviews within or across clinical domains. When topics cannot be clustered or when a maximal modeling approach to VOI is deemed impractical or undesirable, the next step is to consider minimal modeling VOI. A minimal modeling approach to VOI is only possible when some data are readily available on comprehensive outcome measures for the clinical or policy decision that is to be informed. Finally, if none of the other VOI methods are feasible, the algorithm proposes considering the use of full modeling VOI. Since a full modeling approach to VOI would likely be more costly than a systematic review, this approach will be worthwhile only when a potentially valuable but costly clinical trial or other (observational) study for collecting additional primary data on a particular topic is so likely to be planned that performing a VOI analysis for research design and sample size calculations is likely anyway. As we discuss further under Other Issues, below, in that case, it may be useful to simply perform a full modeling VOI study immediately.

Figure 3. Algorithm for identifying the effective and efficient approach to calculating VOI in informing priorities for systematic reviews



VOI: value of information

Stage 1: Use of Conceptual VOI to Bound Value in Systematic Reviews and Formal Quantification of VOI

The first stage of the algorithm we propose is to assess the conceptual VOI of performing a systematic review in an individual review topic. With this approach, information on each of the conceptual elements (e.g., the expected change in uncertainty about treatment benefits from evidence synthesis, and the durability of such review findings) is used to determine the population-level VOI from the review of evidence from existing research studies in order to provide informative bounds on the value of systematic reviews in individual topics without formally quantifying such VOI estimates through more complex modeling exercises. When information is available that suggests that any of these elements approximates zero, the product of these terms (and hence the VOI) will almost always be zero unless some other element is exceptionally large. For topics in which the values for the conceptual VOI are low, it is not likely that prioritizing and reviewing evidence in a systematic review would be an effective means of research spending.

To assess whether the conceptual VOI is likely to be low, research on VOI elements at this stage of the algorithm is meant to quickly identify any conceptual elements that have values that approximate zero. A pragmatic method for this would be to assess the values for each of the elements of VOI through a quick scan, followed by a more comprehensive search for data on values in the elements initially identified as likely to be low in the quick scan. Such information may be available from the literature identified through MEDLINE[®]/PubMed, national statistics bureaus, the National Health Institutes, registries and post marketing surveillance studies, or the use of expert opinion (see also Table 2). The order in which the value of each of the conceptual elements of VOI is assessed could be determined by the ease with which information on these elements can be collected. For example, population size is relatively easy to determine, while information on implementation or durability of review findings may be more difficult to find. Given that VOI will be low if any of these elements approach zero, it may be most efficient to use judgment about whether any of these elements are likely close to zero and then focus initially on those conceptual elements of VOI until any one of them is found to approach zero.

Stage 2: Consideration of Maximal Modeling VOI When Topics Cluster Within or Across Clinical Domains

For systematic review topics in which modeling cannot be excluded because of low conceptual VOI, the second stage of the algorithm considers whether a maximal modeling approach offers a possibility to simultaneously analyze the value of performing systematic reviews on separate but related topics clustering in a particular clinical domain. The clustering of topics may be based on the specific relationship of particular diseases and their treatments, perhaps along the lines of pathophysiology or clinical pathways, for which one often relies on the opinions from experts. For example, the screening, diagnosis and treatment of patients with prostate cancer can be perceived as topics clustering in the domain of prostate cancer. The single comprehensive models used for maximal modeling VOI are often organized around disease and treatment processes or health care programs.

By simultaneously calculating the value of multiple systematic reviews, the costs of performing VOI are minimized across the individual review topics. While maximal models may have to be newly constructed, it may be more efficient to use existing models for this purpose.

Examples of such models would include the Coronary Heart Disease Policy Model or perhaps one of the decision-analytic models like CORE Diabetes Model or CDC-RTI Cost-Effectiveness model he already available in diabetes care.^{15,112-114} In identifying models that are already available in the clinical domain of interest, and that are applicable for maximal modeling approaches to VOI, expert opinion, environmental scans, or literature searches may be useful. Clearly, an existing model may need to be adapted before applying it to perform VOI in a specific decision context, for example, by adjusting or updating data input. To evaluate maximal models, simulation or bootstrapping can be performed using software like MS Excel, Stata or WinBUGS. A maximal modeling approach to VOI may be particularly desirable when multiple potential uses of the model could be envisioned. In effect, this may be especially relevant in the context of prioritizing systematic reviews because such approaches to evidence synthesis are often set up to identify research gaps and direct the planning of new research.

Even when individual topics for systematic reviews can be clustered, maximal modeling approaches to VOI to prioritizing systematic reviews and other research studies may still be considered impractical or undesirable. This may be because of the perceived burden to constructing new ‘maximal’ models or adapting existing ones, or because of the limited appreciation of establishing a more sustainable infrastructure for future VOI analyses. In those situations where a choice is made to not use maximal modeling VOI, the algorithm suggests to assess the value in systematic review topics individually rather than simultaneously, starting with the consideration of applying minimal modeling VOI to identify research priorities. For example, for a clinical question that could be clustered with other topics to apply a maximal modeling approach, but for which data to apply minimal modeling VOI might be readily available, a minimal modeling approach might be preferred on the basis of speed with which it could be applied if a decision about starting a trial was being actively considered.

Stage 3: Use of Minimal Modeling VOI When Data on Comprehensive Outcomes Measures Are Available

The third stage of prioritizing systematic reviews among individual, potentially valuable review topics is to consider performing VOI calculations with only minimal modeling based on data on comprehensive outcomes measures (e.g., life expectancy, QALYs, and costs or net benefits) that can be used to readily address the clinical or health policy decision in question. The data needed for such a minimal modeling approach to VOI may often be available from existing clinical trials, observational studies, or meta-analyses. It may be thereby useful to break down the term minimal modeling into no modeling (i.e., when comprehensive outcomes are directly measured), and limited modeling (i.e., when some modeling is needed to calculate the comprehensive outcomes measure, for example by combining quality of life with life expectancy). VOI calculations based on minimal modeling can be done via bootstrapping/simulation using raw data or distributions for health outcomes on costs, and survival data, or even through equation-based computations. Minimal modeling VOI can thereby be implemented in software like R, Stata or WinBUGS, and templates for these types of analyses are readily available.⁷

As noted above, if a VOI study already exists in a topic area, measures for VOI can also be derived from these studies. This requires careful attention as to whether the evidence on specific diseases and/or treatments in these studies is readily applicable to the specific context in which a particular clinical question is to be addressed. If no such studies can be found and no

comprehensive measures of relevant outcomes are readily available, the next step would be to consider the use of a full modeling approach to VOI to prioritize systematic reviews.

Stages 4 and 5: Use of Full Modeling VOI When Additional Collection of Primary Data Is Expected to Be Both Valuable and Costly

For systematic review topics in which the VOI algorithm suggests the potential for full modeling of a particular disease, its treatment and the different health states, it is important to consider whether further research is likely to be performed. The basic challenge in using full modeling VOI to prioritize a systematic review is that the construction of full models is too burdensome and a costly way to perform VOI to inform decisions about prioritizing low-cost studies such as systematic reviews. It would not make sense to perform a costly VOI study just to decide not to do a relative inexpensive systematic review since it makes more sense just to perform the systematic review.

Our algorithm suggests the use of a full modeling approach to VOI only when it seems so likely that further research is planned for collecting additional primary data, and this research is likely to be costly enough that it will make sense to perform a full modeling VOI study. VOI is then done both to prioritize the systematic review topic and help the efficient design of relevant studies, for example by suggesting appropriate sample size in trials, the most relevant outcomes to measure, or the appropriate length of followup of patients and patient cohorts. If that VOI analysis suggests that further research is not likely to reveal any evidence or is too costly, prioritization exercises for systematic reviews are not likely to be valuable. In practice, the work involved in performing the full modeling VOI may overlap so greatly with the work needed to perform the systematic review, that they will effectively both be completed. As such, it is hard to argue that the full modeling VOI is being used to prioritize the systematic review. Nevertheless, it would make sense to perform the full modeling VOI at this stage and since this may suggest that a systematic review could be of low value (perhaps compared with a review focusing on some part of the decision problem, or compared with studying the problem at all), it is still the case that the full modeling VOI might result in the decision not to complete a full systematic review.

Other Issues in the Use of VOI Estimates to Prioritize Systematic Reviews

In prioritizing topics nominated for systematic review, a differentiation can be made between (1) those topics for which estimates of the population-level VOI are provided through maximal, minimal or full modeling; (2) those topics for which conceptual VOI indicates that there is no or limited value in the review of evidence; and (3) those topics for which application of VOI does not appear practical so that approaches other than VOI need to be used to inform priorities for systematic reviews. Under the assumption that resources or budgets are fungible between research and other uses, a strict economic analysis might suggest performing all systematic reviews for which VOI is calculated to exceed the costs associated the review and synthesis of existing evidence. However, if the costs of systematic reviews vary and the resources or budgets for research are limited, priority has to be given to performing the systematic review or set of

reviews that maximizes the returns (i.e., population-level VOI net of the expected costs of systematic reviews) of research spending.

In practice, with typical levels of resources available to perform systematic reviews, the costs of performing systematic reviews may be so small relative to their benefits, or the capacity to perform systematic reviews may be so limited, that their costs can usually be neglected in prioritizing reviews. Priority setting may then rely solely on the assessment of population-level VOI of systematic reviews. When comparing the value of systematic reviews across individual topics or clusters of topics, however, it is important that estimates for the population-level VOI reflect the size of the affected patient populations, the probability of implementation of specific treatments or interventions, and the durability of evidence that would come from the review. Standardization should also account for potential differences in the perspective and time horizon of analysis, the use of health outcomes, costs, utilities as well as threshold values for cost-effectiveness or willingness-to-pay for an effectiveness outcome. Although the construction of full models may perhaps provide most accurate indication of the value of research to address a particular clinical question, lower cost VOI methods (i.e., conceptual VOI, maximal modeling, and minimal modeling) probably more often have practical and valuable application in informing priorities in systematic reviews.

Notably, the initial stage in prioritizing systematic reviews, prior to any use of the algorithm, is to generate a list of nominated review topics. This may be done on an ad-hoc basis or by more systematic approaches like environmental scans, literature searches or Delphi techniques. Since failure to consider a sufficiently large set of potential review topics may result in assigning high priority to a topic that would have received lower priority had additional topics been considered, it is critical that the list of topics nominated for systematic review include as many potential topics as possible.

Conclusion

In minimizing the costs of VOI as part of an overall strategy to use VOI to inform priorities for systematic reviews, we propose an algorithm that describes a multistage process to identify the effective and efficient approaches to performing value of information analysis. This process begins with conceptual VOI to identify when VOI of a systematic review is likely to be very low, followed by the clustering of review topics and consideration of the use of maximal models, and then consideration of minimal modeling using comprehensive outcome measures of the benefit of the alternative treatments or health interventions under study if data permits. Although full models may aid in the planning and design of research studies, we find rather limited conditions for its use in prioritizing systematic reviews. The valuable application of a full modeling approach to VOI is limited primarily to instances where a such an approach appears likely to be applied in any case because it seems very likely that a review would result in suggesting that a costly trial will be needed for which a full modeling VOI would be a logical investment. The algorithm we propose attempts to provide a systematic strategy with which to consider the use of VOI to prioritizing systematic reviews.

Application

This section describes our efforts to assess the potential utility of applying the algorithm we developed for identifying the effective and efficient use of VOI in informing priorities for systematic reviews. We apply the algorithm for a selection of topics nominated to the AHRQ EPCs for systematic review. We explore whether application of our algorithm suggest that conceptual VOI, maximal modeling, minimal, or full modeling VOI may be useful in prioritizing systematic reviews. We also illustrate the application of these approaches in a few selected topics to illustrate how each of the lower cost approaches to VOI might be applied. We find that the application of the algorithm may be useful in selecting the appropriate VOI methods to inform priorities for systematic reviews that reduce the burden of the practical application of VOI.

Methods

To assess its potential utility of our proposed algorithm, we applied it to attempt to identify appropriate VOI methodology to inform priorities for topics nominated to the AHRQ EPCs for systematic review in 2009. Topics for possible systematic reviews are generated through a nomination process described by Whitlock et al.⁴, and are then narrowed through triage meetings. The topic nominations were extracted from the minutes of the topic triage meetings at AHRQ.¹¹⁵ We considered only those topics that were reported to meet AHRQ's criteria for relevance to its research or programmatic domain as well as the information requirements for topic nomination. The algorithm was not applied for topics that were addressed in research or programmatic activities already undertaken by the AHRQ EPCs, and/or duplicated with other topics already discussed in triage meetings before 2009. For each topic with potential for review, we applied the multistage algorithm to choose among conceptual VOI, minimal modeling, maximal modeling or full modeling as the effective and efficient approach to VOI for identifying the priority of that specific review topic (Appendix G). To populate each of the stages of the algorithm, we used information from a variety of sources, including the minutes of the topic triage meetings, clinicaltrials.gov, Google Scholar and MEDLINE[®]/Pubmed.

In a series of pilot studies, we illustrate and discuss how the application of conceptual VOI, maximal modeling and minimal modeling can be useful substitutes for full modeling VOI in applying VOI to inform priorities for systematic reviews while recognizing the costs of VOI and minimizing those costs. The two examples of conceptual VOI address review topics relating to (1) administering ketogenic diet in epileptic children, and (2) structuring of practice in community-based psychiatric care. The use of a maximal modeling approach to VOI is discussed with respect to its potential application for simultaneously addressing multiple questions about the value of systematic reviews in topic nominations clustered in diabetes care. Minimal modeling VOI is applied to assess the value of information from updating a review of evidence on non-invasive versus invasive mechanical ventilation in acute respiratory failure. To demonstrate the application of full modeling VOI to inform priorities for systematic reviews, we refer to our review of VOI studies in the theory section of this report. This is because our analysis above suggests that a decision to fully model a disease and treatment process will generally be made primarily for the purpose of efficiently designing trials or other (observational) studies that are likely to be planned for the collection of additional primary data following the performance of a systematic review.

Results

Identification of Topics Nominated for Systematic Review

In 2009, 73 topics were nominated for systematic reviews to the AHRQ EPCs. Of these, 10 topics did not fit within the AHRQ's EHC Program and/or failed to meet minimum information requirements for topic nomination. Another 11 topics were already addressed by existing research or programmatic activities. Eleven out of the remaining 52 topics were not considered for algorithm application because they were duplicates of earlier topics discussed. In total, 41 topics were identified as having potential for review, and were used to evaluate the potential utility of our algorithm in selecting VOI methods for prioritizing systematic reviews. These topics primarily covered questions about the comparative effectiveness of treatments or health interventions, and included a wide range of clinical domains, including pain management, cardiovascular diseases and cancer. The set of topics seemed broadly representative of topics typically nominated to the AHRQ EPCs for systematic review.

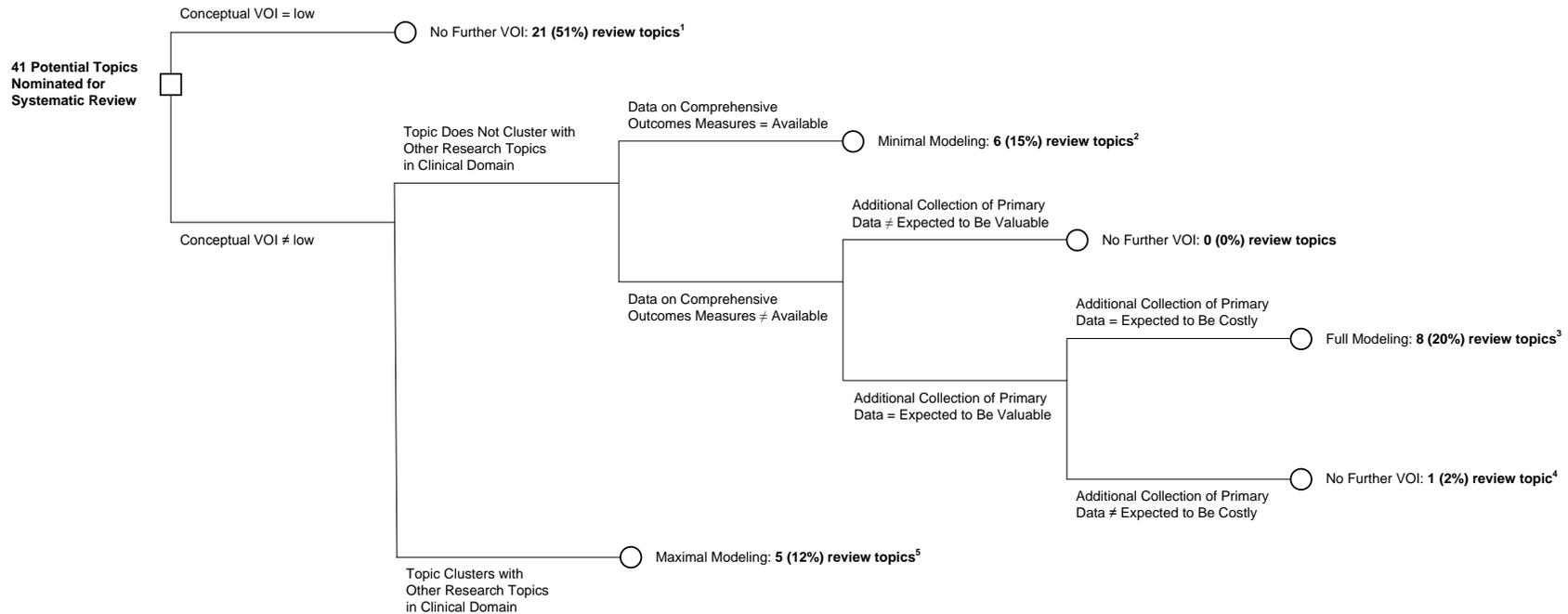
Approaches to VOI in Prioritizing Systematic Reviews

As shown in Figure 4, each of the different approaches to VOI (i.e., conceptual VOI, maximal modeling, minimal modeling, and full modeling) was judged as having some applicability within an overall strategy of applying VOI to inform priorities among the topics nominated to AHRQ for systematic review in 2009.

By using information on the elements that determine the population-level VOI of a systematic review, we found that a conceptual approach to VOI suggested the informative value in formally quantifying VOI through modeling to be low in 21 (51%) nominated review topics. In most of these topics (86% of 21 topics), the review and synthesis of evidence was not expected to produce any valuable insights because of the lack of trials or other (observational) studies comparing treatment or health intervention options under consideration. Data or information to describe the potential limits in the implementation and durability of systematic review evidence were more difficult to find, although some variation in clinical care and coverage or payment policies may frequently be anticipated. One (5%) topic, the use of supplementary pharmacological therapy in phenylketonuria, was identified in which a very small incident population of about 2000 patients per year and the lack of any primary research suggesting long-term improvement in quality of life from reduced phenylalanine concentrations and dietary phenylalanine restrictions from supplementary pharmacological therapy (e.g., sapropterin dihydrochloride) has not been demonstrated in any primary research study yet,^{116,117} argued for lower priority in spending on a systematic review compared with the other topics considered.

In the 19 (49% of 41 topics) systematic review topics in which modeling could not be excluded because of low conceptual VOI, we found that maximal modeling or minimal modeling approaches to VOI frequently offered lower cost alternatives to typical full modeling VOI when informing priorities among possible systematic reviews.

Figure 4. Application of algorithm for identifying the effective and efficient approaches to VOI to inform priorities for topics nominated to the AHRQ EPCs for systematic review in 2009



¹ Topics: 1) Electroconvulsive Therapy in Elderly; 2) Specialized Wheelchairs for Patients; 3) Upright MRI; 4) Vagus Nerve Simulation for Depression; 5) Family Involvement in Hospital Discharge Planning; 6) Treatment of Glaucoma; 7) Home Oxygen Therapy; 8) Prevention and Early Detection of Skin Cancer; 9) Treatment of Neovascular Age-Related Macular Degeneration; 10) Herbal Therapies for Cholesterol Reduction; 11) Ketogenic Diet for Epileptic Children; 12) Dietary Supplements in Elderly taking Cardiovascular Drugs; 13) DVT Prophylaxis for Special Populations; 14) Complementary and Alternative Medicine for Benign Prostatic Hyperplasia; 15) Hormone Therapy for Treatment of Menopausal Symptoms; 16) School-Based vs Outpatient Speech Therapy for Children; 17) Multimodal Pain Management in Adults; 18) Anesthesia in Infants; 19) Phenylalaninerestricted Diet for Phenylketonuria; 20) Surgical Treatment of Chronic Pelvic Pain; 21) Practice Structuring in Community-Based Psychiatric Care.

² Topics: 1) Occupational and Physical Therapy; 2) Antipsychotics for ADHD; 3) Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure; 4) Allergen-Specific Immunotherapy; 5) Acute Migraine Treatment in Emergency Settings; 6) Prophylactic Treatment of Migraine with Alzheimer's Medication.

³ Topics: 1) H2RAs and PPIs for GERD; 2) Self-Measured Blood Pressure Monitoring; 3) Pharmacologic Therapies for Management of Crohn's Disease; 4) Prevention of Venous Thromboembolism in Orthopedic Surgery; 5) Biologics vs Conventional Systemic Treatments for Moderate and Severe Psoriasis; 6) Effectiveness of Nurse Case Managers; 7) Procalcitonin-guided Therapy for Sepsis; 8) Physician Outreach via Email and Internet Networking

⁴ Topic: 1) Antinuclear Autoantibody and Rheumatoid Factor Testing.

⁵ Topics: 1) Urinary Incontinence; 2) Blood Glucose Control; 3) Noninvasive Technologies for Diagnosis of CAD in Women; 4) Mental Health Support for Juvenile (Type 1) Diabetes Mellitus; 5) Natriuretic Peptide Measurement in Heart Failure;

ADHD: attention deficit hyperactivity disorder; AHRQ: Agency for Healthcare Research and Quality; CAD: coronary artery disease; DVT: deep vein thrombosis; EPCs: Evidence-based Practice Centers; GERD: gastroesophageal reflux disease; H2RAs: histamine receptor antagonists; MRI: magnetic resonance imaging; PPIs: proton pump inhibitors; VOI: value of information.

The application of maximal models is a potentially valuable approach to VOI in 5 (12%) systematic review topics, as these topics were found to cluster with other review topics within or across diverse clinical domains. These clusters of topics concerned patient management in urinary incontinence, coronary artery disease, heart failure, and diabetes (2x). In addition to the clustering of multiple topics for systematic reviews, a maximal modeling approach to VOI was also found to be feasible in a single review topic or intervention for which multiple uses could be anticipated. One of example this related to the measurement of natriuretic peptides that comprised a single topic with potential value in the management of congestive heart failure for both the diagnosis of patients and control in treatment. As such, a single comprehensive model could be constructed with which to simultaneously assess the value in the reviews of evidence on the alternative uses of peptide measurement.

In almost one-third (30%) of the systematic review topics, comprehensive outcome measures were found to be readily available, and minimal modeling could be used to provide estimates of VOI in these topics. For example, the value of performing a review on the comparative effectiveness of allergen-specific immunotherapy as supplement to usual care could be assessed using the 10-year follow up data on asthma incidence that was available from the Preventive Allergy Treatment study.¹¹⁸ A similar approach could be applied using the results from an existing meta-analysis reporting pooled odds ratios for headache relief from acute migraine treatment (non-opioids versus opioids) in emergency settings.¹¹⁹ Direct replication of these data or perhaps limited modeling exercises in which asthma incidence data or headache relief scores are related to quality of life and/or life expectancy could facilitate low-cost and rapid assessments of VOI in performing systematic reviews, or updates of reviews, on these topics that could be of use in priority setting.

Full modeling VOI was found to be potentially valuable in 8 (20%) of the 41 potential review topics nominated to AHRQ EPCs. In these topics, the planning of further research was anticipated to be most likely, and the trials or (observational) studies for additional data collection were expected to be both valuable and costly. As a result, the construction of full models of the disease and treatment processes in these topics was thought to aid in identifying most relevant evidence gaps and establishing efficient research designs. The formal quantification of VOI based on a full modeling approach would not be an efficient spending of research funds in antinuclear autoantibody and rheumatoid factor testing in children with musculoskeletal pain. The review and synthesis of existing evidence on the prevalence of musculoskeletal pain from rheumatic causes is likely to reveal useful information to guide diagnostic testing in children in primary care settings and may suggest proceeding with further collection of prevalence data. However, since many practice registries and ongoing studies exist in this area, performing such analysis of prevalence is likely to be too inexpensive to justify using a full modeling VOI approach.

Applications of Conceptual VOI

To demonstrate the value of a conceptual approach to VOI, we discuss two nominated systematic review topics for which information on different elements of population-level VOI (i.e., uncertainty reduction versus the implementation and durability of evidence) provide bounds on the value expected from performing a systematic review. We have selected: (1) ketogenic diet for epileptic children, and (2) structuring of practice in community-based psychiatric care as examples in which zero or low conceptual VOI suggest low priority without formally quantifying the value of reviews in the topics.

Limited Reduction in Uncertainty: Ketogenic Diet in Children with Epilepsy

One condition under which a conceptual approach to VOI can provide informative bounds on the value of a systematic review is when there is no benefit expected in this because there is no available comparative effectiveness evidence to synthesize. This seems to be the case for the review of evidence on ketogenic diet in children with intractable or refractory epilepsy. In the U.S., about 2.1 million children are diagnosed with epilepsy each year.¹²⁰ In 55 percent of these patients, pharmacotherapy is not effective and seizures persist. A subset of these patients may benefit from ketogenic diet with increased seizure control, reduced adverse effects, and the containment of medical costs.^{121,122} While the population expected benefits from review of evidence is sizable, there is limited guidance on how to administer ketogenic diet (e.g., dosing, duration and vitamin supplements) and considerable variation exists in clinical care.¹²³ Perhaps because of this, we found no trial comparing ketogenic diet against anti-epileptic drugs for refractory or intractable epilepsy. The long-term adverse effects of the dietary treatments are also typically unknown. Even if trials or other (observational) studies did exist that were sufficiently similar, the rapid emergence of newer antiepileptic drugs with improved efficacy and convenience would reduce the durability of the value of any findings from a review.¹²¹ We found that the potential for reducing uncertainty in benefits of treatment through performing a systematic review on ketogenic diet is likely very low because of the lack of comparability in existing studies. This issue arose frequently in many other review topic nominations.

Low Probability of Implementation and Limited Durability of Information: Practice Structuring in Community-Based Psychiatric Care

Implementation issues and a limited durability of review findings from systematic reviews can bound the value in performing VOI to prioritize among possible review topics. As an example of this, we found that a conceptual approach to VOI suggests a low value in the review of evidence on the comparative effectiveness of practices structuring in community-based based psychiatric care, in which 30- or 45-minute checks complemented with traditional psychotherapy are considered as alternatives to standard 15-minute medication checks. This topic has a large relevant population, with 25 million independent visits to psychiatrists in 2006, and 3.18 percent of the U.S. population using outpatient therapy as of 2007.^{124,125} Many psychiatric patients with prescriptions interact with their physicians only during monthly 15-minute medication checks. This has become standard practice due to coverage or payment policies by Medicaid and insurance companies. We found no research, no trial, or no observational study in which the comparative effectiveness of alternative ways of structuring psychiatric practice is evaluated. The lack of head-to-head comparisons due to differences in indication, condition, and severity makes it unlikely that conducting a systematic review is going to impact practice. Moreover, the research agenda on psychiatric services is likely to be heavily influenced by the IOM meeting on Initial National Priorities for Comparative Effectiveness Research,¹²⁶ which makes the findings, if any, of a systematic review on this topic less likely to be durable. The apparent barriers to changing standard practice and the limited durability of review evidence suggest that this topic will have a low VOI. Even though a system review may still have potential value in identifying evidence gaps and priorities for future research in this area, it is not clear that a systematic

review is per se needed given the ease with which it is possible to determine that comparative effectiveness evidence on practices structuring for psychiatric care is lacking.

Application of a Maximal Modeling Approach to VOI: Multiple Topics Clustering in Diabetes Care

Some of the best examples of maximal modeling as an effective and efficient approach to VOI are likely to be in management of common chronic diseases or clinical conditions, such as diabetes. Diabetes-related research, which may include systematic reviews that synthesize evidence from the many studies in this domain, is expected to be highly valuable because of the major health and costs burden that diabetes imposes on the U.S. population.^{127,128} Almost 26 million people suffer from diabetes, of which 90–95 percent have (adult-onset) diabetes type 2, while the others suffer from insulin-dependent diabetes type 1.¹²⁹ Patient management of either form of diabetes is typically complex, using multiple assessment tools and interventions. These can include screening and preventive measures in different at-risk groups or the whole population, diagnostics tools such as oral glucose tolerance tests, fasting blood glucose tests or glycosylated hemoglobin, and insulin therapy or medication medical or dietary or lifestyle interventions. Diabetes is highly associated with hypertension and hypercholesterolemia, and obesity, making interventions to address these comorbid factors critical to the management of diabetes.^{130,131} Between 2008 and 2010, the AHRQ EPCs received 10 nominations for systematic review on 7 separate topics related to diabetes. Of these, 2 topics pertained to diabetes type 1⁹, 4 topics to diabetes type 2¹⁰, and 1 topic pertained to both types of diabetes¹¹. With numerous nominations of topics that can be clustered within the single domain of diabetes care, this suggests the consideration of constructing a maximal model that describes the relationship between these topics and interventions and that can be used to simultaneously assess the potential value of multiple systematic reviews. Of note, both the National Cancer Institute and the National Heart Lung and Blood Institute have recently explored the use of maximal modeling approaches to VOI as a means to prioritize research in the major disease areas of interest to them.^{132,133}

Diabetes is a particularly suitable disease candidate for maximal modeling because a number of models have already been developed and validated, and could potentially be used to facilitate VOI analysis. For example, the CORE Diabetes Model could be of use in simultaneously addressing VOI in systematic review topics that relate to both diabetes type 1 and type 2.^{112,113} This model is based on data from the Diabetes Control and Complications Trial, and simulates the long term health and economic consequences of treatments and interventions in diabetes types 1 and 2 to support clinical and policy decisionmaking, with the option to consider various diabetes complications like stroke, hypoglycemia, and end stage renal disease.¹³⁴ For diabetes type 2, we also refer to the CDC-RTI Cost-Effectiveness model and the University of Michigan model. This first model could potentially be used to analyze VOI in both preventive measures and treatment interventions in diabetes type 2, and includes features to simulate diabetes prescreening and the impact of prediabetes.¹¹⁴ The second model might aid in predicting the onset and progression of type 2 diabetes, and has additional features that would allow to

⁹ Topics: Mental Health Support for Juvenile (Type 1) Diabetes Mellitus; Daily Insulin Injections or Insulin Pump Therapy with and without Continuous Glucose monitoring.

¹⁰ Topics: Tight Management vs. Loose Control of Blood Glucose for Hospitalized Patients with Type II Diabetes; Comparative Effectiveness of Short- and Long-Acting Insulin and Insulin Analogs for Adults with Type 2 Diabetes Mellitus; Harms and Benefits of Different Possible Combinations of Medications for the Treatment of Dyslipidemia in Adults with Type 2 Diabetes; Therapies for Impaired Glucose Tolerance to Prevent Progression to Type 2 Diabetes.

¹¹ Topic: Point-of-Care Testing for Glycated Hemoglobin.

simultaneously assess the value that can be expected from studying the effect of screening, diagnostic tools, and treatment compliance on outcomes.¹³⁵ When relying on one or more of the existing diabetes models to address multiple questions on VOI, it might be important to adapt these models to the specific context in which decisions are made about the priority of systematic reviews on various topics related to diabetes type 1 and type 2. For example, both the CDC-RTI and the University of Michigan model are populated with data from the United Kingdom Prospective Diabetes Study¹³⁶ and therefore would require adjustment or updating to provide estimates of VOI that reflect the U.S. population of diabetes patients.

Application of a Minimal Modeling Approach to VOI

To assess the potential of minimal modeling approaches to provide information on the value expected from performing systematic reviews, we discuss one new clinical empirical application that requires “no modeling.” In this application, we studied the comparative effectiveness of noninvasive positive pressure ventilation versus standard therapy in acute respiratory failure. We chose this application as an example in which data on comprehensive outcome measures, i.e., both in-hospital patient mortality and costs, are available that allow direct replication of these data to estimate the population-level VOI of updating the review of evidence on this topic.

Use of Available Data on Comprehensive Outcome Measures: Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure

In the U.S., more than 850,000 patients are admitted to the hospital with acute respiratory failure each year.¹³⁷ Next to acute cardiogenic pulmonary edema and other indications, these admissions most frequently concern exacerbations of chronic obstructive pulmonary disease (COPD). Standard medical therapy in these patients includes supplemental oxygen, bronchodilators, antibiotics, corticosteroids, and diuretics. A recent meta-analysis, pooling data from 11 studies, found that noninvasive positive pressure ventilation (NPPV), as supplement to initial therapy, reduce in-hospital patient mortality (relative risk: 0.45; 95% confidence interval [CI], 0.30–0.60) and length of hospital stay (difference: -1.94 days; 95% CI: 3.87–0.01) during acute exacerbations of COPD.¹³⁸ Because the benefits of NPPV are not known with certainty and additional costs (+\$7,012) are associated with administering NPPV in patients, the expense of masks and oxygen supplementation, the training of clinical staff, and the acquisition of ventilators and monitoring systems, further research could potentially aid in informing treatment choice in acute respiratory failure.

Given this background, we sought to examine whether a minimal modeling approach to VOI could provide useful data on the priority for an update of the review of evidence on the comparative effectiveness of NPPV versus standard therapy for acute respiratory failure in patients with COPD.

To estimate population-level VOI, we replicated summary data available from Quon et al.¹³⁸ on the relative risk of in-hospital mortality and difference in the length of hospital stay through simulation in WinBUGS, assuming independent, (log)normal distributions for the both (Table 7; Appendix H). The population expected value of updating a review on acute respiratory treatment ($pEVI$) was established as the difference between the population expected value of perfect information given meta-analysis data ($pEVPI_{prior}$) and that with predicted outcomes for additional

patient samples that could come from the review update ($pEVPI_{post}$). To calculate net benefit of treatment alternatives on a per patient basis, we accounted for the gain in life-years assuming a baseline mortality of 25% and an age-adjusted life expectancy of 4.4 years for patients admitted to hospitals with respiratory failure and whom require ventilation (mean age: 67 years), and subtracted the difference in costs of hospital stay and treatment from the product of life-years saved and the willingness-to-pay or cost-effectiveness threshold.¹³⁸⁻¹⁴⁰ For all model evaluations of VOI to achieve convergence, we discarded initial 50,000 ‘burn-in’ sample iterations, and based inferences on further runs of 50,000 iterations.

The analysis of VOI was performed from a societal perspective, in which the opportunity costs for labor is not expected to differ between NPPV and standard treatment because of the pensionable age of patients with hospital admissions for acute exacerbations of COPD. In establishing the population level value of updating the earlier meta-analysis, only a limited proportion of patients with acute exacerbations is expected to receive NPPV in practice (i.e., probability of implementation = 11%), while 13 percent of patients is expected to be intolerant to non-invasive ventilation because of claustrophobia or frequent productive cough. In addition, we assumed the information from the potential review update to be durable over a time horizon of 5 years, and used a discount rate of 3 percent. The results of our analysis are represented in an acceptability curve and expected VOI curves over a range of threshold values for cost-effectiveness on the basis of which a treatment decision could be made.

As shown in Figure 5, the population expected VOI suggests that performing a systematic review to provide more precise estimates on the net benefit of NPPV compared with standard treatment in exacerbations of COPD is unlikely to be valuable over a wide range of threshold values for cost-effectiveness. Specifically, the $pEVI$ is not expected to exceed the expected costs of \$300,000 for a review update for a cost-effectiveness threshold less than \$8000 or over \$26,000 per life-year saved. For a more common threshold of \$50,000 per life-year saved, the supplementary use of NPPV in acute respiratory failure is recommended without further research to inform this treatment decision. This is because of the statistically significant effect of treatment alternatives on in-hospital mortality-risk and hospital stay from meta-analysis.¹³⁸ The upper bounds on the value that can be expected from further research ($pEVPI_{prior}$) broadly range from \$554,500 to \$149.30 million for threshold values around \$15,000/life-year for which the decision about optimal treatment of acute respiratory would change. Essentially, these VOI calculations are not very different from some standardized VOI estimates available, ranging from \$2 million to \$125 billion, for other studies.⁷ The population value of updating a review on acute respiratory treatment ($pEVI$) varies considerably with the additional sample of patients that may be found. This value decreases with larger sample sizes because it then becomes less predictable what the outcomes of the review would be.

We conclude that performing VOI through minimal modeling reveals that there is limited value to be expected from reducing uncertainty about the comparative effectiveness of NPPV versus standard therapy in acute respiratory failure. Based on these results, the updating of an earlier meta-analysis on treatment effects would seem to merit low priority, especially when the resources or budgets for research are limited and other systematic reviews exist for which VOI is calculated to exceed the costs of performing these reviews. The minimal modeling exercise in acute respiratory failure took just a few days of work, as opposed to what we expect would be months for a typical full-modeling approach to VOI.

Table 7. Details of application for minimal modeling approach to VOI in acute respiratory failure

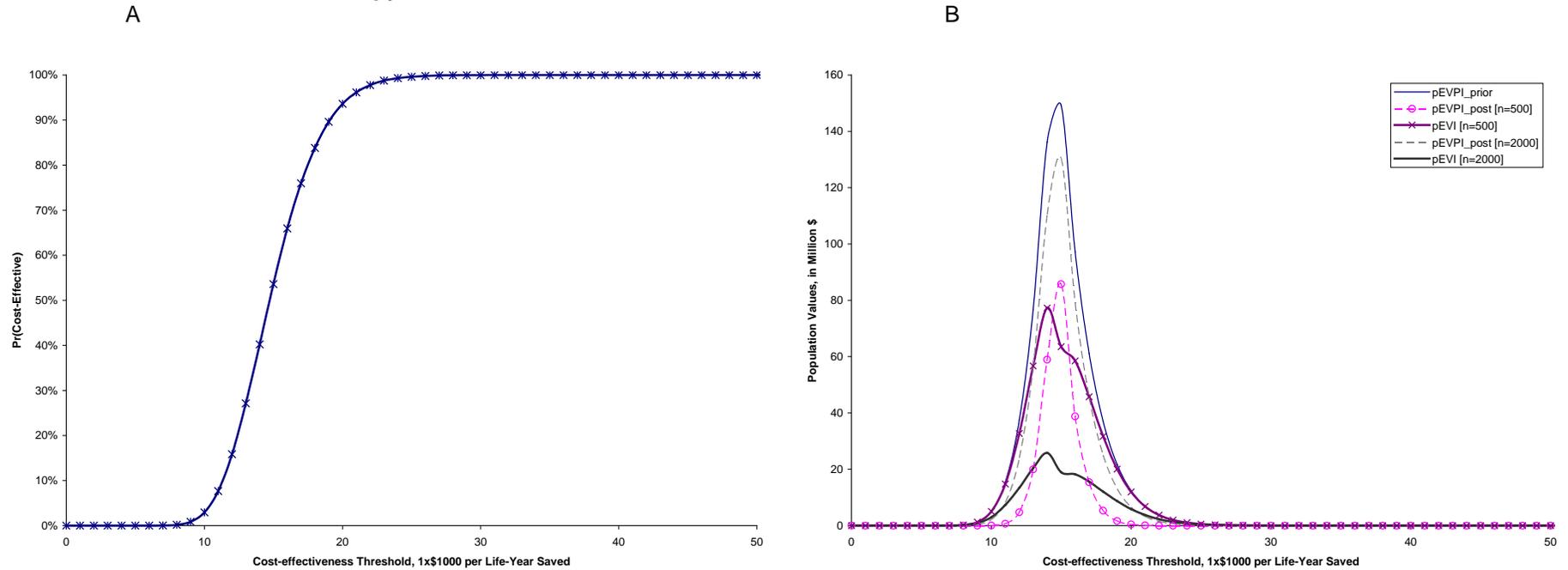
Application	Noninvasive Positive Pressure Ventilation Versus Standard Therapy
Minimal Modeling	Direct replication through parametric simulation of data in WinBUGS [Appendix H]
Setting	U.S.
Perspective	Societal
Data	Baseline in-hospital mortality rate in patients with respiratory failure: 25% [138] Costs of hospital stay: \$600 per day [141] Administration Costs of NPPV: \$17,711 [†] [142] Costs of standard therapy: \$10,699 [†] [142] Life-expectancy patients surviving respiratory failure: 4.4 years [§]
	Implementation of NPPV in hospitals: 11% [143] Non-toleration to NPPV by patients: 13% [144] Durability of information: 5 years [assumption]
	<i>Evidence from Available Meta-Analysis for Prior Analysis</i> [138] - Relative risk of in-hospital mortality: 0.45 (95% CI: 0.30, 0.60; sample size: 940) - Difference in length of hospital stay: -1.94 days (95% CI: -0.01, -3.87; sample size, 956)
	<i>Assumptions regarding Additional Review Findings for Posterior Analysis</i> - Additional samples of patients: 500, 1000, 2000, 3000, 4000, 5000, 6000 patients
Incidence	850,000 hospital admissions per year [137]
Time horizon	5 years (durability = 1,0 for all years over this time horizon)
Discounting	3%
Cost-effectiveness threshold	λ : 0-\$100,000 per life-year saved
VOI results	<i>Prior Analysis</i> - $pEVPI_{prior} = \$149,30$ million* - $Pr(\text{Net Benefit} > 0) = 0.54^*$
	<i>Posterior Analysis</i> - $pEVPI_{post} = \$85,7$ million* - $pEVI = \$63,6$ million* - Population-level returns of systematic review = \$63,3 million*, with expected costs of systematic review = \$300,000
	* λ : \$15,000 per life-year saved (~ICER)

CI: confidence interval; ICER: incremental cost-effectiveness ratio of NPPV compared with standard therapy; NPPV: Noninvasive Positive-Pressure Ventilation; pEVI: population expected value of information from review update with predicted outcomes for additional sample of 500 patients [138]; $pEVPI_{post}$: population expected value of perfect information with (posterior) predicted outcomes for review update with additional sample of 500 patients; $pEVPI_{prior}$: population expected value of perfect information prior to updating review, based on available meta-analysis; $Pr(\text{Net Benefit} > 0)$: probability that NPPV is net beneficial (or cost-effective) compared with standard therapy; VOI: value of information; λ : cost-effectiveness threshold.

[†] 2009 \$ costs were calculated by adjusting cost indexations from Keenan et al. [142] for historical currency exchange rates [145] (i.e., average daily over period 01/01/year of study and 12/31/year of study), and consumer price indexations [146,147].

[§] Life expectancy of patients with respiratory failure was calculated as the weighted average over an approximate 75% of patients within 65-74 age group die within 100 days [139], and 25% of patients with an average of 16.8 years of life remaining [140].

Figure 5. Acceptability curve (A) and population expected value of information (B) for comparing noninvasive positive pressure ventilation with standard therapy



pEVI: population expected value of information from review update with predicted outcomes for additional sample of n patients (i.e., $pEVPI_{prior} - pEVPI_{post}$); $pEVPI_{prior}$: population expected value of perfect information prior to updating review, based on available meta-analysis;¹³⁸ $pEVPI_{post}$: population expected value of perfect information with (posterior) predicted outcomes for review update with additional sample of n patients.

Conclusion

Our algorithmic approach to systematizing the use of VOI in prioritizing systematic reviews demonstrated to have potential utility in identifying effective and efficient VOI methods for prioritizing topics nominated to the AHQR EPCs for systematic review. As part of this, conceptual VOI, maximal modeling, and minimal modeling are often found to offer lower cost alternatives to typical full modeling approaches to VOI. In a series of clinically related empirical applications, we described how the use of these alternative approaches to VOI can potentially minimize the burden to the practical application of VOI and aid in setting priorities among all possible systematic reviews. As such, VOI may improve the effectiveness of research spending on systematic reviews.

Discussion

General Findings

In this study, we sought to assess whether a systematic approach to the use of VOI to inform priorities for systematic reviews could be developed with the potential to improve the effectiveness of research spending on systematic reviews. We found a growing body of literature applying VOI to inform research priorities, and identified 78 published VOI studies, among which full modeling of the disease and its treatment – rather than less complex and less expensive VOI approaches - is the dominant approach to analysis. Despite the availability of some lower cost approaches to VOI, however, we found that VOI has seldom been applied to inform priorities for systematic reviews. Our review of the priority-setting processes in 13 major U.S. and international organizations revealed that VOI or its elements are not explicitly quantified when performing and/or funding systematic reviews, though ideas implicit in VOI principles are commonly applied, with the exception of durability of evidence. We identified that the high costs, also in terms of complexity, data, expertise and time requirements, of the most common (full-modeling) approaches to VOI are generally unlikely to be worthwhile when prioritizing systematic reviews but that lower cost VOI methods may be worthwhile under some circumstances. To this end, we developed an algorithm that describes a multistage process for identifying the effective and efficient approaches to performing VOI in systematic reviews. From assessing the potential utility of this algorithmic approach in topics nominated to AHRQ’s EPCs, we found that conceptual VOI, maximal modeling, and minimal modeling may often offer lower cost alternatives to full modeling approaches to provide estimates of value of systematic reviews. In a series of clinically related empirical applications, we described how the use of these lower cost methods could minimize the burden to practical application of VOI and aid in setting priorities among all possible systematic reviews for which resources are limited.

Information Requirements of Application of Algorithm to VOI

Our results suggest that the algorithm to systematizing the use of VOI when prioritizing systematic reviews can be applied with only limited information requirements. Indeed, in applying the algorithm in review topics nominated to AHRQ in 2009, we found that a great deal of information needed to populate the multistage process to deciding about VOI was already generated as part of the triage process undertaken by the AHRQ EPCs. That is, the population of patients whom may benefit from the review outcomes was typically specified, while the potential benefits and uncertainty reduction in treatment alternatives and health interventions are considered as part of the EHC Program selection criteria relating to the “appropriateness,” “importance,” and “impact” of potential review topics. In addition, AHRQ topic briefs provided data – albeit that this primarily concerned qualitative information – on variation in care and the potential for change in practice, the development of clinical guidelines and that of ongoing or recently completed research, which can address potential limits on the implementation and durability of systematic review findings. In effect, our review of prioritization processes showed that the conceptual elements that determine the value of evidence synthesis are considered by most organizations involved in systematic review activities, even though variation exists in how these information elements are operationalized and measured. Data collection on comprehensive measures for health outcomes, costs and/or net benefits of treatments or health interventions, and that on the prospects of future research may require additional literature searches, environmental

scans or expert elicitation. Where this information is available, decisions about whether and how to analyze the value of information from performing systematic reviews readily follow from the algorithm.

Applicability of Algorithm to Select VOI Approaches

Because the development of our algorithm is based on general principles of VOI, the use of this algorithm may aid in identifying effective and efficient approaches to estimate the value of research also in contexts other than that of systematic reviews where VOI is considered for informing research priorities. Generally, our algorithmic approach seems to be advantageous in low-cost research efforts where budget limitations urge some prioritization. Aside from systematic reviews, such efforts may involve surveys for the prevalence or incidence of particular diseases or clinical conditions, or small-scale pilot studies of treatments, behavioral or delivery interventions. When applying VOI in a context of high-cost studies or combinations or series of studies that require substantial funding, the algorithm may find its most useful application in considering information on the probability of implementation, durability of research evidence and other conceptual elements that determine the population value of research so as to ensure that studies only receive funding when these are indeed expected to produce value. Examples of high-cost studies in which a more systematized use of VOI could be useful pertain not only to costly randomized controlled clinical trials but also to observational studies of policy changes or large-scale social experiments in which patients are randomly assigned to different forms of coverage. Regardless of the costs of research, the application of the algorithm would guide a systematized use of VOI when time and resources, including data and expertise, to perform VOI are limited.

Applicability of Approaches to Calculating VOI

Our reviews and the applications suggest several situations in which lower cost methods, that is, conceptual VOI, maximal modeling or minimal modeling, may substitute full modeling approaches in an overall strategy of VOI to inform research priorities, which may include the performance of systematic reviews.

In providing informative bounds on the value of research, conceptual VOI is most likely to be useful when there is evidence suggesting low values in any of the multiplicative elements that determine the population-level VOI. Such situations may occur when the clinical use or implementation of research outcomes is prevented due to barriers such as a lack of knowledge or resistance by clinicians and/or patients, or strict coverage or payment policies. Another example would be in the case of rare diseases for which the value from research is limited because of the small population of patients affected. Unless the value for any of the elements of VOI equals zero, there may be some uncertainty associated with the decisions to rule out value in specific research studies or systematic reviews. As noted earlier, however, the consideration of a conceptual approach to VOI seems prudent before investing in more complex modeling to formally quantify the value of information in a particular intervention or research topic.

Substantial investments necessary to construct single comprehensive ‘maximal’ models that can simultaneously address multiple questions of VOI are only valuable in situations where multiple uses of these models can be anticipated. This is typically the case in more complex or chronic diseases like diabetes or cardiovascular disease in which health outcomes and resources use could be affected by multiple clinical conditions and interventions. A maximal modeling

approach would allow the costs of modeling for current topics to be minimized, and may facilitate rapid and low-cost assessment of VOI for future topics. In effect, it could be worthwhile investing in building an infrastructure or research network, perhaps based on those decision models already available in a clinical domain, to collect and analyze relevant information from research projects in which the performance of VOI may aid in identifying evidence gaps and efficient designs of new research or adaptive trials.

Minimal modeling can be used to estimate the value in research topics when comprehensive outcome measures on the treatments or health interventions under comparison are readily available from trials, observational studies or meta-analyses. One example would involve a study that follows patient cohorts over the course of a particular disease and its treatment until death and that records all outcomes, like survival, quality of life and/or costs, relevant to address the clinical or policy decision in question. Another is when a study measures comprehensive outcomes data, from a trial in which survival is similar between two arms after some point, but survival or quality of life up to that point might differ. As illustrated in the new application of a minimal modeling approach to VOI in acute respiratory failure and earlier analyses, direct replication or bootstrapping of these data to address the value of information can be easily implemented in software such as WinBUGS or Stata.⁷ Alternatively, modeling can be minimized when a trial or data set is available that can require only modeling of survival or other limited modeling exercises (e.g., utility mapping or approximation of cost) to generate comprehensive measures of health outcomes, costs, or net benefit that would readily allow VOI calculations in research topics.

We found very limited conditions for the use of typical full modeling approaches to VOI for research prioritization. This is typically only the case when further research is potentially valuable but costly, and the analysis of uncertainty in the effects of treatment or interventions on outcomes need to be sufficiently accurate so that this can aid in identifying relevant evidence gaps and the efficient design of new studies. In most situations, the construction of a full model of a disease and treatment process for analyzing the value expected from low cost studies, including systematic reviews, is most likely too costly to outweigh the returns expected from prioritizing among possible research projects and performing the actual research.

Limitations of VOI Approach to Research Prioritization

In practice, prioritizing research, including systematic reviews, is not simply a task of performing VOI and balancing VOI estimates against each other. One of the reasons is that decision makers and other stakeholders in the prioritization process often have divergent values and preferences related to health and health care, and these different perspectives may affect how decisions about research spending are made. For example, we found that some decisions about the priority of topics nominated to AHRQ EPCs for systematic review deviated from those decisions that would come from applying our algorithmic approach to VOI.¹⁴⁸ Indeed, these deviations can be explained in part because, in practice, some criteria like the burden of disease, variation in care, or equity considerations sometimes receive more weight than others in prioritizing research. In addition, some review topics passed through the selection process at AHRQ with the intent to refine the scope of these topics or develop technical briefs without recommending systematic reviews. In formally quantifying the value of information as an unweighted product of a selection of elements, VOI may not fully recognize the importance of alternative perspectives on the role of formal approaches to valuing research may play within the larger context of research prioritization and health care decisionmaking. Thus, we propose that

our algorithm be used as a complement to, rather than as a substitute for, the judgment of informed decision makers.

In addition to the perhaps more selective nature of VOI, other limitations of an overall strategy of VOI to prioritizing research studies and systematic reviews should be noted. First, VOI analyses may often have to be restricted to establishing upper bounds (e.g., EVPI or pEVPI) on the value of research because it is difficult to predict the potential information that could result from new research. This is especially true in systematic reviews in which evidence synthesis may lead to greater uncertainty about the benefits of treatments or health interventions than that was anticipated before performing the systematic review. Predicting the value of systematic reviews becomes even more difficult when these are set up to explore heterogeneity in outcomes and patient groups that may be important to reflect in clinical guidance, coverage or payment policies, and directing further research. Even though measures of perfect information can provide useful indications of which systematic reviews or research studies are potentially worthwhile, it is preferred to come up with some estimate of research outcomes that can be balanced against the costs of research so as to sufficiently inform prioritization decisions about research funding. As illustrated in our minimal modeling analysis of value of information, this prediction or distribution of outcomes of particular research may be based on assumptions for the notional additional sample of patients or perhaps expert elicitation.¹⁴⁹ Finally, current VOI approach to valuing research projects is limited by the fact that it does not explicitly account for ongoing activities that seek to promote the implementation of research outcomes into clinical practice.^{11,12} These activities may comprise the development of clinical practice guidelines or implementation strategies like patient counseling, medical education or academic detailing of clinicians, and payment incentives or reminders. Aside from the effect that active implementation of research may have on clinical behavior or performance and thus on health outcomes and resource use, the costs of investing in such activities would have to be considered in developing meaningful estimates of the value of research.

Future Directions of Research

Incorporation of VOI in Priority-Setting Processes

Among its primary advantages, VOI motivates decision makers and others involved in the process of research prioritization to explicate criteria relevant for priority-setting, and to provide quantified measures for making decisions about research spending. The use of VOI may lend transparency and credibility to prioritization decisions, especially if it is used as a precursor to scrutinizing objective data on the value of health research and to further subjective discussion. As a result, VOI seems to complement current subjective and more objective approaches to prioritizing research studies and systematic reviews. In essence, the results of our study suggest the implementation of a two-stage process by which VOI is incorporated into current prioritization processes. At first, information on each of the conceptual elements of VOI is used to “rule out” conducting research on topics that are expected to have low conceptual value of information. In a second stage, practical quantitative VOI methods are employed to assess the relative value of research projects that can be used in the ranking of these projects. Such a two-stage approach to the use of VOI seems applicable in the triage process for systematic reviews currently undertaken by the AHRQs EPCs. To allow for a broad perspective in valuing research, the approach to VOI can thereby be extended to incorporate the heterogeneity and weighing of different aspects of priority setting. For example, consideration of rare but catastrophic events or

equity considerations can be included by weighting the expected net benefits appropriately, for example by adjusting the measure of health benefit accordingly. The expected value of individualized care may be especially important in cases in which heterogeneity in clinical or economic consequences of particular treatments or interventions is a critical concern.⁶⁷ In extending the use of VOI in prioritization research, this type of analysis could aid not only in generating new research topics that would follow from modeling exercises that are constructed to provide estimates of VOI, but also in valuing research on topics within existing topics. For example, value of information analysis could address the value of studying the effect of medication switching on outcomes in patients with schizophrenia so as to inform clinical decisionmaking about treatment algorithms in these types of patients.

Standardization of VOI Calculations

Implementation of VOI in priority-setting practice would require standardizing population-level VOI analyses if these are to be used to compare research projects and make prioritization decisions. To this end, it is critical that VOI estimates reflect appropriate assumptions about key parameters, ranging from disease-specific ones for measuring health outcomes, costs and utilities to more general assumptions, such as the perspective and time horizon of analysis, discount rates, and the broad population of patients being considered. In addition, standardized methodology needs to be developed for assessing the probability of implementation and durability of research evidence. A useful method for this may be the use of expert elicitation. The potential for elicitation exercises may extend to predicting research outcomes and correlation in information across topics and studies, providing guidance on how to structure complex decision-analytic models or adjust or update existing ones, and the appropriate weighting of conceptual elements of VOI. Standardization and transparency in the reporting of VOI studies would allow policymakers and others to critically assess the potential relevance of VOI indications from other settings to addressing their own decisions.

Evaluation of the Use of VOI for Prioritizing Health Research

Because resources invested in performing VOI may essentially be invested directly in resolving clinical questions or providing health care, it seems important to evaluate whether a systematized use of VOI in research prioritization processes is indeed valuable. One way to study this would be to assess whether that process is useful to decision makers and other stakeholders prioritizing systematic reviews and would lead them to make decisions about the priority of systematic review that are different from the decisions they would have made without information about VOI. The latter could be evaluated by taking a retrospective look at the differences between prioritization decisions made in practice and those decisions that would come from ranking based on VOI estimates, an example of this is given by the work prepared by Whitlock and Eder.¹⁴⁸ Discrete choice experiments may also be useful for eliciting whether prioritization decisions change—albeit in “hypothetical” scenarios—with estimates of VOI being presented along with evidence on other decision criteria like burden of disease, and for different values of these different criteria. One approach to assess the usefulness of VOI would be to convey survey decision makers and others involved in research prioritization in order to obtain feedback on whether VOI aids in organizing evidence to inform priority setting, and perhaps in communicating decisions about the focus of research and priority of particular research projects to the general public. Perhaps most importantly, it should be evaluated whether a new approach

to research prioritization in which VOI is considered changes decisions that produces systematic reviews and other research studies that are more valuable to stakeholders, particularly in terms of health outcomes and resource use. To empirically evaluate this, the use of VOI would need to be incorporated into current priority-setting processes and then the outcomes of those processes would need to be systematically analyzed.

Conclusion

We conclude that consideration of VOI principles and methods may have a useful role in informing priorities for systematic reviews. VOI seems likely to be able to help decisionmakers and others involved in the priority-setting process to explicate criteria and provide quantified measures of expected value that can be used to prioritize systematic reviews. Since AHRQ and other decisionmaking bodies and research funding agencies are investing greater resources in generating topics to consider for systematic review and it is unclear whether resources to perform all possible systematic reviews will be available, approaches to research prioritization such as VOI seem likely to become increasingly important. A systematized use of VOI in which an algorithm guides the choice among conceptual VOI, maximal, minimal and full modeling would minimize the burden to the practical application of VOI and ensure maximum benefit from research spending in terms of population health.

Abbreviations and Variables

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CADTH	Canadian Agency for Drugs and Technologies in Health
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DEPC	Duke Evidence-based Practice Center
DERP	Drug Effectiveness Review Project
EHC	Effective Health Care
ENBS	expected net benefit from sampling
ENG	expected net gain of performing a trial
EPCs	Evidence-based Practice Centers
EVI	expected value of information
EVPI	expected value of perfect information
EVPPPI	expected value of partial perfect information
EVSI	expected value of sample information
ICER _{trial}	incremental cost-effectiveness ratio of performing a trial
NHS	National Health Services
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NIHR HTA	National Institute for Health Research Health Technology Assessment program
NPPV	noninvasive positive pressure ventilation
OHTAC	Ontario Health Technology Advisory Committee
Osteba	Basque Office for Health Technology Assessment
pENBS	population expected net benefit of sampling
pENG	population expected net gain of performing a trial
pEVI	population expected value of information
pEVPI	population expected value of perfect information
pEVPPPI	population expected value of partial perfect information
pEVSI	population expected value of sample information
QALY	quality-adjusted life-year
SBU	Swedish Council on Technology Assessment in Health Care
SIGN	Scottish Intercollegiate Guidelines Network
TEP	technical expert panel
UC	University of Chicago
USPSTF	U.S. Preventive Services Task Force
VOI	value of information
WHO	World Health Organization
ZonMw	Netherlands Organisation for Health Research and Development

Variables (in Order of Appearance in Text)

$pEVI$	population expected value of information from a particular set of information I from a research study or systematic review, in monetary terms
β'	discount rate for the future benefits and costs of information over time period t , $\beta' \in [0,1]$
Dur_t	probability that information from a particular research study or systematic review is durable at time period t , $Dur_t \in [0,1]$
Pop_j	size of patient population expected to benefit from health intervention j , $Pop_j \in [0, \infty]$
$Im p_{j,t}$	probability of implementation of health intervention j at time period t with and additional set of information I on parameter values θ' , $Im p_{j,t} \in [0,1]$
$E_{\theta'} NB[j, \theta]$	expected net benefit of health intervention j with additional set of information I on parameter values θ , in monetary terms
$Im p_{j,t}$	probability of implementation of health intervention j at time period t , $Im p_{j,t} \in [0,1]$
$E_{\theta} NB[j, \theta]$	expected net benefit of health intervention j with uncertain parameter values θ , in monetary terms
EVI	expected value of information from a particular set of information I from a research study or systematic review, in monetary terms
I	particular set of information from a research study or systematic review, on parameter values θ
j	particular health intervention (including a clinical guideline or an implementation strategy), or set of mutually exclusive health care interventions, $j \in [1, 2, \dots, J]$
λ	threshold value for cost-effectiveness or willingness-to-pay (e.g., \$ per additional life-year or quality-adjusted life-year)
$E_{\theta} O(j, \theta)$	expected outcomes of health intervention j with uncertain parameter values θ , in terms of life expectancy, quality of life or any other health outcome
$E_{\theta} C(j, \theta)$	expected costs of health intervention j with uncertain parameter values θ , in \$
t	time period for which a particular clinical or health policy decision is relevant, in years
Π_t	population expected returns from performing value of information analysis to identify the priority for a particular research study or systematic review, in monetary terms
$EVPI$	expected value of perfect information, in monetary terms
$EVPPPI$	expected value of perfect partial information, in monetary terms
C_t	costs of performing a particular research study, which may include a systematic review, at time period t , in \$
C_{vor}	costs of performing value of information calculations, in \$

References

1. Laupacis, A. and S. Straus, Systematic reviews: time to address clinical and policy relevance as well as methodological rigor. *Annals of Internal Medicine*, 2007. 147(4): p. 273-4.
2. Chambers, D., et al., Maximizing the impact of systematic reviews in health care decision making: a systematic scoping review of knowledge-translation resources. *Milbank Q*, 2011. 89(1): p. 131-56.
3. Perrier, L., et al., Interventions encouraging the use of systematic reviews by health policymakers and managers: A systematic review. *Implement Sci*, 2011. 6(1): p. 43.
4. Whitlock, E.P., et al., AHRQ series paper 3: identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the effective health-care program. *J Clin Epidemiol*, 2010. 63(5): p. 491-501.
5. Claxton, K., Bayesian approaches to the value of information: implications for the regulation of new pharmaceuticals. *Health Economics*, 1999. 8(3): p. 269-74.
6. Meltzer, D., Addressing uncertainty in medical cost-effectiveness analysis implications of expected utility maximization for methods to perform sensitivity analysis and the use of cost-effectiveness analysis to set priorities for medical research. *Journal of Health Economics*, 2001. 20(1): p. 109-29.
7. Meltzer, D.O., et al., Minimal Modeling Approaches to Value of Information Analysis for Health Research. *Med Decis Making* 2011;31(6):E1-E22.
8. Fleurence, R.L. and D.J. Torgerson, Setting priorities for research. *Health Policy*, 2004. 69(1): p. 1-10.
9. Philips, Z., et al., Priority setting for research in health care: an application of value of information analysis to glycoprotein IIb/IIIa antagonists in non-ST elevation acute coronary syndrome. *International Journal of Technology Assessment in Health Care*, 2006. 22(3): p. 379-87.
10. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998;18(2 Suppl):S68-80.
11. Fenwick, E., K. Claxton, and M. Sculpher, The value of implementation and the value of information: combined and uneven development. *Medical Decision Making*, 2008. 28(1): p. 21-32.
12. Hoomans, T., et al., Value of information and value of implementation: application of an analytic framework to inform resource allocation decisions in metastatic hormone-refractory prostate cancer. *Value in Health*, 2009. 12(2): p. 315-24.
13. Willan, A.R. and S. Eckermann, Optimal clinical trial design using value of information methods with imperfect implementation. *Health Economics*, 2010. 19(5): p. 549-61.
14. Meltzer, D.O., A. Basu, and H.Y. Meltzer, Comparative effectiveness research for antipsychotic medications: how much is enough? *Health Aff (Millwood)*, 2009. 28(5): p. w794-808.
15. Weinstein, M.C., et al., Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *Am J Public Health*, 1987. 77(11): p. 1417-26.
16. Griffin S, Welton NJ, Claxton K. Exploring the research decision space: the expected value of information for sequential research designs. *Med Decis Making*. 2010;30(2):155-62.
17. Tappenden, P., et al., Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-beta and glatiramer acetate for multiple sclerosis. *Health Technology Assessment (Winchester, England)*, 2004. 8(27): p. iii, 1-78.
18. Ades AE, Mavranzouli I, et al. Network meta-analysis with competing risk outcomes. *Value Health*. 2010;13(8):976-83.
19. Conti S, Claxton K. *Med Decis Making*. 2009 Nov-Dec;29(6):643-60. Epub 2009 Jul 15. Dimensions of design space: a decision-theoretic approach to optimal research design.

20. Myers, E., et al., Evaluating the Potential Use of Modeling and Value-of-Information Analysis for Future Research Prioritization Within the Evidence-based Practice Center Program., P.b.t.D.E.-b.P.C.u.C.N. 290-2007-10066-I., Editor. 2011, AHRQ Publication No. 11-EHC030-EF.: Rockville, MD.
21. Meltzer, D., et al., Minimal Modeling Approaches to Value of Information Analysis for Health Research. Methods Future Research Needs Report No. 6. 2011, AHRQ Publication No. 11-EHC062-EF.: Rockville, MD.
22. Ramsey, S.D., D.K. Blough, and S.D. Sullivan, A forensic evaluation of the National Emphysema Treatment Trial using the expected value of information approach. *Med Care*, 2008. 46(5): p. 542-8.
23. Stevenson, M.D., A. Scope, and P.A. Sutcliffe, The cost-effectiveness of group cognitive behavioral therapy compared with routine primary care for women with postnatal depression in the UK. *Value in Health*, 2010. 13(5): p. 580-4.
24. Detsky, A.S., Using cost-effectiveness analysis to improve the efficiency of allocating funds to clinical trials. *Stat Med*, 1990. 9(1-2): p. 173-84.
25. Forbes, C., et al., A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer. *Health Technology Assessment (Winchester, England)*, 2002. 6(23): p. 1-119.
26. Girling, A.J., et al., Modeling payback from research into the efficacy of left-ventricular assist devices as destination therapy. *International Journal of Technology Assessment in Health Care*, 2007. 23(2): p. 269-77.
27. Townsend, J., M. Buxton, and G. Harper, Prioritisation of health technology assessment. The PATHS model: methods and case studies. *Health Technology Assessment (Winchester, England)*, 2003. 7(20): p. iii.
28. Willan, A.R. and E.M. Pinto, The value of information and optimal clinical trial design. *Statistics in Medicine*, 2005. 24(12): p. 1791-1806.
29. Eckermann, S. and A.R. Willan, Expected value of information and decision making in HTA. *Health Economics*, 2007. 16(2): p. 195-209.
30. Willan, A. and M. Kowgier, Determining optimal sample sizes for multi-stage randomized clinical trials using value of information methods. *Clin Trials*, 2008. 5(4): p. 289-300.
31. Eckermann, S. and A.R. Willan, Globally optimal trial design for local decision making. *Health Economics*, 2009. 18(2): p. 203-16.
32. Willan, A.R., Clinical decision making and the expected value of information. *Clin Trials*, 2007. 4(3): p. 279-85.
33. Barton, G.R., A.H. Briggs, and E.A. Fenwick, Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfect information (EVPI). *Value in Health*, 2008. 11(5): p. 886-97.
34. Fenwick, E., et al., Assessing the impact of censoring of costs and effects on health-care decision-making: an example using the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Value in Health*, 2008. 11(3): p. 365-75.
35. Groot Koerkamp, B., et al., Value of information analysis used to determine the necessity of additional research: MR imaging in acute knee trauma as an example. *Radiology*, 2008. 246(2): p. 420-429.
36. Koerkamp, B.G., et al., Value of information analyses of economic randomized controlled trials: the treatment of intermittent claudication. *Value in Health*, 2010. 13(2): p. 242-50.
37. Omenn, G.S., Assessment of human cancer risk: challenges for alternative approaches. *Toxicol Pathol*, 2001. 29 Suppl: p. 5-12.
38. Oostenbrink, J.B., et al., Expected value of perfect information: an empirical example of reducing decision uncertainty by conducting additional research. *Value in Health*, 2008. 11(7): p. 1070-80.
39. Goeree, R., et al., Health technology assessment and primary data collection for reducing uncertainty in decision making. *J Am Coll Radiol*, 2009. 6(5): p. 332-42.
40. Singh, S., et al., Value of information of a clinical prediction rule: informing the efficient use of healthcare and health research resources. *International Journal of Technology Assessment in Health Care*, 2008. 24(1): p. 112-9.

41. Henriksson, M., F. Lundgren, and P. Carlsson, Informing the efficient use of health care and health care research resources - the case of screening for abdominal aortic aneurysm in Sweden. *Health Economics*, 2006. 15(12): p. 1311-22.
42. Martikainen, J.A., et al., Economic evaluation of temozolomide in the treatment of recurrent glioblastoma multiforme. *Pharmacoeconomics*, 2005. 23(8): p. 803-15.
43. Coyle, D. and J. Oakley, Estimating the expected value of partial perfect information: a review of methods. *Eur J Health Econ*, 2008. 9(3): p. 251-9.
44. Iglesias, C.P. and K. Claxton, Comprehensive decision-analytic model and Bayesian value-of-information analysis: pentoxifylline in the treatment of chronic venous leg ulcers. *Pharmacoeconomics*, 2006. 24(5): p. 465-78.
45. Sculpher, M. and K. Claxton, Establishing the cost-effectiveness of new pharmaceuticals under conditions of uncertainty-- when is there sufficient evidence? *Value in Health*, 2005. 8(4): p. 433-46.
46. Rao, C., et al., Economic analysis of esophageal stenting for management of malignant dysphagia. *Dis Esophagus*, 2009. 22(4): p. 337-47.
47. Fleurence, R.L., Setting priorities for research: a practical application of 'payback' and expected value of information. *Health Economics*, 2007. 16(12): p. 1345-57.
48. Dong, H., D. Coyle, and M. Buxton, Value of information analysis for a new technology: computer-assisted total knee replacement. *International Journal of Technology Assessment in Health Care*, 2007. 23(3): p. 337-42.
49. Xie, F., et al., Results of a model analysis to estimate cost utility and value of information for intravenous immunoglobulin in Canadian adults with chronic immune thrombocytopenic purpura. *Clin Ther*, 2009. 31(5): p. 1082-91; discussion 1066- 8.
50. Groot Koerkamp, B., et al., Uncertainty and patient heterogeneity in medical decision models. *Med Decis Making*, 2010. 30(2): p. 194-205.
51. Claxton, K., et al., Bayesian value-of-information analysis. An application to a policy model of Alzheimer's disease. *International Journal of Technology Assessment in Health Care*, 2001. 17(1): p. 38-55.
52. Hassan, C., et al., Value-of-information analysis to guide future research in the management of the colorectal malignant polyp. *Dis Colon Rectum*, 2010. 53(2): p. 135-42.
53. Collins, R., et al., A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer. *Health Technology Assessment (Winchester, England)*, 2007. 11(2): p. iii-iv, xv-xviii, 1-179.
54. Fenwick, E., et al., An iterative Bayesian approach to health technology assessment: application to a policy of preoperative optimization for patients undergoing major elective surgery. *Medical Decision Making*, 2006. 26(5): p. 480- 96.
55. Oakley, J.E., et al., Simulation sample sizes for Monte Carlo partial EVPI calculations. *Journal of Health Economics*, 2010. 29(3): p. 468-77.
56. Claxton, K.P. and M.J. Sculpher, Using value of information analysis to prioritise health research: some lessons from recent UK experience. *Pharmacoeconomics*, 2006. 24(11): p. 1055-68.
57. Wilson, E., et al., Cost-utility and value-of-information analysis of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg*, 2010. 97(2): p. 210-9.
58. Teerawattananon, Y., M. Mugford, and V. Tangcharoensathien, Economic evaluation of palliative management versus peritoneal dialysis and hemodialysis for end-stage renal disease: evidence for coverage decisions in Thailand. *Value in Health*, 2007. 10(1): p. 61-72.
59. McKenna, C., et al., Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis. *Health Technology Assessment (Winchester, England)*, 2009. 13(24): p. iii-iv, ix-xi, 1-90.

60. Grutters, J.P., et al., The cost-effectiveness of particle therapy in non-small cell lung cancer: exploring decision uncertainty and areas for future research. *Cancer Treat Rev*, 2010. 36(6): p. 468-76.
61. Fox, M., et al., The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model. *Health Technology Assessment (Winchester, England)*, 2007. 11(47): p. iii-iv, ix-248.
62. Rodgers, M., et al., Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*, 2008. 12(34): p. iii-iv, xi-xiii, 1-198.
63. McKenna, C., et al., A systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for postmyocardial infarction heart failure. *Health Technology Assessment (Winchester, England)*, 2010. 14(24): p. 1-162.
64. Griebisch, I., et al., Comparing the clinical and economic effects of clinical examination, pulse oximetry, and echocardiography in newborn screening for congenital heart defects: a probabilistic cost-effectiveness model and value of information analysis. *International Journal of Technology Assessment in Health Care*, 2007. 23(2): p. 192-204.
65. Karnon, J., Planning the efficient allocation of research funds: an adapted application of a non-parametric Bayesian value of information analysis. *Health Policy*, 2001. 61(3): p. 329-47.
66. Rogowski, W., et al., The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis. *Health Technology Assessment (Winchester, England)*, 2009. 13(31): p. iii-iv, ix-xi, 1-77.
67. Basu, A. and D. Meltzer, Value of information on preference heterogeneity and individualized care. *Medical Decision Making*, 2007. 27(2): p. 112-27.
68. Claxton, K., et al., A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technology Assessment (Winchester, England)*, 2004. 8(31): p. 1-103, iii.
69. Colbourn, T., et al., Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses. *Health Technology Assessment (Winchester, England)*, 2007. 11(29): p. 1-226, iii.
70. Colbourn, T.E., et al., Preventive strategies for group B streptococcal and other bacterial infections in early infancy: cost effectiveness and value of information analyses. *BMJ*, 2007. 335(7621): p. 655.
71. Bansback, N., et al., Statin therapy in rheumatoid arthritis: a cost-effectiveness and value-of-information analysis. *Pharmacoeconomics*, 2009. 27(1): p. 25-37.
72. Galani, C., et al., Uncertainty in decision-making: value of additional information in the cost-effectiveness of lifestyle intervention in overweight and obese people. *Value in Health*, 2008. 11(3): p. 424-34.
73. Rojnik, K. and K. Naversnik, Gaussian process metamodeling in Bayesian value of information analysis: a case of the complex health economic model for breast cancer screening. *Value in Health*, 2008. 11(2): p. 240-50.
74. Hassan, C., et al., Value-of-information analysis to guide future research in colorectal cancer screening. *Radiology*, 2009. 253(3): p. 745-52.
75. Peck, S.C. and R. Kavet, Research strategies for magnetic fields and cancer. *Risk Analysis*, 2005. 25(1): p. 179-88.
76. Wailoo, A.J., et al., Cost-effectiveness and value of information analyses of neuraminidase inhibitors for the treatment of influenza. *Value in Health*, 2008. 11(2): p. 160-71.
77. Black, C., et al., The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*, 2009. 13(52): p. 1-148.

78. Grutters, J.P., et al., Decision-Analytic Modeling to Assist Decision Making in Organizational Innovation: The Case of Shared Care in Hearing Aid Provision. *Health Serv Res*, 2008.
79. Speight, P.M., et al., The cost-effectiveness of screening for oral cancer in primary care. *Health Technology Assessment (Winchester, England)*, 2006. 10(14): p. 1-144, iii-iv.
80. Bojke, L., et al., Identifying research priorities: the value of information associated with repeat screening for age-related macular degeneration. *Medical Decision Making*, 2008. 28(1): p. 33-43.
81. Castelnovo, E., et al., The cost-effectiveness of testing for hepatitis C in former injecting drug users. *Health Technology Assessment (Winchester, England)*, 2006. 10(32): p. iii-iv.
82. Robinson, M., et al., Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling. *Health Technology Assessment (Winchester, England)*, 2005. 9(27): p. iii-iv.
83. Philips, Z., K. Claxton, and S. Palmer, The half-life of truth: what are appropriate time horizons for research decisions? *Medical Decision Making*, 2008. 28(3): p. 287-99.
84. Smith, K.J., et al., Cost-effectiveness of alternative outpatient pelvic inflammatory disease treatment strategies. *Sex Transm Dis*, 2007. 34(12): p. 960-6.
85. Garside, R., et al., Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. *Health Technology Assessment (Winchester, England)*, 2006. 10(8): p. 1-142.
86. Smits, M., et al., Minor head injury: CT-based strategies for management--a cost-effectiveness analysis. *Radiology*, 2010. 254(2): p. 532-40.
87. Hewitt, C., et al., Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis. *Health Technology Assessment (Winchester, England)*, 2009. 13(36): p. 1-145, 147-230.
88. Kee, F., et al., The value of positron emission tomography in patients with non-small cell lung cancer. *Eur J Radiol*, 2010. 73(1): p. 50-8.
89. Grant, A., et al., The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastroesophageal reflux disease - a UK collaborative study. The REFLUX trial. *Health Technology Assessment (Winchester, England)*, 2008. 12(31): p. 1-181, iii-iv.
90. Bojke, L., E. Hornby, and M. Sculpher, A comparison of the cost effectiveness of pharmacotherapy or surgery (laparoscopic fundoplication) in the treatment of GORD. *Pharmacoeconomics*, 2007. 25(10): p. 829-41.
91. Karnon J, Carlton J, et al. Informing disinvestment through cost-effectiveness modelling: is lack of data a surmountable barrier? *Appl Health Econ Health Policy*. 2009;7(1):1-9.
92. Hunink, M.G., Decision making in the face of uncertainty and resource constraints: examples from trauma imaging. *Radiology*, 2005. 235(2): p. 375-83.
93. Noorani, H.Z., et al., Priority setting for health technology assessments: a systematic review of current practical approaches. *International Journal of Technology Assessment in Health Care*, 2007. 23(3): p. 310-5.
94. INAHTA. Global Networking for Effective Healthcare, <http://inahta.episerverhotell.net/News-archive/Website-Launch/> [Accessed: 2012 Feb 10].
95. AHRQ, Fiscal Year 2011, D. Justification of Estimates for Appropriations Committees, Editor. 2011.
96. Husereau, D., M. Boucher, and H. Noorani, Priority setting for health technology assessment at CADTH. *International Journal of Technology Assessment in Health Care*, 2010. 26(3): p. 341-7.
97. CADTH, 2008-2009 Annual Report, C.A.f.D.a.T.i. Health., Editor. 2010.
98. NICE, Topic Selection Programme Process Manual, N.I.f.H.a.C. Excellence., Editor. 2008.
99. NIHR, Identifying and prioritising HTA research., N.H.T.A. programme., Editor.
100. USPSTF. U.S. Preventive Services Task Force (USPSTF) Procedure Manual. Section 2: Topic Selection, Prioritization, and Updating. 2008; www.uspreventiveservicestaskforce.org/uspstf08/methods/procmmanual2.htm [Accessed: 2012 Feb 10].

101. World Health Organization. WHO Guideline Review Committee, WHO Handbook for Guideline Development. Geneva, 2010.
102. Oxman, A.D., H.J. Schunemann, and A. Fretheim, Improving the use of research evidence in guideline development: 2. Priority setting. *Health Res Policy Syst*, 2006. 4: p. 14.
103. Cochrane. Priority-Setting Workshop, . in 16th Cochrane Colloquium: Evidence in the Era of Globalisation. 2008. Freiburg, Germany.
104. Oortwijn, W.J., et al., Priority setting for health technology assessment in The Netherlands: principles and practice. *Health Policy*, 2002. 62(3): p. 227-42.
105. SIGN, SIGN 50: A guideline developer's handbook, S.I.G. Network, Editor. 2008.
106. SBU. Selecting Topics www.sbu.se/en/About-SBU/Selecting-topics/ [Accessed: 2012 Feb 10].
107. Goeree, R., et al., Health technology assessment and primary data collection for reducing uncertainty in decision making. *J Am Coll Radiol*, 2009. 6(5): p. 332-42.
108. Rico, R. and J. Asua, The prioritization of evaluation topics of health - primary research (Structured abstract). *The Cochrane Library Health Technology Assessment Database* 2008(1).
109. Neumann, PJ. Emerging lessons from the drug effectiveness review project. *Health Aff (Millwood)*, 2006. 25(4): p. W262-71.
110. McDonagh, M., Drug Effectiveness Review Project (DERP): Systematic Review Methods and Procedures. 2010.
111. Noorani, H., Personal Communication. Topic Identification (AHRQ Cancer Comparative Effectiveness Review).
112. Palmer, A.J., et al., Validation of the CORE Diabetes Model against epidemiological and clinical studies. *Curr Med Res Opin*, 2004. 20 Suppl 1: p. S27-40.
113. Palmer, A.J., et al., The CORE Diabetes Model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin*, 2004. 20 Suppl 1: p. S5-26.
114. The Diabetes Prevention Program: baseline characteristics of the randomized cohort. The Diabetes Prevention Program Research Group. *Diabetes Care*, 2000. 23(11): p. 1619-29.
115. AHRQ. EHC Scientific Resource Center Secure Website. 2011; Access permission required. www.kpchr.org/ehc/ [Accessed: 2012 Feb 10].
116. National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and Management, October 16-18, 2000.
117. Hegge KA, Horning KK, et al. Sapropterin: a new therapeutic agent for phenylketonuria. *Ann Pharmacother*. 2009 Sep;43(9):1466-73.
118. Jacobsen L, Niggemann B, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62(8):943-8.
119. Friedman BW, Kapoor A, et al. The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials. *Ann Emerg Med*. 2008;52(6):705-13.
120. French, J.A. and T.A. Pedley, Clinical practice. Initial management of epilepsy. *N Engl J Med*, 2008. 359(2): p. 166-76.
121. Keene, D.L., A systematic review of the use of the ketogenic diet in childhood epilepsy. *Pediatr Neurol*, 2006. 35(1): p. 1-5.
122. Mandel, A., et al., Medical costs are reduced when children with intractable epilepsy are successfully treated with the ketogenic diet. *J Am Diet Assoc*, 2002. 102(3): p. 396-8.
123. Kossoff, E.H., International consensus statement on clinical implementation of the ketogenic diet: agreement, flexibility, and controversy. *Epilepsia*, 2008. 49 Suppl 8: p. 11-3.
124. Olfson, M. and S.C. Marcus, National trends in outpatient psychotherapy. *Am J Psychiatry*, 2010. 167(12): p. 1456-63.
125. Mojtabai, R. and M. Olfson, National trends in psychotherapy by office-based psychiatrists. *Arch Gen Psychiatry*, 2008.65(8): p. 962-70.
126. Institute of Medicine (U.S.). Committee on Comparative Effectiveness Research Prioritization., Initial national priorities for comparative effectiveness research. 2009, Washington, D.C.: National Academies Press. xxiii, 227 p.
127. Gaede, P., et al., Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*, 2003. 348(5): p. 383-93.

128. Jones, A.P., et al., Understanding diabetes population dynamics through simulation modeling and experimentation. *Am J Public Health*, 2006. 96(3): p. 488-94.
129. A.D.A.. Diabetes Statistics. <http://www.diabetes.org/diabetes-basics/diabetes-statistics/> 2011 [Accessed: 2012 Feb 10].
130. Simon, K.C., et al., Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology*, 2007. 69(17): p. 1688-95.
131. Sowers, J.R., M. Epstein, and E.D. Frohlich, Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*, 2001. 37(4): p. 1053-9.
132. U.S. National Cancer Institute, Cancer Intervention and Surveillance Modeling Network (CISNET) <http://cisnet.cancer.gov/> [Accessed: 2012 Feb 10].
133. U.S. National Heart Lung and Blood Institute. NHLBI Working Group on Value of Information Modeling [Executive Summary]. 2010. www.nhlbi.nih.gov/meetings/workshops/info-modeling.htm [Accessed: 2012 Feb 10].
134. A.D.A.. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. *The DCCT Research Group. Diabetes*, 1986. 35(5): p. 530-45.
135. Zhou, H., et al., A computer simulation model of diabetes progression, quality of life, and cost. *Diabetes Care*, 2005. 28(12): p. 2856-63.
136. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia*, 1991. 34(12): p.877-90.
137. AHRQ, HCUPnet, Healthcare Cost and Utilization Project. <http://hcupnet.ahrq.gov/> [Accessed: 2012 Feb 10].
138. Quon, B.S., W.Q. Gan, and D.D. Sin, Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. *Chest*, 2008. 133(3): p. 756-66.
139. Cox, C.E., et al., Differences in one-year health outcomes and resource utilization by definition of prolonged mechanical ventilation: a prospective cohort study. *Crit Care*, 2007. 11(1): p. R9.
140. Statistics, U.S.N.C.f.H., National Vital Statistics Reports (NVSr), in U.S. Census Bureau, Statistical Abstract of the United States. 2011. p. 78.
141. Stanford RH, Shen Y, McLaughlin T. Cost of Chronic Obstructive Pulmonary Disease in the Emergency Department and Hospital: An Analysis of Administrative Data from 218 US Hospitals. *Treat Respir Med*. 2006;5(5):343-9.
142. Keenan, S.P., et al., Noninvasive positive pressure ventilation in the setting of severe, acute exacerbations of chronic obstructive pulmonary disease: more effective and less expensive. *Crit Care Med*, 2000. 28(6): p. 2094-102.
143. Esteban A, Ferguson ND, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med*. 2008 Jan 15;177(2):170-7.
144. Ram FSF, Picot J, et al Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD004104. DOI: 10.1002/14651858.CD004104.pub3.
145. OANDA. Historical Exchange Rates. 2011.
146. Labor, U.D.o. Bureau of Labor Statistics, CPI Inflation Calculator. http://www.bls.gov/data/inflation_calculator.htm [Accessed: 2012 Feb 10].
147. Bank, W. Data: United States. 2011; <http://data.worldbank.org/country/united-states> [Accessed: 2012 Feb 10].
148. Whitlock EP and Eder M. EHC Topic Selection: Potential Role of Value of Information Analyses. Agency for Healthcare Research and Quality, EPC Meeting [presentation], 2011
149. Bojke, L., et al., Eliciting distributions to populate decision analytic models. *Value in Health*, 2010. 13(5): p. 557-64.

Appendix A. Search Criteria from Previous VOI and Priority-Setting Reports

Myers, E., et al., Evaluating the Potential Use of Modeling and Value-of-Information Analysis for Future Research Prioritization Within the Evidence-based Practice Center Program. 2011, AHRQ Publication No. 11-EHC030-EF.: Rockville, MD [20].

Search #1: Designed to identify articles addressing methods of priority setting, using the following search strategy (no date restrictions, search date October 22, 2010): ("Research"[Mesh] OR "Health Services Research"[Mesh]) AND (exercise[title/abstract] OR tool[title/abstract] OR tools[title/abstract] OR model[title/abstract] OR models[title/abstract] OR method[title/abstract] OR methods[title/abstract] OR "models, theoretical"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "resource allocation"[MeSH Terms] OR "investments/economics"[MeSH Terms]) AND ("health priorities"[MeSH Terms] OR "priority setting"[title/abstract] OR "research priorities"[title/abstract] OR "research priority"[title/abstract])

Search #2: Designed to identify articles specifically addressing VOI, using the following search strategy (no date restrictions, search date December 1, 2010): "value of information"[title/abstract] AND (("Decision Making"[Mesh] OR "Decision Theory"[Mesh]) OR ("Research"[Mesh] OR "Health Services Research"[Mesh]) OR research[title/abstract])

Meltzer, D., et al., Minimal Modeling Approaches to Value of Information Analysis for Health Research. Methods Future Research Needs Report No. 6. 2011, AHRQ Publication No. 11-EHC062-EF.: Rockville, MD [21].

Search #1: We searched the MEDLINE database for English-language publications from January 1, 1990 to June 3, 2010, using the following exact search terms (in all fields): "value of information," "value of additional information," "value of information analysis," "expected value of perfect information," "EVPI," "expected value of partial perfect information," "EVPPI," "Bayesian approach to uncertainty," or "value of research."

Search #2: Our grey literature search was limited to Internet sites of different health technology assessment (HTA) organizations and institutions in the United States, Canada, the U.K., Australia/New Zealand, The Netherlands, and Germany. Web sites were searched for: (1) VOI methods guidance intended to aid authors in completing a HTA, and (2) examples of VOI applications in individual HTA and systematic review publications.

Appendix B. Data Extraction Form for VOI Studies

Reference(s)				
Approach to Calculating VOI	Full Modeling / Minimal Modeling, Subtype 'No Modeling' / Minimal Modeling, Subtype 'Limited Modeling' / No Modeling / Maximal Modeling, specify:			
	Decision Tree / Markov Model / NOT STATED / Other, specify:			
	Development of New Model / Extension or Adaptation of Existing Model / Other, specify:			
	Single / Multiple Technologies	Single / Multiple Disease(s)	Single / Multiple Domain(s)	
Use of Evidence from Systematic Review(s) for VOI Calculations	NOT STATED / Not Done / Done, specify:			
Application	Comparison:			
	Setting:	US / UK / Canada / Australia / The Netherlands / Other, specify:		
	Perspective:	Societal / Third Party Payer / Patient / NOT STATED / Other, specify:		
	Time Horizon:	Lifetime / Other, specify:		
	Year of Analysis:	Specify:		
	Discounting:	Costs	NOT STATED / STATED, specify:	
		Benefits	NOT STATED / STATED, specify:	
Purpose of VOI	Analysis of Decision Uncertainty / Analysis of Uncertainty in Element(s) of Decision / Identification of Research Priorities / Generation of Topics for Research / Value in Specific Research / Design of Specific Research / NOT STATED / Other, specify:			
Consideration of Information on Conceptual Elements when Calculating VOI	Benefits of Decision	NOT STATED / STATED, specify:		
	Reduction in Uncertainty:	NOT STATED / STATED, specify		
	Probability of Implementation:	NOT STATED / STATED, specify		
	Durability of Information:	NOT STATED / STATED, specify		
	Size of Patient Population:	NOT STATED / STATED, specify		
	Discounting:	NOT STATED / STATED, specify		
	Existing VOI studies	NOT STATED / STATED, specify		
VOI Results	EVI / EVSI / EVPI / EVPPI / ENBS / Other, specify: pEVI / pEVSI / pEVPI / pEVPPI / pENBS / Other, specify: Specification of results:			
Conclusions on VOI	Specify:			
Application of VOI Results to Prioritize New Evidence Synthesis Research, including Systematic Review(s)	NOT STATED / Not Done / Done, specify:			
Consideration of Information on Conceptual Elements when Interpreting VOI Results	NOT STATED / Not Done / Done, specify:			
Comparison of VOI Results with Other Approaches to Research Prioritization	NOT STATED / Not Done / Done, specify:			
Comparison of VOI Results with Other VOI Studies	NOT STATED / Not Done / Done, specify:			

EVI: expected value of information, EVSI: expected value of sample information; EVPI: expected value of information; EVPPI: expected value of partial perfect information; ENBS: expected net benefit of sampling; pEVI: population expected value of information, pEVSI: population expected value of sample information; pEVPI: population expected value of information; pEVPPI: population expected value of partial perfect information; pENBS: population expected net benefit of sampling

Appendix C. Extracted Data on Clinically Related VOI Applications (N=72) in Value of Information Studies (M=77)

Reference(s)	[22]	[23]	[24]
Approach to Calculating VOI	<ul style="list-style-type: none"> - Minimal Modeling, Subtype "Limited Modeling" [i.e., LYs gained (long term) modeled using DEALE method] - NOT STATED, NOT STATED, newly developed - Single technology, single disease, within single clinical domain 	<ul style="list-style-type: none"> - Minimal Modeling, Subtype "Limited Modeling" [i.e., QALYs modeled by mapping from EPDS scores to utility values (SF-6D) and multiplying these values by appropriate time period, based on PoNDER trial data] - Simulation/bootstrapping, NA, newly developed - Single technology, single disease, within single clinical domain 	<ul style="list-style-type: none"> - Minimal Modeling, Subtype "Limited Modeling" [i.e., LYs saved modeled using modified DEALE method] - Equation-based computations, NA, newly developed - Single technology, single disease, single clinical domain
Use of Systematic Review(s)	NOT STATED	Done, systematic review was performed on clinical efficacy of group cognitive behavior therapy (gCBT)	Not Done, trial evidence was used
Application	Lung-volume-reduction surgery (LVRS) versus medical therapy (MT) for patients with severe emphysema	gCBT versus routine primary care for women with postnatal depression (PND)	Comparison of 5 trials in cardiovascular medicine (LRC, RCT-portion of CASS, MRFIT, ISAM, Canadian aspirin in unstable angina trial)
Setting	U.S.	U.K.	US
Perspective	NIH / CMS	NHS	NOT STATED
Primary Purpose of VOI	To evaluate potential utility of EVI in informing decision to fund NETT [demonstration of VOI methods]	NOT STATED	NOT STATED [demonstration of method for estimating cost-effectiveness of proposed trials]
Time Horizon, Year of Analysis, Discounting	10 years, 1996, 3% (both costs and effects)	10 years, 2008, NOT STATED	NOT STATED, NOT STATED, NOT STATED
Pre-Conceptual VOI:			
Difference in Benefits	No expected survival benefits, more treatment costs and more QoL for LVRS versus MT [multiple references]	Reduction of physician contact time and increase in number of available places for treatment in gCBT versus individual CBT [no reference]	NOT STATED
Reduction in Uncertainty	NOT STATED	NOT STATED	NOT STATED
Probability of Implementation	NOT STATED	NOT STATED	All patients in target population receive intervention with positive trial [assumption]
Durability of Information	10 years [pre-NETT survey]	10 years [assumption]	NOT STATED
Size of Patient Population	20k LVRS procedure per year [assumption]	120k women with PND per year [Office for National Statistics, 2005; Morrell et al., 2009]	15k – 5M per year [no reference]
Discounting	NOT STATED	NOT STATED	NOT STATED
Existing VOI Studies	NOT STATED	NOT STATED	NA
VOI Results	<ul style="list-style-type: none"> - pEVPI* = \$46.0M - pEVS† = \$41.0M - pENBS* = -\$19.0M, SS = 1250 per arm * λ = \$50k/QALY 	<ul style="list-style-type: none"> - EVPI* = £53.50, pEVPI* = £64M - EVPP† = £26.59 for costs of gCBT, £22.70 for gradient of relationship between EPDS and SF-6D * λ = £30k per QALY 	- ICERs of trials = \$5461-102k per LY
Conclusion on VOI	Some doubt that investing time and effort in EVI analysis would have altered decision process about trial funding	pEVPI would sufficiently cover costs of undertaking further research to obtain more robust data	ICERs of proposed trials are considerably smaller than ICERs of interventions with proven effectiveness
Prioritization of Systematic Review(s)	Not Done, specific to NETT	NOT STATED	Not Done, specific to trials
Post-Conceptual VOI	NOT STATED	Implementation: Implications in terms of effectiveness and cost of women wishing to move from individual to group treatment and vice versa should be assessed Other: no comparison is made with individual CBT	Implementation: Dissemination of intervention after successful positive trials is more complicated than 0-100% function Other: Variation across trials in ICERs is associated with choice of one design feature, i.e., clinically important difference
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NA
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

QALY: quality-adjusted life year; LY: life-year; λ: cost-effectiveness threshold; NA: not applicable; DEALE: Declining Exponential Average Life Expectancy; EPDS: Edinburgh Postnatal Depression Score; EVPI: expected value of perfect information; pEVPI: population expected value of perfect information; pEVS†: population expected value of sample information; pENBS: population expected net benefit of sampling; EVPP†: expected value of partial perfect information; pEVPP†: population expected value of partial perfect information; SS: sample size; ICER: incremental cost-effectiveness ratio; NIH: National Institute of Health; CMS: Centers for Medicaid and Medicare Services; NHS: National Health Services; NETT: National Emphysema Treatment Trial; LRC: Lipid Research Clinics-Coronary Primary Prevention Trial; CASS: Coronary Artery Surgery Study; MRFIT: Multiple Risk Factor Intervention Trial; ISAM: Intravenous Streptokinase in Acute Myocardial Infarction Trial; QoL: quality-of-life

Reference(s)	[25]	[14]	[26]
Approach to Modeling	- Minimal Modeling, Subtype "Limited Modeling" [i.e., LYs gained modeled using exponential distributions] - Simulation/bootstrapping, NOT STATED, newly developed - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "Limited Modeling" [i.e., LYs gained modeled using pooled estimates from meta-analysis; incidence: distribution of survival curves and steady-state lifetime prevalence] - Simulation/bootstrapping, cohort analysis, newly developed - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "Limited Modeling" [i.e., LYs gained modeled using exponential (constant hazard) distribution, with mean survival from REMATCH (in OMM) and separate distributions for LVAD failures/successes] - Equation-based computations, NA, newly developed - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Done, systematic reviews were performed on clinical effectiveness and cost-effectiveness of liposomal doxorubicin for second-line treatment of advanced ovarian cancer, after failure of platinum-based regimens	Not Done, evidence was used from CATIE trial	Not Done, evidence was used from REMATCH trial
Application	Liposomal doxorubicin versus topotecan as second-line treatment in patients with advanced ovarian cancer	Perphenazine (first-generation antipsychotics) versus all second-generation antipsychotics for patients with schizophrenia	Left ventricular assist devices (LVADs) implantation optimal medical management (OMM) in patients with end-stage heart failure (ESHF)
Setting	U.K.	U.S.	U.K.
Perspective	NHS	NIH	Health care provider
Primary Purpose of VOI	Not Stated	To calculate expected value of research to further reduce uncertainty about costs and benefits of first- and second-generation antipsychotics and implications for design of future studies in area	To assess value of discovering actual size of survival benefit in LVADs with OMM
Time Horizon, Year of Analysis, Discounting	5 years, 2000, 6% (both costs and effects)	Lifetime, 2002, 3% (both costs and effects)	10 years, 2007, 3% (both costs and effects)
Pre-Conceptual VOI:			
Difference in Benefits	Non-significant difference in majority of clinical outcomes between liposomal doxorubicin and topotecan [Gordon et al., 2001; Schering-Plough, 2001], with significantly less costs for the first [Smith et al., 2001; Schering-Plough, 2001]	Diminished risk of extrapyramidal symptoms and costliness in second-generation antipsychotics, with tendency of some second-generation drugs to produce weight gain and blood-lipid abnormalities [CATIE trial]	Evidence of efficacy and effectiveness for first-generation device is convincing, but assessments of cost-effectiveness of treatment compared with OMM was unfavorable [Rose et al., 2001; Rawlins and Culyer, 2004; Anon, 2004]
Reduction in Uncertainty	NOT STATED	Uncertainties in effectiveness in controlling psychotic symptoms, and some evidence cognition improvement in second-generation antipsychotics [CATIE trial]	Second-generation nonpulsatile pumps offer good prospects [Kirkin and Holman, 2006], and third-generation pumps can generate significant additional health benefit [Hoshi et al., 2006].
Probability of Implementation	NOT STATED	Not Stated	NOT STATED
Durability of Information	5 years [no reference]	30 years [no reference]	5 years [no reference(s)]
Size of Patient Population	3000 patients per year [no reference]	52.6k [CATIE trial]	15k patient with ESHF per year [Dominguez et al., 1990]
Discounting	6%	NOT STATED	3.5% [no reference(s)]
Existing VOI Studies	NOT STATED	NOT STATED	NOT STATED
VOI Results	- EVPI* = £800, pEVPI* = £10.7M * λ = £30k per LY	- pEVPI* = \$308B - pENBS* = \$13.8B, SS = 4000-4500 per arm * λ = \$50k per QALY	- EVPI* = £6, pEVPI* = £775k * λ = £30k per QALY, device costs = £60k [Siegenthaler et al., 2005]
Conclusion on VOI	Appropriately designed trial could potentially represent good value for money with collection of utilities likely to be important.	Future research is likely to be of immense value, particularly relating uncertainty on effects of treatments on costs, and very large sample sizes will be needed to address such uncertainty.	A trial of second-generation LVADs would represent value for money in UK setting
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	Not Stated
Post-Conceptual VOI	Benefits differences: QoL is not considered in the analysis	Benefits differences: medication switching in CATIE and treatment algorithms are not considered in analysis	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

QALY: quality-adjusted life year; LY: life-year; λ: cost-effectiveness threshold; NA: not applicable; EVPI: expected value of perfect information; pEVPI: population expected value of perfect information; pENBS: population expected net benefit of sampling; SS: sample size; NIH: National Institute of Health; CMS: Centers for Medicaid and Medicare Services; NHS: National Health Services; QoL: quality-of-life; CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness; REMATCH: Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart Failure; QoL: quality of life.

Reference(s)	[27[a]]	[27[b]]	[27 [c]]
Approach to Modeling	- Minimal Modeling, Subtype "Limited Modeling" [i.e., scenario analysis, varying assumptions around trial evidence and implementation of CMSW service] - Equation based computations, NA, NA - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "Limited Modeling" [i.e., scenario analysis, varying assumptions around trials evidence and implementation of stabilization protocol] - Equation based computations, NA, NA - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "Limited Modeling" [i.e., scenario analysis, varying trial evidence and implementation of early elective surgery] - Equation based computations, NA, NA - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Application	Postnatal midwifery support service and standard current midwifery visits versus midwifery visits alone	Pre-hospital intravenous fluid replacement versus stabilization alone in adults with serious trauma	Early surgery versus a period of ultrasound surveillance for patients aged 60–76 years with small AAAs
Setting	U.K.	U.K.	U.K.
Perspective	NOT STATED	NHS	NHS
Primary Purpose of VOI	NOT STATED	Not Stated	
Time Horizon, Year of Analysis, Discounting	5 years, 1994, 6% (costs) and 2% (effects)	10 years, 1998, NOT STATED	5/10 years, 1990, NOT STATED
Pre-Conceptual VOI:	<p>Difference in Benefits Extra costs for CMSW services and trial [no reference], point improvement in GHP profile of SF-36 [assumptions, scenario analyses] Scenarios are weighted [assumptions]</p> <p>Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population 6114 maternities per year in health authority [UK Birth Statistics, 1995]</p> <p>Discounting Existing VOI Studies 2% [for trial costs] NA</p>	<p>Extra costs for stabilization protocol and trial [no reference], reduction in patient mortality [assumptions, scenario analyses] Scenarios are weighted [assumptions]</p> <p>Different implementation scenarios for trial outcomes and no trial [assumptions, scenario analyses] 10 years [assumption] Number of trauma patients treated by a non-metropolitan ambulance service [no reference] NOT STATED NA</p> <p>NOT STATED NA</p>	<p>Extra costs for surgery [reference to literature], reduction in patient mortality and improvement in QoL [assumptions, scenario analyses] Scenarios are weighted [assumptions]</p> <p>Different implementation scenarios for trial outcomes and no trial [assumptions, scenario analyses] 5/10 years [assumptions] 2000 [no reference]</p> <p>NOT STATED NA</p>
VOI Results	- ICER of trial: £2-3.50/ per +1-point GHP profile of SF-36	- ICER of trial: £3000-4330/life saved	- ICER of trial: £20k/life-year saved
Conclusion on VOI	Trial should be funded, but with design changes to 1) detect a significant change in breast-feeding rates or in postnatal depression; and 2) consider subgroups of women at relatively high risk	Trial would be cost-effective when considering predicted reductions in mortality	Expected payback to trial is marginally positive, with expected small savings in both life and costs
Prioritization of Systematic Review(s)	Not Done, specific to trial	Not Done, specific to trial	Not Done, specific to trial
Post-Conceptual VOI	NA	NA	NA
Comparison with Other VOI Studies	NA	NA	NA
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

CMSW: community midwifery support worker; NA: not applicable; AAAs: abdominal aortic aneurysms; GHP: General Health Perception; QoL : quality-of-life; ICER: incremental cost-effectiveness ratio.

Reference(s)	A: [28[a)]; B: 29; C: [30[a)]; D: [31]; E: [13[a)]	F: 28[b]; C: 30[a]	[13[b)]
Approach to Modeling	- Minimal Modeling, Subtype "No Modeling" [i.e., direct measurement of QALYs] - Equation-based computations, parametric, NA - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "No Modeling" [i.e., direct measurement of QALYs] - Equation-based computations, parametric, NA - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "No Modeling" [i.e., direct measurement of dyspepsia symptoms] - Equation-based computations, parametric, NA - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Not Done, data were used from trial [Hutton et al., 2003]	Not Done, data were used from trial [Tannock et al., 1996; Bloomfield et al., 1998]	Not Done, data were used from trial [Chiba et al., 2002]
Application	Early (week 34) versus late (week 37) external cephalic version (ECV) in pregnant women presenting in breech position	Prednisone plus mitoxantrone versus prednisone alone in patients with hormone-resistant prostate cancer	Omeprazole plus metronidazole/clarithromycin versus omeprazole plus placebos in patients with dyspepsia
Setting	A,B,C,E: North America; D: U.S., U.K. and Australia	Canada	Canada
Perspective	All: Societal	Societal	Societal
Primary Purpose of VOI	NOT STATED [Demonstration of methods A+C: for sample size calculations; B: for delaying decision making; D: for global trial design; and E: for VOI with imperfect implementation]	NOT STATED [Demonstration of methods for sample size calculations]	NOT STATED [Demonstration of methods for VOI with imperfect implementation]
Time Horizon, Year of Analysis, Discounting	All: 20 years. NOT STATED, A: NOT DONE / B,C,D,E: NOT STATED	NOT STATED, NOT STATED, F: NOT DONE / C: NOT STATED	12 months, 1999, NA
Pre-Conceptual VOI:			
Difference in Benefits	QALYs and costs for comparators are given, and calculated for INBs [Hutton et al., 2003]	QALYs and costs for comparators are given, and calculated for INBs [Tannock et al., 1996; Bloomfield et al., 1998]	Reduction in dyspepsia symptoms in omeprazole plus metronidazole/clarithromycin relative to omeprazole plus placebos [Chiba et al., 2002]
Reduction in Uncertainty	Variance and covariance in QALYs, costs and INBs are calculated [Hutton et al., 2003]	Variance and covariance in QALYs and costs is given, and calculated for INBs [Tannock et al., 1996; Bloomfield et al., 1998]	Variance and covariance in symptom reduction is calculated [Willan, 2004]
Probability of Implementation	A,B,C,D: NOT STATED E: Probability of implementation is portrayed as function of z-statistic [assumptions, sensitivity analysis]	NOT STATED	Probability of implementation is portrayed as function of z-statistic [assumptions, sensitivity analysis]
Durability of Information	A,B,C,E: 20 years [no reference] D: NOT STATED	NOT STATED	20 years [no reference]
Size of Patient Population	A: NOT STATED B,E: 50k [assumptions] C: 100k [assumptions] D: 50k (U.S.), 10k (U.K.), 3k (Australia) [assumptions] NOT STATED	F: 10k [assumption], C: 60k [assumption]	50k [no reference]
Discounting Existing VOI Studies	NOT STATED	NOT STATED NOT STATED	NOT STATED NOT STATED
VOI Results	A: pENG = \$0.7M, SS = 346/arm* B: pENG = \$0.4M, SS = 284/arm* ⁵ C: pENG = \$1.4M, SS = 155/arm (stage 1), 124/arm (stage 2)* D: Global pENG = 0, global SS = 0/arm (U.S.), 0, 0/arm (U.K.), \$0.9M, 339/arm (Australia) E: pENG = 38.2M, SS = 489/arm* [†] * λ = \$1000/non-caesarian delivery (U.S. and U.K.); \$750 (Australia) ⁵ Reversal cost = \$ 2.0 M [†] γ = 0.67, β = 2.33	F: pENG = \$0, SS = 0/arm* C: pENG = \$1.6M, SS = 66/arm (stage 1), 163/arm (stage 2)* * λ = \$20k per QALY	- pENG = \$8.0M, SS = 109 per arm * * λ = \$1000 per year without/minimal dyspepsia symptoms, γ: 0.67, β = 2.33
Conclusion on VOI	-	F: Prednisone plus mitoxantrone should be adopted based on current evidence; C: NOT STATED	NOT STATED
Prioritization of Systematic Review(s)	Not Done, recommendations specifically relate to trials	Not Done, recommendations specifically relate to trials	Not Done, recommendations specifically relate to trials
Post-Conceptual VOI	A,B,C,D,E: NOT STATED	NOT STATED	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	A,C: Comparison with results of frequentist approach to SS calculations B: Comparison with VOI calculations without delay option D: Comparison with VOI calculations for local trial design E: Comparison with VOI calculations with perfect implementation	Comparison with results of frequentist approach to sample size calculations	NOT STATED

QALY: quality-adjusted life year; INBs: incremental net benefits; λ: cost-effectiveness threshold; NA: not applicable; pENG: population expected net gain; SS: sample size,

Reference(s)	[32]	[33]	[34]
Approach to Modeling	- Minimal Modeling, Subtype "No Modeling" [i.e., direct measurement of risk of cardiovascular event] - Equation-based computations, NA, newly developed - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "No Modeling" [i.e., direct measurement of QALYs] - Simulation/bootstrapping, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "No Modeling" [i.e., direct measurement of LYs gained] - Simulation/bootstrapping, cohort simulation, newly developed - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Not Done, evidence used from HOPE study	Not Done, evidence used from trial [Goeree et al. 2002]	Not Done, evidence used from AFFIRM trial
Application	Ramipril (ACE inhibitor) versus management strategies of placebo in patient over 55 years at risk of heart disease	Comparison of seven different management strategies for GERD	Rate- versus rhythm-control treatments for persons with atrial fibrillation
Setting	U.S. and Canada	Canada	US
Perspective	Government/private donation-based or philanthropic agency	Provincial government payer	Third-party payer
Primary Purpose of VOI	To illustrate optimal sample size determination [Demonstration of application of VOI methods for SS calculations]	To show how decision uncertainty should be presented and interpreted [Demonstration of application of CEACs, CEAF and VOI methods]	To know at which particular realization decision uncertainty will resolve [Demonstration of impact of censoring adjustment on decision making]
Time Horizon, Year of Analysis, Discounting	4.5 years [HOPE study], NOT STATED, 3% (costs)	1 year, 2000, NA	5.65 years, 2002, 3% (both costs and effects)
Pre-Conceptual VOI:	Benefits of Decision Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI studies	NOT STATED NOT STATED NA NA NA NA NA NA	Rhythm-control was both more costly and less effective than rate-control [AFFIRM trial] NOT STATED NOT STATED 5 years [no reference] 500k [2.3M] [Go et al., 2001; Greenlee et al., 2005] 3% NOT STATED
VOI Results	- Threshold number of patients benefiting from technology = 4.8M (U.S.); 2.28M (Canada)* * λ = \$10k per cardiovascular event saved	- EVPI = \$14* * λ = \$50k per QALY	- pEVPI: \$23M* * λ = \$50k/life-year
Conclusion on VOI	NOT STATED	CEAF, along with EVPI, should be calculated to present optimal decision and decision uncertainty calculated; uncertainty can increase when probability of optimal option being cost-effective also increases.	Censoring adjustment may impact decision to fund additional research, because pEVPI varies with censoring scenarios
Prioritization of Systematic Review(s)	NOT STATED	NA	NOT STATED
Post-Conceptual VOI	NOT STATED Other VOI Studies: NOT STATED	NA Other VOI studies: NA	NOT STATED Other VOI studies: NOT STATED
Reflection on Other Methods for Research Prioritization	Done, VOI methods for calculating SS are compared with likelihood methods (test of hypothesis and confidence intervals) for doing so.	NA	NOT STATED

NA: not applicable; ACE: angiotensin converting enzymes; SS: sample size; λ : cost-effectiveness threshold; EVPI: expected value of perfect information; population expected value of perfect information; QALY: quality-adjusted life-year; LYs: life-years; AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management

Reference(s)	[35,92[a]]	[36]	[37]
Approach to Modeling	- Minimal Modeling, Subtype "No Modeling" [i.e., conversion of EuroQoL-scores into utility values using Dolan tariff] - Simulation/bootstrapping, parametric, newly developed - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "No Modeling" [i.e., conversion of EQ5D-scores to utilities using Dutch scoring algorithm] - Simulation/bootstrapping, cohort analysis, newly developed - Single technology, single disease, within single clinical domain	- Minimal Modeling, Subtype "No Modeling" [i.e., specificity and sensitivity of testing based on assumptions] - Equation-based computations, NA, newly developed - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Not Done, trial evidence was used [Nikken et al., 2005]	Not Done, trial evidence was used	Not Done, predictions were based on Lave-Omenn model [Omenn et al., 1995]
Application	Radiography and magnetic resonance (MR) imaging versus radiography alone in patients with acute knee trauma (in an ED setting)	Endovascular revascularization versus supervised exercise training for patients with intermittent claudication	National Toxicology Program (NTP) carcinogenicity test versus MultiCASE prediction of potential carcinogenic risk
Setting	The Netherlands (NL) / European Union (E.U.)	The Netherlands	U.S.
Perspective	Societal	Societal	NOT STATED
Primary Purpose of VOI	To help guide future outcomes research with use of prospective data from RCT	1) To design optimal study, and 2) To demonstrate VOI analysis of patient-level data from RCT to guide future research.	To determine features for carcinogenicity testing to be more economically efficient and socially justifiable judgments with testing than without testing
Time Horizon, Year of Analysis, Discounting	6 months, 2000, NA	12 months, 2005, NA	NOT STATED, 2001, NA
Pre-Conceptual VOI:	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI studies	6 month follow up of 189 patients revealed significant difference in costs and small transient significant difference in outcomes between [Nikken et al., 2005] See Benefits difference NOT STATED 10 years [assumption] 20k (NL) / 561k (EU) [assumptions] 3% NOT STATED	Improvement in QALYs and higher costs in revascularization versus exercise group [Spronk et al., 2008] Non-significant difference in net benefit in revascularization versus exercise group [Spronk et al., 2008] NOT STATED 5 years [assumption] 10k patients per year [assumption] 3% NOT STATED
VOI Results	- EVPI = €2.1*, pEVPI: €365k (NL) / €10.2M (E.U.)* - pENBS = NA (NL) / €3.8M, SS = 2500/arm (E.U.)* * λ = €80k/QALY	- pEVPI = €11.0M* - pENBS = €7.3M, SS = 475 per arm* * λ = €80k per QALY	- pEVPI = \$62.0M* * λ = \$1.0M per false positive and \$10.0M per false negative testing
Conclusion on VOI	Optimal study design involves trial with 3500 patients per arm, collecting data on QALYs, cost of overnight hospital stay, and friction costs	More research is justified with 1) optimal study collecting data on QALE and additional admission costs for 525 patients per arm, and 2) VOI analysis providing explicit framework to determine optimal SS and identify key parameters for design of future trials.	- If likelihood chemical is carcinogenic > 50%, use of rodent bioassay is more costly than classifying chemicals as carcinogens without further testing. - If concordance of rodent bioassay to true effect in humans < 70%, or likelihood of chemical being carcinogenic < 10%, social cost is less if classify all as noncarcinogenic. - If testing were not done, it would be necessary to implement an "as low as reasonably achievable" approach to exposure reduction.
Prioritization of Systematic Review(s)	Not Done, specific to trial design	NOT STATED	NOT STATED
Post-Conceptual VOI	Population and durability: Both annual population potentially benefiting from research and durability of technology are influential and uncertain Other clinical studies are expected to result in up to 100-fold higher VOI, with prioritization ultimately depending on portfolio of potential studies submitted to funding agency, VOI and research budget.	Decision uncertainty: not all available evidence pertaining to decision is considered as trial evidence is used ENBS can be compared with other (unrelated) study proposal, where study proposals with a higher ENBS should be reimbursed first and funding is justified for any study proposal with ENBS > 0.	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

EVPI: expected value of perfect information; pEVPI: population expected value of perfect information; pENBS: population expected net benefit of sampling; SS: sample size; QALY: quality-adjusted life-year; QALE: quality-adjusted life-expectancy.

Reference(s)	[38]	[39]	[40]
Approach to Modeling	- Full modeling - Markov model, NOT STATED, existing model published earlier by authors - Single technology, single disease, within single clinical domain	- Full modeling - Decision tree, NOT STATED, updating of existing model - Single technology, single disease, within single clinical domain	- Full modeling - Decision tree, cohort simulation, new model - Single technology, single disease, within clinical domain
Use of Systematic Review(s)	Not Done, evidence from multiple trials was used [Vincken et al., 2002; Casaburi et al., 2002; Brusasco et al., 2002]	Done, evidence was used from review on clinical efficacy of drug-eluting stents (DES) versus baremetal stents (BMS) [Bowen et al., 2005]	Not Done, data from trials were used [Christenson et al., 2004; Christenson et al., 2006]
Application	Comparison of bronchodilators (i.e., tiotropium, salmeterol or ipratropium) in moderate to very severe COPD	DES versus BMS in coronary artery disease	EPDR versus usual care (i.e., clinical judgment alone) for detecting ACS patients at emergency departments with chest discomfort
Setting	The Netherlands	Canada (Ontario)	Canada
Perspective	Health care	Third party payer	Ministry of Health
Purpose of VOI	To determine impact of actually collecting additional data on utilities on overall model uncertainty	To determine the value of continuing data collection beyond [Tu et al., 2007]	To aid decision to conduct further research to validate EDPR [Demonstration of use of VOI analysis]
Time Horizon, Year of Analysis, Discounting	5 years, 2001, 4% (costs), 1.5% (effects)	2 years, 2007, 5% (both costs and effects)	30 days, 2003, NA
Pre-Conceptual VOI:	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI studies	NOT STATED Paucity of existing data, generalizability of efficacy evidence [Bowen et al., 2005] NOT STATED 5, 10, 15 years [assumptions, sensitivity analysis] NOT STATED NOT STATED NOT STATED	NOT STATED Uncertainty about both cost and outcome parameters of EDPR exists NOT STATED 1, 2, 5 years [assumptions, sensitivity analysis] 500k per year [Heart and Stroke Foundation of Canada, 2000] 3% NOT STATED
VOI Results	- $EVPI_{\text{before data collection}}^* = \text{€}1985$, $EVPI_{\text{after data collection}}^* = \text{€}1077$ - EVPPI: highest for utilities, transition probabilities between COPD severity stages * $\lambda = \text{€}20k$ per QALY	- $pEVPI > 0$ for $\lambda > \$40k$ per QALY - EVPPI: highest for revascularization rates DES and BMS	- $pEVPI^* = \$CAD16.3M$ * $\lambda = \$CAD20k$ per QALY
Conclusion on VOI	VOI analysis identified parameters for which additional research is most worthwhile. After conducting additional research on utilities, EVPI was substantially reduced.	Continuation of data collection is worthwhile for $\lambda > \$40k$ per QALY, particularly focusing mortality in patients treated with DES or BMS	Health and monetary benefits of conducting further research into EDPR are likely to outweigh costs of conducting research, even in short-term
Prioritization of Systematic Reviews	NOT STATED	Not Done, specific in Field Evaluation Studies	NOT STATED
Post-Conceptual VOI	Decision uncertainty: some forms of uncertainty may not have been considered in analysis, e.g., new EQ-5D utilities from multinational trial, heterogeneity of COPD population, and disease state transitions. Other: Difference between EVPI and sum of EVPPIs complicates interpretation of VOI analysis	NOT STATED	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

COPD: Chronic Obstructive Pulmonary Disease; EPDR: Early Disposition Prediction Rule; ACS: acute coronary syndrome; EVPI: expected value of perfect information; EVPPI: expected value of partial perfect information; pEVPI: population expected value of perfect information; λ : cost-effectiveness threshold; QALY: quality-adjusted life-year

Reference(s)	[41]	[42]	[43]
Approach to Modeling	- Full modeling - Markov model, cohort simulation, previously published by authors - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, NOT STATED, previously developed by authors - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	NOT STATED	Done, for clinical outcomes data	NOT STATED
Application	Screening versus non-screening for abdominal aortic aneurysm	Temozolomide (TMZ) versus procarbazine, lomustine plus vincristine (PCV) chemotherapy for glioblastoma multiforme (GBM) and anaplastic astrocytoma	Entacapone versus usual therapy in advanced Parkinson's disease
Setting	Sweden	Finland	Canada
Perspective	Societal	Health care payer / Societal	Health care system / societal
Primary Purpose of VOI	To guide research priorities regarding policy issue of screening for AAAs [Demonstration of application of VOI methods]	To evaluate the value of new information for reducing uncertainty related to choice of treatment between TMZ and PCV	To aid in demonstrating the use of alternate methods (UNLI, single MCS, two-stage MCS, quadrature method, difference method) for estimating EVVPI and to allow replication of results if desired. [demonstration of methods for estimating EVVPI]
Time Horizon, Year of Analysis, Discounting	Lifetime, 2003, 3% (both costs and effects)	Lifetime, 2001, 5% (both costs and effects)	5 years, 2001, 5% (both costs and effects)
Pre-Conceptual VOI:			
Benefits of Decision	Screening reduces abdominal aortic aneurysm-related mortality in men [SBUAlert, 2005] Cost and effectiveness of screening program with a particular design (inviting 65-year-old males once) [SBUAlert, 2005] NOT STATED	NOT STATED No available data comparing cost-effectiveness of TMZ and PCV NOT STATED	NOT STATED NOT STATED NOT STATED
Reduction in Uncertainty	10 years [assumption] 40k (with 5% prevalence of AAA 5 in men > 65 ys) [Scott R et al., 1991, Vardulaki et al., 1998, Statistical Sweden, 2003]	10 years [assumption] 168 new cases of GBM, with 1000 high-grade gliomas, per year [using US estimates]	NOT STATED NOT STATED
Probability of Implementation	3%	5%	NOT STATED
Durability of Information	NOT STATED	NOT STATED	NOT STATED
Size of Patient Population			
Discounting			
Existing VOI Studies			
VOI Results	- pEVPI* = €300k - pEVVPI* = nearly all uncertainty stems from rupture probability * λ = €30k per QALY	- (maximum) pEVPI* ≈ €4.1M * λ = €32.4k per QALY	- EVVPI measures for alternative calculative methods (UNLI, single MCS, two-stage MCS, quadrature method, difference method)
Conclusion on VOI	Given information available on overall cost-effectiveness of screening, it appears unlikely that any further research regarding would be worthwhile.	Future research would potentially be cost-effective if costs of research were < €4.1 M	All measures for estimating EVVPI are subject to Monte Carlo error. EVVPI estimates converge to same value with increasing replications for the different methods
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Post-Conceptual VOI	Structural uncertainty: authors stated that this is not considered in analysis	NOT STATED	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	Done, Technical brief by SBU required more evidence of costs-effectiveness of screening, whereas VOI indicates that focusing on the probability of rupture seems to be most reasonable way of using research resources if more information should be acquired	NOT STATED	NOT STATED

pEVPI: population expected value of perfect information; pEVVPI: population expected value of partial perfect information; EVVPI: expected value of partial perfect information λ: cost-effectiveness threshold; QALY: quality-adjusted life-year; AAAs: abdominal aortic aneurysms

Reference(s)	[44]	[45,11[a]]	[46]
Approach to Modeling	- Full modeling - Markov model, cohort simulation, newly developed - Single technologies, single disease, within single clinical domain	- Full modeling - Decision tree, NOT STATED, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Decision tree, NOT STATED, newly developed - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Done, identification of RCT data from earlier systematic review of pentoxifylline (vs placebo) for venous leg ulcer [Jull et al., 2002], and meta-analysis on odds-ratio of healing	Done, meta-analyses of probability of 5% weight loss at 3 months, probability of 10% weight loss at 6 months, and weight loss at 12 months	Done, meta-analysis of clinical outcomes previously done by authors [Yakoub et al., 2008]
Application	Oral pentoxifylline versus placebo as an adjunct to compression for venous leg ulcers	Orlistat versus dietary management in treatment of obesity	Covered versus uncovered self-expanding metal stents (SEMS) for the palliation of malignant dysphagia
Setting	U.K.	U.K.	U.K.
Perspective	NHS	NHS	Third party payer
Purpose of VOI	a) To explore decision uncertainty regarding cost-effectiveness of oral pentoxifylline; b) to determine contribution of findings from trial [Dale et al., 1990] to reduce decision uncertainty regarding cost-effectiveness of pentoxifylline [i.e., posterior analysis]; c) to provide information regarding future research.	To inform decision about further research and establish value of reducing uncertainty surrounding individual parameters [Demonstration of VOI (and VOIM) methods]	To investigate and quantify the uncertainty associated with the results of our analysis
Time Horizon, Year of Analysis, Discounting	1 year, 2004, NA	1 year, NOT STATED, NA	1 year, NOT STATED, NA
Pre-Conceptual VOI:	Benefits of Decision	Pentoxifylline drug provides additional benefits to compression and is possibly effective for patients not receiving compression [Jull et al., 2002]	NOT STATED
	Reduction in Uncertainty	See Benefits differences	Quality of evidence of probabilities of weight loss, weight loss, utilities and costs is very low and substantial uncertainty surrounding these estimates exists [O'Meara, 2002].
	Probability of Implementation	NOT STATED	No impact (0%) evidence/information on implementation [Note: estimate of implementation (50%) used for VOIM analysis][TAR and guidance documents]
	Durability of Information	10 years [expert opinion]	8 years [no reference]
	Size of Patient Population	1.5 / 1000 prevalence (or 62k at any time) of venous leg in population > 18 years [Callam et al., 19983]	11k prevalent and 11k annual incidence [TAR and guidance documents]
	Discounting	6%	Done, rate: NOT STATED
	Existing VOI Studies	NOT STATED	NOT STATED
VOI Results	<i>Prior analysis (i.e., including [Dale et al., 1999])</i> - pEVPI = £128.2k, £127.1k, £126.7k for $\lambda = \text{£}0, \text{£}100, \text{£}500$ per QALY <i>Posterior analysis (i.e., including [Dale et al., 1999])</i> - pEVPI = low values for $\lambda = \text{£}0\text{-}2500$ per QALY	- EVPI* = £24, pEVPI = £2M, EVPI _{realizable} * = £0 for with $\lambda = \text{£}30.0k$ per QALY - pEVVPI = changes in HRQoL, due to modification in body weight ¹ , resource use ² with $\lambda = \text{£}21.4k$ per QALY (ICER) ¹ highest, ² relatively high	- pEVPI* = \$35.6k * $\lambda = \$50k$ per QALY
Conclusion on VOI	Posterior degree of uncertainty associated with use of does not justify conduct of further research. Pentoxifylline was already associated with large probability of being not only clinically but also cost effective, if not cost saving before [Dale et al., 1999]	pEVPI suggests further research may be required to support adoption of orlistat, but pEVVPIs indicate this may not need to have experimental design.	Further comparative analysis of currently available covered and uncovered SEMS has little value, although evaluating other palliative treatments for malignant dysphagia may be justified.
Prioritization of Systematic Review(s)	Not Done, recommendation are made specific to trials	Not Done, advice for observational surveys in HRQoL changes, and experimental designs in expected loss of body weight at 12 months	NOT STATED
Post-Conceptual VOI	Costs of research: £380k for [Dale et al., 1999]	Difference in benefits: Where INB are small, returns available from research are small.	Further research: cost of trial on clinical efficacy of covered SEMS will likely exceed maximum pEVPI
Comparison with Other VOI Studies	NOT STATED	pEVPI for zanamivir are higher than for orlistat due to difference in population size	NOT STATED
Reflection on Other Research Prioritization Methods	Yes, comparison with [Dale et al., 1999], in previous priority setting	NOT STATED	NOT STATED

pEVPI: population expected value of perfect information; pEVVPI: population expected value of partial perfect information; QALY: quality-adjusted life-year; λ = cost-effectiveness threshold; EV

Reference(s)	[47[a]]	[47[b]]	[48]
Approach to Modeling	- Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Decision tree, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, cohort simulation, previously published by authors [Dong et al., 2006] - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Done, using data from published systematic reviews on effectiveness of vitamin D and calcium, and of hip protectors [Fleurence, 2004]	Done, data was used from systematic review on effectiveness of pressure-relieving devices [Fleurence 2005]	Done, systematic review on clinical outcomes and cost-effectiveness of TKR conducted
Application	Comparison of vitamin D only, calcium only, vitamin D and calcium, hip protectors only, vitamin D and calcium and hip protectors and no treatment in prevention of osteoporotic fractures in men and women >70 years [Demonstration of 'payback' approach and VOI methods in prioritizing research]	Comparison of high-specification foam mattresses (standard care), alternating pressure mattress overlays and alternating pressure mattress replacements for prevention of pressure ulcers [Demonstration of 'payback' approach and VOI methods in prioritizing research]	Computer-assisted (CAS) total knee replacement (TKR) versus conventional TKR
Setting	U.K.	U.K.	U.K.
Perspective	NHS	NHS	NOT STATED
Primary Purpose of VOI	To assess whether conducting research was cost-effective and should take priority over other areas of research.	To assess whether conducting research was cost-effective and should take priority over other areas of research.	To measure upper limit on returns to future research and to identify parameters for which future research may be warranted.
Time Horizon, Year of Analysis, Discounting	Lifetime, 2000, 6% (both costs and effects)	12 wks, 2003, NA	10 years, NOT STATED, 3.5% (both costs and effects)
Pre-Conceptualization of VOI	Benefits of Decision Reduction in Uncertainty Population of Patients Probability of Implementation Durability of Information Discounting Existing VOI Studies	NOT STATED Lack evidence on efficacy and cost-effectiveness of pressure-relieving devices [multiple references] Population: 5-32% prevalence in UK hospitals [Kaltenthaler et al, 2001], with incidence varying according to setting, patient case mix, severity of illness, and other contextual factors [Lyder, 2003] Various implementation scenarios used in payback method [sensitivity analysis] 5 years [assumption] NOT STATED NOT STATED	Improvement in accuracy and precision of component and mechanical axis alignment with CAS, cost-saving and small QALY advantage [multiple references] Multiple sources of uncertainty, e.g., utility values, costs, transition probabilities, and effect of CAS [Dong et al., 2006], long term evidence from RCTs 44.9k TKR operations per year [National Joint Registry for England and Wales, 2005] NOT STATED 5, 10, 15, 20 years [assumptions, sensitivity analysis] 3.5% NOT STATED
VOI Results	- pEVPI* = £730M for males and females - pEVPPPI* = £501M for females * λ = £30k per QALY	- pEVPI* = £608M * λ = £30k per QALY	- EVPI* = £21.4, pEVPI* = £8.3M - pEVPPPI* = £5.6M for utility parameters, £20k for transition probabilities relating to CAS-TKR, £5k for transition probabilities related to conventional TKR * λ = £30k per QALY, durability = 10 years
Conclusion on VOI	Research would be potentially cost-effective in osteoporosis in populations considered.	Research would be potentially cost-effective in pressure ulcer areas in populations considered.	From U.K. perspective, it is likely to be worthwhile to have additional research related to patient utilities at different health states. Further research related to transition probabilities may only be of value from a more global perspective.
Prioritizing of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Post-Conceptualization of VOI	Benefits differences: wider range of subgroup analyses could have been conducted. Implementation: payback and VOI methods need to address issue of impact of research on clinical practice and feasibility of applying methods in practice. Decision modeling: systematic application and feasibility of complex modeling exercises for prioritizing between all disease areas have to be considered, as well as the accessibility of these methodological approaches to individuals setting research agendas. Costs of VOI: priority setting exercises have costs that need to be justified in presence of scarce resources. Generalisability: results may not be applicable to non-UK settings Other VOI studies: NOT STATED	Benefits differences: wider range of subgroup analyses could have been conducted. Implementation: payback and VOI methods need to address issue of impact of research on clinical practice and feasibility of applying methods in practice. Decision modeling: systematic application and feasibility of complex modeling exercises for prioritizing between all disease areas have to be considered, as well as the accessibility of these methodological approaches to individuals setting research agendas. Costs of VOI: priority setting exercises have costs that need to be justified in presence of scarce resources. Generalisability: results may not be applicable to non-UK settings Other VOI studies: NOT STATED	Population and durability: annual size for relevant patient population and time horizon are critical parameters and can only be a matter of judgment. Other: special attention should be paid to generalizing results to other countries
Comparison with Other VOI Studies	Generalisability: results may not be applicable to non-UK settings Other VOI studies: NOT STATED	Generalisability: results may not be applicable to non-UK settings Other VOI studies: NOT STATED	Other VOI studies: NOT STATED
Reflection on Other Research Prioritization Methods	Done, explicit comparison with payback methods	Done, explicit comparison with payback methods	NOT STATED

pEVPI: population expected value of perfect information; pEVPPPI: population expected value of partial perfect information; EVPI: expected value of perfect information; λ: cost-effectiveness threshold; QALY: quality-adjusted life-years

Reference(s)	[49]	[50]	[51]
Approach to Modeling	- Full modeling - Markov model, NOT STATED, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, cohort simulation, update from existing model - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, NOT STATED, extension/adaptation of developed - Single technology, single disease, within single clinical domain
Use of Systematic Review	Done, meta-analyses were done using evidence on clinical parameters from previous review [Chen et al., 2008]	NOT STATED	Not done
Application	Intravenous immunoglobulin (IVIg) versus oral prednisone in persistent chronic immune thrombocytopenic purpura (ITP)	Multidetector computed tomographic angiography (CTA) versus conventional catheter coronary angiography (CA) for diagnosing coronary heart disease (CHD)	Donepezil versus no treatment in mild to moderate Alzheimer's disease
Setting	Canada	US	US
Perspective	Publicly funded health care system	Health care system	Societal
Primary Purpose of VOI	NOT STATED	NOT STATED [Demonstration of methods to analyze uncertainty and patient heterogeneity]	To inform important policy issues such as setting research priorities, establishing technically efficient research design, and informing efficient regulatory framework. [Demonstration of VOI methods]
Time Horizon, Year of Analysis, Discounting	Lifetime, 2007, 5% (both costs and effects)	Lifetime, NOT STATED, NOT STATED	210 wks, NOT STATED, NOT STATED
Pre-Conceptualization of VOI	Benefits of Decision Reduction in Uncertainty Population of Patients Likelihood of Implementation Durability of Information Discounting Existing VOI Studies	More effective than high-dose methylprednisolone and oral prednisone in adults with severe ITP [Godeau et al., 2002] NOT STATED NA NOT STATED NOT STATED NOT STATED NOT STATED	Trial proofs efficacy (<24 weeks) of donepezil [Rodgers et al., 1998] > 24 weeks efficacy, economic and QoL data on donepezil is not collected in trial [Rodgers et al., 1998] 872k AD patients [U.S. census projections] NOT STATED 2-8 years [Claxton and Thompson, 1999] NOT STATED NOT STATED
VOI Results:	- EVPI* = 0 - EVPPI* = 0 * λ = \$CAN30k per QALY	- pEVPI* = \$61M - pEVVPI* = \$42M for utility of nonspecific chest pain, \$32M for costs of CA, \$25M for costs of CTA, \$14M for TPR of CTA * λ = \$50k per QALY	- pEVPI* = \$339M - pEVVPI* = \$270M for efficacy duration (ED), \$93M for RRR > 24 wks, \$84M for RRR < 24 wks, \$39M for drop out rate * λ = \$50k per QALY, ¹ most relevant
Conclusion on VOI	Current evidence can be regarded as sufficient to support decision that prednisone is cost-effective treatment for adults with persistent chronic ITP, and no future research is warranted.	NOT STATED	Additional experimental research on ED is potentially cost-effective.
Prioritizing of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Post-Conceptualization of VOI	Benefits differences: administration and distribution costs of IVIg were not included in analysis Further research: empirical evidence related to impact of treatments on patients' utility would be worthwhile Other VOI studies: NOT STATED	NOT STATED	Other: observational data on efficacy duration, RRR > 24 wks, RRR < 24 wks and drop out rate are vulnerable to selection bias requiring experimental design or econometric solutions to selection bias
Comparison with Other VOI Studies	Other VOI studies: NOT STATED	Other VOI Studies: NOT STATED	Other VOI Studies: NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

EVPI: expected value of perfect information; EVVPI: expected value of partial perfect information; pEVPI: population expected value of perfect information; pEVVPI: population expected value of partial perfect information; λ: cost-effectiveness threshold; QALY: quality-adjusted life-year

Reference(s)	[52]	[53,12]	[54]
Approach to Modeling	- Full modeling - Decision tree, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Decision tree, NOT STATED, newly developed - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Done, pool-data analysis of prevalence of residual disease in low risk and high risk groups based on systematic review [Cooper et al., 1995]	Done, systematic review of clinical effectiveness and cost-effectiveness of docetaxel plus prednisone/prednisolone versus other chemotherapy regimens, best supportive care or placebo	Done, systematic review of trials and the cost analyses on preoperative optimization (pre-opa)
Application	Postendoscopic surgery versus waiting strategy in low-risk (LR) colorectal malignant polyps	Comparison of docetaxel plus prednisone/prednisolone with other chemotherapies and palliative care for advanced metastatic hormone-refractory prostate cancer (mHRPC)	Comparison of pre-op with dexamethasone (d), pre-op with adrenaline (a) and standard patient management in high-risk surgical patients
Setting	U.S.	U.K.	U.K.
Perspective	Societal	NHS	NOT STATED
Primary Purpose of VOI	To quantify expected value of obtaining more information on optimal therapeutic strategy for LR malignant polyp and to identify key uncertain parameters deserving prioritized research.	To determine the costs of uncertainty associated with adoption decision	To determine before time of commissioning whether most recent trial on pre-op was potentially worthwhile (prior analysis), and to readdress, with updated trial results whether further research is potentially worthwhile (posterior analysis). [Demonstration of VOI methods for EVPI and EVPII calculations]
Time Horizon, Year of Analysis, Discounting	Lifetime, NOT STATED, NOT STATED	Lifetime, 2003-4, 3.5% (both costs and effects)	2 years, NOT STATED, NOT STATED
Pre-Conceptualization of VOI	Benefits of Decision Reduction in Uncertainty Population of Patients Likelihood of Implementation Durability of Information Discounting Existing VOI Studies:	Modeled clinical and economical advantage of surgery of LR malignant polyp [Wilcox and Beck, 1987] Sensitivity of model outputs to several variables, such as surgical mortality, residual disease, or operative efficacy [Wilcox and Beck, 1987] 14k patients with malignant polyps [multiple references] NOT STATED 5 years [assumption] 3% NOT STATED	NOT STATED 2748 patients per year [Cancer Research UK, 2008] NOT STATED [Note: estimates of adherence are provided for VOIM calculations] 1.5 years [timelines surrounding NICE appraisal of atrasentan] 3.5% NOT STATED
VOI Results	- EVPI* = \$16.7k, pEVPI* = \$1099.4M - EVPII* = \$14.8k for combination among histological accuracy, residual disease, and surgical mortality * λ = \$150k per life-year gained	- pEVPI = £13.36M* * λ = £20k per QALY	<i>Prior analysis:</i> - EVPI* = £350, pEVPI* = £48M - pEVPII* = £48M for short term costs, £37M for costs and survival with pre-opa, £1.7M for costs and survival with pre-opd and standard care) <i>Posterior analysis:</i> - EVPI* = £650, pEVPI* = £67M * λ = £30k per QALY
Conclusion on VOI	Further research, specifically addressing major areas of uncertainty, is needed.	Further research is potentially valuable but costs of research need to be taken into account when deciding about allocation resources for research purposes	Incorporation of trial data reduced uncertainty of expected cost and expected survival duration, but this reduction in parameter uncertainty did not translate into reduction in decision uncertainty.
Prioritizing of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Post-Conceptualization of VOI Comparison with Other VOI Studies	NOT STATED Other VOI Studies: NOT STATED	NOT STATED Other VOI Studies: NOT STATED	NOT STATED Other VOI Studies: NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

EVPI: expected value of perfect information; pEVPI: population expected value of perfect information; EVPII: expected value of partial perfect information; pEVPII: population expected value of partial perfect information; λ: cost-effectiveness threshold; QALY: quality-adjusted life-year

Reference(s)	[17, 55, 56(i)]	[57]	[58]
Approach to Modeling	- Full modeling - Markov model, NOT STATED, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Decision tree, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, cohort simulation, newly developed - Single technologies, single disease, within single clinical domain
Use of Systematic Review(s)	Done, systematic review of relative risks of relapse and disease progression of interferon beta and one trial of glatiramer acetate [Chilcott et al., 2003b]	Done, data on probabilities of events is extracted from Cochrane review [Gurusamy and Samraj, 2006; Gurusamy et al., 2009]	Done, only 1 RCT found on relative efficacy of peritoneal dialysis (PD) and hemodialysis (HD)
Application	Disease-modifying therapies (DMT) (interferon-beta 1a, interferon-beta 1b and glatiramer acetate) versus conventional treatment for multiple sclerosis	Early laparoscopic cholecystectomy (ELC) versus delayed laparoscopic cholecystectomy (DLC) for acute cholecystitis	Comparison of providing PD as initial treatment followed by HD if complications/switching occur; providing HD followed by PD if complications/switching occur and palliative care in end-stage renal disease (ESRD)
Setting	UK	UK	Thailand
Perspective	NHS	NHS	Both National Health Security Office and Societal
Primary Purpose of VOI	To test algorithm to estimate EVPI bias and confidence interval width for specified number of inner and outer samples [demonstration of algorithm for computing predicted bias and confidence intervals for Monte Carlo based estimates]	NOT STATED	To determine whether different values of particular input parameter lead to different optimum decisions, and if so, how much expected loss under alternative optimum decisions varies
Time Horizon, Year of Analysis, Discounting	20 years, NOT STATED, 6% (cost), 1.5% (benefits)	1 year, 2006, NA	Lifetime, 2004, 3.5% (both costs and effects)
Pre-Conceptual VOI	Difference in Benefits	NOT STATED	NOT STATED
	Reduction in Uncertainty	NOT STATED	NOT STATED
	Probability of Implementation	NOT STATED	NOT STATED
	Durability of Information	10 years [no reference]	10 years [no reference]
	Size of Patient Population	800 DMTs per year [Richards et al., 2002; NICE, 2003, personal communication]	13k laparoscopic cholecystectomies per year [no reference]
	Discounting	3.5%	3.5%
VOI Results	Existing VOI Studies	NOT STATED	NOT STATED
		- EVPI* = £8855, pEVPI* = £86.21M - Bias in EVPPI for mean costs associated with EDSS 9.5 health state: £456-20 for 500-10k inner samples, 1000 outer samples. - 95% CIs for EVPPI for mean costs associated with EDSS 9.5 health state: £1729-371 for 100-100k outer samples, 1000 inner samples * λ = £10k per QALY	- pEVPI* = £18.8M - pEVVPI* = only worthwhile reducing uncertainty in QoL * λ = £20k per QALY
Conclusion	Further research is merited on impact of IFN-β and glatiramer acetate, focusing on relationship between EDSS and cost of care, that between EDSS and QoL, therapy drop off rate, impact of therapies on disease progression, and eligibility for and uptake of DMTs Algorithm is easily and generally applied to compute predicted bias and confidence intervals for Monte Carlo based estimates of EVPPI in decision models. Infeasibly long computation times would be required for accurate EVPI estimates and Gaussian process meta-model was required to emulate original model and produce much quicker model runs [Tappenden et al., 2004]	There is potential to gain from further research to inform decision, particularly relating to QoL estimates for different health states. Additional research into other model parameters is unlikely to change model conclusions.	NOT STATED
Prioritizing of Systematic Review(s)	Not Done, although further information on costs of particular EDSS states and therapy drop off rates may be obtained through non-experimental designs, further useful information on impact of DMTs on disease progression and health outcomes would be most reliably obtained through long-term RCT including direct assessment of QoL.	NOT STATED	NOT STATED
Post-Conceptual VOI	NOT STATED	Further research: research recommendations from economic analysis relate only to specific decision question of whether to recommend ELC over DLC for acute cholecystitis, other research recommendations beyond specific question are outside scope of analysis.	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

EVPI: expected value of perfect information; pEVPI: population expected value of perfect information; EVPPI: expected value of partial perfect information; pEVVPI: population expected value of partial perfect information; λ: cost-effectiveness threshold; QALY: quality-adjusted life-year

Reference(s)	[59]	[60]	[61]
Approach to Modeling	- Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Done, systematic review of clinical effectiveness of and cost-effectiveness	Done, transition probabilities were derived for each cycle from systematic review and meta-analysis [Grutters et al., [in press]]	Done, systematic review(s) on clinical effectiveness, cost analyses and economic evaluations of cardiac resynchronisation therapy (CRT) (compared with (optimizing atrioventricular delay (OPT))
Application	Enhanced external counterpulsation (EECP) versus no treatment in adults with chronic stable angina	Particle therapy, both protons and carbonions versus best currently available treatments for (stage 1) non-small-cell lung cancer (NSCLC)	Pairwise comparisons of CRT-P (inserting a pulse generator) versus OPT alone, CRT-D (including automatic implantable cardioverter defibrillator [ICD]) as OPT alone, CRT-P versus CRT-D in heart failure
Setting	U.K.	The Netherlands	U.K.
Perspective	NHS and Personal Social Services	Health care	NHS
Primary purpose of VOI	To assess the potential value of future research on EECP.	To assess the value of additional research, and for which topics further research is most valuable.	To calculate total VOI estimate for differing levels of WTP
Time Horizon, Year of Analysis, Discounting	Lifetime, 2008, 3.5% (both costs + effects)	5 years, 2007, 4% (costs), 1.5% (effects)	Lifetime, 2005, 3.5% (both costs and effects)
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	More efficacious in refractory stable angina and heart failure, better patient outcomes, adverse events [multiple references] Limited evidence on short- and longer-term QoL, risk of cardiovascular event, costs and generalizability of evidence on EECP [no reference] NOT STATED 10 years [assumption] 68k prevalence and 5128 annual incidence of angina [Michael Chester, Liverpool Hope University, personal communication, 2008; British Heart Foundation, 2007] 3.5% NOT STATED	NOT STATED NOT STATED NOT STATED 7 (CRT-P) / 6 (CRT-D years) [approximations] 6300 patients per year [assumption] NOT STATED NOT STATED
VOI Results	- EVPI* = £440.16; pEVPI* = £48.7M - EVVPI* = £784.68 for 1-year QoL improvement; £379.80 for probability of sustaining QoL benefits in subsequent years; £0.00 for repeat top-up procedures; pEVVPI* = £86.9M for 1-year QoL improvement; £42.1M for probability of sustaining QoL benefits in subsequent years; £0.00 for repeat top-up procedures. - maximum EVSI* > £ 87.9M, maximum ENBS*: £ 87.9M at optimal SS of 900 patients over 4-year trial period * λ = £20k per QALY	- EVPI* = €7,784, pEVPI* = €22M - pEVVPI* (most valuable) = €16M for effectiveness of carbon-ion therapy, other valuable parameter groups = effectiveness of SBRT and the treatment costs (the number of fractions per treatment. * λ = €80k per QALY	CRT-P v OPT - EVPI* = £157, pEVPI* = £6.2M - maximum pEVVPI* = £2.4M for all HRs and £1.1M for all survival curves CRT-D v OPT - EVPI* = £917, pEVPI* = £31.8M - maximum pEVVPI* = £17.8M for all HRs, £7.2M for all survival curves, £19.2M for SCD and £2.0M for death due to worsening HF. CRT-D v CRT-P - EVPI* = £1697, pEVPI* = £67.6 million - maximum pEVVPI* = T £50.5M for all HRs, £19.6M for SCD and £36.7M for death due to worsening HF. * λ = £30k per QALY
Conclusion on VOI	Long-term follow-up trials in both angina and heart failure warranted, particularly focusing on QoL and adverse events and efficacy of EECP in patients with truly refractory severe angina. Future trials should take account of existing angina guidelines and ensure correct selection of patients for EECP therapy, i.e. only after education, comprehensive rehabilitation and real optimization of medication.	Further research is needed to reduce existing uncertainty, particularly relating to effectiveness of particle therapy in NSCLC. However, collecting clinical evidence requires particle facilities. Therefore, it might be worthwhile to invest in particle facility, which should initially be used for clinical research only.	Suggestions for further research: prediction of non-responders (systematic reviews of current evidence and further primary studies), appropriate use of CRT-D devices; NYHA classes I and II (RCTs), long-term safety data (observational studies)
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	Done, for prediction of non-responders
Post-Conceptual VOI	Future research: if ENBS (£87.9M) > fixed costs of research, proposed 4-year clinical trial with equal allocation can be considered cost-effective.	NOT STATED	Decision uncertainty: relative clinical effectiveness and cost-effectiveness CRT-D versus CRT-P devices is uncertain due to limited head-to-head evidence.
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

EVPI: expected value of perfect information; pEVPI: population expected value of perfect information; EVVPI: expected value of partial perfect information; pEVVPI: population expected value of partial perfect information; λ: cost-effectiveness threshold; QALY: quality-adjusted life-year; QoL: quality-of-life.; SS: sample size

Reference(s)	[62]	[63]	[64]
Approach to Modeling	- Full modeling - Decision Tree + Markov Model, cohort simulation, newly developed - Single technology, single disease, single clinical domain	- Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full modeling - Decision tree, cohort simulation, newly developed - Single technology, single disease, within clinical domain
Use of Systematic Review(s)	Done, systematic reviews were done of clinical studies and economic evaluations of catheter ablation for AF and typical atrial flutter.	Done, systematic review on clinical events, side effects and cost-effectiveness evidence on spironolactone, eplerenone, canrenone or potassium canrenoate	Done, systematic review of prevalence at screen and birth, test performance, and risk of cardiovascular collapse
Application	Radio frequency catheter ablation (RFCA) (without long-term antiarrhythmic drug (AAD use)) versus long-term antiarrhythmic drug (AAD) treatment alone in adults with paroxysmal atrial fibrillation (AF) (patients with a CHADS2 score of 1)	Comparison of spironolactone, eplerenone and standard care without aldosterone antagonist for postmyocardial infarction	Comparison of a) clinical examination alone, b) pulse oximetry in addition to clinical examination, and c) screening echocardiography in addition to clinical examination for newborn screening of congenital heart defects (CHD)
Setting	UK	UK	UK
Perspective	NHS	NHS	NHS
Primary Purpose of VOI	To explore the implications of the uncertainty associated with the cost-effectiveness of RFCA	To determine need for further research to identify research questions critical to decision-making and to help inform design of future studies	To investigate which research priorities would be of greatest value in reducing uncertainty regarding future newborn screening policies
Time Horizon, Year of Analysis, Discounting	Lifetime, 2006, 3.5% (both costs and effects)	Lifetime, 2008-09, 3.5% (both costs and effects)	1 year, 2000/1, NA
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	Reduction of symptoms [NICE guidance, 2004; Earley and Schilling, 2006] NOT STATED NOT STATED Lifetime, 5 years [assumptions, sensitivity analysis] 1000 per year [as potential exemplary population for particular decision context] NOT STATED NOT STATED	Antenatal screening programs have potential to identify CHD [Bricker et al., 2000] Effectiveness of screening strategies in preventing collapse or death—before diagnosis—of infants with treatable but life-threatening defects is uncertain [no reference] NOT STATED [note: cost-effectiveness analysis accounts for screening rates] 5 years [assumption] 549.6k newborns per year [based on number hospital deliveries in 2000/2001] 6% Existing VOI Studies: NOT STATED
VOI Results	- EVPI* = £2.02, pEVPI* = £17.4k - EVVPI* = £0.25, pEVVPI* = £371.47 for utilities of NSR and AF health states * λ = £30k per QALY	- EVPI = £1876, pEVPI = £484.9M - pEVVPI : majority of decision uncertainty due to relative treatment effects of mortality * λ = £20k per QALY	- pEVPI* = £744k (life threatening malformation), £14.4M (clinically significant malformation) - pEVVPI* = £557k (life threatening malformation) and £11.3M (clinically significant malformation) for detection rates of pulse oximetry, £0 (life threatening malformation) and £5.0M (clinically significant malformation) for screening echocardiography, and £275k (life threatening malformation) and £5.3M (clinically significant malformation) for screening test costs. * λ = £50k per timely diagnosis
Conclusion on VOI	Further research in area is likely to be of significant value, with most value directed towards obtaining more precise estimates of QoL of patients following RFCA and AAD.	Potential value to the NHS in undertaking additional research, particularly on relative treatment effects of mortality between eplerenone and spironolactone; An adequately powered, well-conducted head-to-head RCT directly comparing differences in mortality, as well as hospitalisations, additional data on non-fatal events and side effects, between spironolactone and eplerenone is likely to provide value for money.	Further research is required before pulse oximetry to clinical examination is recommended as policy, targeting at reducing uncertainty around detection and false-positive rates for pulse oximetry
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Post-Conceptual VOI	Durability: marked variations in VOI based on alternative assumptions (lifetime and 5 years).	NOT STATED	Benefits differences: disbenefits and QoL losses associated with false-positive screening results could not be quantified. Decision uncertainty: paucity of studies comparing longer-term outcomes between screened and unscreened populations NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	Both: NOT STATED	NOT STATED	NOT STATED

Reference(s)	[65]	[92[b]]	[66]
Approach to Modeling	- Full modeling - Decision tree, discrete event simulation, using previously develop published by authors - Single technology, single disease, within single clinical domain	- NOT STATED - NOT STATED - NOT STATED	- Maximal modeling [i.e., model describes short term/acute care (acute percutaneous coronary intervention (PCI) and (repeated) revascularization, risk stratification, and long term drug treatment in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS)] - Decision Tree + Markov model, cohort simulation, extension/adaptation previous model [Main et al., 2004] - Multiple technologies, single disease, within single clinical domain
Use of Systematic Review(s)	Done, review of clinical effectiveness of tamoxifen [Karnon and Brown, 2002]	NOT STATED	Done, systematic reviews of randomised controlled trials (RCTs) and economic evaluations of clopidogrel and prasugrel, plus publications relating to withdrawal of clopidogrel
Application	Tamoxifen alone versus tamoxifen and chemotherapy in node positive, postmenopausal women < 65 years with early breast cancer	Computed tomography rule (i.e., CT in only patients at high risk (requiring neurosurgical intervention) versus CT in patients at high and medium risk (with brain injury no CT)) versus predictions by physician themselves in minor head injury	Comparison of a) clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months; b) clopidogrel as an adjunct to standard therapy (including aspirin) for 6 months; c) clopidogrel as an adjunct to standard therapy (including aspirin) for 3 months; d) clopidogrel as an adjunct to standard therapy (including aspirin) for 1 month; e) standard therapy (including aspirin) alone in non-ST-elevation acute coronary syndrome (NSTE-ACS)
Setting	U.K.	U.S.	U.K.
Perspective	NHS	NOT STATED	NHS
Primary Purpose of VOI	To value collection of additional information to inform treatment decision to provide tamoxifen alone versus tamoxifen and chemotherapy in node positive, postmenopausal women < 65 ys [Demonstration of VOI methods using non-parametric techniques]	To present and illustrate tools that can help in setting priorities for research [Demonstration of application of VOI analysis]	To establish the potential value and feasibility of future research into the optimal duration of clopidogrel treatment
Time Horizon, Year of Analysis, Discounting	Lifetime, 2000, 6% (costs) and 1.5% (benefits)	NOT STATED, 2002, NOT STATED	Lifetime, 2005-6, 3.5% (both costs and effects)
Pre-Conceptual VOI	Benefits of Decision Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	Reduction in CT head use [no reference] NOT STATED NOT STATED 10 years [assumption] 200k per year [Coyle et al., 2003] NOT DONE NOT STATED	Absolute benefit of clopidogrel, relative to standard care, appeared to decline > 12 months [Main et al., 2004] Absence of robust data of potential rebound effect on withdrawal of clopidogrel therapy and time lapse, price of generic clopidogrel is subject to considerable uncertainty [Main et al., 2004] NOT STATED 10 years [assumption] 60k [Philips et al., 2006] 3.5% Only reference to other HTA programmes and related VOI Studies [Claxton et al. Pilot study 2005; Philips et al., 2006]
VOI Results	- EVPI _{episodic} * = £239.08, pEVPI* = £7.1M - EVSI _{episodic} * = £154.5, pEVSI* = £4.7M (both SS = 2000) * Sampling cost = £2.0M, pENBS* = £2.7M (both SS) * λ = £5k per QALY	- EVPI* = CAN\$3, pEVPI = CAN\$60M * λ = NOT STATED	- pEVPI* = £108.5M, £77.1M, £20.4 for all patients, high-risk, low risk patients (on patent) - pEVPPPI*: £89.1M for effectiveness, £1.3M for epidemiology, £3.3M for cost (all patients, on patent) * λ = £30k per QALY
Conclusion on VOI	Research resources allocated to trials comparing tamoxifen and chemotherapy versus tamoxifen alone in node positive, postmenopausal women would provide substantial net benefits	NOT STATED	The results of VOI demonstrate considerable variation in potential value of research
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	Not Done, RCT on impact of duration of clopidogrel treatment on withdrawal rebound is discussed
Post-Conceptual VOI	Population: assumptions regarding size of patient population impacted pEVPI estimates. Other: decisions to fund research should be based on a comparison of relative net benefits of alternative areas of research. Durability: standardized methods for estimation of durability of research need to be developed, building in factors relating to trial recruitment time, time to inform all model parameters, and re-estimation of relevant patient population for every length of follow-up. Other: different model structures may need to be adopted to inform immediate resource decision and VOI analysis	NOT STATED	Implementation: changes in routine clinical practice may mean that VOI results may be less generalizable in particular risk groups. Durability: there is uncertainty in relation to typical duration of health technology life cycles Other: Dichotomous approach to risk stratification impacted VOI.
Comparison with Other VOI Studies	NOT STATED	NOT STATED	More widespread use of VOI to broader range of applications would provide additional benchmarks of value for money of research into range of alternative decision problems
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

Reference(s)	[11[c]]	[11[b]]	[67]
Approach to Modeling	- NOT STATED - Decision tree, NOT STATED, NOT STATED - Single technology, single disease, within single clinical domain	- Full Modeling - Decision tree, NOT STATED, NOT STATED - Single technology, single disease, within single clinical domain	- Full modeling - NOT STATED, NOT STATED, newly developed - Single technology, single disease, within single clinical domain
Use of Systematic Review(s)	Done, estimates of effectiveness were based on reported meta-analysis of RCT evidence	Done, estimates of effectiveness were based on reported meta-analysis of RCT evidence	Done, reviews and meta-analyses for model parameters
Application	Prophylactic extraction versus deliberate retention of wisdom teeth	Zanamivir versus usual care in high-risk patients when influenza	Watchful waiting vs radical prostatectomy vs external-beam radiation therapy for prostate cancer (moderately differentiated cancer in 65 old male)
Setting	U.K.	U.K.	U.S.
Perspective	NHS	NHS	Societal
Primary Purpose of VOI	NOT STATED [Demonstration of application of framework for VOI and value of implementation framework]	NOT STATED [Demonstration of application of framework for VOI and value of implementation framework]	NOT STATED [Demonstration of application of EVIC calculations]
Time Horizon, Year of Analysis, Discounting	NOT STATED, NOT STATED, NOT STATED	NOT STATED, 2000–2001, NOT STATED	NOT STATED, 2003, 3% (both costs and effects)
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	NOT STATED NOT STATED No impact (0%) evidence/information on implementation [Note: estimate of implementation (0%) used for VOIM analysis][TAR and guidance documents] 8 years [no reference] 136k annual incidence [TAR and guidance documents]	NOT STATED NOT STATED Individualized care NOT STATED 23.8k annual incidence of moderately differentiated cancer of 550 per 100,000 in US pop 4.33 [US Census, 2000] NOT STATED NOT STATED
VOI Results	Done, Rate NOT STATED NOT STATED	Done, Rate NOT STATED NOT STATED	NOT STATED
Conclusion on VOI	- EVPI* = £0, pEVPI* = £0 - EVPI _{Individualized} * = £0 * λ = £30k per QALY	- EVPI* = £6, pEVPI* = £5.6M - EVPI _{Individualized} * = £0 * λ = £30k per QALY	- EVIC (pop): \$70.0M*; EVIC (pop) for parameters: 62.1M (anxiety), 23.8M (impotence) * \$50 k per QALY
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Post-Conceptual VOI	NOT STATED	Difference in benefits: Where INB are small, returns available from research are small.	NOT STATED
Comparison with Other VOI Studies	NOT STATED	• EVPI for zanamivir are lower than for orlistat due difference in INB • pEVPI for zanamivir are higher than for orlistat due to difference in population size	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

TAR: technology assessment report; EVIC: expected value of individualized care

Reference(s)	[68[a],56[a]]	[68[b],56[b]]	[68[d],56[c]]
Approach to Modeling	- Full modeling - Decision tree, NOT STATED, newly developed - Single technology, single disease, within single domain	- Full modeling - Decision tree, NOT STATED, newly developed - Single technology, single disease, within single domain	- Maximal modeling (i.e., model describes urinary tract infections (UTIs), progression of renal scarring, development of end-stage renal disease (ESRD), transplant and dialysis for ESRD onset) - Markov model, NOT STATED, newly developed - Multiple technologies, multiple diseases, within single clinical domain
Use of Systematic Review(s)	Done, estimates for effectiveness of manual chest physiotherapy interventions based on review [Hondras et al., 2003]	Done, estimates for effectiveness of manual chest physiotherapy interventions based on review [Jones and Rowe, 2003]	Done, evidence from systematic review was used to structure decision model [Down 2003], evidence from systematic review was used to estimate frequency of UTI with antibiotic treatment [Williams et al., 2003] and systematic searches for natural history were performed
Application	Manual chest physiotherapy interventions (i.e., massage therapy, chiropractic spinal manipulation (CSM) and physical therapy) versus no intervention in asthmatic children and asthmatic adults treated in community and asthmatic children treated in hospital	Manual chest physiotherapy interventions (i.e., autogenic drainage, active breathing, heat lamp and chest percussion with drainage) versus no intervention in adults with COPD	Long-term (3-year) treatment with trimethoprim, nitrofurantoin or cotrimoxazole versus intermittent short-term antibiotic treatment for recurrent UTI prophylaxis.
Setting	UK	UK	UK
Perspective	NHS	NHS	NHS
Primary Purpose of VOI	To assess potential value of future research	To assess potential value of future research	To assess potential value of future research
Time Horizon, Year of Analysis, Discounting	30 days, NOT STATED, NA	30 days, NOT STATED, NA	3 years, NOT STATED, NOT STATED
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies		
	NOT STATED Evidence on manual chest physiotherapy techniques in asthma patients is insufficient, and RCTs on effects of manual therapies on clinically relevant outcomes is needed [Hondras et al., 2003] NOT STATED 5, 10, 15 years [assumptions, sensitivity analysis] 1 in 8 children, 1 in 13 adults [National Asthma Campaign asthma audit, 2001] 3.5% NOT STATED	NOT STATED Evidence on effect manual chest physiotherapy techniques on pulmonary functions in COPD is insufficient [Jones and Rowe, 2003] NOT STATED 5, 10, 15 years [assumptions, sensitivity analysis] NOT STATED [based on Scottish Parliament, 2001 and Office for National Statistics, 2002] 3.5% NOT STATED	Long term antibiotics reduce risk of recurrent UTI in children [Williams et al., 2003] Evidence for widespread use of long-term prophylactic antibiotics was weak [Williams et al., 2003] NOT STATED 10 years [assumption] 8.4% and 1.7% of girls and boys aged 7 years, with 30% having recurrent UTIs [Winberg et al., 1975] 3.5% NOT STATED
VOI Results	- pEVPI* = £14.5M for children treated in community, £0 for adult treated in community; £1.2M for children treated in hospital - pEVPI* = £14.2M for effect of massage on FEV ¹ (for children treated in community); £0 for all parameters (for adult treated in community); £1.2M for effect of physical therapy on length of hospital stay (for children treated in hospital) * λ = £30k per QALY, durability = 10 years	- pEVPI* = £0 - pEVPI* = £0 * λ = £30k per QALY, durability = 10 years	- pEVPI* = £2.24M and £0.61M for girls aged 3 with no VUR and with VUR, £0.69M and £0.54M for girls aged 1 with no VUR and with VUR, £2.24M and £0.61M for boys aged 3 with no VUR and with VUR, £0.69M and £0.54M for boys aged 1 with no VUR and with VUR - pEVPI* = £2.25 for effect of prophylaxis on frequency of UTI (for girls aged 3 years), £1.77 for information on long term effect (>6 months) (for girls aged 1 year), effect of all prophylactic treatment are important in boys * λ = £30k per QALY, durability = 10 years
Conclusion on VOI	Further research will be potentially cost-effective in asthmatic children treated in community and hospital. as EVPI is likely to exceed costs of research. In both cases experimental design is required while CSM children in community should be excluded as comparator and LOS for children in hospital should be included as end-point in any proposed research designs. Additional research is unlikely to be cost-effective in asthmatic adults in hospital.	Additional research is unlikely to be cost-effective, as cost of research are likely to exceed the pEVPI	Additional primary research may be required for selected patient groups (particularly girls with no VUR), particularly head-to-head comparisons of either cotrimoxazole and trimethoprim or all three antibiotics with longer follow-up (6 months to 3 years)
Prioritization of Systematic Review(s)	No, recommendations focus on RCT design	NA	NOT STATED
Post-Conceptual VOI	Benefits differences; other measures of respiratory function may be important, rather than only linking FEV1 and EQ-5D.	Benefits differences: uncontrolled placebo effects in trials might overestimate FEV1 outcomes; costs of physiotherapy equipment are excluded from analysis. Population: application of all-age average incidence rates to the total population of England and Wales may overestimate adult COPD patients.	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

Reference(s)	[69,70]	[71]	[72]
Approach to Modeling	- Maximal modeling [i.e., model describes screening, vaccination and treatment of group B streptococcal (GBS) and other (non-BGS) bacterial infections in early infancy] - Decision tree, cohort simulation, newly developed by authors - Multiple technologies, multiple diseases, within single clinical domain	- Maximal modeling [i.e., model combines coronary heart disease (CHD) model predicting events (angina, unstable angina, myocardial infarction and death) from rheumatoid arthritis (RA) with model predicting outcome of changes in disease activity on variables such as QoL] - Markov model, cohort simulation, newly developed by authors - Single technology, multiple diseases, across multiple clinical domains	- Maximal modeling - [i.e., model predicts coronary heart disease and stroke on the basis of different conditions (including 'normal', 'hypertension', 'diabetes', 'hypercholesterolemia')] - Markov model, cohort simulation, published earlier by authors - Single intervention, multiple diseases, across multiple clinical domains
Use of Systematic Review(s)	Done, systematic reviews and meta-analyses were performed on natural history of disease and effectiveness of testing, treatment and vaccination	Not Done, evidence was used from multiple other sources	Done, systematic reviews performed on effectiveness of lifestyle intervention
Application	Comparison of prenatal testing for GBS (by polymerase chain reaction or culture), prepartum antibiotic treatment (intravenous penicillin or oral erythromycin), and vaccination during pregnancy to prevent GBS and other bacterial infections in early infancy	Statin therapy plus conventional disease-modifying anti-rheumatic drug (DMARD) versus DMARD alone in females with RA	Lifestyle intervention (including dietary counseling and physical exercise) versus standard care in overweight and obese patients
Setting	U.K.	U.S.	Switzerland
Perspective	NHS	Health care payer	Societal
Primary Purpose of VOI	To determine the cost-effectiveness of further research and identify research priorities	To determine VOI on determinants in order to help guide future research directions on statin use in RA.	To assess uncertainty in cost-effectiveness of intervention and to determine if further research is necessary based on current information.
Time Horizon, Year of Analysis, Discounting	Lifetime, 2005, NOT STATED (costs), 3% (QALYs)	10 years, 2005, 5% (both costs and effects)	60 years, 2006, 3% (both costs and effects)
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	Reduction of both cardiovascular risks and RA disease activity via lipid-lowering and anti-inflammatory benefits [McCarey et al., 2004], substantial costs of implementing statin therapy policy. Magnitude of long-term net benefits of statins [McCarey et al., 2004] NOT STATED NOT STATED 2.1M patients with RA, potentially receiving statin therapy [Lawrence et al., 1999] NOT STATED NOT STATED	Lifestyle intervention safely improves metabolic abnormalities [Pritchett et al., 2005] NOT STATED All subjects developing hypertension, diabetes, and hypercholesterolemia are diagnosed and treated [assumption] 10 years [assumption] 32k overweight, 18k obese patients (30-60 years, excluding those with comorbidities) [Swiss Federal Statistical Office, 2006] 3% NOT STATED
VOI Results	- pEVPI* = £67.3M (including vaccination), £29.0M (excluding vaccination) * λ = £25k per QALY	- pEVPI* = \$2322.6M for change in DAS28/CRP (0 to <6 months), \$1003.8M for health utilities associated with HAQ/DAS28, \$831.6M for change in DAS28/CRP (6 to <12 months), \$191.1M for change in DAS28/CRP (≥12 months) * λ = \$50k per QALY	- maximum EVPI = CHF198 in overweight patients, CHF100 in obese patients, maximum pEVPI = CHF6.8M in overweight patients, CHF3.2M in moderate obese patients - pEVPI: higher in overweight than in moderate obese patients, depending on age and sex, with maximum of CHF 4.7M for utilities in females aged 30 years
Conclusion on VOI	pEVPI is substantial and exceeds cost of most proposed research in clinical area, with main uncertainty relating to vaccine efficacy.	More research is valuable before deciding on cost-effectiveness of statin therapy in RA, focusing on refining precise RA disease-activity benefits and health-utility changes associated with statin therapy, over > 12 months.	Lifestyle intervention can be regarded as cost-effective only in certain situations depending on sex, age group, and λ. Further investigations are necessary to evaluate cardiovascular risk factors in overweight and obese people, and patients' preferences on weight loss treatments.
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	NOT STATED
Post-Conceptual VOI	Benefits differences: exclusion of adverse effects of antibiotics and organizational costs to implement (or reverse) new intervention from analysis Decision uncertainty: change over time of prevalence of maternal colonization, and proportion of EOGBS compared with EO non-GBS pathogens in maternal risk groups, accuracy of PCR testing	Benefits differences: exclusion of risk reduction of stroke in statins from analysis [Law et al., 2003]; use of 6-month study results on outcomes such as cardiovascular events and deaths only; upcoming availability of generic, less expensive statins.	Benefits differences, decision uncertainty and population: Allocation of funds between lifestyle intervention and standard care in the prevention and treatment of obesity and future research depends on 1) λ, 2) decision uncertainty, 3) size of the eligible population and 4) age, sex, and BMI of patients.
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Comparison with Other Research	NOT STATED	NOT STATED	NOT STATED
Prioritization Methods			

Reference(s)	[73]	[74]	[75]
Approach to Modeling	- Maximal modeling [i.e., model describes screening, diagnosis and treatment of breast cancer] - Markov model, cohort analysis, extension of existing model by authors - Multiple technologies, single disease, within single clinical domain	- Maximal modeling [i.e., model describes screening, surveillance and colorectal cancer (CRC) treatment] - Markov model, cohort simulation, newly developed by authors - Multiple technologies, single disease, within single clinical domain	- Full modeling [i.e., model describes mechanism of action and effect of electric and magnetic field [EMF] on childhood leukemia and available options to reduce health risk] - Decision tree, computational equations, newly developed by authors - Multiple technologies, single disease, within single clinical domain
Use of Systematic Review(s)	Not Done, data were used from Cancer Registry of Slovenia	NOT STATED	Not Done
Application	Comparison of 36 mammography breast cancer screening policies, differing in age eligibility criteria and screening interval, and no-screening	Comparison of screening strategies for CRC, including colonoscopy, computed tomographic (CT) colonography, flexible sigmoidoscopy, and barium enema examination	Comparison of no action, insulation and service entrance to reduce risk in possible mechanisms of action (i.e., magnetic fields, contact current and spurious) of EMF on childhood leukemia
Setting	Slovenia	US	US
Perspective	Health care sector	Societal	Homeowner
Primary Purpose of VOI	To determine whether allocation of resources into further research of breast cancer screening is warranted; also, to identify the parameters for which the information would be most valuable. [Demonstration of use of Multiple Linear Regression (MLR) and Gaussian Process (GP) metamodels for reducing computing time]	To quantify the expected value of obtaining more information on the optimal test for CRC screening and to identify the key sources of uncertainty that merit prioritization for future research.	To investigate implications of uncertainty as to which mechanism of actions of EMF on childhood leukemia is valid.
Time Horizon, Year of Analysis, Discounting	Lifetime, 2004, 3% (both costs and effects)	Lifetime, 2008, 3% (both costs and effects)	NOT STATED, NOT STATED, NOT STATED
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	NOT STATED Lack of evidence on efficacy of techniques in preventing CRC [multiple references] NOT STATED 5 years [estimation] 15.5M subjects eligible and adherent to CRC screening per year, excluding those screened in past [Pickhardt et al., 2008] 3% NOT STATED	Residual exposure and costs of option to reduce health risk vary [assumptions] Both mechanism of action of EMF on childhood leukemia and strength of any association of contact current and risk are uncertain [assumptions, scenario analyses] NOT STATED NOT STATED 2M houses with 1.8 children < 10 years [Statistical Abstract US, 2002] NOT STATED NOT STATED
VOI Results	- pEVPI : €100-500M for $\lambda = \text{€}10\text{-}40\text{k}$ per QALY - EVVPI: cancer sojourn times account for majority of decision uncertainty - Computation time* (with 500 inner / 10k outer level simulations) = 47 days for GP metamodels, 47*1/0.3% for original model, 5.6 days for MLR metamodeling * for all six parameter groups	- EVPI* = \$216, pEVPI* = \$1,5291.2M - EVVPI* = \$166 for adherence, \$66 for natural history-transition rate, \$179 for both adherence and natural history adherence rate * $\lambda = \text{\$}100\text{k}$ per life-year gained	- EVPI* = \$233, \$101, \$145 per house for different strategies of learning on mechanism and effect, pEVPI* = \$200-500M * $\lambda = \text{\$}2\text{k}$ for reduction of leukemia probability by 10^{-3}
Conclusion on VOI	Further research is warranted, with cancer sojourn times having highest priority for future research.	Choice of optimal test has large societal impact and should be top priority for further research, particularly to adherence to screening. Until more information is obtained, colonoscopy should be implemented.	NOT STATED
Prioritization of Systematic Reviews	NOT STATED	NOT STATED	NOT STATED
Post-Conceptual VOI	Population: Low incidence of breast cancer and relatively small population hinders sampling for pilot study of mammography breast cancer screening Other: Timeliness of data collection (e.g., cancer sojourn times) makes delaying decision about screening policy irrational. Other: Metamodels increase accessibility of extensive VOI analysis for computationally expensive health economic models and reject computational expense as reason for omission of such analysis	Population: nearly 50% U.S. population > 50 years is expected to benefit because of low penetration of CRC screening	Costs of VOI: identification of "problem" houses is assumed to be without costs. Accrual of information: information provision is assumed to be instantly available and completely precise, cost of collecting information of different reliability is neglected Risk behavior: every homeowner is assumed to have same opinion with regard to mechanism and odds ratio and same degree of risk aversion. NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Comparison with Other Research	NOT STATED	NOT STATED	NOT STATED
Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

Reference(s)	[76]	[77]	[78]
Approach to Modeling	- Full modeling [i.e., model describes both decision making process about antiviral drug treatment (at population, health professional and patient level) and disease progression] - Decision tree, cohort simulation, newly developed by authors - Single technology, single disease, within single clinical domain	- Full modeling [i.e., model includes glucosamine for management of pain and restoration of function and knee replacement arthroplasty] - Markov model, cohort simulation, newly developed by authors - Multiple technologies, single disease, within single clinical domain	- Maximal modeling [i.e., model describes organizational aspects of providing hearing aids and progression of hearing impairment] - Markov model, cohort simulation, newly developed by authors - Multiple technologies, single disease, within single clinical domain
Use of Systematic Review	Done, meta-analyses were performed for review evidence on effectiveness of antiviral drug treatment and disease progression	Done, systematic reviews on clinical effectiveness of glucosamine sulphate or hydrochloride and chondroitin sulphate were performed	Not Done, data were use from cohort study [Grutters et al., 2007]
Application	Comparison of amantadine, zanamivir, oseltamivir with no treatment in suspected influenza	Glucosamine sulphate versus current care in slowing or arresting progression of knee osteoarthritis (OA)	Private dispensers versus ear-nose-throat (ENT) specialists and audiological centers (ACs) for hearing aid provision.
Setting	U.K.	U.K.	The Netherlands
Perspective	NHS	NHS	Societal
Primary Purpose of VOI	To identify future research priorities	To investigate worth of commissioning further research on cost-effectiveness of therapy	To calculate worth of acquiring additional information through further research, and to examine for which parameters further research is most valuable
Time Horizon, Year of Analysis, Discounting	21 days, 2001, NA	Lifetime, 2007-8, 3.5% (both costs and effects)	Lifetime, 2006, 3% (both costs and effects)
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	NOT STATED NOT STATED NOT STATED 10 years [assumption] 500k knee OA patients per year [assumption] 3.5% NOT STATED	NOT STATED Capability of private dispensers to identify persons requiring medical care, cost reduction of transfer of tasks, maintaining quality of care [no reference(s)] NOT STATED 10 years [no reference(s)] 1.2M (i.e., all persons > 50 ys with hearing complaints, without hearing aid [Central Bureau for Statistics, 2007]) NOT STATED NOT STATED
VOI Results	- EVPI = local maxima at λ = £11k for amantadine and £40k for oseltamivir, pEVPI* = £2M - pEVPI* > £500 only for QoL for untreated influenza * λ = £30k per QALY, durability = 15 years	- pEVPI = £600M for λ = £30k per QALY - Most important parameters in EVPI: QoL gain and TKR probability associated with therapy	- EVPI* = €87, pEVPI* = €100M, - EVPI* = most valuable parameter: whether persons with hearing complaints seek help sooner with private dispenser, other valuable parameters: probability of private dispenser referring patients to ENT specialist, probability of undetected pathology detected before harm done, utility scores. * λ = €40k per QALY
Conclusion	Only at higher λ s EVPI becomes substantial for number of parameters that could only be examined through comparative studies.	Further research would be beneficial, with priorities in QoL (glucosamine sulphate vs placebo), structural outcomes and knee arthroplasty	NOT STATED
Prioritization of Systematic Reviews	NOT STATED	NOT STATED	NOT STATED
Post-Conceptual VOI	Benefit differences: cost of administering treatments can be lowered e.g., by nurse / telephone prescriptions or "over the counter" sales. Maximal modeling: methods need to be developed to recognize interaction between decisions, e.g., for different patient groups Population, durability and discounting: size of population, time horizon and discount rate are uncertain. Decision uncertainty: EVPI for proportion of ILI that is true influenza and rate of influenza A / overall influenza indicates both value of parameter uncertainty and seasonal variability. Implementation: improving near patient testing might enable better targeting of antivirals (with GPs better distinguishing influenza correctly). Structural uncertainty: EVPI depends on specification of decision model and characterization of uncertainty.	Benefit differences: cost changes arising from changes in QoL were not modeled owing to lack of data. Decision uncertainty: EVPI may be related to SS and map between health status instruments for QoL values Research design: nationally, representative cohort survey to determine the current level of TKR surgery would help generalizability of model results	NOT STATED
Comparison with Other VOI Studies	Other VOI Studies: NOT STATED	Other VOI Studies: NOT STATED	Other VOI Studies: NOT STATED
Comparison with Other Research Prioritization Methods	NOT STATED	NOT STATED	NOT STATED

Reference(s)	[79]	[80,68[c],56[d]]	[81]
Approach to Modeling	- Maximal modeling [i.e., model describes screening, diagnosis and treatment of oral cancer] - Markov model, cohort simulation, newly developed - Multiple technologies, single disease, single clinical domain	- Full modeling [i.e., model describes screening, diagnosis and treatment of age-related macular degeneration (AMD)] - Markov model, cohort simulation, newly developed by authors - Multiple technologies, single disease, within single clinical domain	- Maximal modeling [i.e., model describes testing, diagnosis and treatment of hepatitis C (HCV), and long term disease progression] - Decision tree + Markov model, cohort simulation, newly developed by authors - Multiple technologies, multiple diseases, within single clinical domain
Use of Systematic Review	Done, systematic reviews were performed on test performance, effectiveness and cost-effectiveness of screening for oral cancer and precancer	Done, estimates for decline in visual acuity were based systematic review as part of NICE TAR [Mears et al., 2003]	Done, systematic reviews were performed on natural history of HCV; acceptability of testing procedures and adherence to antiviral treatment; effectiveness of antiviral treatment and costs of long-term complications of HCV and treatment of advanced liver disease; and QoL.
Application	Comparison of no screening with a range of alternative screening strategies for oral cancer, based on a one-off prevalence screen, including invitational and opportunistic programs in both primary medical and dental locations	Comparison of weekly self-screening following 1st eye involvement with neovascular AMD with no screen but diagnosis and treatment of eligible AMD following self-referral to an ophthalmologist and a strategy of no screening and no photodynamic therapy (PDT)	Systematic case-finding for HCV in a general case of and three specific health service settings (i.e., general practice, prisons and services for people who misuse drugs and alcohol) among former injecting drug users (IDUs)
Setting	UK	UK	UK
Perspective	NHS	NHS	NHS
Primary Purpose of VOI	To determine the costs of uncertainty associated with the decision to adopt screening strategy	To inform NCCHTA about need for additional evidence to support guidance issued by NICE on use of PDT for AMD and, in particular, whether research recommendations by NICE, for evaluation of screening for AMD, should be regarded as priority [demonstration of VOI methods]	NOT STATED
Time Horizon, Year of Analysis, Discounting	Lifetime, 2002-3, 3.5% (both costs and effects)	10 years, 2000 [Smith et al., 2004], 3.5% (both costs and effects)	Lifetime, 2004, 6% (costs), 1.5% (QALYs)
Pre-Conceptual VOI			
	Difference in Benefits	NOT STATED	NOT STATED
	Reduction in Uncertainty	NOT STATED	NOT STATED
	Probability of Implementation	NOT STATED	NOT STATED
	Durability of Information	10 years [assumption]	5, 10, 15 years [assumptions, sensitivity analysis]
	Size of Patient Population	22.2M (prevalent population aged 40-79 years) + 0.8M per year (incident population <40 years) [Office for National Statistics, 2003]	5000 new, previously undiagnosed cases per year [Meads et al., 2002]
	Discounting	3.5%	3.5% [HM Treasury, 2003; NICE, 2004]
	Existing VOI Studies	NOT STATED	Authors state that NICE based research recommendations not on any formal analysis.
VOI Results	pEVPI* = £277M (assuming treatment has no effect on malignant transformation rate [MTR]) EVPPPI* = £45 for MTR, £3 for stage-shift, £9 pp for self-referral (assuming treatment has no effect on the MTR) * λ = £30k per QALY	pEVPI* = £6.95M (20/40 visual acuity), £14.75M (20/80) pEVPPPI = £1.35M (effect PDT on expected QALYs) (20/40 visual acuity), £2.83M (effect PDT on expected QALYs), £1.05M (effect no PDT on expected QALYs) (20/80) * λ = £30k per QALY, durability = 10 years	pEVPI* = £16.9M pEVPPPI* = £14.2M (for utilities) * λ = £30k per QALY
Conclusion on VOI	Further research is likely to be of significant value, with most value in obtaining more precise estimates of MTR	Further research may be potentially cost-effective, as EVPI may exceed research cost. More evidence about effect of PDT on QoL would be most valuable, e.g. through randomized trials (effect of PDT on QALYs) or surveys of QoL	Priorities for further research (in priority order) include: 1) pilot studies of case-finding strategies; 2) researching treatment with combination therapy of PegIFN and ribavirin or approaches to behavioural modification; 3) monitoring of scale and progress of HCV epidemic and estimating number and type of IDUs; 4) investigation of harm reduction through advice on alcohol intake; 5) research on life expectancy and utilities in HCV and treatments; 6) studies on hepatitis nurse specialists and research on knowledge and attitudes of clinicians and current and former IDUs towards HCV testing and treatment; 7) studies on influence of diabetes and obesity on disease progression.
Prioritization of Systematic Reviews	NOT STATED	Following presentation of analysis, systematic review and DAM of screening for AMD treatment was commissioned by NCCHTA	NOT STATED
Post-Conceptual VOI	Benefits Differences: EVPI is highly sensitive to impact of treatment on reducing MTR.	Structural uncertainty: structural assumptions in model affected EVPI quite substantially.	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	NOT STATED	Descriptive comparison of differences between priority setting by NICE and VOI, stating that research recommendations by NICE should have included a component to identify patients with 1st eye AMD.	NOT STATED

Reference(s)	[82, 9, 83, 56[e], 56[f]]	[84]	[85]
Approach to Modeling	- Full modeling - Decision tree + Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	- Full Modeling - Markov model, NOT STATED, newly developed - Single technology, multiple disease, single clinical domain	- Maximal modeling [i.e., model describes surveillance, diagnosis and treatment of Barrett's oesophagus] - Markov model, cohort simulation, newly developed - Multiple technologies, single disease, within single clinical domain
Use of Systematic Review(s)	- Done, systematic reviews of clinical effectiveness and economic evaluations of glycoprotein IIb/IIIa antagonists (GPAs) and meta-analysis of relative risk reductions (RRRs)	- Not Done, evidence was used from multiple other sources	- Done, systematic reviews were performed on effectiveness and cost-utility of endoscopic surveillance of Barrett's oesophagus
Application	Comparison of 1) GPAs as part of initial medical management of non-ST elevation acute coronary syndrome (ACS); 2) GPAs in patients with planned PCI, where GPAs are started once a decision to undertake PCI has been made; 3) GPAs as an adjunct to PCI, where the agent is used at the time of PCI or is started up to 1 hour before the procedure; and 4) usual care (no use of GPA)	Comparison of antibiotic regimens (including Ceftriaxone, Doxycycline, Metronidazole, Cefoxitin, Levofloxacin, Ofloxacin) for mild to moderate pelvic inflammatory disease (PID)	Comparison of surveillance regimen for patients with Barrett's oesophagus with no surveillance
Setting	U.K.	U.S.	U.K.
Perspective	NHS	Societal	NHS
Primary Purpose of VOI	To guide research decisions within a given area	To provide guidance for further investigation of outpatient PID treatment effectiveness differences among recommended regimens.	To identify the most important areas of uncertainty to inform prioritisation of further research.
Time Horizon, Year of Analysis, Discounting	Lifetime, 2000/01, 6% (costs), 2% (effects)	10 years, 2004, 3% (both costs and effects)	20 years, 2004, 6% (cost) and 1.5% (costs)
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI studies:	≈ 4-fold differences in cost exist between least and most expensive of recommended regimen [Drug Topics Red Book, 2004] there is little evidence of significant differences in short-term cure rates and no evidence for differences in long-term PID complication outcomes between treatments as head-to-head studies are lacking [CDC, 2006] NOT STATED [Note: Medication adherence is element of model] 10 years [no reference] 750k PDI cases per year [Sutton et al., 2005] NOT STATED NOT STATED	NA Evidence for effectiveness of surveillance of Barrett's oesophagus is weak and varied [Somerville, 1990]; some evidence that patients may not comply well with surveillance programmes [Eckardt et al., 2001] NOT STATED 10 years [assumption] 5692 newly diagnosed patients with Barrett's oesophagus eligible for surveillance per year [multiple references] 6% [no reference] NOT STATED
VOI Results	- pEVPI* = £20.032M - pEVVPI* = £17.741M for relative risk associated with strategy 1 * λ = £30k per QALY, durability = 10 years	- maximum acceptable cost per research subject (i.e., EVPI / SS for detecting a given difference in treatment effects and costs of antibiotics): \$146, \$984, \$1319 for 1% (n = 313.9k), 5% (n = 12.6k), 10% (n=3132), respectively * λ = £50k per QALY; \$50 difference in costs of antibiotics	- EVPI = £148, pEVPI = £6.6M - EVVPI = £32.86, pEVVPI = £4.1M for post-surgical recurrence rates (in both arms), £108.64 and £4.8M (for progression rate ACO to symptomatic ACO) * λ = £30k per QALY
Conclusion	Future research should be directed toward reducing uncertainty associated with relative risk of death in ACS patients prescribed GPAs and not undergoing PCI procedure in acute phase	Further research is needed to investigate differences in antibiotic effectiveness for modifying PID complication risk, since relatively small differences can have great impact, both clinically and economically.	There is considerable benefit in research reducing uncertainty within the model, with costs not being important areas of uncertainty, and transitions having much greater impact than utility data.
Prioritization of Systematic Review(s)	NOT STATED	NOT STATED	Done, VOI may be considered relatively high if further research were to be confined to small observational studies or further research synthesis or relatively low if commissioners were to proceed with large RCT running over many years
Post-Conceptual VOI	Population: EVPI necessarily depends on annual incidence Durability: selection of time horizon, change in price and information, and entry of new technologies have substantial impact on estimates of pEVPI Other: Inclusion of additional comparator (clopidogrel) in analysis had marked impact on potential value of future research; type of future research required can differ between heterogeneous groups of patients NOT STATED	NOT STATED	Population and durability: EVPI depends on size of the population affected and the expected lifetime of the technology
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Reflection on Other Research Prioritization Methods	Done, comparison of NICE's research recommendations based on the Appraisal Committee's understanding of the major gaps in the evidence with VOI results are broadly consistent, with VOI suggesting that key area of uncertainty relates to the relative effectiveness of GPA versus standard medical management, and also in comparison with clopidogrel.	NOT STATED	NOT STATED

Reference(s)	[86]	[87]	[88]
Approach to Modeling	- Full modeling [i.e., model describes diagnosis, prediction and treatment of minor head injury (MHI) and disease progression] - Markov model, cohort simulation, newly developed	- Maximal modeling [i.e., model describes screening, identification and treatment of postnatal depression (PND) and (dis)continuation to PND treatment] - Decision tree, NOT STATED [Monte Carlo simulation], newly developed model	- Maximal modeling [i.e., model describes pre-operative assessment, surveillance and treatment of non-small lung cancer (NSCLC)] - Markov model, cohort simulation, extending existing model (decision tree) [Bradbury et al., 2002]
Use of Systematic Review	Multiple technologies, single disease, within single clinical domain NOT STATED	Multiple technologies, single disease, within single clinical domain Done, Systematic reviews were conducted on validity, acceptability, clinical effectiveness and cost-effectiveness of methods for identifying PND	Multiple technologies, single disease, within single clinical domain Done, systematic reviews of both clinical effectiveness and economic evaluations of FDG-PET in NSCLC with regard to mediastinal staging, and meta-analysis of diagnostic accuracy
Application	Comparison of 1) computed tomography (CT) performed in all patients with MHI, (b) CT performed selectively according to the NOC, (c) CT performed selectively according to the CCHR, (d) CT performed selectively according to the CHIP rule, and (e) CT not performed	Edinburgh Postnatal Depression Scale (EPDS) (cut points 7–16) and Beck Depression Inventory (BDI) (cut point 10) versus current practice for identifying postnatal depression (PND)	Positron emission tomography vs mediastinoscopy for pre-operative assessment of NSCLC
Setting	US	UK	Scotland
Perspective	Societal	NHS/personal social services	NOT CLEAR
Purpose of VOI	To evaluate whether further research to uncertainty regarding patient outcomes would be required and/or justified	To assist in prioritizing future research and to identify most valuable areas NHS	To explore how uncertainty in patient-derived utility and possible uncertainty surrounding accuracy of technology might affect decision to adopt one or other strategy
Time Horizon, Year of Analysis, Discounting	Lifetime, 2006, 3% (both costs and effects)	12 months, 2006/7, NA	30 ys, NOT STATED, NOT STATED
Pre-Conceptual VOI	Difference in Benefits Reduction in Uncertainty Probability of Implementation Durability of Information Size of Patient Population Discounting Existing VOI Studies	Compared with clinical observations, CT is less costly and equally effective for the clinical management of pts with MHI [multiple references] Prediction rules have wide 95% CI (83%-100%) [multiple references] NOT STATED 5 years [no reference] 300M people [US Census Bureau, Not Stated] 3% NOT STATED	Divergent outcomes in RCTs (only 2) on clinical effectiveness of FDG-PET [multiple references] See Benefits differences NA NOT STATED NOT STATED NOT STATED NOT STATED
VOI Results	EVPI* = \$1759, pEVPI* = \$7 billion EVPPi* = \$1703 for long-term functional outcomes, \$1498 for outcome of patients with non-neurosurgery lesion, \$187 for outcome of patients with neurosurgery lesion * λ = \$75k per QALY	pEVPI* = £40.08M pEVPPi* = £9.03M for treatment parameters, £3.18M for EPDS and BDI (all cut points) sensitivity/specificity, £2.89M for PDS (all cut points) sensitivity/specificity. * λ = £30k per QALY, durability = 10 years	EVPI = £9.72, £24.35, £45.05, £76.42 for age 50, 60, 70, 80* * λ = £30k per QALY
Conclusion	More research is warranted to increase certainty about long-term patient outcomes after MHI. Until such research is conducted, routine use of CT in all patients with MHI is justified	At higher λs there appeared markedly higher potential value associated with further research more generally and also specifically around: diagnostic test performance (primarily related to the use of the EPDS); treatment strategies for confirmed PND; the impact of PND on HRQoL; and other epidemiological data, e.g., prevalence rates and routine case detection.	Uncertainty about patient preferences and attitudes to decision-making exceeds uncertainty about accuracy of PET for indication, and research should focus on this
Prioritization of Systematic Reviews	NOT STATED	NOT STATED	NOT STATED
Post-Conceptual VOI	Generalisability of findings: VOI based on cost data from the Netherlands	Comparators: full range of potentially feasible strategies was not considered.	NOT STATED
Comparison with Other VOI Studies	NOT STATED	NOT STATED	NOT STATED
Comparison with Other Methods for Priority Setting	NOT STATED	NOT STATED	NOT STATED

Reference(s)	[89,90][pre-trial model]]	[91]
Approach to Modeling VOI	<i>Pre-trial</i> - Full modeling - Markov model, cohort simulation, newly developed - Single technology, single disease, within single clinical domain	<i>Post-trial</i> - Full modeling - Markov model, cohort simulation, adaptation from pre-trial model - Single technology, single disease, single clinical domain
Use of Systematic Review	Done, reviews and meta-analyses for HRQoL (measured by the EQ-5D) in relation to gastro-oesophageal reflux disease (GERD), and transition probabilities	Done, systematic reviews were performed on prevalence and natural history, screening methods, effectiveness of treatment options, and health-related quality-of-life issues relating to amblyopia and strabismus
Application	Surgery (laparoscopic fundoplication (LF) vs long-term medical therapy in gastro-oesophageal reflux disease (GERD)	Comparison of six alternative screening options for amblyopia comprising screening in children at different ages (3, 4, and 5 years) and using alternative sets of test (visual acuity (VA) testing and cover-uncover test, with and without autorefraction)
Setting	U.K.	U.K.
Perspective	NHS	NHS
Purpose of VOI	To estimate the value of conducting additional research that would reduce parameter uncertainty	To identify major areas of uncertainty and so inform future research priorities in disease area
Time Horizon, Year of Analysis, Discounting	<i>Pre-trial</i> 30 years, 2004, 3.5% (both costs and effects)	<i>Post-trial</i> Lifetime, 2006, 3.5% (both costs and effects)
Pre-Conceptual VOI	Difference in Benefits <i>Pre-trial</i> Evidence on costs and cost-effectiveness of LF vs medication differ among studies, no UK studies comparing laparoscopic fundoplication with PPIs using a generic HRQoL measures Reduction in Uncertainty <i>Pre-trial</i> See Benefits differences Probability of Implementation <i>Pre-trial</i> NOT STATED Size of Patient Population <i>Pre-trial</i> NA Durability of Information <i>Pre-trial</i> NOT STATED Discounting <i>Pre-trial</i> NOT STATED Existing VOI Studies <i>Pre-trial</i> NOT STATED	<i>Post-trial</i> Inclusion of results REFLUX-trial <i>Post-trial</i> Inclusion of results REFLUX-trial <i>Post-trial</i> 160k [National Statistics, 2005]
VOI Results	<i>Pre-trial</i> - EVPI = £15.1k* - EVPPI = £11.3k for QoL implications of medical or surgical therapies * λ = £30k per QALY	<i>Post-trial</i> pEVPI = £300M, pEVPPPI = £160M (HRQoL, surgery and medical), £50M (HRQoL, after surgery failure)
Conclusion	<i>Pre-trial</i> Further research could be potentially worthwhile, particularly focusing on HRQoL in medical management or post-surgery	<i>Post-trial</i> continued follow-up of randomised trial would be valuable, particularly collecting data on long-term HRQoL and prognosis of patients
Prioritization in Systematic Reviews	NOT STATED	NOT STATED
Post-Conceptual VOI	<i>Pre-trial</i> Size of Patient Population: EVPI will exceed cost of further investigation, as REFLUX population is likely to be sizeable	<i>Post-trial</i> Probability of Implementation: surgical capacity and availability of trained surgeons may hinder implementation
Comparison with Other VOI Studies	NOT STATED	NOT STATED
Comparison with Other Approach to Research Prioritization	NOT STATED	NOT STATED

HRQoL: health-related quality of life; NHS: National Health Services

Appendix D. Potentially Relevant Health Care Decisionmaking Bodies and Research Funding Agencies

FROM THE UNIVERSITY OF CHICAGO REPORT [21]:

1. Programs for Assessment of Technology in Health (PATH) Research Institute – Canada*
2. Medical Services Advisory Committee (MSAC) – Australia*
3. Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-D) – Australia*
4. Health Services Assessment Collaboration (HSAC) – New Zealand*
5. Dutch Health Care Insurance Board (CVZ) – Netherlands*
6. German Institute for Quality and Efficiency in Health Care (IQWiG) – Germany*

FROM THE DUKE EVIDENCE-BASED PRACTICE CENTER REPORT [20]:

National Institutes of Health: Centers, Programs, and Individual Institutes

7. Division of Program Coordination, Planning and Strategic Initiatives, Office of Director, NIH*
8. Office of AIDS Research
9. Office of Behavioral and Social Sciences Research (OBSSR)
10. Office of Strategic Coordination (OSC), Office of Director, NIH
11. Office of Research in Women's Health
12. National Cancer Institute (NCI)
13. National Eye Institute (NEI)
14. National Heart, Lung and Blood Institute (NHLBI)[§]
15. National Human Genome Research Institute (NHGRI)
16. National Institute of Aging(NIA)
17. National Institute of Alcohol Abuse and Alcoholism (NIAAA)
18. National Institute of Allergy and Infectious Diseases (NIAID)[§]
19. National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS)*
20. National Institute of Biomedical Imaging and Bioengineering (NIBIB)*
21. National Institute of Child Health and Human Development (NICHD)
22. National Institute on Deafness and other Communication Disorders (NIDCD)*
23. National Institute of Dental and Craniofacial Research (NIDCR)
24. National Institute of Digestive and Kidney Diseases (NIDDK)*
25. National Institute of Drug Abuse (NIDA)
26. National Institute of Environmental Health Science (NIEHS)
27. National Institute of General Medical Sciences (NIGMS)*
28. National Institute of Mental Health (NIMH)
29. National Institute of Neurological Disorders and Stroke (NINDS)*
30. National Institute of Nursing Research (NINR)*
31. NIH Consensus Statements

Agency for Healthcare Research and Quality (AHRQ)

32. United States Preventive Services Task Force (USPSTF)*
 - They select topics, but commission the EPCs to do systematic reviews*
33. Developing Evidence to Inform Decisions about Effectiveness Network (DeCIDE) Centers
34. Centers for Education & Research on Therapeutics (CERTs)
35. Topic Selection for Systematic Reviews (EPCs)*

Other U.S. Government Sponsors of Research

36. Centers for Disease Control and Prevention (CDC)*
37. Centers for Medicare and Medicaid Services (CMS)
38. Veterans Administration (VA)*

- VA Technology Assessment Program*
39. U.S. Food and Drug Administration (FDA)*
 40. U.S Agency for International Development (USAID)

International Agencies and Groups

41. National Institute for Clinical Excellence (NICE) – UK*
42. Cochrane reviews and protocols*
43. Canadian Agency for Drugs and Technologies in Health (CADTH) – Canada*
44. Institutes for Health Services and Policy Research (IHSPR) – Canada*
45. German Research Foundation
46. German Federal Ministry of Education and Research
47. Australian Research Council
48. World Health Organization (WHO)*

Non-governmental Sponsors of Research

49. American Cancer Society
50. Bill and Melinda Gates Foundation
51. Robert Wood Johnson Foundation
52. American Heart Association
53. March of Dimes*

FROM NOORANI et al 2007 [93]:

54. Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) – Alberta, Quebec*
55. Alberta Heritage Foundation for Medical Research (AHFMR) – Alberta, Canada*
56. Unit of Health Economics and Health Technology Assessment (HunHTA) – Hungary*
57. Israel Center for Technology Assessment in Health Care (ICTAHC) – Israel*
58. Medical Advisory Secreteriat/ Ontario Health Technology Advisory Committee (MAS/OHTAC) – Ontario, Canada*
59. NIHR Coordinating Centre for Health Technology Assessment (NCCHTA) – UK*
 - Now called NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)*
60. *NHS Quality Improvement Scotland* (NHS QIS) – Scotland, UK*
61. Basque Office for Health Technology Assessment (OSTEBA) – Spain*
62. Swedish Council on Health Technology Assessment (SBU) – Sweden*
63. The Medical and Health Research Council of The Netherlands (ZonMW) – Netherlands*

OTHER

64. American Society for Clinical Oncology (ASCO) – U.S.*
65. Centre for Reviews and Dissemination (CRD) – U.K.*

* Agencies that perform systematic reviews of health care

§ Agencies that develop clinical practice guidelines for which they synthesize evidence.

Appendix E. Data Extraction Form for Priority-Setting Processes in Health Care Decisionmaking Bodies and Research Funding Agencies

Details of Body / Agency	Name : _____ Setting: _____ Scope: _____ National / Regional _____ Public / Private Budget: NOT STATED / STATED, specify _____
Primary Purpose of Decision Making and/or Research Funding	Technology Coverage / Clinical Information Provision and Practice Guideline Development / Evidence Generation and Synthesis, including Systematic Reviews / Evidence Generation and Synthesis, not including Systematic Reviews / Implementation of Care / Further Research / Other, specify: _____
Priority Setting Specific to Research (circle all relevant and provide specification(s))	Primary Data Collection / Review of Evidence, including Systematic Reviews / Review of Evidence, not including Systematic Reviews / Not Done / NOT STATED Specification(s): _____
Perspective of Research Priority Setting	Societal / Third Party Payer / Patient / NOT STATED / Other, specify: _____
Research Topic Generation (select all relevant and provide specification(s))	Nomination / Environmental Scan / Expert Opinion / Literature Search / Other / Not Done / NOT STATED Specification(s): _____
Methods Applied in Prioritizing Research (circle all relevant and provide specification(s))	Subjective Judgment (including Consensus Based Approaches) / Burden of Disease (Cost of Illness) / Payback of Research / Variation in Practice / Value of Information / Multi-Criteria / Other / NOT STATED / Not Done Specification: _____
Application of VOI (circle all relevant)	Analysis of Uncertainty in (Elements) of Decision / Identifying Topics for Research / Guidance for Further Research / Identifying Research Priorities / Value in Specific Research / Design of Specific Research / Not Applied / NOT STATED / Other, specify: _____
Guidance on VOI Application	Provided, describing Approaches to Modeling / Provided, not describing Approaches to Modeling / Not Provided / NOT STATED
Criteria Applied in Prioritizing Research (circle all relevant and provide specifications)	Difference in Benefits of Health Technologies / Availability of Evidence or Controversy or Uncertainty around This / Burden of Disease or Costs of Illness / Size of Patient Population or Inclusiveness / Availability of Alternatives, Timeliness/Feasibility of Review or Durability of Technology Use / Implementation of Health Technologies or Variation in Practice / Specific (Expected) Interests of Stakeholders or Ethical, Legal or Social Issues / Payback of Research or Value of Information / NOT STATED / Other, specify _____
Generation of Evidence by Body or Agency	Funded Only / Conducted Only / Funded and Conducted / Funded and Conducted by Others, specify _____ / NOT STATED
Synthesis of Evidence by Body or Agency	Funded Only / Conducted Only / Funded and Conducted / Funded and Conducted by Others, specify _____ / NOT STATED
Decision Making by Body or Agency	Advice Only / Decision Making Only / Both Advice and Decision Making / None / NOT STATED
Involvement of Stakeholders in Priority Setting Process	Topic Generation / Research Prioritization and Design / Evidence Generation and Synthesis / Decision Making / Not Done / NOT STATED
Identification of Main Stakeholders in Priority Setting Process	Patients / Health Professionals and Institutions / Manufacturers / Insurers / None / NOT STATED / Other, specify _____

Appendix F. Extracted Data From Priority Setting Processes in Different Organizations (K=13)

Name of Body or Agency	AHRQ EHC program [4,95]	CADTH HTA [96,97]
Setting	National, public	National, public funding, but independent
Budget	FY 2011 AHRQ total = ~\$611 million, \$25 million of which is for evidence synthesis	FY 2010 CADTH total = ~\$24 million, with \$5 million for the HTA program
Overall purpose/ mission of agency	"AHRQ's EHC program was authorized in 2003 by the US Congress to conduct and support research on outcomes, comparative clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services."	"to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers." (website)
Types of materials and research produced by body or agency	Evidence Generation and Synthesis, including Systematic Reviews	Clinical Information provision, evidence generation and synthesis, including systematic reviews
Does the agency make policy decisions or give advice to decision-makers?	Advice only	Advice only
Is <i>new evidence</i> funded or conducted by body or agency?	Funded and conducted (HSR, non-clinical)	None
Is <i>evidence synthesis</i> funded or conducted by body or agency?	Funded and conducted (by EPCs)	Conducted only
Primary purpose / targeted audience of evidence synthesis	to "rigorously summarize existing research studies so that health and health care decisions by practitioners, policymakers, and patients are more evidence based"	We tailor our evidence-based reports and information products to support and inform those who make decisions about health policy and purchasing, service management, and clinical practice. (website)
Stated perspective of priority setting process	"stakeholder perspectives, scientific perspectives, and the programmatic authority vested in AHRQ"	"The selected topics usually are of national interest to the publicly funded health care system." (website)
Scope/ range of topics for priority-setting exercises	All topics	All topics
Sources for Topic Generation	Nominations, expert opinions, literature search	Nomination, Expert opinion, environmental scans, other (formal surveys)
Methods Applied in Prioritizing Research	Subjective judgment, multi-criteria (including burden of disease, and variation in practice or care)	Other: Multi-criteria decision analytic approach called the analytic hierarchy process- involved an objective multi-criteria ranking, and information is then given to an advisory committee to deliberate at a face to face meeting.
Application of VOI (see Apdx D)	Not stated	Not stated
Guidance on VOI application	Not stated	Not stated
Criteria applied in prioritizing research	Availability of evidence, burden of disease, cost of illness, size of patient population, feasibility, variation in practice, Public or provider interest, Potential impact	Difference in Benefits of Health Technologies, Availability of Evidence, Burden of Disease, availability of alternatives, timeliness, variation in practice, expected interest, Other: budget impact, controversial nature of proposed technology, economic impact, ethical, legal, or psychosocial implications.
Involvement of Stakeholders in Priority-setting process	Topic generation, research prioritization and design, evidence generation and synthesis	Topic generation, research prioritization and design
Identification of Main Stakeholders in the PS Process	Patients, Health Professionals and Institutions, Insurers	Health professionals and institutions, insurers

Name of Body or Agency	NICE [98]	NIHR HTA program [99]
Setting	National, public funding, but independent	National, public
Budget	FY 2009 total ~\$70 million	FY 2010/11 ~£992m (US\$1600m) for NIHR total, ~£88m (US\$142m) for HTA program
Overall purpose/ mission of agency	NICE "is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health. NICE produces guidance in three areas of health: public health, health technologies, and clinical practice"	"The HTA programme produces independent research information on the effectiveness, costs and broader impact of healthcare treatments and tests to meet the needs of those who plan, provide or receive care in the NHS."
Types of materials and research produced by body or agency	Clinical Information provision and practice guideline development, evidence generation and synthesis, including systematic reviews, Implementation of Care	Evidence Generation and Synthesis, including Systematic Reviews
Does the agency make policy decisions or give advice to decision-makers?	Advice, but "the NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals."	Advice only
Is new evidence funded or conducted by body or agency?	Funded and conducted (HSR, non-clinical)	Funded and Conducted (methods)
Is evidence synthesis funded or conducted by body or agency?	Funded and Conducted	Funded and Conducted
Primary purpose / targeted audience of evidence synthesis	NICE produces three versions of its technology appraisals: the full appraisal for health professionals and NHS bodies, the quick reference guide for health professionals, and information for the public is written for using suitable language for people without specialist medical knowledge.	"to meet the needs of those who plan, provide or receive care in the NHS."
Stated perspective of priority setting process	to "ensure NICE's work programmes address topics of importance to patients, professionals and the health of the public and help them make the best use of NHS resources"	Not stated
Scope/ range of topics for priority-setting exercises	Topics divided into 8 "selection panels" for different clinical domains (does not include new cancer drugs, separate program)	Topics divided into 6 advisory panels for different types of technology (diagnostics vs. prevention vs. external devices vs. pharmaceutical, etc.)
Sources for Topic Generation	Nomination, Expert opinion, environmental scans, literature search, other (solicitations at meetings and conferences)	Nomination, Expert opinion, environmental scans
Methods Applied in Prioritizing Research	Subjective judgment, multi-criteria (including burden of disease, payback of research, variation in practice)	Subjective judgment, multi-criteria (including burden of disease and value of research)
Application of VOI (see Apdx D)	Not stated	Not stated
Guidance on VOI application	Not stated	Not stated
Criteria applied in prioritizing research	Availability of evidence, burden of disease, costs of illness, timeliness/feasibility of review, variation in practice, expected interest of stakeholders, ethical, legal, or social issues.	Burden of Disease and costs of illness, size of patient population, timeliness, feasibility of review, ethical, legal, or social issues, payback of research
Involvement of Stakeholders in Priority-setting process	Topic generation, research prioritization and design, evidence generation and synthesis	Topic generation, research prioritization and design
Identification of Main Stakeholders in the PS Process	Patients, Health Professionals and Institutions, manufacturers, insurers	Health professionals and institutions, other: lay people

Name of Body or Agency	USPSTF [100]	World Health Organization [101]
Setting	National, public	Global
Budget	FY2009 ~\$7.1 million	N/A
Overall purpose/ mission of agency	"Task Force recommendations are intended to improve clinical practice and promote the public health. The Task Force's scope is specific: its recommendations address primary or secondary preventive services targeting conditions that represent a substantial burden in the United States and that are provided in primary care settings or available through primary care referral."	"WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends."
Types of materials and research produced by body or agency	Evidence Generation and Synthesis, including Systematic Reviews	Clinical Information provision and practice guideline development, evidence generation and synthesis, including systematic reviews, Implementation of Care
Does the agency make policy decisions or give advice to decision-makers?	Advice only	Advice only
Is <i>new evidence</i> funded or conducted by body or agency?	None	Funded and conducted (HSR, and some clinical)
Is <i>evidence synthesis</i> funded or conducted by body or agency?	Funded	Conducted only
Primary purpose / targeted audience of evidence synthesis	"While the main audience for Task Force recommendations is the primary care clinician, the recommendations also have relevance for and are widely used by policymakers, managed care organizations, public and private payers, quality improvement organizations, research institutions, and patients."	"Recommendations that can impact upon health policies or clinical interventions are considered guidelines for WHO purposes"
Stated perspective of priority setting process	Not stated	Not stated
Scope/ range of topics for priority-setting exercises	All topics (within primary and secondary preventative services)	All topics, but divided into groups based on tracks
Sources for Topic Generation	Nomination, Expert opinion	Nomination, Expert opinion, environmental scans
Methods Applied in Prioritizing Research	Subjective judgment, multi-criteria (including burden of disease and value of research)	Subjective judgment, multi-criteria (including burden of disease)
Application of VOI (see Apdx D)	Not stated	Not stated
Guidance on VOI application	Not stated	Not stated
Criteria applied in prioritizing research	Availability of evidence or controversy, burden of disease, size of patient population, timeliness/feasibility of review, variation in practice, other: need for a balanced portfolio	Availability of evidence or controversy, burden of disease and cost of illness, size of patient population, timeliness/feasibility of review, variation in practice, ethical, legal, or social issues, other: policy relevance, topics that require system changed, opportunity costs
Involvement of Stakeholders in Priority-setting process	Topic generation	Topic generation, research prioritization and design
Identification of Main Stakeholders in the PS Process	Not stated	Not stated

Name of Body or Agency	Cochrane [102]	ZonMW [103]
Setting	Global	National, public
Budget	N/A	FY 2000 ~\$7 million
Overall purpose/ mission of agency	"The Cochrane Collaboration, established in 1993, is an international network of people helping healthcare providers, policy makers, patients, their advocates and carers, make well-informed decisions about human health care by preparing, updating and promoting the accessibility of Cochrane Review"	"The Health Care Efficiency Research programme [administered by ZonMw] actively promotes research on the recognition, assessment and implementation of cost-effective interventions and fosters generalisation of knowledge"
Types of materials and research produced by body or agency	Evidence Generation and Synthesis, including Systematic Reviews	Evidence Generation and Synthesis, including Systematic Reviews
Does the agency make policy decisions or give advice to decision-makers?	Advice only	Advice only
Is <i>new evidence</i> funded or conducted by body or agency?	None	None
Is <i>evidence synthesis</i> funded or conducted by body or agency?	Conducted only	Conducted only
Primary purpose / targeted audience of evidence synthesis	"Cochrane Reviews are designed to facilitate the choices that practitioners, consumers, policy-makers and others face in health care."	"The projects are commissioned to provide information for evidence-based policy making on the governmental level and should also promote evidence-based use of the relevant health technologies at the practice level."
Stated perspective of priority setting process	Not stated	Policy-makers ("The Health Care Insurance Board is restricting societal relevance to policy relevance from their perspective")
Scope/ range of topics for priority-setting exercises	No single process- each review group does it's own independently, variety of processes)	All topics
Sources for Topic Generation	Nomination, Expert opinion, environmental scans, literature search, other (using the Database of Uncertainties)	Nomination, not clearly stated
Methods Applied in Prioritizing Research	Subjective judgment, multi-criteria, burden of disease ("using health indicators (i.e. mortality or incidence to prioritize reviews")	Multi-criteria, burden of disease, some subjective judgment
Application of VOI (see Apdx D)	Not stated	Not stated
Guidance on VOI application	Not stated	Not stated
Criteria applied in prioritizing research	Availability of evidence, burden of disease, size of patient population, timeliness, feasibility, variation in practice, other: importance to developing countries	Burden of disease and cost of illness, size of patient population, other (direct costs of intervention per patient, additional aspects with an impact on health policy (e.g. uncontrolled diffusion)
Involvement of Stakeholders in Priority-setting process	Topic generation, selection of criteria, research prioritization and design	Research prioritization and design
Identification of Main Stakeholders in the PS Process	Health professionals and institutions, patients/consumers.	Health professionals and institutions, insurers

Name of Body or Agency	SIGN [104]	SBU [104]
Setting	National	National, public
Budget	~£1 (US\$1.6m) as of April 2007	---
Overall purpose/ mission of agency	"The Scottish Intercollegiate Guidelines Network (SIGN) was established in 1993 by the Academy of Royal Colleges and their Faculties in Scotland, to develop evidence based clinical guidelines for the National Health Service in Scotland"	"In 1992, SBU was commissioned as an independent public authority for the critical evaluation of methods used to prevent, diagnose, and treat health problems."
Types of materials and research produced by body or agency	Clinical Information provision and practice guideline development, Evidence Generation and Synthesis, including Systematic Reviews	Evidence Generation and Synthesis, including Systematic Reviews
Does the agency make policy decisions or give advice to decision-makers?	Advice only	Advice only
Is <i>new evidence</i> funded or conducted by body or agency?	None	None
Is <i>evidence synthesis</i> funded or conducted by body or agency?	Conducted only	Conducted only
Primary purpose / targeted audience of evidence synthesis	"They are designed to help practitioners assimilate, evaluate and implement the ever increasing amount of evidence and opinion on best current practice... guidelines can assist healthcare professionals in making decisions about appropriate and effective care for their patients."	"Reports by SBU are intended for those who make important choices regarding which healthcare options to use. Target groups include professional caregivers, healthcare administrators, planners, and health policy makers. The findings also concern many patients and their families."
Stated perspective of priority setting process	Not stated	"In HTA, the technology is analyzed from several perspectives and includes the ethical, social, and economic consequences of that technology. The most prominent part of HTA has been to determine cost-effectiveness to improve "value-for-money" in health care."
Scope/ range of topics for priority-setting exercises	All topics (clinical guidelines, not just research), but divided into specialty subgroups of children, cancer, CVD, mental health, primary care	All topics
Sources for Topic Generation	Nomination, Expert opinion, environmental scans	Nomination, Expert opinion, environmental scans
Methods Applied in Prioritizing Research	Subjective judgment, multi-criteria (including burden of disease, and variation in practice)	Subjective judgment, multi-criteria (including burden of disease)
Application of VOI (see Apdx D)	Not stated	Not stated
Guidance on VOI application	Not stated	Not stated
Criteria applied in prioritizing research	Burden of disease, variation in practice, Availability of evidence, Public or provider interest, Potential impact	Availability of evidence or controversy, burden of disease, size of patient population, ethical, legal, or social issues, ,Public or provider interest
Involvement of Stakeholders in Priority-setting process	Topic generation, research prioritization and design, evidence generation and synthesis	Topic generation
Identification of Main Stakeholders in the PS Process	Health professionals and institutions, patients/consumers.	Health professionals and institutions, patients/consumer, insurers

Name of Body or Agency	OHTAC [106]	Osteba [107]
Setting	Regional, public	Regional, public
Budget	N/A	N/A
Overall purpose/ mission of agency	"The OHTAC's mandate is to undertake reviews of health technologies as requested by hospitals, community-based health services, or the MOHLTC and make recommendations to the deputy minister of health regarding the uptake and diffusion of these technologies."	"To contribute to the appropriate use of existing and future health technology [and] to provide information on safety, efficacy, effectiveness, accessibility, and equity about different technologies, as required by decision makers in the Basque Country."
Types of materials and research produced by body or agency	Clinical Information provision and practice guideline development, Evidence Generation and Synthesis, including Systematic Reviews	Evidence Generation and Synthesis, including Systematic Reviews
Does the agency make policy decisions or give advice to decision-makers?	Advice only	Advice only
Is <i>new evidence</i> funded or conducted by body or agency?	None	None
Is <i>evidence synthesis</i> funded or conducted by body or agency?	Funded	Conducted only
Primary purpose / targeted audience of evidence synthesis	The reviews are conducted primarily to be used by the OHTAC to make recommendations on adoption and coverage, but they are also published and open to anyone.	Osteba's reports are used by the Health Department for policy making and by hospitals, clinicians and private care providers to improve medical practice and the organization of healthcare delivery.
Stated perspective of priority setting process	Not stated	Not stated
Scope/ range of topics for priority-setting exercises	All topics (focus on health technologies, not information systems or drugs in the Ontario Drug Benefit Program)	All topics
Sources for Topic Generation	Nomination	Expert Opinion
Methods Applied in Prioritizing Research	Subjective judgment, multi-criteria	Subjective judgment, multi-criteria (burden of disease and variation in practice)
Application of VOI (see Apdx D)	Not stated	Not stated
Guidance on VOI application	Not stated	Not stated
Criteria applied in prioritizing research	Difference in benefits of health technologies, Burden of disease and cost of illness, availability of alternatives, (other: must be licensed by Health Canada)	Burden of disease or cost of illness, size of patient population, variation in practice, timeliness, expected interest of stakeholders
Involvement of Stakeholders in Priority-setting process	Topic generation, research prioritization and design	Topic generation, research prioritization and design
Identification of Main Stakeholders in the PS Process	Health professionals and institutions, insurers, other (academics in health economics and ethics)	Health professionals and institutions, patients were invited but did not attend

Name of Body or Agency	DERP [108,109]
Setting	National, independent organization
Budget	"Participating organizations all contribute the same amount—\$96,600 per year for three years—to finance the \$4.2 million project."
Overall purpose/ mission of agency	"The Drug Effectiveness Review Project (DERP) is an alliance of fifteen states and two private organizations, which have pooled resources to synthesize and judge clinical evidence for drug-class reviews."
Types of materials and research produced by body or agency	Evidence Generation and Synthesis, including Systematic Reviews
Does the agency make policy decisions or give advice to decision-makers?	Advice only; some member organizations can make their own policy decisions
Is <i>new evidence</i> funded or conducted by body or agency?	None
Is <i>evidence synthesis</i> funded or conducted by body or agency?	Conducted only
Primary purpose / targeted audience of evidence synthesis	Some reports are open to the public, but some materials are just produced for membership organizations. "The DERP reports are not usage guidelines. They are not an endorsement or recommendation for any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports."
Stated perspective of priority setting process	Not stated (presumably the DERP membership, which does include a lot of state Medicaid programs, uses them- and it is known that the AARP is adapting them for consumer reviews.)
Scope/ range of topics for priority-setting exercises	Pharmaceuticals
Sources for Topic Generation	Nomination
Methods Applied in Prioritizing Research	Subjective judgment
Application of VOI (see Apdx D)	Not stated
Guidance on VOI application	Not stated
Criteria applied in prioritizing research	Not applicable: "In selecting which therapeutic categories to review, DERP participants give priority to certain types of classes: those accounting for a large share of pharmacy budgets; those consisting of multiple drugs; those with substantial off-label use; and those with recent additions of costly drugs."
Involvement of Stakeholders in Priority-setting process	Topic generation, research prioritization and design
Identification of Main Stakeholders in the PS Process	Insurers that are member orgs, manufacturers.

Appendix G. Application of Multistage Algorithm to VOI for Prioritizing Topics for Systematic Reviews

Topic	Difference in Benefits	Reduction in Uncertainty	Probability of Implementation	Durability of Information	Size of Patient Population	Comprehensive Outcome Measures	Prospects for Further Research	Prioritization of Topic
Urinary Incontinence (UI): Natural History and Risk Factors of UI, Effective Strategies for Identification and Prevention, and (Long Term) Effectiveness of Treatment, Patient Adherence and Overcoming Barriers	<i>Prevention:</i> - Limited/no information found <i>Treatment:</i> - Resolution in UI through different interventions: pooled risk differences range from 0.11 to 0.18 [Shamliyan et al., 2007] - Potential for improvement in QoL [Shamliyan et al., 2007]	<i>Prevention:</i> - Limited/no information found <i>Treatment:</i> - Resolution in UI through different interventions: pooled risk differences 95% CI range from 0.07 to 0.22 [Shamliyan et al., 2007]	Limited/no information found	Limited/no information found	26.0M [Shamliyan et al., 2007; NIH, 2007]	NA	NA	MAXIMAL MODELING [single topic, multiple uses]
Blood Glucose Control	-	-	-	-	25.8M [National Diabetes Fact Sheet, 2011]	-	-	MAXIMAL MODELING [clustering of topic with other topics within clinical domain]
Noninvasive Technologies for Diagnosis of CAD in Women	- Reduction in mortality - No substantiate diagnostic accuracy [in exercise myocardial perfusion and exercise echo] in women vs men [Metz et al., 2007] - Multicomponent CMR stress test can accurately diagnose CAD in women [Klem 2008]	- Insufficient power to detect differences in event rates between gender subgroups [Metz et al., 2007] - Limited data available for clinical indication of risk stratification in asymptomatic women; limited data support the sue of CMR in detection of CHD in symptomatic women [Mieres et al., 2007]	Controversy about noninvasive testing among clinicians, depending on question being addressed with test [http://heartdisease.about.com/od/coronaryarterydisease/a/no-ninvasiveCAD.htm]	- Emergence of biomarkers, gentech and technnologies - Multicomponent CMR	8.1M [AHA, 2009]	Limited / no information found	Trialing is complex and costly, perhaps unethical	MAXIMAL MODELING [clustering of topic with other topics within clinical domain]
Mental Health Support for Juvenile (Type 1) Diabetes Mellitus	-	-	-	-	- Prevalence: 0.215M Incidence 0.015M	-	-	MAXIMAL MODELING [clustering of topic with other topics within clinical domain]
Natriuretic Peptide Measurement in Management of Heart Failure: BNP and NT-proBNP to Diagnose/Monitor and Guide Treatment and Management of Heart Failure	<i>Diagnosis</i> - Potential for rule out cardiac dysfunction, diagnosis OR: 27.7 [Ewald et al., 2008] <i>Treatment</i> - Treatment overall hazard ratio for mortality: 0.69 [Felker et al., 2009] - Improvement in QALYs [Morimoto et al., 2004] - Decrease in costs of health care without increasing patient risk	<i>Diagnosis</i> - Diagnosis OR 95%CI: 21.6–35.6 [Ewald et al., 2008] <i>Treatment</i> - Treatment overall hazard ratio 95% CI: 0.55-0.86 [Felker et al., 2009] - Differences exist between current guidelines, RCTs, and recent meta-analyses on topic	- Increase in use of natriuretic plasma peptide measurement expected from current availability of simpler assay methods [Cowie et al., 2002]	- Several prospective studies ongoing confirm the utility of a natriuretic peptide-guided therapeutic strategy	Prevalence: 5.0M [NHLBI, 2009]	- No comprehensive outcomes available - No indication of VOI from existing studies	<i>Treatment</i> - large randomized trials are recommended [Balion et al., 2004].	MAXIMAL MODELING [single topic, multiple uses]
Electroconvulsive Therapy (ECT) in Elderly: Comparative Effectiveness of ECT vs Medication, Psychotherapy, and Combination Therapy as 1st Line Treatment in Elderly with Severe Depression	- Significant reduction of depressive symptoms in short-term - Increase in adverse effects, including cognitive disorders and cardiovascular risks [Gardner and O'Connor, 2008; Fraser et al., 2008] - Reduction of economic burden of depression [Greenhalgh et al., 2005]	- No research study / systematic review found on topic - Limited evidence on long-term benefits of ECT - Limited guidance on ECT for treatment of depression	- Limited awareness and acceptability of ECT - Limited accessibility to ECT due to disparities in mental health insurance, poor diagnosis / referral in primary care, and insufficient geriatric mental health workforce [APA, 2008]	- No trials ongoing / recently completed fully addressing topic [clinicaltrials.gov] - Potential changes in administration of ECT (e.g., inpatient versus outpatient)	7.9M [APA, 2008]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Specialized Wheelchairs for Patients: Assessment	Limited/No information available [Topic Brief, 2009; Interagency Wheelchair Work Group, 2004]	Limited / no information available [Topic Brief, 2009; Interagency Wheelchair Work Group, 2004]	Large variation in reimbursement policies for these devices in Medicare and Medicaid [Topic Brief, 2009]	Many types of wheelchairs exist, ranging in (customized) features and costs [Topic Brief, 2009]	2.3-3.9M [Simpson et al., 2008]	NA	NA	NO CONCEPTUAL VOI [No Difference in Benefits; No Reduction in Uncertainty]
Upright MRI: Comparative Effectiveness of Upright versus Conventional (Axial Loading) MRI in Diagnosis of Patients with Spinal Pain and Scoliosis	- Potential improvement in validity and accuracy of diagnosis - Improvement in patient satisfaction/accommodation	No comparative studies / systematic reviews exists [Skelly et al., 2007]	- Limited diffusion of uMRI in clinical practice [Skelly, et al., 2007] - Substantial investment costs for uMRI [\$1.55M] - Different coverage policies exist between health plans	NA	55.3M [Skelly et al., 2007]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Vagus Nerve Stimulation (VNS) for Depression: Comparative Effectiveness in 2nd Line Treatment for Depression in Children	- Potential reduction of symptoms of depression - Increase in adverse effects, incl. dyspnea and infection [AAFP, 2007]	- No comparative studies / systematic reviews exists - No guideline recommendations on use of VNS in children	Limited/no information available	Limited/no information available	18.0M [only for subpop children < 18] 3-5% major depression in childr [AAFP, 2007]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Family Involvement in Hospital	- Potential for reduction of	No research studies / systematic reviews	No standardization in hospital	Limited/no information	Incidence: >1.7M	NA	NA	NO CONCEPTUAL VOI

Topic	Difference in Benefits	Reduction in Uncertainty	Probability of Implementation	Durability of Information	Size of Patient Population	Comprehensive Outcome Measures	Prospects for Further Research	Prioritization of Topic
Discharge Planning: Comparative Effectiveness of Family Involvement in Hospital Discharge Planning vs "Traditional" Models of Discharge Planning for Mental Health and Psychiatric Services	hospitalization and readmissions - Potential for improvement of patient satisfaction, (medication) compliance, and cost containment - No "traditional" models of hospital discharge for patients with mental health illness	found relevant to topic [MEDLINE@Pubmed, Google Scholar]	discharge practice	found	hospital discharges of patients with serious mental disorders per year [DeFrances et al., 2008]			[No Difference in Benefits, No Reduction in Uncertainty]
Treatment of Glaucoma: Comparative Effectiveness of Combinations of Surgery, Laser and Pharmaceutical Treatment of Primary Open-Angle Glaucoma (POAG) in Minority Groups and Vulnerable Populations	- Improvement of intraocular pressure and visual function outcomes - Reduction of medication costs of POAG [Rylander and Vold, 2008]	1 research study found relevant to topic [AGIS, 2004]	Limited/no information found	13+ trials ongoing/recently completed relevant to topic [clinicaltrials.gov]	Incidence: 2.0M * % minority/vulnerable per year [Schmier et al., 2007]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty; Limited Durability of Information]
Home Oxygen Therapy: Comparative Effectiveness of Home Oxygen Therapy in Infants and Children with Bronchopulmonary Dysplasia (BPD) Chronic Neonatal Lung Disease (CNLD)	- Reduction in risk of sudden infant death, frequency of desaturation and pulmonary hypertension - Improvement in QoL, neurodevelopment growth and palliative care for hypoxemia - Increase in risk of adverse pulmonary outcomes for too much oxygen [MacLean and Fitzgerald, 2006] - Substantial costs of home and supplemental oxygen therapy	- 2 trials with limited outcomes and short follow-up, not specific to children receiving home oxygen therapy [Askie et al., 2003; STOP-ROP, 2000] - Large variation in guideline recommendations and measurements used for oxygen saturation in children	- Coverage decisions for pediatric home oxygen therapy vary by Medicaid program - Significant variation in clinical care and controversy about what constitutes appropriate care	Limited/no information found	0.01M [Hazinski, 2003]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty; Limited Probability of Implementation]
Practice Structuring in Community-Based Psychiatric Care: Comparative Effectiveness of 30 or 45-Minute Checks Complemented with Traditional Psychotherapy vs Standard 15-Minute Medication Checks	- No research studies / systematic reviews found relevant to topic [MEDLINE@Pubmed, Google Scholar]	- No research studies / systematic reviews found relevant to topic [MEDLINE@Pubmed, Google Scholar]	- 15-minute medication check is a widespread practice - Reinforcement of medication check by reimbursement issues/managed care - Controversy about medication check [Bohnert et al., 2006; Lambert, 2000; Moffic and Steven, 2006]	- Institute of Medicine (IOM) study ongoing [Institute of Medicine, 2009]	26.2M [Cherry et al., 2008]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty; Limited Probability of Implementation]
Prevention and Early Detection of Skin Cancer: Comparative Effectiveness of Non-Invasive Tests vs Biopsy for Diagnosis of Skin Cancer	- Potential for reduction of mortality - Potential for quick and painless detection	No research studies / systematic reviews found relevant to topic [MEDLINE@Pubmed, Google Scholar]	Variation in clinical care exists [Charles et al., 2005]	Limited/no information found	Incidence: 1.1M per year [ACS, 2007]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Treatment of Neovascular Age-Related Macular Degeneration (AMD): Comparative Effectiveness of VEGF Inhibitors vs Other Treatments for Neovascular AMD	- Potential for improvement in visual acuity [AAO, 2008] - Potential for reduction in costs of AMD treatment [AAO, 2008]	- > 3 systematic reviews on effectiveness of individual treatment options [e.g., Cochrane, 2009; HTA CADTH, 2008] - No direct comparison of all treatment options and no long term comparative effectiveness - Guidelines recommend patient preferred treatment [AAO, 2008]	Variation in practice due to costs of treatment, co-payments and patient preferences [AAO, 2008]	- Multiple research studies ongoing / shortly completed [clinicaltrials.gov] - Research funding for comparative effective research from National Eye Institute	- Prevalence: 1.8M [AAO, 2008] - Incidence: 0.2M [AAO, 2008]	NA	NA	NO CONCEPTUAL VOI [Limited Durability of Information]
Herbal Therapies for Cholesterol Reduction: Comparative Effectiveness of Herbal Treatment vs Medication for Hyperlipidemia	Efficacy and safety of dietary supplements remains unclear [Knox and Gaster, 2007]	No comparative effectiveness studies / systematic reviews found, except from those relating to red yeast rice for which FDA placed warning [Liu et al., 2006]	(Off-label) use of dietary supplements in 50% US-population [Knox and Gaster, 2006]	Several research studies ongoing/recently completed [clinicaltrials.gov]	38.6M [National Center of Health Statistics, 2005]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Ketogenic Diet (KD) for Epilepsy: Comparative Effectiveness of KD vs Medication and Surgery as 1st Line Management in Children with Intractable or Refractory Epilepsy	- (Potential for) increase in seizure control [Keene, 2006] - (Potential for) reduction in adverse effects, including suicide [Keene, 2006] - (Potential for) reduction in medical costs [Mandel et al., 2002]	- No randomized or controlled, prospective trial available relevant to topic - Limited data on long-term adverse effects of KD - Very limited guidance on patient selection, initiation and management of KD - Debate about appropriate comparator KD	Variation in administration of ketogenic diet, incl. dosing and duration [Kossoff, 2008]	Emergence of newer antiepileptic drugs with improved efficacy and convenience [Keene, 2006]	2.1M [French and Pedley, 2008]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Dietary Supplements (DS) in Elderly taking Cardiovascular Drugs: Comparative Effectiveness of DS Adjunctive to Pharmacotherapy in Elderly with Cardiovascular Diseases	Potential interaction between DS and cardiovascular agents	- No research study / systematic review found related to topic - Guidelines recommend information collection on DS by clinicians but do not provide guidance on check for interaction with pharmacotherapy [Miller et al., 2007]	Generalization of research findings on benefits of DS and translation into effective treatments may be difficult because of lack of (FDA) regulation	Limited/no information found	26.0M [Yeh et al., 2006]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
DVT Prophylaxis for Special Populations already Identified for Prophylaxis: Low Molecular Weight Heparin (LMWH) vs Unfractionated Heparin (UFH)	- No difference in renal failure between [Dentali et al., 2008] - No difference for any outcomes across trials [Bump et al., 2009]	Statistically significant evidence, based on cohort study [Dentali et al., 2008]	Variation in clinical practice exists, in both types and design of studies [e.g., Dentali et al., 2008; Bump et al., 2009]	Changes in administration of prophylaxis to be expected, e.g., at home and oral [Weitz, 2009]	Incidence: 0.35M	NA	NA	NO CONCEPTUAL VOI [No Difference in Benefits; No Reduction in Uncertainty]
Complementary and Alternative Medicine (CAM) for Benign Prostatic Hyperplasia (BHP): Comparative Effectiveness of CAM vs Pharmacotherapy for BHP	- Potential for symptom relief and delay of surgery - Potential interaction of CAM with pharmacotherapy	Limited/no research studies / systematic review found related to long term outcomes	- Important variation in clinical care and controversy about what constitutes appropriate care - Guideline do not recommend use of CAM [AUA, 2009]	CAMUS trial ongoing on topic	8.0M [McVary, 2007; NID, 2009]	NA	NA	NO CONCEPTUAL VOI [Limited Durability of Information]

Topic	Difference in Benefits	Reduction in Uncertainty	Probability of Implementation	Durability of Information	Size of Patient Population	Comprehensive Outcome Measures	Prospects for Further Research	Prioritization of Topic
			- Lack of standardization and (FDA) regulation of use of herbal supplements					
Hormone Therapy for Treatment of Menopausal Symptoms: Comparative Effectiveness of Delivery Techniques for Hormone Replacement Therapy for Menopausal Symptoms	- Improvement of QoL [Farquhar et al., 2009] - Reduction of menopausal symptoms [Canderelli et al., 2007; Nelson et al., 2007] - Increase in adverse effects, incl. risks of cancer, heart diseases, and stroke [Nelson et al., 2007; Farquhar et al., 2009]	- Varying outcomes (over time) in QoL differences between 4 studies related to topic [Farquhar et al., 2009] - Follow-up in 4 studies is < 3 years [Farquhar et al., 2009]	- Variation in administration (e.g., dosage and duration) of hormonal therapy [Nelson, 2008] - Reduction in prescription rates [Nelson, 2008]	29 research studies ongoing/recently completed relevant to topic [clinicaltrials.gov]	Incidence: 1.5M per year [Canderelli et al., 2007]	NA	NA	NO CONCEPTUAL VOI [Limited Durability of Information]
School-Based vs Outpatient Speech Therapy for Children: Comparative Effectiveness	Limited / no information found	No studies / reviews relevant to topic found	- Speech therapy predominantly school-based (> 98%) [ASHA, 2008] - Substantial variation in administration/delivery of therapy (e.g., duration and intensity) [ASHA, 2008]	Limited/no information found	4.5M [Law et al., 2003]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Multimodal Pain Management Programs for Chronic Mixed-Cause, Non-Cancer Neuropathic Pain in Adults: Comparative Effectiveness of Comprehensive/Multidisciplinary/ Interdisciplinary Pain Programs vs Single Therapies	- Potential for improvement in pain management and QoL [APC, 2007] - Potential for reduction in costs [Gatchel and Okifuji, 2006]	No studies / reviews found relevant to topic [MEDLINE@PubMed, Google Scholar]	- Important variation in clinical care - Controversy exists about appropriate clinical care	Limited/no information found	20.4-45.4M [APS, 2009; Gatchel and Okifuji, 2006]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Anesthesia in Infants: Long Term Comparative Effectiveness of Regional vs General Anesthesia	Potential reduction in risk of apnea	- No studies / reviews addressing long term neurodevelopmental outcomes - No comprehensive, up-to-date guidance	Choice of anesthesia is typically determined by procedure type	- Development of research protocol and guideline on topic [Cochrane, 2009; NICE, 2009] - 2 ongoing trials addressing topic [clinicaltrials.gov]	Incidence: 1.5M surgeries per year	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty, Limited Durability of Information]
Phenylalanine-restricted Diet for Phenylketonuria (PKU): comparative effectiveness of a phenylalanine restricted diet (with medical foods, amino acids and micronutrients supplements) vs pharmacological therapy such as Kuvan	- Reduction in risk of nutritional deficiencies and dietary restrictions - Potential improvement in quality of life - Increase in adverse effects, incl. headache and abdominal pain - Substantial costs of pharmacologic therapy (<57-200k) [Pollack, 2009]	- Insufficient data to evaluate use of tyrosine supplements and protein substitutes - Response to treatment with Kuvan 20-56%, cannot be pre-determined by laboratory testing (e.g., genetic testing) [US FDA, 2009] - No guidelines or consensus on optimal levels of blood phenylalanine [FDA Center for Drug Evaluation and Research, 2007]	- Variation in clinical care, particularly regarding precise level of phenylalanine restriction and diet relaxation - No up-to-date guidelines exist for dietary and pharmacologic management of PKU, except from NIH consensus statement [NIH, 2000]	There is need for powered RCT [NIH, 2000]	Incidence: 0.002M [NIH, 2001]	NA	NA	NO CONCEPTUAL VOI [Small Patient Population; No Reduction in Uncertainty]
Nonsurgical vs Surgical Treatment of Chronic Pelvic Pain: comparative effectiveness of surgical vs non-surgical treatment	- Reduction of pain and other symptoms - Reduction of productivity losses [Kuligowska et al., 2008]	- No studies found directly comparing surgical vs non-surgical treatment [Cheong and Howard, 2007] - No standardized definition on CPP exists - Guidelines vary in detail of recommendations [Fall et al., 2004; RCOG, 2005; Jarrell et al, 2005]	Significant variation in clinical practice exists	Limited/no information available	24.9M [Latthe et al., 2006; Matthias et al., 2002]	NA	NA	NO CONCEPTUAL VOI [No Reduction in Uncertainty]
Occupational and Physical Therapy: comparative effectiveness of physical and rehabilitative therapy for adults with knee pain secondary to osteoarthritis (OA)	- Improvement in pain relief / control, physical functioning and prevention of disability [e.g., Bjordal et al., 2007; Jamtvedt et al., 2008] - Potential for improvement in QoL [Fitzgerald and Oatis, 2004] - Improvement in adherence to treatment modalities by clinicians and patients [Fitzgerald and Oatis, 2004] - Reduction of economic burden of OA [CDC, 2010]	- 80+ studies / 4+ reviews on intermediate outcomes [incl. Bjordal et al., 2007; Jamtvedt et al., 2008; Fransen et al., 2008] - No study / review focusing on patient-centred functional outcomes - Guidelines recommend exercise [AAOS, 2008]	- No standardization of treatment [Fitzgerald and Oatis, 2008] - Improvement in adherence expected from patient-centered outcomes - Variation in coverage of treatment by health plans	Revision of guideline recommendations in 2012 [AAOS, 2008]	Prevalence: 13.0M [CDC, 2010; AAOS, 2008]	Table 3 [Jamtvedt et al., 2008]	NA	MINIMAL MODELING
Antipsychotics for ADHD: comparative effectiveness of antipsychotics vs stimulant medication in children with ADHD	- Improvement in control of aggressiveness and disruptiveness [Aman et al., 2002; Snyder et al., 2002] - Increase of adverse effects, incl. cardiovascular-related and metabolic disturbance [McIntyre and Jerrell, 2008]	- 10 RCTs relevant to topic [e.g., Aman et al., 2002] - No systematic review exist - Most guidelines do not address use of antipsychotics in treating ADHD; and only recommend use when aggressive comorbidities exist or in very severe cases of ADHD [Taylor et al., 2004]	Limited/no information found	4 RCTs ongoing/recently completed (fully) relevant to topic [clinicaltrials.gov]	5.4M [Armenteros et al., 2007]	- Comprehensive outcomes: [Table 4 in Aman et al., 2002] - Potential indication of VOI [Meltzer et al., 2009]	NA	MINIMAL MODELING
Noninvasive Positive Pressure Ventilation (NPPV) for Acute Respiratory Failure: comparative effectiveness in COPD and ACEPE patients	- Decrease in need for invasive endotracheal intubation: -65% [Quon et al., 2008] - Reduction in risk of in-hospital mortality (RR): -55% [Quon et al., 2008] - Reduction in length of hospital stay	- Decrease in need for invasive endotracheal intubation: 95% CI: 0.26-0.47 [Quon et al., 2008] - Reduction in RR: 95% CI: 0.30-0.66 [Quon et al., 2008] - Reduction in LoS: 95% CI: 0.0-3.9days	- Great variation of use between hospitals and regions: max 11% use [Nava and Hill, 2009] - Non-tolerance by patients: 13-19%	Limited/No information available	12.0M [COPD], 1.0M [ACPE]	Measures for RR and LoS [Quon et al., 2008]	NA	MINIMAL MODELING

Topic	Difference in Benefits	Reduction in Uncertainty	Probability of Implementation	Durability of Information	Size of Patient Population	Comprehensive Outcome Measures	Prospects for Further Research	Prioritization of Topic
	during acute COPD exacerbations (LoS): -1.9 days [Quon et al., 2008]	[Quon et al., 2008]						
Allergen-Specific Immunotherapy: Comparative effectiveness of allergen-specific immunotherapy plus standard vs. standard alone for allergy diseases in asthmatic and asthma-prone children	- Reduction of asthma symptoms and medication, OR: 4.6 of not developing asthma [Jacobsen et al., 2007]; 3.8 in grass-pollen allergic children [Novembre et al., 2004] - Increase in risk of adverse events	- Reduction of asthma symptoms and medication, OR 95% CI: 1.5-13.7 of not developing asthma [Jacobsen et al., 2007]; 1.5-10.0 in grass-pollen allergic children [Novembre et al., 2004] - 2 systematic reviews and 24 trials	Variation in and debate about most appropriate administration of (sublingual or subcutaneous) administration of immunotherapy [Van Wijk et al., 2007]	14 studies ongoing / recently completed relevant to topic [clinicaltrials.gov]	Prevalence: 50.0M [American Academy of Allergy, 2011]	Reduction of asthma symptoms and medication, OR and 95% CI with 10 year follow-up: not developing asthma [Jacobsen et al., 2007]; in grass-pollen allergic children	NA	MINIMAL MODELING
Acute Migraine Treatment in Emergency Settings: comparative effectiveness of non-opioids and opioids in emergency departments (ED)	- Improvement in relief of pain and symptoms (incl. vomiting and nausea) of migraine [Friedman and Grosberg, 2009] - Reduction of economic burden of migraine [Kalra and Elliot, 2007]	11+ studies / 3 systematic reviews relevant to topic [Colman et al., 2004; Bailey et al., 2008; Friedman et al., 2008]	- Considerable variation in clinical practice [Vinson, 2002; Colman et al., 2004] - Guidelines caution against the use of opioids as 1st line treatment [ICSI, 2009]	> 4 studies ongoing/recently completed [clinicaltrials.gov]	Incidence: 1.0M ED presentations per year [Vinson, 2002]	Pooled odds ratios for headache relief [Friedman et al., 2008]	NA	MINIMAL MODELING
Prophylactic Treatment of Migraine with Alzheimer's Medications	- Some improvement in frequency and severity of migraines with only few side effects [Nicolodi et al., 2002; Bigal et al., 2008] - Reduction in productivity loss (\$19.6B per year [Burton et al., 2009])	- 3 observational studies on memantine [Bigal et al., 2008; Spengos et al., 2008; Charles et al., 2007], 1 on donepezil [Nicolodi et al., 2002] - No guidance for off label use of Alzheimer's medications for migraine prevention	- Current utilization in 38% patients eligible for prophylactic treatment: 13% [Silberstein et al., 2009]	No trial ongoing / recently completed relevant to topic [clinicaltrials.gov]	22.7-34.0M [Silberstein, 2009]	Observational studies: frequency of migraine and severe pain [Bigal et al., 2008; Nicolodi et al., 2002]	NA	MINIMAL MODELING
H2RAs and PPIs for GERD: a) comparative effectiveness of H2RAs and PPIs for treatment of GERD; b) effectiveness of algorithm for LT treatment of GERD (i.e., combination PPIs and H2RAs); and c) cost-effectiveness of medical management and surgical options for treatment of GERD	- Improvement in symptoms and QoL, maintenance of healed erosive esophagitis, and prevention of - Reduction in costs of health care	Uncertainty in LT comparative effectiveness and costs of combined treatment regimens (PPI and H2RAs)	- PPIs dominate prescribing practice - Some endoscopic interventions are no longer in use - Some concerns with OTC treatments for GERD - Worldwide variation in guidance on LT treatment of GERD	Limited / no information available	45.4 - 99.9M	- No comprehensive outcome measures found - Indication of VOI: [Barton et al., 2008; Grant et al., 2008]	Trial is potentially valuable	FULL MODELING
Self-Measured Blood Pressure Monitoring: comparative effectiveness of self-measured blood pressure monitoring vs clinic measurements in patients with hypertension	- Improvement in measurement and monitoring of blood pressure [Stergiou et al., 2004; Appel et al., 2002]; systolic blood pressure: 4.2 mm HG [Cappuccio et al., 2004] - Improvement of adjustment and adherence to therapy [Stergiou et al., 2004; Appel et al., 2002; Ogedegbe and Schoenthaler, 2006] - Increase in adverse effects, incl. obsessiveness of patients and inappropriate disease management [Pickering et al., 2008]	- 15+ trials / 5 observational studies - Improvement in measurement and monitoring of blood pressure [Stergiou et al., 2004; Appel et al., 2002]; systolic blood pressure: 95% CI 1.5-6.9 mm HG [Cappuccio et al., 2004]	- Rapid increase in use of SMBP [Pickering et al., 2008] - Inconsistent guideline recommendations on use of SMBP - Coverage of SMBP only by limited number of health plans - No CMS decision on use of SMBP	Limited / no information available	65.0M [Pickering et al., 2008]	- No comprehensive outcome measures found - No indication of VOI from existing studies	Trial is potentially valuable	FULL MODELING
Pharmacologic Therapies for Management of Crohn's Disease: comparative effectiveness of post-operative treatment options for patients	- Improvement in QoL, control and prevention of inflammation, symptom relief, remission of disease and postponing need for surgery - Increase in side effects and risk associated with them - Reduction in cost burden of disease (\$8.2k-18.9k per patient, or \$3.6B-15.5B US budget impact per year [Kappelman et al., 2003; Yu et al., 2008])	- 1 meta-analysis available comparing single treatments vs placebo, or vs single treatment [Patil et al., 2008; Doherty et al., 2009] - No standard regimen to prevent relapse of Crohn's after surgery [Rena et al., 2008], or to define disease severity [AAFP, 2010]	- Variation in clinical practice due to heterogeneity in symptoms, course of disease and prognosis among patients [Rena et al., 2008]	1+ trials for new experimental drugs ongoing [clinicaltrials.gov]	Prevalence: 0.5M [Kappelman et al., 2007; CCFR, 2009]	- Meta-analysis: clinical recurrence and surgery recurrence in 23 RCTs - No indication of VOI from existing studies	Trial is potentially valuable	FULL MODELING
Prevention of Venous Thromboembolism (VTE) in Orthopedic Surgery: comparative effectiveness of prophylaxis in patients undergoing major orthopedic surgery (TKR, THR, HFS)	- Reduction in risk of DVT and PE - Increase in adverse side effects, incl. bleeding - Reduction in economic burden of VTE	- Inconsistent outcome measures / results [Geerts et al., 2008; AAOS, 2008]	- Substantial variation in use of prophylaxis in clinical practice: < 52% [Yu et al., 2007] - Payment by regulatory bodies, e.g. CMS - Controversy among clinicians, and contradictory guidelines exist [Geerts, 2008; AAOS, 2008]	Multiple trials / studies ongoing / recently completed [clinicaltrials.gov]	- Incidence of PE: 0.1M per year > Number of orthopedic surgeries - max bound 1/0.4*0.25M at risk / surgical procedures [Geerts et al., 2008]	- No comprehensive outcome measures found - No indication of VOI from existing studies	Trial is potentially valuable but likely costly	FULL MODELING
Biologics vs Conventional Systemic Treatments for Moderate and Severe Psoriasis:	- Reduction in chronic inflammation of skin and psychosocial disability - Improvement in QoL	- Only 3 RCTs found relevant to topic - No trial evidence on long-term safety and efficacy of biologic and nonbiologic	Limited / no information found	Limited / no information found	Prevalence: 7.5M [Menter et al., 2008]	- No comprehensive outcome	Trial is potentially valuable	FULL MODELING

Topic	Difference in Benefits	Reduction in Uncertainty	Probability of Implementation	Durability of Information	Size of Patient Population	Comprehensive Outcome Measures	Prospects for Further Research	Prioritization of Topic
Comparative Effectiveness	<ul style="list-style-type: none"> - Reduction on costs burden of disease and productivity loss (\$1500 per year) [Fowler et al., 2008] - Substantial cost difference between biologics (\$13k-30k) and conventional systemic treatment [Sizto et al., 2009] 	treatments for moderate-to-severe psoriasis				<ul style="list-style-type: none"> - measures found - No indication of VOI from existing studies 	but likely costly	
Effectiveness of Nurse Case Managers: Comparative Effectiveness	<ul style="list-style-type: none"> - Improvement in quality of care - Reduction in health care utilization and costs 	Insufficient evidence / inconsistent results [Owens et al., 2007; Latour et al., 2007]	Limited / no information found	Limited / no information found	All patients	<ul style="list-style-type: none"> - No comprehensive outcome measures found [due to limited follow up] - No indication of VOI from existing studies 	Substantial value in more research	FULL MODELING
Procalcitonin-Guided Therapy for Sepsis: Comparative Effectiveness for Diagnosis and Management vs. Standard Therapy	<ul style="list-style-type: none"> - Reduction in antibiotics therapy duration (pooled OR: 0.506) and antibiotic exposure (weighted mean difference: 2.785) without harmful effects for patients (pooled OR: 0.838) [Tang et al., 2009] - Reduction of economic burden of disease with increase in costs of hospitalization [Martin and Wheeler, 2009] 	<ul style="list-style-type: none"> - Reduction in antibiotics therapy duration (pooled OR: 95% CI 0.290-0.882, p = 0.016) and antibiotic exposure (weighted mean difference: 95% CI 1.225-4.345, p = 0.000) without harmful effects in terms of patient mortality (pooled OR 95% CI 0.571-1.229, p = 0.365) [Tang et al., 2009] 	<ul style="list-style-type: none"> - Limited / no information about utilization of biomarkers in clinical practice - Clinical use of PCR-guided therapy remains controversial [Tang et al., 2009] 	4 CCTs/RCTs ongoing/recently completed relevant to topic [clinicaltrials.gov]	Incidence: 0.75M per year [Lever and Mackenzie, 2007]	<ul style="list-style-type: none"> - No comprehensive outcome measures found - No indication of VOI from existing studies 	Trial is potentially valuable	FULL MODELING
Physician Outreach via Email and Internet Networking: Effectiveness on Patient Outcomes and Treatment Adherence	<ul style="list-style-type: none"> - Improvement in patient satisfaction/convenience - Improvement in QoL and process measures, incl. treatment adherence - Reduction in costs of health services [Leong et al., 2005] 	Limited / no information available	<ul style="list-style-type: none"> - 5.5-9.2% patient access to physicians conducting internet or email consults [Sciamanna et al., 2003] - 55% discontinued use of internet communication tool over 1.5 years [Wu et al., 2006] 	Limited / no information available	All patients	<ul style="list-style-type: none"> - No comprehensive outcomes measures found - No indication of VOI from existing studies 	Trials are expected to be complex and costly	FULL MODELING
Antinuclear Autoantibody and Rheumatoid Factor Testing: Comparative Effectiveness in Children with Musculoskeletal Pain	Reduction of false positive tests	<ul style="list-style-type: none"> - No evidence on epidemiology and determinants of pain - No guidelines on testing 	Limited / no information found	Limited / no information found	3.8-15.0M	<ul style="list-style-type: none"> - No comprehensive outcomes measures found - No indication of VOI from existing studies 	Observational study on prevalence data is potentially valuable	NO FULL MODELING [Observational Study for Additional Primary Data Collection is Expected to Be Relatively Inexpensive]

Appendix H. Minimal Modeling VOI in Acute Respiratory Failure in WinBUGS

#MODEL: COMPARATIVE EFFECTIVENESS OF Noninvasive Positive Pressure Ventilation vs STANDARD THERAPY

```
model
{
# MODELS FOR PRIOR ANALYSIS

lnrr_prior ~ dnorm(mu_lnrr_prior, tau_lnrr_prior)
ilos_prior ~ dnorm(mu_ilos_prior, tau_ilos_prior)

for (i in 1 : 101)          # threshold value for cost-effectiveness (*1000-1000)
{
NB_prior[i] <- exp(lnrr_prior)*(1-exp(-bmr))*le*(i*1000-1000)/pow((1+beta), (le-1)) + ilos_prior*c_ilos - c_nppv
PrCE_prior[i] <- step(NB_prior[i])
pEVPI_prior.1[i] <- max(-NB_prior[i], 0)*((time*imp*dur*pop)/pow((1+beta), (time-1)))
pEVPI_prior.2[i] <- max(0, NB_prior[i])*((time*imp*dur*pop)/pow((1+beta), (time-1)))
}

# MODELS FOR SAMPLE & POSTERIOR ANALYSIS

for (nsc in 1:7)
{
n[nsc] <- max(500, (nsc-1)*1000) # expected additional sample of patients for review update

ybar_tau_lnrr[nsc] <- 1/((1/tau_lnrr_prior)*n_lnrr/n[nsc])

ybar_lnrr[nsc] ~ dnorm(lnrr_prior, ybar_tau_lnrr[nsc])
mu_lnrr_post[nsc] <- (ybar_lnrr[nsc]*ybar_tau_lnrr[nsc]/(tau_lnrr_prior + ybar_tau_lnrr[nsc]))
+ (mu_lnrr_prior*tau_lnrr_prior/(tau_lnrr_prior + ybar_tau_lnrr[nsc]))

ybar_tau_ilos[nsc] <- 1/((1/tau_ilos_prior)*n_ilos/n[nsc])

ybar_ilos[nsc] ~ dnorm(ilos_prior, ybar_tau_ilos[nsc])
mu_ilos_post[nsc] <- (ybar_ilos[nsc]*ybar_tau_ilos[nsc]/(tau_ilos_prior + ybar_tau_ilos[nsc]))
+ (mu_ilos_prior*tau_ilos_prior/(tau_ilos_prior + ybar_tau_ilos[nsc]))

for (k in 1 : 101)          # threshold value for cost-effectiveness (*1000-1000)
{
NB_post[nsc, k] <- exp(mu_lnrr_post[nsc])*(1-exp(-bmr))*le*(k*1000-1000)/pow((1+beta), (le-1)) + mu_ilos_post[nsc]*c_ilos - c_nppv
PrCE_post[nsc, k] <- step(NB_post[nsc, k])
pEVPI_post.1[nsc, k] <- max(-NB_post[nsc, k], 0)*((time*imp*dur*pop)/pow((1+beta), (time-1)))
pEVPI_post.2[nsc, k] <- max(0, NB_post[nsc, k])*((time*imp*dur*pop)/pow((1+beta), (time-1)))
}
}

# DATA

list(mu_lnrr_prior = -0.80,      # mean log relative risk of in-hospital mortality
tau_lnrr_prior = 31.98,        # precision of distribution of log relative risk, 1/var() = 1/(ln(0.30)-ln(0.60))/2*1.96)^2
mu_ilos_prior = 1.94,         # mean difference in length of hospital stay
tau_ilos_prior = 1.03,        # precision of distribution of length of hospital stay, 1/var() = 1/(3.87-0.01)/2*1.96)^2
bmr = 0.25,                   # baseline in-hospital mortality rate
le = 4.4,                     # life expectancy, years
c_nppv = 7012,                 # costs of administring NPPV, $
c_ilos = 600,                  # costs of hospital stay per day, $
time = 5,                     # time horizon of analysis, years
dur = 1,                      # durability of information
imp = 0.10,                   # implementation of NPPV, probability of implementation x tolerability of NPPV, 0.11*0.87
pop = 850000,                 # number of hospital admissions per year
beta = 0.03,                  # discount rate
n_lnrr = 940,                 # sample of patients included in prior systematic review [Quon et al., 2008]
n_ilos = 956,                 # sample of patients included in prior systematic review [Quon et al., 2008]
end
```