Value-of-Information Analysis for Patient-Centered Outcomes Research Prioritization

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I. Introduction

The purpose of this document is to discuss the potential use of value-of-information analysis (VOI) as a tool for research priority setting for the Patient-Centered Outcomes Research Institute (PCORI). The paper is divided into six sections. First, we provide a brief description of VOI, using an example based on the standard cost-effectiveness framework. Next, we review the existing literature on the application of VOI to research prioritization in health care settings, followed by a discussion of challenges to VOI identified in this literature. In the fourth section, we discuss the unique challenges to the use of VOI for research prioritization by PCORI, in particular, the desirability of alternatives to cost-effectiveness as a decision threshold, followed by some proposed solutions to these challenges. Finally, we provided suggestions for evaluating these potential solutions within PCORI's research agenda.

II. Description of VOI

VOI is an approach to research prioritization which uses Bayesian methods to estimate the potential benefits of gathering further information (through more research) before making a decision. In "classic" decision analysis, the optimal choice between two or more strategies is the one with the highest expected value; for each strategy, the expected value is calculated by multiplying the probability of a given outcome by the value of that outcome. Because this calculation is almost always an estimate made on the basis of imprecise or incomplete data, the result is more properly referred to as the *expected value given current information*. The underlying uncertainty in the data raises the possibility that a decision made on the basis of the expected value given current information may be incorrect. Using Bayesian methods, it is possible to calculate the *expected value given perfect information*—in other words, the outcome if the optimal decision were made every time. The difference between these two values is the *expected value of perfect information* (EVPI), the upper bound of the opportunity cost of making

a wrong decision; any effort to improve the quality of available data that costs less than the EVPI is worth pursuing.

A. Example Based on the Standard Cost-Effectiveness Framework

We can compare two hypothetical treatments, A and B, for a potentially fatal disease. Although VOI for health care research has traditionally been performed using a cost-effectiveness framework, where the optimal decision is based on a willingness-to-pay (WTP) threshold defined in terms of cost per quality-adjusted life year (QALY) saved,[1-5] the approach requires only that an "optimal" decision be defined—how that decision is defined is less important (the implications for this for PCORI are discussed in the last two sections). For this example, we assume that the initial costs of the two treatments are identical, so that the only costs that need to be considered are those associated with failed treatment or treatment complications, and our primary outcome is unadjusted life expectancy. We also assume that no randomized trials have been performed, and that the only available data on treatment effectiveness and complication rates are from two case series of 50 (Treatment A) and 100 (Treatment B) patients, while data on mortality after a complication is available from an administrative dataset of 1000 patients. For the purposes of this example, we do not consider the effects of inadequate study design on uncertainty and focus only on sample size; we also do not consider the effects of uncertainty in cost estimates. Table 1 shows the available "data," including 95 percent confidence intervals, and Figure 1 shows a simple decision tree used to estimate the expected value given this data.

Table 1. Input Variables and Values for Treatments A and B

Parameter	**Treatment A (95% CI)**	**Treatment B (95% CI)**
Cure rate	94% (86.0 to 98.6%)	90% (83.5 to 95.0%)
Life expectancy if cured	20 years	
Life expectancy if treatment fails	5 years	

Parameter	Treatment A (95% CI)	Treatment B (95% CI)
Costs of managing treatment failure	$50,000	
Overall complication rate	20% (10.0 to 27.5%)	5% (2.1 to 10.1%)
Mortality rate after complication	10% (8.2 to 12.0%)	
Cost of complication	$10,000	
Costs associated with fatal complication	$50,000	

Abbreviation: CI = confidence interval

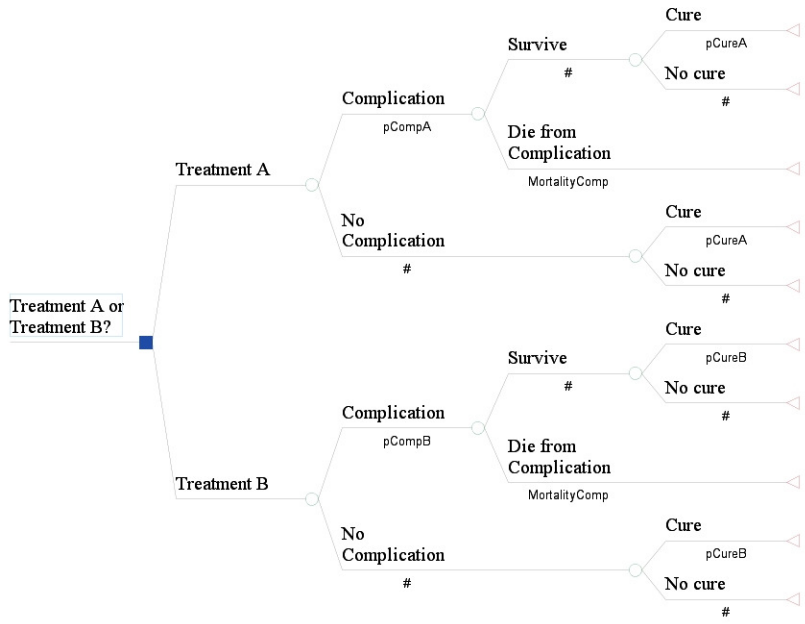


Figure 1. Schematic of decision tree used in example. pCompA = complication rate for treatment A, pCompB = complication rate for treatment B, MortalityComp = mortality rate after experiencing a complication, pCureA = probability of cure with Treatment A, pCureB = probability of cure with

Treatment B, "#" = 1-the probability of the branch above the "#".

Table 2 shows the expected values based on the mean value of the parameters. Treatment A results in better overall life expectancy because of the higher cure rate, but has higher overall costs because of a higher complication rate, resulting in an incremental cost-effectiveness ratio of $692 per year of life saved.

Table 2. Expected Values of Outcomes of Interest Given Treatment A or B

Outcome	Treatment A	Treatment B
Mean life expectancy	18.72 years	18.40 years
Mean costs	$10,940	$10,725
Mortality from complications of treatment	2.0%	0.5%

In a setting where the optimal decision is based on cost-effectiveness, Treatment A would be preferred based on these results if a decisionmaker were willing to pay at least $692 for each year of life saved. An alternative to incremental cost-effectiveness ratios for comparing different options across varying WTP thresholds is net benefits, expressed as either net monetary benefits (NMB) or net health benefits (NHB). Both measures integrate costs, effectiveness, and WTP into a single number. For example, NMB is defined as

Willingness-to-pay threshold * Net quality-adjusted life expectancy – Net costs

At any given WTP, the option with the highest NMB is "optimal"; in Table 2, the NMB for Treatment A at a WTP threshold of $600 (less than the incremental cost-effectiveness ratio of $692) would be ($600*18.72) – $10,940, or $292, while for Treatment B it would be ($600*18.40) – $10,725, or $315, and Treatment B would be preferred; at a threshold of $750 (a value higher than the incremental cost-effectiveness ratio), the corresponding values would be $3,100 for Treatment A and $3,075 for Treatment B, and Treatment A is "optimal."

However, even at a single WTP, the possibility that Treatment B would be preferred cannot be ruled out given the wide confidence intervals for both effectiveness and complication rates. In probabilistic sensitivity analysis (PSA), multiple simulations are performed; drawing the value for each parameter from a distribution based on the available data or expert input at the beginning of each simulation. The expected value is the mean of all the simulations and should approximate the expected value estimated from the means of each parameter. The advantages of PSA include quantification of the uncertainty surrounding the expected value, and, in the context of decisionmaking, an estimate of the probability of making an incorrect decision based on the available information.

Table 3 shows the results of 10 simulations from our original example, at a WTP threshold of $750.

Table 3. Outcomes from 10 Simulations of Treatment A and B Assuming a WTP Threshold of $750

Simulation Number	Net Benefits Treatment A	Net Benefits Treatment B	Maximum Net Benefits	Preferred Strategy	Opportunity Cost
1	$4,180	$4,306	$4,306	B	$0
2	$2,273	$2,415	$2,415	B	$0
3	$7,095	$4,507	$7,095	A	$2,588
4	$3,186	$4,017	$4,017	B	$0
5	$3,504	$3,433	$3,504	A	$72
6	$5,698	$6,740	$6,740	B	$0
7	$4,762	$3,718	$4,762	A	$1,044
8	$3,960	$1,919	$3,960	A	$2,041
9	$5,071	$5,964	$5,964	B	$0
10	$1,904	$5,123	$5,123	B	$0
Expected value (mean of simulations 1–10)	$4,163	$4,214	$4,789		$575

Abbreviation: WTP = willingness-to-pay

Each simulation draws the values for effectiveness, complication rates, and mortality from the distributions determined by the sample size. The mean value for all the simulations is the expected value—for Treatment A, $4,163, and, for Treatment B, $4,214. Based on the expected

NMB, Treatment B is the preferred option. However, in 4 of the 10 simulations, Treatment A had the higher NMB. If we knew the results of each simulation, we would choose the option with the highest net benefit *in that simulation*. In this case, the expected value would be the mean of the maximum values for the entire set of simulations, or the expected value given perfect information. The difference between this value ($4,789) and the expected value given current information ($4,214) is the expected value of perfect information (EVPI, $575).

Alternatively, this can be considered as the opportunity cost based on making the wrong decision. If we choose Treatment B based on its higher expected value, there is a 40 percent chance that we would be wrong; the difference between the net benefits of A and B in each simulation where A was preferred (numbers 3, 4, 7, and 8 in Table 3) represents the opportunity cost of choosing B based on its expected value; the expected overall opportunity cost is the mean of these, or $575 (identical to the value obtained by subtracting the expected value given current information from the expected value given perfect information).

Further research might result in a narrower range of parameter values for both treatments—the higher the EVPI, the more worthwhile it would be to invest in further research. Note that the EVPI is dependent on the WTP threshold—in general, the EVPI will be highest at values of the threshold where there is the greatest uncertainty about the optimal decision. The decision model generates estimates of the EVPI for individual “patients”; these can then be converted to a population-level estimate based on the number of potential patients, the time horizon under which the intervention will be used, and an appropriate discount rate. If the expected costs of research to reduce uncertainty are less than the population EVPI, then further research could be considered. At the simplest level, using the example above, the EVPI value of $575 would be multiplied by the expected number of patients who would be candidates for Treatment A or Treatment B over a given future time horizon, incorporating an appropriate discount rate; this value represents the upper bound of what would be reasonable to spend to reduce uncertainty

surrounding Treatments A and B. As a tool for research prioritization, the population EVPI has two main potential applications: (a) as a "go/no go" threshold for deciding whether further research is worthwhile; and (b) in theory, as a way to compare the "cost-effectiveness" of research across different interventions, or even across different clinical problems or therapeutic areas.

The partial EVPI, or *expected value of partial perfect information* (EVPPI), is a further extension of this concept. In this case, the EVPPI for a specific variable or group of variables is estimated, usually by holding the value of that variable or group of variables constant and performing the rest of the probabilistic analyses; the results provide an estimate of the cost-effectiveness of reducing uncertainty for specific variables. The higher the EVPPI, the more important reducing uncertainty for that particular parameter is for reducing uncertainty about the overall decision. Figure 2 shows the EVPPI for treatment effectiveness, complication rates, and mortality from complications at varying WTP thresholds for the example above.

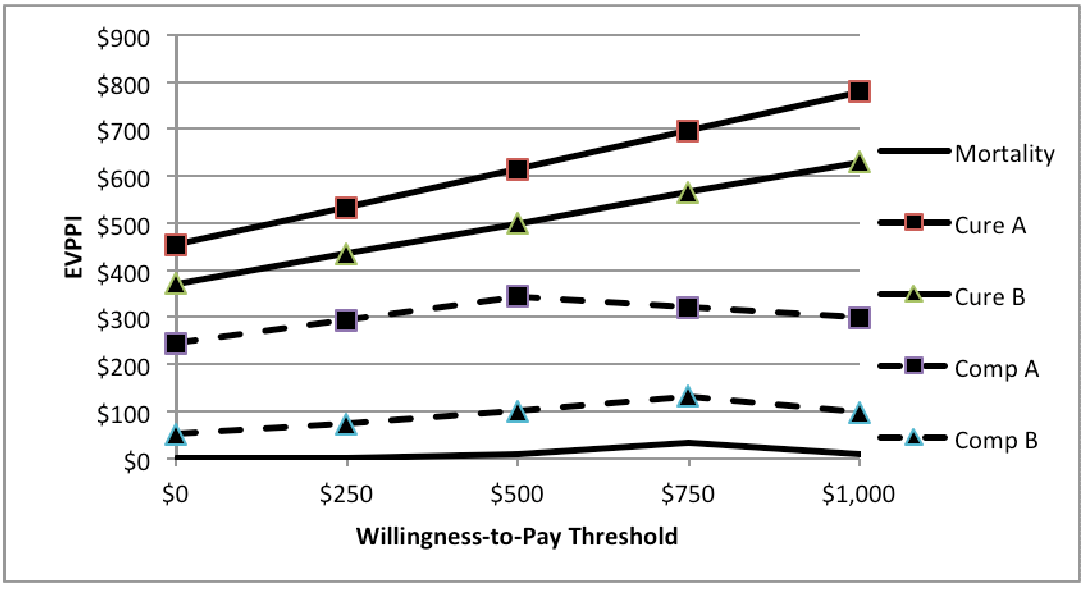


Figure 2. EVPPI at varying WTP thresholds for uncertain parameters. Cure A = cure rate of Treatment A; Cure B = cure rate of Treatment B; Comp A = complication rate of Treatment A; Comp B = complication rate of treatment B; Mortality = mortality rate after complications.

In this example, the mortality rate for complications has a very low EVPPI, in part because of the greater precision of the already existing data. Complication rates are next in importance, with rates associated with Treatment A having a higher EVPPI (because of lower precision). Effectiveness has the highest EVPPI, with Treatment A again having the highest value. Therefore, it follows that reducing uncertainty about the relative effectiveness of the two treatments has the highest priority, followed by complication rates. These values can be used to inform study designs, including sample size needs.[1,6-13]

B. Summary

In summary, VOI is a method for estimating the impact of uncertainty on the likelihood of making an incorrect decision. By estimating the overall EVPI based on the currently available data, policymakers can estimate the value of any further research prior to making a decision. By estimating the EVPPI for specific components of the uncertainty, policymakers can estimate the relative value of research on those components. The next section reviews specific published applications of VOI within the health care setting.

III. Current State of VOI in Health Care Research Prioritization

A. Literature Search Methods

Search Strategy

To identify published literature relevant to this review, we performed a search of the PubMed® database using search terms relevant to VOI. We also reviewed all included references from a prior study performed by our research group in which we evaluated the use of modeling techniques, including VOI analysis, for research prioritization.[14] Details of the search

strategy used, a flow diagram depicting the results of the search and screening process, and lists of included and excluded articles are provided in Appendix A.

Inclusion and Exclusion Criteria

At the title-and-abstract screening level, articles were included if they met the following criteria:

- Published in English language from January 1, 1990, to the present
- Describe an explicit priority-setting process which employs either VOI or decision modeling in another format, or provide explicit discussion or examples of VOI analyses

Articles were excluded if they focused on establishing priorities for providing health services rather than prioritization of research.

We retrieved the full text of all potentially relevant literature included at the title-and-abstract level and conducted a second review for inclusion and exclusion. For inclusion at the full-text stage, articles were required to meet the following criteria:

- Available in English
- Full publication (excluding articles only available as abstracts)
- Published January 1, 1990 to present
- Either
    1. describes an explicit priority-setting process which employs either VOI or decision modeling in another format, or
    2. provides explicit discussion or examples of VOI analyses
- Focused on research prioritization (excluding prioritization of health services or other topics)
- Includes a formal framework or process for research prioritization
- Includes specific research prioritization recommendations (excluding articles that provide only a description of a framework/ process)

- Prioritization is VOI- or decision analysis-based
- Context is relevant to PCORI

Study Selection

Two investigators independently reviewed each title and abstract for potential relevance; articles included by either investigator underwent full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to include or exclude the article for data abstraction. When the paired reviewers arrived at different decisions about whether an article met criteria for inclusion, or about the reason for exclusion, we reached a final agreement through review and discussion among investigators. Full-text articles meeting eligibility criteria were included for data abstraction. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc., Manotick, ON, Canada).

Data Abstraction

We developed a data abstraction form in Distiller SR for collecting data from all included studies. Abstractors worked in pairs: the first abstracted the data, and the second reviewed the article and the accompanying abstraction form to check for accuracy and completeness. Disagreements were resolved by consensus or by assistance from a third, arbitrating member of the study team. Abstracted data elements are listed in Appendix B.

Additional Analysis Based on Web of Science Search

To explore the potential impact and translation of the VOI studies we identified and their findings we performed a Web of Science search to determine the number of published studies that cited our included VOI papers. These studies were then evaluated to determine whether they were methods papers, systematic reviews, or cost-effectiveness analyses, or if they could potentially represent primary research on a topic informed by the VOI.

B. Literature Search Findings

Table 4 illustrates the results of the search. The majority of the identified VOIs included patient preferences or behaviors (usually as part of a QALY) as one of the outcomes or key probabilities; of these, approximately half identified these parameters as one of the three most important sources of uncertainty (i.e., had high EVPPI).

Table 4. Characteristics of Existing VOI Literature

Sponsor	Number of VOI Papers (% of all VOI)	Studies with Patient Preferences Included (% of VOI Papers by Sponsor)	Studies That Cite Patient Preferences as Important* (% of VOI Papers by Sponsor Where Patient Preferences Included)
UK NICE	28 (34)	27 (96)	10 (37)
Other non-U.S. government	17 (21)	14 (82)	6 (43)
U.S. government	9 (11)	7 (78)	4 (57)
Other**	28 (34)	19 (68)	8 (42)
TOTAL	82 (100)	67 (82)	28 (42)

*Includes studies that listed uncertainties related to patient preferences/adherence within the top three parameters requiring future research
**Includes studies funded through academic, advocacy groups, or industry sources, and those where the sponsor was either unclear or unreported.
Abbreviations: NICE = National Institute for Health and Clinical Excellence; VOI = value-of-information analysis

Based on the available evidence, the greatest experience with the use of VOI for prioritization by research sponsors is in the UK with 28 of the 82 (34%) included papers being supported by the National Institute for Health and Clinical Excellence (NICE) within the UK's Health Technology Assessment (HTA) program; an additional 18 studies were not specifically funded by NICE but were performed by authors within the UK through other research funding mechanisms. There does not appear to be any meaningful experience in the United States other than small pilot studies. Of particular interest to PCORI, patient-centered outcomes such as quality of life, or patient behaviors such as adherence to recommendations, had high EVPPIs in approximately half of the papers where these parameters were included as an outcome.

Even within the UK, however, the extent to which VOI analyses have specifically informed coverage decisions or funding for studies judged to be worthwhile on the basis of VOI is unclear. Of the 556 articles citing the included VOI papers identified in the Web of Science, only 40 were not methods papers, systematic reviews, or cost-effectiveness analyses, and—based on their title, abstract, and date of publication—could potentially represent primary research on a topic informed by the VOI. However, none of these papers specifically cited the VOI as a justification for the study or as a validation of the importance of the results. Technically, VOI is clearly feasible for patient-centered research and is able to generate potentially useful estimates of EVPI and EVPPI. However, there are challenges to the broader use of VOI by the research community which have been consistently identified. The next section describes these general challenges, focusing on broad issues rather than specific unresolved methodological debates.

IV. General Challenges to the Use of VOI for Research Prioritization

A. Resources Needed to Develop Appropriate Models.

Conducting a VOI requires extensive resources, including:

- Personnel: Expertise is required in the clinical area being studied, in the evaluation and synthesis of literature and other data sources, in computer decision modeling, and in the use of VOI and its associated analyses itself. Centers with the appropriate mix of expertise are limited; indeed, our review showed that 38% of all the identified VOI papers were authored by one of only three groups (20 studies from the University of York, 7 from Erasmus University Medical Center, and 4 from University of Chicago).
- Time: The parameter inputs for a VOI require, at the very least, a systematic review of the literature, and often involve primary data analysis and synthesis (for example,

of cost data) as well. If such a review has not preceded the decision to utilize VOI, time must be budgeted for this review. Model building, validation, and calibration also require substantial amounts of time. Finally, because of the need to use probabilistic analytic methods, the physical time required to perform VOI can be substantial.

- Computing resources: The time required to perform VOI can be reduced with more powerful computers, or with distributed computing, but this requires additional investment in hardware and software programming.

In some cases, a "minimal modeling" approach to VOI can be used which requires substantially less investment. As described by Meltzer and colleagues,[15] minimal modeling appears to be most useful when an intervention affects quality of life alone (eliminating the need to model survival or other clinical outcomes); when a study follows cohorts of patients randomized from the time of treatment to death and records all relevant outcomes; or when outcomes data are available from a study in which survival or quality of life differ up to a certain point, then become similar. This approach is unlikely to be applicable for interventions for chronic disease, where followup to death is uncommon, and, as the authors note, estimating the EVPPI for specific parameters is impossible without a decision model. Another disadvantage is the inability to use the same model to evaluate different interventions, populations, or other scenarios by revising the model parameters.

As the authors point out, even a minimal modeling approach requires an investment of resources that could otherwise potentially be used to fund direct research to answer research questions. Whether the substantial investment required to incorporate VOI into research prioritization by PCORI would ultimately lead to a more efficient use of resources is unclear, but there may be methods to provide some empiric data, which we discuss in the final section.

B. Scope of VOI

There are numerous potential ways that VOI can be used to inform research priorities, but some of these are likely to be more feasible than others.

- Prioritizing across disease areas: In theory, population EVPIs could be estimated for broad classifications of diseases and conditions (e.g., cancer versus heart disease versus pregnancy-related conditions), or within narrower categories (e.g., breast versus ovarian versus prostate cancer), and these estimates used to allocate resources (for example, to the appropriate National Institutes of Health [NIH] institutes). However, the technical challenges and resources required to develop the comprehensive set of models needed to generate reasonable estimates across diseases and conditions make this impractical for the foreseeable future. In the shorter term, VOI is likely to be limited to condition-specific prioritization decisions.
- Prioritizing within a condition: For conditions where several broad categories of intervention are potentially available, it may be possible to compare the relative value of further research within each category. For example, attempts at identifying effective screening strategies for ovarian cancer have consistently failed,[16,17] and modeling studies suggest that this is largely due to the natural history of the disease rather than inadequate screening technology.[18,19] VOI comparing the EVPI for further research into screening relative to primary prevention strategies or improved treatments for ovarian cancer could help inform the relative allocation of resources.
- Prioritizing specific comparative effectiveness research: The most common application of VOI to date has been in identifying whether further research is justified prior to adapting a particular intervention, and which specific areas contribute most to uncertainty, and it seems likely that this will remain the most common application for some time. This suggests that initial applications of VOI may fall within areas where

there are already existing and generally well-accepted models (such as cervical, breast, prostate, colorectal cancer, cardiovascular disease, and HIV); however, these areas may not necessarily be the ones where the potential benefits of VOI are greatest.

- Prioritizing attributes of patient experience common to multiple conditions: One potential category where comparison of VOI results across different diseases or conditions might be useful is in prioritizing research into different aspects of patient experiences with the healthcare system that affect multiple conditions. In this case, the between-condition comparisons could focus on relative ranking, rather than specific EVPIs or EVPPIs. For example, adherence to recommendations is likely to be important to the overall effectiveness of screening for a variety of conditions. If uncertainty about the impact of specific attributes of a physician/health system experience on adherence is consistently highly ranked in terms of EVPPI in VOI analyses of screening for multiple conditions, further research into those attributes might have greater overall impact than for attributes that are more unique to a given condition.

C. Stakeholder Engagement

Feedback from decisionmakers and stakeholders from both the UK NICE experience [20] and the much smaller Agency for Healthcare Research and Quality (AHRQ) pilot of the use of VOI performed by the Duke Evidence-based Practice Center[14] was generally positive, but several consistent themes were noted (many of these were also noted in a review of the use of modeling in systematic reviews conducted by the University of Minnesota for AHRQ) :[21]

- Lack of familiarity with the methodology*:* The majority of stakeholders are not familiar with decision modeling, Bayesian techniques, or VOI. This is particularly true in the U.S. setting. To the extent that analysts are able to provide appropriate background materials, this can be somewhat ameliorated, but this requires additional time and effort on the part of the analysis team. Ultimately, if VOI is to be part of the prioritization process, methods

for providing basic training in the principles of VOI are required; in the context of PCORI, special efforts may be needed for patient representatives, particularly if these come from outside the advocacy/policy community.

- Timing of VOI*:* One of the Duke pilot projects involved stakeholders who had recently participated in a consensus-based approach to research prioritization. Although all of the stakeholders felt the VOI results were helpful, they were evenly divided on whether the VOI results would have been more helpful as background prior to beginning the consensus process, or as something to be integrated into the consensus approach as part of an iterative process.

  In the setting of a research sponsor such as PCORI, VOI could be performed prior to a solicitation for research proposals, with the solicitation specifically requesting proposals only in those areas identified as having acceptable EVPI/EVPPI. Alternatively, VOI could be performed after an initial review of proposals as part of the funding decision, with proposals with higher EVPI/EVPPIs receiving higher priority for funding. In either case, the sponsor would need to specify specific areas of research interest that could be incorporated into a model for VOI. Another possibility would be to encourage, or even require, investigators to include a VOI analysis as part of the rationale for their proposals.

D. Heterogeneity and Equity

VOI has typically been performed using a population-level perspective. However, differences between individuals or subgroups in the probability of different outcomes, or in preferences for different outcomes, can have substantial effects on VOI results.

- Heterogeneity in probability of outcomes*:* Different subgroups may have different results based on the probability of different outcomes. For example, in one of the Duke pilot studies, the individual EVPI for further research in non-hysterectomy treatment for

uterine fibroids was somewhat higher for African-American women than for white women, because of a higher incidence of fibroids at younger ages.[14] Because the overall incidence is so much higher in African-American women, this does not substantially affect the relative population-level EVPIs; however, for conditions with less striking disparities, or for conditions affecting a smaller subgroup, it is possible that population EVPIs would be lower. This issue is especially important if population-level EVPIs are used to prioritize research across different conditions or diseases—rare conditions would inevitably rank lower, raising issues of how to balance overall burden of disease, the potential population benefits of reducing uncertainty for a particular condition, and equity.

- Heterogeneity in patient preferences for outcomes*:* There may be variation between subgroups in the distribution of patient preferences for different outcomes. For example, the relative importance of quality of life and survival may vary between individual cancer patients,[22] and the "average" optimal choice may be suboptimal for a substantial proportion of patients.[23] Again, equity considerations need to be balanced with the absolute size of the relevant subgroup and the magnitude of preference differences when using population-level EVPI for research prioritization. On the other hand, the basic approach behind estimating VOI can be helpful in identifying the value of considering patient preferences, through estimation of the expected value of individualized care (EVIC),[24] which calculates the value of "research" into elicitation of individual patient preferences; for example, Basu and Meltzer found a very high value for eliciting individual patient preferences prior to treatment for prostate cancer in 65 year old men compared to treatment based on population-level preference data.[24]
- Heterogeneity in patient preferences for other attributes of care*:* Variability in preferences for other attributes of care beyond outcomes is also important, but has not been systematically incorporated into VOI. If preferences for these attributes affect

behavior, these can be incorporated into models as probability parameters—for example, as mentioned above, the potential effect of different attributes of screening tests on adherence to colorectal cancer screening had the largest EVPPI of any parameter in a recent cost-effectiveness/VOI analysis.[25] However, other attributes are not readily captured within QALY framework; many women have very strong preferences for the labor and delivery process, but converting these preferences into utilities based on elicitation via standard gamble or time trade-off has questionable face validity. Alternative approaches, such as discrete choice experiments,[26-28] may be a useful alternative for capturing patient values for a range of relevant attributes.

E. Effect of Resolving Uncertainty on Patient and Provider Choices

A fundamental assumption underlying VOI is that research resolving uncertainty will lead to improved clinical decisionmaking. However, recent experience in the US suggests that new evidence is often met with substantial resistance from both patients and providers,[29-31] especially for treatments that have already been incorporated into practice. The VOI approach can be extended to incorporate the relative value of interventions to increase adherence to evidence-based practice (the expected value of implementation;[10,32,33] such an analysis might suggest that research into methods for improving adherence should have a higher priority than research into clinical effectiveness; such research may or may not be part of PCORI's research portfolio, but knowing that improved implementation is more important than improved certainty about effectiveness is useful in either case.

These general challenges to the use of VOI are faced by any organization seeking to utilize the method for research prioritization.[2] However, there are some unique challenges to PCORI, especially related to how to use VOI when decision making based on an explicit cost-effectiveness threshold is not currently an option.

V. Specific Challenges to the Use of VOI by PCORI

Patient-centered outcomes research is defined by PCORI as research that:

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, or health delivery system interventions to inform decisionmaking, highlighting comparisons and outcomes that matter to people;
- Is inclusive of an individual's preferences, autonomy and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life;
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination; and
- Investigates (or may investigate) optimizing outcomes while addressing burden to individuals, resources, and other stakeholder perspectives.[34]

VOI can certainly address all of these areas, although the last is the one where there has been the greatest experience. Although the final research agenda and evaluation criteria for PCORI have not yet been published, preliminary indications are that specific disease areas will not be targeted; instead, the research portfolio will be divided between five broad themes—clinical effectiveness, improving health systems, communication and dissemination, fairness/addressing disparities, and accelerating patient-centered research.[35] VOI can be used to inform research priorities for the first four areas, and, to the extent that greater use of VOI might lead to the development of a more efficient research process, investment in VOI resources can potentially contribute to the fifth as well.

Table 5 shows proposed prioritization/review criteria for research for PCORI, and specific ways in which VOI could potentially be used to help evaluate each domain.

Table 5. Potential Use of VOI in Proposed PCORI Evaluation Criteria

PCORI Evaluation Criteria	Potential Use of VOI
Impact on health of individuals and populations	Population EVPI allows comparison across conditions. Population EVPPI allows comparison of specific components of uncertainty within a condition/intervention
Probability of improvability via research	EVPPI can estimate relative impact of different parameters; feasibility of research requires additional judgments
Inclusiveness of different sub-populations	Effect of differences in sub-populations can be explicitly modeled.
Current gaps in knowledge/variations in care	VOI explicitly addresses the relative importance of different gaps in knowledge, and can be extended to incorporate variation in care.
Impact on health system performance	Depending on definition, "health system performance" can be incorporated into VOI
Current health disparities	Effect of reducing existing disparities can be explicitly modeled
Potential to influence decision-making at the point of care	VOI explicitly considers impact of reducing uncertainty in specific parameters affecting decisions; usefulness depends on extent to which this uncertainty actually drives decision-making
Responsiveness to expressed needs	N/A
Fits PCORI definition	N/A
Novel use of technology	N/A
Efficient use of research resources	VOI explicitly compares relative value of different research areas, allowing resources to be directed to areas of greatest impact

Abbreviations: EVPI = expected value of perfect information; EVPPI = expected value of partial perfect information; N/A = not applicable; PCORI = Patient-Centered Outcome Research Institute; VOI = value of information

VOI has the potential to be a useful tool for PCORI in developing a research agenda. However, in addition to the general issues related to VOI identified in Section III above, the current ambiguity about how cost-effectiveness research and the use of quality-adjusted life expectancy as an outcome fit within PCORI's research portfolio[36-38] suggests that alternative approaches may need to be considered, or used alongside the "classic" approach. Although this is not an insurmountable challenge, and may have some advantages compared to "classic" VOI, the lack of a monetized decision threshold makes it almost impossible to directly translate VOI findings into a research budget—decisionmakers will need to incorporate other criteria besides the quantitative rankings from alternative VOI approaches in making funding decisions. Although this would be true with monetized VOI results as well, the lack of a specific relationship between the value of the research and the research budget makes the process somewhat more

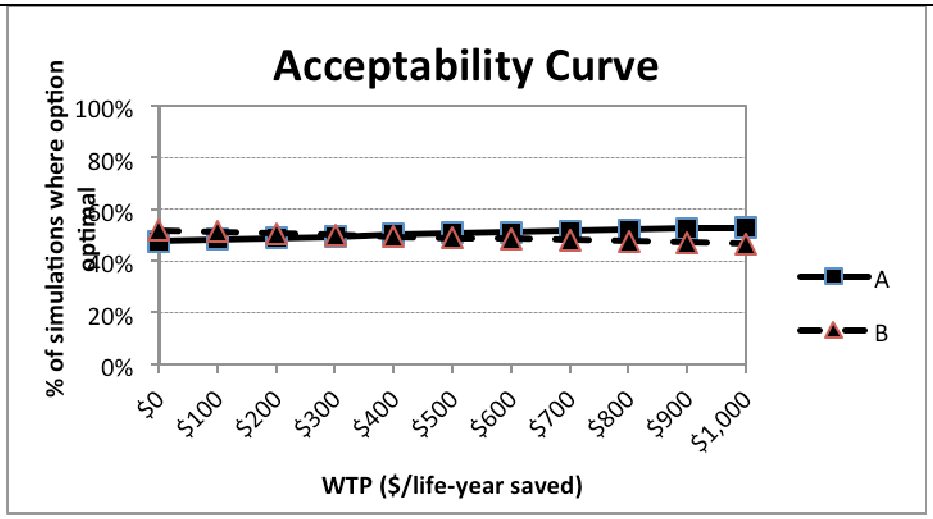
difficult (of course, since VOI results are not currently used, this would not represent a change from the status quo).

Ultimately, the underlying purpose of VOI for health care is to help decide whether further research will increase the likelihood of a given stakeholder making an optimal decision, given his or her preferences for the inevitable trade-offs between clinical benefits and harms, and economic costs. Incremental costs per QALY or NMB are simply methods for summarizing these trade-offs. In principle, alternative summary measures can be used. Options for the use of VOI outside of a cost-effectiveness framework include:

- Using cost-benefit analysis: There are a variety of alternative approaches to valuing preferences for non-market goods such as health care, including stated preference methods such as contingent valuation and discrete choice experiments (where questionnaires are used to elicit preferences for different states or attributes), and revealed preference (where preferences are inferred from observed data such as the time and costs associated with travel).[39] Such approaches are commonly used in the economic evaluation of environmental and safety regulation, and could potentially be applied to the health care setting.[40] Individual- or subgroup-level variations in the distribution of preferences can be incorporated into models. Another advantage of this approach is that using data from certain stated preference methods such as discrete choice would greatly facilitate incorporating preferences for different nonclinical attributes of a choice (e.g., surgical versus nonsurgical management when "hard" outcomes are similar) into the model, especially compared to QALYs.[26,27] The basic approach to estimating EVPI and EVPPI would be similar.[41] Finally, because the principles and language of cost-benefit analysis are familiar to policymakers from their use in other settings that affect health, a cost-benefit framework may facilitate communication of the results of VOI in some settings.

- Using “harm-benefit ratios” or multiple other criteria: If costs are not to be considered at all, a VOI approach could still be used. For example, the incidence of specific harms could be considered as “costs” in the numerator, with clinical benefits in the denominator; specific weights could be used for different harms and benefits. The effect of uncertainty of different parameters on the “optimal” outcome could still be quantified and used to help with decisions, as long as decision makers are willing to specify an acceptable threshold. Figure 3 illustrates this using the hypothetical example from Section I. The first panel (A) is a cost-effectiveness acceptability curve, where the Y-axis represents the proportion of simulations where a given option had the highest NMB, and the Y-axis represents a WTP threshold. In the second panel (B), the analysis was conducted using total complication incidence as the numerator and life expectancy as the denominator, while the third panel (C) uses fatal complication incidence as the denominator.

A.



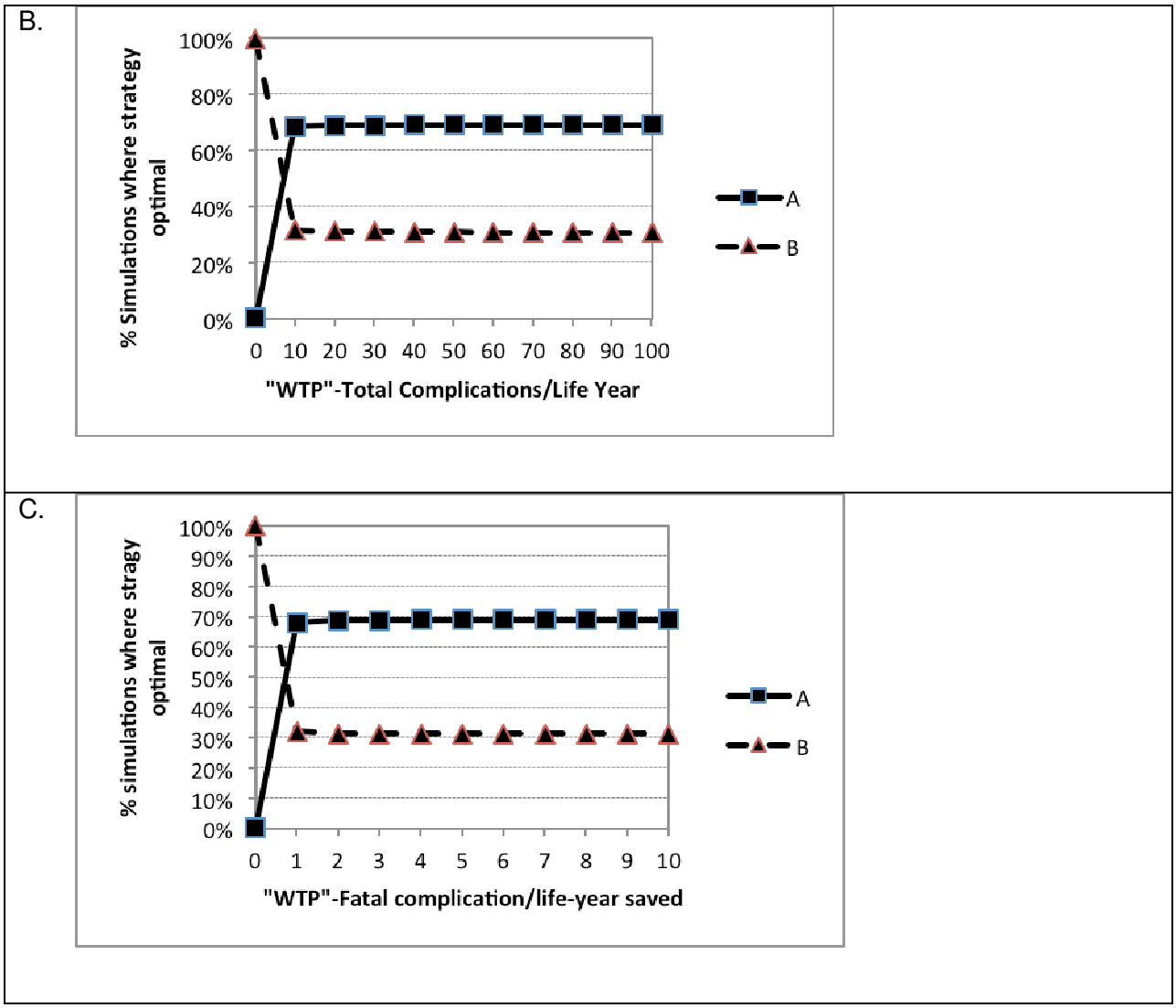


Figure 3. Acceptability curves for (a) cost per life-year saved, (b) total complications per life year saved, and (c) fatal complications/life-year saved from the example given in Section I. Graphs show the percentage of simulations where Treatment A (squares) or B (triangles) was optimal at a given threshold for WTP for an extra year of life-saved in terms of costs, complications, or fatal complications.

There have been a variety of methods proposed as alternatives to cost-effectiveness for quantifying the joint distribution of benefits and harms,[42-47] some of which include probabilistic analyses, but we did not identify any examples where the results of these methods were used to

help with research prioritization. Challenges to this approach include the need for decisionmakers to explicitly identify thresholds for the trade-offs, as well as the difficulty in translating these results into a research budget; however, costs—whether from a societal, payer, or patient perspective—could readily be incorporated. This approach might be particularly helpful in quantifying uncertainty and identifying research priorities in the setting of evidence-based guidelines or recommendations where costs are not explicitly considered, such as those by the U.S. Preventive Services Task Force (USPSTF). Models are increasingly used to help inform the recommendations; using VOI to quantify uncertainty might be especially helpful when the optimal trade-offs between benefits and harms is not clear, or when a surrogate for harm (such as unnecessary invasive diagnostic procedures)[48,49] is used. Multi-criteria decision analysis (MCDA), another method borrowed from environmental policymaking,[50,51] may have the most promise; there has been some pilot work with using MCDA in a health care setting, but primarily in the context of coverage decisions[42,47] or individual decisionmaking;[52] it should be possible to expand this approach to address research prioritization.

These options are not mutually exclusive, and, indeed, a single VOI analysis could potentially incorporate all of them—each approach is an attempt to improve decisionmaking by clarifying the trade-offs involved in making a decision now compared to putting off the decision and collecting more data. The inputs and outputs are similar across the various approaches, with the main difference being the way that the individual components of the decision—harms, benefits, and costs—are aggregated to facilitate decisionmaking. It is likely that, in many if not most cases, the results will be quite similar no matter which approach is taken. In that case, the best approach is probably the one that is easiest to communicate to decisionmakers, researchers, and patients.

VI. Recommendations

We believe that VOI has significant potential as a tool for research prioritization by PCORI, despite both the general challenges to its application and the challenges specific to its use by PCORI described in this paper. Addressing these challenges is certainly feasible, but will require investment of resources. We suggest the following initial steps by PCORI:

A. Formal Discussions/Conference with Other Policymakers

The ultimate success of VOI as a tool will require a critical mass of both methodologists able to perform VOI, and policy makers comfortable enough with the approach to be able to use the results of VOI. Whether and when this critical mass develops will be driven by the extent to which VOI is adopted by research sponsors. PCORI should engage with other research sponsors with experience with VOI (particularly NICE). We are aware of ongoing pilot work to incorporate VOI into prioritization by one of the cooperative trials groups sponsored by the National Cancer Institute (NCI),[53] and of active interest on the part of the National Heart, Lung, and Blood Institute (NHLBI).[54,55] Development of a common research agenda and implementation plan by major sponsors would both increase overall efficiency and help accelerate development of the necessary infrastructure to fully utilize VOI.

B. "Comparative Effectiveness"/Proof of Principle of VOI

In order to justify the investment in developing this infrastructure, it would be helpful to have better evidence that the use of VOI will ultimately lead to more efficient use of research resources. As noted above, there is no evidence that VOI has actually been used to make decisions about research funding. One way to make a more compelling case for greater use of VOI would be to directly compare the results of prioritization based on VOI to current practice.

Our search identified one such "forensic" analysis, which compared the estimated VOI of a completed trial based on information available at the time of study design to the actual cost of

the trial and concluded that the investment was worthwhile;[56] the NHLBI Working Group on VOI has suggested similar analyses.[54] However, VOI is designed to help with decisions prospectively—retrospective analysis of a single study may provide some insight into whether the decision to fund that study was appropriate from a VOI perspective, but it does not provide any useful information about whether funding that study was appropriate *compared to the other alternatives available at the time.*

A more informative analysis would be to use VOI to evaluate the choices made in resource allocation. Possible designs include:

- Within a single study, compare funded sample size to optimal sample size based on expected value of sample information.
- Using a completed request for applications/proposals for a condition where there is an existing model which can be adapted for VOI (and with appropriate protections for confidentiality and the peer review process), compare rankings of the proposals based on VOI to both the final peer review scoring for "significance" and to the ultimate funding decision by the sponsor.
- Alternatively, the above-described comparison could be performed prospectively, in parallel with an ongoing review.

C. Developing a Specific Strategy for VOI

The first two steps will help PCORI decide whether the investment required to optimally incorporate VOI into its research prioritization is worthwhile. Once this decision is made, a more detailed strategy for developing VOI capacity can be formulated. This would include decisions about appropriate decision criteria, the timing of VOI relative to evaluation of research proposals, and the nature of the infrastructure to support VOI for PCORI.

D. Parallel Development/Evaluation of VOI and Value of Implementation

Finally, as discussed above, scientific uncertainty alone is not the sole (or, in many cases, the major) contributor to variability in practice, inefficiency, or excess costs. Investment in research that does not result in practice change is ultimately not the best use of resources, no matter how high the EVPI. Any use of VOI by PCORI needs to include a "value of implementation" component so that, when appropriate, research resources are directed towards understanding and overcoming barriers to the use of evidence by patients and providers prior to obtaining the evidence itself.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
EVIC	expected value of individualized care
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
HTA	Health Technology Assessment
MCDA	multi-criteria decision analysis
NCI	National Cancer Institute
NHB	net health benefit
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NMB	net monetary benefit
PCORI	Patient-Centered Outcomes Research Institute
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
USPSTF	U.S. Preventive Services Task Force
VOI	value-of-information analysis
WTP	willingness-to-pay

Appendix A. Literature Search and Screening Results

PubMed® Search Strategy

Search date: November 3, 2011

Exact search string:

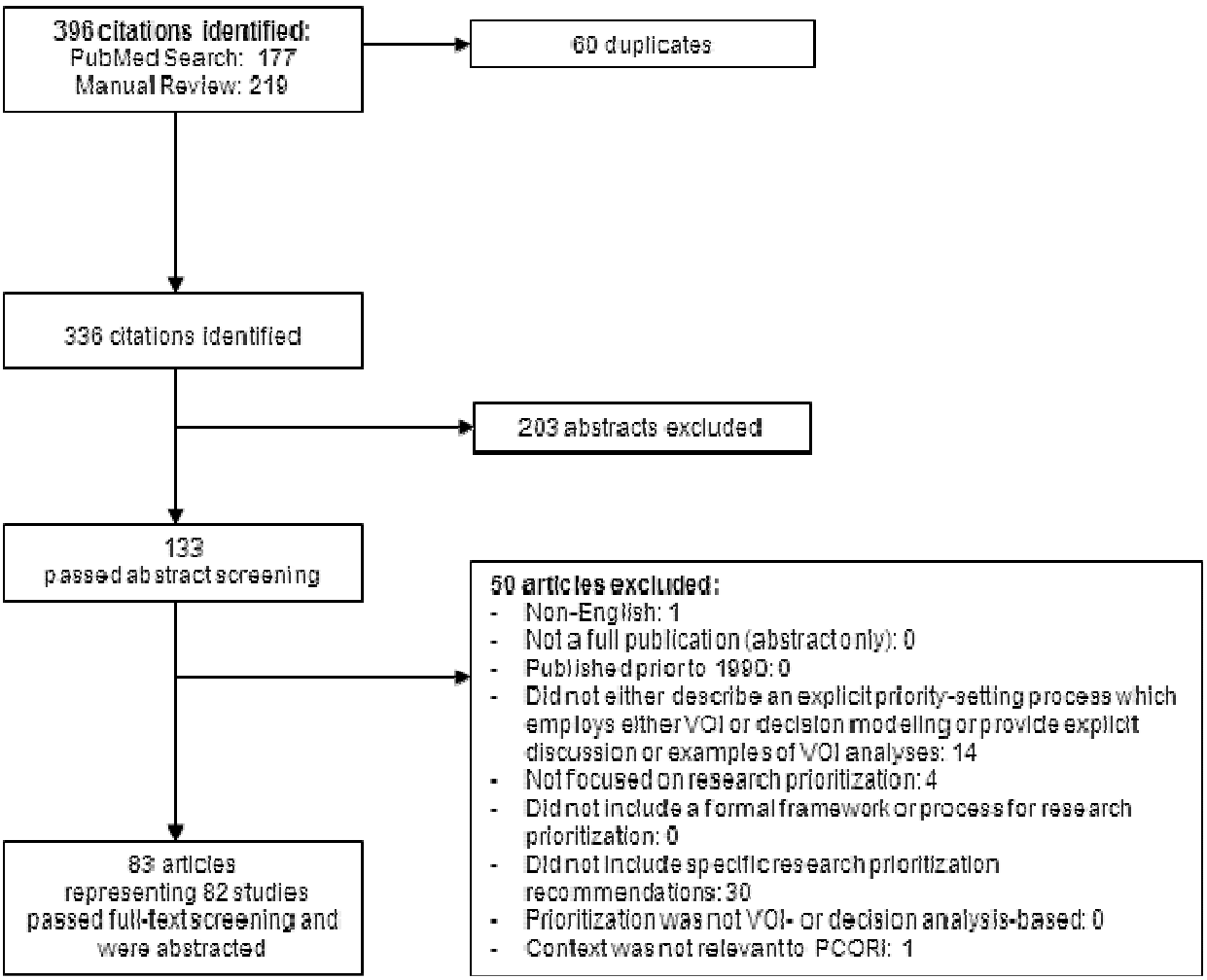
((("value of information"[ALL] OR "Value of Additional Information"[ALL] OR "Value of Information Analysis"[ALL] OR "Expected Value of Perfect Information"[ALL] OR "EVPI"[ALL] OR "EVPPI"[ALL] OR "Expected Value of Partial Perfect Information"[ALL] OR "Bayesian Approach to Uncertainty"[ALL] OR "Value of Research"[ALL])) AND (("Decision Making"[MH] OR "Decision Theory"[MH]) OR ("Research"[MH] OR "Health Services Research"[MH]) OR research[TIAB])

Set #	Terms	# of Results
#1	Search (("value of information"[ALL] OR "Value of Additional Information"[ALL] OR "Value of Information Analysis"[ALL] OR "Expected Value of Perfect Information"[ALL] OR "EVPI"[ALL] OR "EVPPI"[ALL] OR "Expected Value of Partial Perfect Information"[ALL] OR "Bayesian Approach to Uncertainty"[ALL] OR "Value of Research"[ALL]))	**337**
#2	Search (("Decision Making"[MH] OR "Decision Theory"[MH]) OR ("Research"[MH] OR "Health Services Research"[MH]) OR research[TIAB])	**1078887**
#3	Search #1 AND #2	**177**

Literature Screening Results

Figure A1 summarizes the results of our literature search and screening.

Figure A1. Literature flow diagram



Abbreviations: PCORI = Patient-Centered Outcomes Research Institute; VOI = value-of-information analysis

List of Included Studies

Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. Med Decis Making 2004;24(2):207-27. PMID: 15090106.

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List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

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Appendix B. Data Abstraction Elements

I. Study Characteristics
- Last name of first author
- Year of publication
- Study objective
- Indicate region(s) where study was performed (check all that apply):
  - U.S.
  - Canada
  - UK
  - Europe
  - South America
  - Central America
  - Asia
  - Africa
  - Australia/ New Zealand
  - Unclear/ Not reported
  - Other (specify)
- List country(ies) where study was performed
- Analysis type (check all that apply):
  - VOI
  - Other modeling
- Funding organization (check all that apply):
  - NIH
  - AHRQ
  - Other US government (specify)
  - Non-US government (specify)
  - WHO
  - Professional society (specify)
  - Advocacy group or NGO (e.g. AHA, ACS)
  - Industry
  - Academic
  - NICE
  - Unclear/ Not reported
- Primary audience for research priorities (check all that apply):
  - Study sponsor/ funder (e.g. HTA by NICE)
  - Named research funder other than study sponsor
  - Unspecified research funders
  - Other (specify)

II. Patient Preferences
- Measure of patient preferences (check all that apply):
  - Utilities/QALY's
  - Willingness to pay
  - Other (specify)

    - None/ not reported
- Source for patient preferences (check all that apply):
    - Systematic review specifically for this article
    - Cited systematic reviews
    - Non-systematic review specifically for this article
    - Cited non-systematic review
    - Study conducted as part of this project
    - Other (specify)
    - None/ not reported
- Method for eliciting patient preferences (check all that apply):
    - Linear rating scale
    - Time-tradeoff
    - Standard gamble
    - Contingent valuation (willingness-to-pay)
    - Discrete choice/conjoint analysis
    - Other (specify)
    - None/ not reported
- Prioritization method for modeling-based approaches (check all that apply):
    - VOI analysis
    - Cost effectiveness
    - Probabilistic decision analytic model
    - Other (specify)
    - Not specified

III. Importance of Uncertainty About Patient Preferences on Results

- Ranking of at least one patient-centered outcome (including preferences/utilities, adherence) in terms of key uncertainties
    - Top 3
    - Reported, but not in top 3
    - Not important
    - Not reported
- List the reported outcomes/ key uncertainties