WHITE PAPER

Value of Information and Research Prioritization

MARCH 15, 2012

PRESENTED BY:
NORC at the University of Chicago

PREPARED BY:
David Rein, PhD

NORC at the UNIVERSITY of CHICAGO

Table of Contents (Title)

Acknowledgements

This work was sponsored by the Patient Centers Outcomes Research Institute (PCORI). I wish to acknowledge Wilhelmine Miller, Ph.D. of NORC at the University of Chicago for her contributions to Section 5 and her review and comments on this work and David O. Meltzer, M.D., Ph.D. for his reviews and guidance on the final drafts. As noted in the text, Equations 2 through 6 of Section 2 are adapted from Briggs, Claxton, & Schulpher, 2006. The views presented in this White Paper represent those of the author alone and do not reflect the positions, official or otherwise NORC at the University of Chicago or PCORI.

Executive Summary

Value of information (VOI) analysis, a tool of the decision sciences, estimates the potential economic losses associated choosing suboptimal policies when that decision is made with uncertain information. In theory, VOI estimates can be compared across policy areas to identify the most important topics for additional research based on the size of the consequences that would result from an incorrect choice. In practice, the Patient Centered Outcomes Research Institute (PCORI) faces three primary barriers to using VOI for this purpose;

1. Uncertainty exists regarding the statutory requirements or prohibitions against the use of quality adjusted life years (QALYs) for research prioritization purposes,
2. Computational challenges in estimating VOI which impede the ability to easily apply the method to a large number of research topics in a timely manner, and
3. Challenges in standardizing the reporting of results and choices of modeling assumptions in a way that allow easy comparisons between topic areas while maintaining flexibility to incorporate differences between topics.

This white paper explores the issue of using value of information (VOI) to prioritize the allocation of resource funding by PCORI with a focus on the three areas above. The paper finds that the law does not prohibit the use of QALYs for the use of resource prioritization; that computational challenges to scaling VOI research to a large number of topics are tractable and manageable; and that guidelines for the standardization of the creation and presentations of VOI information would facilitate its utilization in research prioritization. The white paper concludes with a list of suggested directions for PCORI to examine to advance the use of VOI for research prioritization. These are categorized into issues related to policy and dissemination, and those related to additional research.

Section 1: Introduction

The Patient Centered Outcome Research Institute (PCORI) was established by Congress as a part of the 2010 Patient Protection and Affordable Care Act (ACA). The institute, which operates as an independent not-for-profit organization, is charged by Congress with assisting patients, clinicians, purchasers, and policy-makers in making informed health decisions.[1] The first set of draft guidance outlining the Institute's categorical research priorities was released January 24, 2012.[2] The Institute operates under intense scrutiny because of the financial implications of comparative-effectiveness research and public confusion and controversy surrounding the ACA. Even organizations that claim to support comparative-effectiveness research have expressed skepticism over the capacity and ability of government-created entities to produce information of value.[3]

In addition to public scrutiny, PCORI also faces the normal budget constraints of having limited resources and near limitless research topics. Rigorous, transparent methods could help PCORI target research to those problems that would most benefit from additional research. Value of information (VOI) analysis is a tool of decision science that can assist research prioritization in a quantified and transparent manner. VOI estimates the potential economic losses associated with selecting the suboptimal choice among two or more policy alternatives when that decision is made with uncertain information. In theory, VOI estimates can be compared across policy areas to rank decisions in terms of the economic consequences that would result from an incorrect choice between policy options. The areas with the greatest potential for adverse consequences would then be given the highest priority for additional research. In practice, however, the computational demands of VOI methods and the lack of standardization across studies has limited the method's use in prioritizing research.[4]

This paper explores the concepts of VOI and how VOI research could be used by PCORI to prioritize research. Section one of the paper provides an introduction to the concept of VOI. Section two discusses issues of VOI estimation. Understanding the methods used to estimate VOI are important in understanding potential issues of scaling and standardizing VOI research for use in research prioritization. Section three discusses the inputs used to expand per person estimates to population estimates. This topic is important to understand because differences in the selection of these inputs could make results from different studies difficult to compare, limiting the usefulness of VOI estimates in prioritizing research. Section four discusses the PCORI legislation, and potential obstacles in using VOI to prioritize research in light of this legislation. Finally, section five summarizes areas worthy of further investigation.

Section 2: What is Value of Information Analysis?

VOI analysis was first developed to support decision analysis in industrial engineering in the mid-1950's and early 1960's.[5] VOI explores the combination of probabilistic and economic outcomes that influence a decision. Decisions about costly alternatives that are made under great uncertainty are obviously more consequential than decisions that are relatively certain or for which the financial impact of making a suboptimal decision is minimal. Expected value of perfect information (EVPI) analysis is a subset of VOI; it incorporates both the uncertainty of the decision and the consequences of choosing incorrectly, by quantifying the difference between the expected net benefits achieved using perfect versus imperfect information.

To understand EVPI, consider that a cost-effective alternative is defined as the intervention with the greatest net benefit, with net benefit defined as

$$NB_j = B_j \cdot \lambda - C_j \quad (1)$$

Where NB is the net benefit, B is the quantity of the benefit under evaluation, λ represents a researcher-defined willing-to-pay value per incremental unit of B, C represents costs, and j references the alternatives under evaluation. In most typical applications, benefits are measured in terms of QALY's gained, but B can represent any benefit of an intervention from years of life saved, to injuries prevented, to years of healthy vision. For health policy questions in the United States λ is commonly set to $50,000 per QALY saved, although no real theoretical justification exists for this value and λ can in fact be set to any value or range of values that are appropriate in making a decision.[6]

In any result, NB_j is measured with uncertainty and thus the cost-effective choice between options is also uncertain. Given that uncertainty, the optimal decision is the intervention with the highest expected net benefit,[7] defined as[1]

$$max_j E_\Theta NB(j, \Theta) \qquad (2)$$

Where Θrepresents the parameter set used to make the decision, and E_Θ refers to the expected value given the parameter set Θ.[8] If decision makers had perfect information, they would of course select the option with the highest actual as opposed to expected net benefit, given a known value of Θ.

$$max_j NB(j, \Theta) \qquad (3)$$

Because the true value of $\Theta$is unknown, the expected value of perfect information is estimated from simulation results as the average maximum net benefit over the possible values of Θ.

$$E_\Theta max_j NB(j, \Theta) \qquad (4)$$

The EVPI is then calculated as the expected value of a decision made with perfect information minus the expected value of a decision made with the existing information.

$$EVPI = E_\Theta max_j NB(j, \Theta) - max_j E_\Theta NB(j, \Theta) \qquad (5)$$

Expected Value of Parameter/Partial Perfect Information

The *expected value of parameter perfect information* (EVPPI, also known as the expected value of partial perfect information) can be calculated for a single or a set of parameters, just as the EVPI can be calculated for the full parameter set used in the model. The EVPPI is often more useful than calculating the EVPI for the full model because many decisions are sensitive to only a few key parameters such as the effectiveness of the intervention, its cost, or the magnitude of the impact of disease on patient quality of life. For example, the cost-effectiveness of

[1] Equations 2 through 6 are adapted from Briggs, Claxton, & Schulpher, 2006.

screening school-aged children for amblyopia is almost entirely driven by the highly uncertain impact of monocular visual impairment on quality of life.[9] Also, while estimating EVPI is not burdensome if a probabilistic decision model is already in place, for the many situations for which none exists developing a model can be prohibitively expensive and time-consuming.

The EVPPI is found by dividing the full parameter set Θ, into a subset φ, for which we wish to learn the value of information, and the remaining parameters ψ, which are allowed to remain uncertain. The EVPPI is then

$$EVPPI_{\varphi} = E_{\varphi} max_j E_{\psi|\varphi} NB(j, \varphi, \psi) - max_j E_{\Theta} NB(j, \Theta) \quad (6)$$

Equation 6 is identical to equation 5, with the exception that the expected value of the decision made with perfect information about all the parameters in the set Θ has been replaced with the expected value of the decision made with perfect information about only the parameters in subset φ.

EVPPI is potentially much more useful for research prioritization than EVPI because it can pinpoint the topics that are most important in making policy choices. Some of these research topics may also have broader applications across a number of conditions. For example, building from the amblyopia example above, research on utility or functionality losses from visual loss might have large implications across a number of visual health policy decisions. Similar examples could involve generalized research on the impact of chronic pain or fatigue, or research on the effect of generic drugs such as avastin on the angiogenesis of tumors. More specific information on which aspects of a decision warrant further investigation is more useful than a more generic finding on uncertainty across all the parameters in a model. Unfortunately, the computational effort involved in estimating EVPPI has limited its policy implementation.

Section 3: Methods to Estimate EVPI and EVPPI

Methods to estimate EVPI and EVPPI can be divided into parametric, nonparametric, and expedited approaches. Differences in the approaches are important to understand because they indicate both the limitations of the data each approach generates and the ability of the approaches to be used to quickly prioritize a large number of research topics (Table 1). Parametric approaches are the easiest to implement, but depend on assumptions regarding the distribution of net benefits that can easily be violated. Non-parametric approaches provide strong estimates of value of information, but depend on the availability and standardization of a probabilistic decision model, and can require substantial processing time. Expedited approaches attempt to abbreviate the time required to establish a decision model or to shorten the computational effort required to estimate EVPPI given a decision model is in place.

Parametric Approaches

Parametric approaches have been developed to estimate the EVPI based on the assumption of normality of the net benefit outcome. This approach estimates EVPI as a function of the willingness-to-pay threshold, the estimated prior mean and standard error of the net benefit, and the integration of the normal curve area under the slope of the loss function. Claxton and Posnett (1996) explain this approach in a paper that estimates the incremental value of additional sampling units with the interest of reducing the standard error of the net benefit of a clinical trial.[10] This direct analytic approach could be used to calculate the EVPI, and with additional work the EVPPI, of many prior cost-effectiveness models provided their net benefits can be assumed to be approximately normal.

However, distributions of net benefits from cost-effectiveness models often lack a parametric distribution, because cost-effectiveness models synthesize parameters with different distributions which have been drawn from multiple sources.[7] Thompson and Nixon (2005) found that distributional assumptions about cost data influenced the determination of cost-effectiveness.[11] In a situation in which statistical tests indicated an adequate fit of the normal or the gamma distribution to the cost data, they found that the choice of one versus the other influenced the cost-effectiveness outcome.[11] This means that researchers must be careful in assuming the normal distribution even in cases where statistical tests indicate that the normal is an adequate fit for the data.

Despite this cautionary evidence, the degree to which parametric approaches create problems for the use of EVPI for research prioritization purposes remain underexplored. Additional methodological research is warranted to explore methods to parametrically estimate EVPI using distributional assumptions other than the normal, and on simulation research to quantify the expected magnitude of error that results from parametric estimates of EVPI using the wrong distributional assumption.

Non-parametric Estimation Approaches

Non-parametric approaches estimate EVPI from Monte Carlo (also known as probabilistic sensitivity analysis) results. While developing a fully probabilistic decision model can be complex and time consuming, generating EVPI from the model's results is fairly straightforward. To do so, the researcher evaluates the maximum net benefit between the model's alternatives for each row of the simulated results. The EVPI is then simply the difference between expected net benefit of the policy selected based on all the results and the expected value of the maximum net benefit possible if we had perfect information about each

row of the simulated results. The EVPI can be evaluated either at a single willingness to pay (WTP) value – if policy makers, such as those in the UK, have articulated a value at which a policy would be considered cost-effective – or across a range of values to observe the shape of the EVPI function with respect to WTP.

Estimating EVPI using parametric approaches could potentially be a viable method for prioritizing research in areas where probabilistic models have been developed. However, the time and effort involved in generating a probabilistic decision model from scratch may preclude its direct application by PCORI to prioritize a basket of research possibilities. A more feasible approach could involve the establishment of guidelines for standardization of nonparametric EVPI results across studies.

In comparison to EVPI, the nonparametric estimation of EVPPI requires substantial additional simulations beyond those conducted to support the baseline analyses. In order to estimate the EVPPI for a particular parameter or subset of parameters φ, the researcher must sample values from the distributions of those parameters, hold those values constant, and then run the simulation allowing the values of ψ to vary to account for their uncertainty. The simulation must be run a sufficient number of times to generate a stable estimate, and then this process must be repeated for the next value of φ until the distribution of φ has been adequately sampled. Unfortunately the number of simulations to adequately sample from the distribution of φ and the number of simulations required to create a stable estimate for each value of φ fluctuate with the type of variable of interest and the level of uncertainty associated with it.

In addition, few applied guidelines or rules of thumb exist to guide practitioners of decision sciences and outcomes research on the estimation of EVPPI. Perhaps as a result of its computational difficulty, few current applied evaluations attempt to estimate EVPPI. A PubMed search of the terms "expected value of perfect parameter information" or "expected value of

partial perfect information" returned only 33 search results, 12 of which were primarily concerned with developing additional methods as opposed to estimating EVPPI related to an applied policy decision.

Expedited Approaches

Expedited estimation approaches refer to a basket of techniques developed or in development to abbreviate the process of estimating EVPI or EVPPI. The parametric estimation of EVPI based on an assumption of normality (above) is an example of a potential expedited approach. Another simple approach to value of information is to place boundaries on the limits of the possible value of information based on the burden of disease. Meltzer (2001) describes a very easy-to-implement approximation of the maximum value of research based on the total disease burden, multiplied by the approximate proportion of that burden that could plausibly be averted through new research on preventive or curative solutions.[12] The obvious limitation to this approach is its speculative nature, as well as the need for burden of disease information and the wide variation in methods used to conduct burden studies.

Minimal modeling is another expedited approach to EVPI and EVPPI calculations. Meltzer and colleagues (2011) review the use of no-modeling and limited modeling approaches to calculating EVPI and EVPPI. A no-modeling approach uses clinical trial information on directly measured costs and QALYs from the time of the intervention initiation until patient death or recovery. In this approach, VOI estimates are created using bootstrapped intervals generated directly from raw clinical data or via parametric assumptions.[4] The authors identified 11 studies that utilized the no modeling approach.

A limited modeling approach can also be applied in situations where treatment affects morbidity or quality of life without an accompanying impact in survival. Meltzer and colleagues

(2011) explain that, provided that QALY impacts have been measured via a valid experimental design, bootstrapped or parametrically defined intervals on effectiveness and costs can be combined in a limited way with survival models to estimate the lifetime EVPI or EVPPI of a given intervention. [4]

The advantages of minimal modeling techniques are the speed of their application when appropriate data are available and to, a lesser extent, the ease in standardizing results generated from studies conducted by different researchers and in different health settings. The most obvious disadvantage is the impossibility of the method when clinical trial data are unavailable. In this case, the development of a decision model is likely to consume less time and resources than the development of a clinical trial.

Also, minimal modeling cannot be used to calculate the EVPI or EVPPI of chronic conditions whose impacts on QALYs and mortality vary across patients and time, a major current limitation. Potentially, future research could focus on standards for developing abbreviated models of complex health conditions for use in developing value of information estimates for research prioritization purposes. Such models could prioritize parsimony, speed of development, and a focus on relevant parameters over fidelity to disease transition states. Abbreviated models could also limit the probabilistic aspects of the model to only those parameters most likely to be evaluated by research, setting other parameters likely to be less important to decision making to their means.

Development of abbreviated models may benefit from methods to decompose complex models into independent simpler models for each of the models' key components. Hazen and Li (2011) provide an example of how a model evaluating cancer treatment options for people infected with HIV could be decomposed into separate simpler models of cancer progression, HIV progression, and background survival rates [13] Estimates of QALYs and costs across the

system were then combined using tractable formulas.[13] Model decomposition has several advantages; it reduces the proliferation of Markov states reducing the overall complexity of the model, and it makes models more transparent for purposes of review. In terms of disadvantages, model decomposition requires an assumption of independence between the components, but this assumption is often true or nearly so. In addition, its implementation is currently technically complex. However, pilot implementations could be developed with the goal of creating guidelines to assist its implementation by applied outcomes researchers.

Possible structural invalidity is the biggest disadvantage of abbreviated models. Developing models that are simpler tend to result in errors of omission or improper characterization of disease progression or treatment. Testing the external validity of abbreviated models could lower the risk of structural invalidity. However, if the purpose of abbreviated modeling is to develop a large number of VOI estimates in a short period of time, then it follows that time for validity testing would also be limited.

There are also several expedited or short cut approaches to estimating EVPPI, given that a probabilistic decision model has already been developed. EVPPI estimates are time consuming primarily because of the need to estimate a large set of so-called inner loop of simulations to adequately represent the full distribution of φ. One possible methodology to expedite EVPPI calculations is quadrature, a procedure in which the researcher samples φ across the percentiles of its distribution and estimates a weighted average of the results.[14] When φ contains only one parameter, quadrature can be achieved by sorting the vector of random parameter estimates by size and then selecting randomly from each percentile of the distribution. The inner loop of the EVPPI simulation is then run one time for each percentile. To save additional time, broader intervals such as deciles can be substituted for percentiles. In cases where φ contains more than one parameter, Latin Hypercube sampling techniques can be used to minimize the number of

samples required to represent the joint distribution of φ.[15] However, when φ contains many parameters, quadrature only marginally improves processing burden over the non-expedited method of estimation.

A second expedited approach to EVPPI estimation is a shortcut 1-level algorithm presented by Brennen and colleagues (2007). Use of this algorithm assumes independence between the parameters, but this is an unarticulated assumption of many decision models. The shortcut algorithm estimates EVPPI by setting all parameters in ψ (the parameters that are not of primary interest) to their mean value for all simulations, while selecting a vector of φ from its prior distribution. After the simulation is run a sufficient number of times to create stable estimates, the EVPPI can be estimated from the single level of analysis in the same manner that EVPI is calculated. The 1-level shortcut offers a substantial savings of effort compared to the traditional 2-level method of estimating EVPPI. It can also be used when parameters are not be fully independent, but the correlations are restricted within φ or within ψ. The method will only result in incorrect estimates when parameters in φ are correlated with parameters in ψ .[14]

Section 4: Expansion of per person results to population results

Most studies of EVPI or EVPPI report results in the manner most relevant to the policy context of the decision and without an explicit articulation of the conditions and choices made to create the estimates. However, these conditions and choices are crucial to understanding the magnitude of the VOI estimate, and efforts to standardize the development and reporting of VOI estimates. At the very least reporting assumptions will be necessary if EVPI is to be used to prioritize research. Meltzer and colleagues (2011) describe the population expected value of information (pEVI) of a given decision as

$$pEVI = \sum_t \beta^t \cdot Durability_t \cdot Implementation_t \cdot Incidence_t \cdot Population_t \cdot EVI \qquad (8)$$

Where pEVI can refer to either the population expected value of perfect or partial perfect information, *t* references the year of the analysis, and EVI is the per person expected value of information. The other terms are defined below, with discussions of how each effects the calculations and possible options to consideration in standardizing their use.

Discount Rate (β)

The discount rate represents the time-preference of the model for benefits that occur today in comparison to benefits that will occur in the future. Discount rates used in cost-effectiveness studies are highly variable across studies, but generally range from 0% to 10%.[16] Gold and colleagues (1996) reviewed a wide range of standards used in the United States to set discount rates before recommending a cost-effectiveness standard of 3%, an approximation of the average shadow price of capital over the long term in the United States.[17] This standard has been widely adopted in United States cost-effectiveness research.

With respect to VOI estimates, the discount rate will determine the extent to which benefits and costs that occur in the future are included in the cost-effectiveness determination.

The effect of the discount rate on the cost-effectiveness will vary depending on how costs and QALYs are distributed across time. In addition, the discount rate changes the net benefit calculation in a non-linear fashion as the rate increases. For these reasons it is not obvious how to systematically adjust published study results that utilize different discount rates in a way that allows for cross-study comparisons.

The discount rate represents a stated preference for future benefits. Because PCORI will be making determinations at a societal level, it is reasonable to expect that this preference would remain consistent across topic areas. PCORI should recommend a standard discount rate to be used for all VOI results. It makes little sense for research teams to select their own discount rate that is different from the societal preference considered by PCORI.

Durability

Durability refers to the waning usefulness of research findings over time. For example, research to reduce the uncertainty regarding the cost-effectiveness of photodynamic therapy with verteporfin for age-related macular degeneration was of use only from approximately the year 2000 until approximately 2007 when the therapy was supplanted by anti-vascular endothelial growth factor treatments – a durability of only 7 years. A challenge in determining durability is the difficulty if not impossibility of predicting which research will have a high degree of durability and which will be supplanted in a number of years.

While it is tempting to create a blanket recommendation of a single durability value (for example 10 years), this ignores that some research, such as a cure for cancer, would likely have a much longer durability and deserve to have those benefits taken into account in a prioritization process. Fortunately durability is relatively easy to adjust for provided researchers provide their per person EVI estimate, and their population and incidence assumptions. The impact of

durability assumptions could be added to univariate sensitivity analyses and researchers submitting information for review could be asked to explicitly justify their baseline durability assumption. Alternatively PCORI could establish durability categories (5 years, 10 years, 20 years, etc), develop guidance on when each category is appropriate, and leave it to individual research teams to select a category and justify their selection.

Implementation

Implementation refers to the challenges of translating new policy decisions into actions in the community. Variations in practice patterns across jurisdictions has been demonstrated for decades.[18] Even for policies that benefit from significant industry and government investment, many areas of the country will lag for years in their adoption of the practice. Calculating VOI requires an assumption regarding the proportion of the target population that will benefit from the decision. Strong prior information on the timing of implementation can guide implementation assumptions for some decisions such as the adoption of vaccines newly recommended by the Advisory Committee on Immunization Practices. For other decisions, implementation assumptions will be more speculative but can still draw from both theoretical and experimental evidence about the utilization of health services. For example, empirical evidence demonstrates that the use of a health technology will be greater when its insurance coverage is mandated.[19]

Like duration, adjusting for implementation is relatively easy provided the researchers provide documentation of per person EVI estimates, and their population and incidence assumptions. Different assumptions about the duration can be included in sensitivity analyses of VOI calculations.

Incidence

Incidence refers to the occurrence of new disease in the years following when the decision is made. Policies regarding new treatment or preventive services will benefit both prevalent cases today as well as new cases that occur during the window of the decision's durability. To accurately estimate the VOI, estimates need to be able to incorporate the benefit gained by future incident cases, or articulate the omission of these cases as a limitation. Incidence is also relatively easy to adjust for provided information is provided on the assumed incidence rates per year and the underlying populations to which these are applied.

Population

Population refers to the number of people included in the target population of interest. Research conducted on specific decisions or health technologies can possibly be applied globally. This might be crucially important in estimating the true value of information on a particular subject. For example, research on the treatment of rare diseases may affect too few people in any one country to justify additional research if valuations were based only on national estimates and only when the global benefits are considered is the research justified. In contrast, given that much public health research is funded by national governments for prioritization purposes, it might make sense to prioritize research based on the benefits that accrue to the citizens of that nation. If PCORI chooses to allow the inclusion of non-domestic benefits then it should provide guidance on the proper inclusion of benefits to other nations and suggest standardized sources of data from which to draw estimates.

Time Horizon

Time horizon refers to number of years into the future the model estimates. Even in situations where information is less durable, current effects of treatment or prevention may result

in benefits for the lifetime of the patient. For example, a case of Hepatitis C, detected and cured based on today's health technologies will continue to benefit that patient even if a better method to detect and cure hepatitis C is developed tomorrow. VOI estimates will be affected by the time horizon used by the model. The advantages of using a shorter time horizon are that generally short-term predictions of events are more accurate than longer term predictions, and that a decision maker may not be interested in benefits that occur in the distant future. Longer time horizons have the advantage of including a more realistic assessment of the benefits and costs of a given decision. Varying time horizons can make comparisons of VOI estimates difficult, and some models cannot be easily adjusted to incorporate shorter time horizons. Also, failing to set a consistent time horizon standard creates the risk of biased outcomes if researchers react by choosing time horizons based on which is most advantageous for a particular policy condition. One approach that PCORI could take is to recommend a standard lifetime time horizon for all VOI estimates, and then adjust the discount rate to manage different valuations of future benefits and the probabilistic parameter assumptions to adjust for future uncertainty.

Section 5: The PCORI legislation and VOI

The methods above and most methodological research on VOI assume that QALYs will be used as the measure of benefit in the net benefit calculations used to create estimates. This is potentially problematic because the ACA directs that PCORI cannot develop or use a dollars-per-QALY amount as a threshold to determine that a type of health care is cost-effective or recommended.[1] Measures similar to QALYs (in that they discount the value of a life because of an individual's disability) are likewise precluded from use in a threshold value. The ACA also prohibits the Medicare program from using QALYs or similar measures as a threshold measure for purposes of coverage, payment, or incentive programs. However, it is not clear just how broadly the prohibition on PCORI's use of QALYs is meant to be.[20] Some have argued that cost-effectiveness analysis, and even the use of QALYs in some application other than a threshold, is not prohibited in PCORI's authorizing legislation.[21] Section 1181(d)(1) of the ACA specifies that

> "The Institute shall identify national priorities for research, taking into account factors of disease incidence, prevalence, and burden … gaps in evidence in terms of clinical outcomes, practice outcomes of care, the potential for new evidence to improve patient health, well-being, and the quality of care, ***the effect on national expenditures associated with a health care treatment, strategy, or health conditions***, as well as patient needs, outcomes, and preferences … The Institute shall establish and update a research project agenda for research to address the priorities identified [above], ***taking into consideration the types of research that might address each priority and the relative value (determined based on the cost of conducting research compared to the potential usefulness of the information produced by research) associated with the different types of research***, and such other factors as the Institute determines appropriate.[emphasis added]"

This wording appears to offer PCORI considerable leeway in the use of QALYs to set research priorities based on VOI calculations. This wording also appears to allow PCORI to be flexible in using QALYs to set research priorities based on VOI calculations. The law neither prohibits nor requires PCORI to use QALYs for research prioritization purposes, although the

use of VOI methods are specifically discussed in other portions of the law. Specifically Section 1181(d)(1) directs PCORI to prioritize research based on the conceptual definition of value of information research, i.e., "cost of conducting research compared to the potential usefulness of the information produced by research." 42 U.S.C. § 1320e(d)(1). Only later in the statute, in Section 1182(e)(3), does the requirement appear that PCORI "shall not develop or employ a dollars-per-quality adjusted life year … as a threshold to establish what type of health care is cost effective or recommended." Thus, while the statute directs PCORI to use VOI research in its definitions section, in a subsequent section, the statute prohibits the use of QALYs for some research functions but not for VOI. This statutory language indicates the writers of the legislation understood that QALYs could be used for VOI as well as for other purposes but chose not to prohibit it for application to VOI. Thus, the use of QALYs for VOI is at least permitted, and perhaps directed, by applicable law.

Still given the public's misunderstanding of QALYs and the hostility of some towards their use in any decision, it is worth considering whether alternative measures of benefits to QALYs might be appropriate. To be acceptable, alternatives would need to fulfill two conditions; the measure would need to:

- Capture disease impacts of morbidity as well as mortality to allow for comparisons across disease states; and
- Be measured in a meaningful continuous or ordinal scale.

One possible alternative to QALYs would be to measure the willingness-to-pay (WTP) to avoid certain health conditions. Recall that the net benefit calculation (Equation 1) multiplies a unit of benefit times a WTP threshold. QALYs have typically been used in place of direct health benefits because they allow us to transform morbidity from a condition to a value that can be compared across health states. For example, through the QALY conversion, the morbidity

from chronic back pain can be compared directly to morbidity from acute episodes of influenza. The ability to weight disparate health conditions and then compare them directly using a standardized unit is the primary benefit of the continued use of QALYs in health economic research. However, the validity of QALYs in grounding cost-effectiveness in welfare theory has been debated.[22, 23]

In contrast, WTP methods estimate the dollar value of a benefit as opposed to its utility weight. Estimating WTP values for each health condition would substitute new common metric, dollars, in place of QALYs, while also negating the necessity of specifying a threshold WTP value in the estimation of VOI. Benefits from a decision could then simply be measured in their natural units (episodes and durations of pain and disability averted). By multiplying those benefits by their WTP estimates, standardized units are created that could be used to compare different forms of morbidity. WTP measures have their own theoretical problems,[24] and the time required to estimate all WTP values needed for research prioritization is prohibitive. However, over the longer term, WTP estimates are more intuitive to a lay audience than QALYs, and may prove to be more politically acceptable.

Another alternative to QALYs could be to substitute one of several health index measures such as the EQ-5D measures in their place. The EQ-5D summarizes five areas of morbidity: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on a scale of 1 to 3, as well as a visual analogue measurement of general health, and a question measuring changes in the condition. The measure combines the individual measures into a single indexed value representing the severity of a health state. The availability of population-normed data allows for estimation of the incremental impact of a health condition. Somewhat problematically, many people interpret the EQ-5D as being synonymous with QALYs measured through more

controversial methods such as time-tradeoff or standard gamble. The EQ-5D may come with the same branding issues as QALYs themselves.

If QALYs or the EQ-5D were infeasible for its use, PCORI could examine the feasibility of developing another health index measure that is customized for the specific research and policy needs of the institute. Because research prioritization depends on the relative value of different choices, the differences in scale between health indexes and QALYs would not impede the ranking of priorities. PCORI could also investigate one of many other health index measures. A large amount of evidence demonstrates the robustness of simple, well-conceived, algorithms in facilitating good decision making.[25]

Section 6: Conclusions and Areas for Additional Research

Value of information research offers a quantifiable and replicable methodology to evaluate the opportunity costs that result from suboptimal decisions. As such it provides a framework within which to understand the relative benefits of research targeted toward different health policy decisions. Rank ordering of research benefits can obviously be used to prioritize or justify research funding. In a more general sense, value of information analysis can simply be used to evaluate the merit of a proposed research endeavor, for example a proposed clinical, in terms of the expected benefits of the research as compared to its costs. In this regard, value of information can be used as a factor to weight applications for funding without the need to directly compare estimates across studies. For example, a minimal requirement for funding could be a demonstration that the benefits of research outweigh its costs. However, currently several barriers may limit the use of VOI research to prioritize research.

The first of these barriers is the uncertainty and misunderstanding regarding the ACA directive on the use of QALYs. Because of the contentious nature of the health care debate and the explicit prohibition of the use of QALYs to set thresholds for insurance purposes, policy makers have understandably have been hesitant to incorporate the use of QALYs for other patient centered outcomes research applications. However, as demonstrated in Section 5 the language of the ACA indicates its writers understood that QALYs could be used for VOI as well as for other purposes but chose not to prohibit the use of QALYs for research prioritization. From this we can conclude that the use of QALYs for VOI is at least permitted, and perhaps directed, by ACA statute.

The second barrier involves conducting VOI research on the scale necessary to prioritize a very large number of research topics. This barrier is caused by the research and development time necessary to create validated and probabilistic decision models for each specified decision

context. Section 3 discusses a variety of methods that can be used to estimate and expedite the estimation of VOI results. These range from enveloping the VOI potential based on disease burden and an expected information gain to the application of algorithms to speed the estimation of VOI using established decision models. In a recent conference paper, Houmans, Siedenfeld, Basu, and Meltzer (2011) outlined an algorithm to guide the staging of VOI research of different levels of intensity.[26] The algorithm lays out a replicable framework through which to consider the sponsorship of VOI research. Topics with conceptually low VOI estimates would not be expected to generate VOI estimates to justify research (research have to be justified on scientific or ethical grounds only). Topics with high VOI potential that overlap with other topics would be nominated as candidates for the development of a full decision model. Topics the fall in between would be evaluated based on data availability and the suitability of abbreviated methods to address the topic.[26] Using Such an algorithm could help prioritize topics for VOI estimation, which would be the first step in creating comparative VOI information for a large range of topics.

The third barrier involves the standardization of VOI estimates across studies. Given the large amount of work to be done, VOI is likely to be conducted in a disseminated fashion and sponsored by government, not-for-profit, and private interests. To facilitate comparisons, PCORI should create guidelines for the standardization of results to allow for comparisons of results across studies. These guidelines should include a combination of prescriptive recommendations regarding VOI factors that are difficult to adjust for in post-publication reviews such as the discount rate and the time horizon that, as well as descriptive guidelines on the optimal presentation of assumptions regarding VOI factors that are easy to adjust for in post-publication reviews.

Suggested Future Directions

Based on the discussion of methods and challenges outlined in this report, PCORI may wish to consider some or all of the following possible future actions. In the areas of policy and dissemination;

1. PCORI should consider requiring that applications for research or clinical grants be supported by a justification based upon the value of the information to be obtained. The methodological rigor required to justify such an application should be allowed to vary based on the magnitude of the research to be conducted. Simpler calculations are likely appropriate for modest requests or pilot projects where full maximal modeling may be required to justify major investment in patient centered outcomes research.

2. In support of the first suggestion, PCORI should consider the development of guidelines to standardize the conversion of person level results to population level estimates. These guidelines should contain information regarding how to present VOI estimates in a way that informs the decision to prioritize a suggested topic for research.

3. PCORI should consider the sponsorship of workshops and the development of teaching materials to facilitate the disseminated estimation of VOI information by the larger research community.

In the area of additional research, PCORI should consider

4. The development of standardized league tables of disease burden that could be used to envelope the VOI for specific disease categories. League tables should be developed using standard methods and using the same data source such as the Medical Expenditure Panel Survey (MEPS) for all disease areas.

5. Support the further development and pilot application of value of information methodology. Such research is justified by the need to develop estimation methods that are achievable by a greater proportion of the health research community, that are more transparent to the public, and that can be applied to a wide range of topic areas quickly. Examples of such areas of inquiry include but are not limited to;
    a. The use of simulated data to conduct research on the type, magnitude, and frequency of errors that occur when parametric methods are used to estimate VOI from net benefits with a variety of distributional assumptions.
    b. Pilot applications of no modeling, minimal modeling, abbreviated modeling, and model decomposition applications that are specifically tailored to quickly and efficiently generate VOI information.
6. The further investigation and pilot development of indexes or measurement techniques of patient centered indicators of preferences between various health-related morbidities.

TABLE1. Advantages and Disadvantages of Possible Approaches to EVPI and EVPPI Estimation

Approach	**Advantages**	**Disadvantages**
Parametric	Simplicity, speed of implementation, accuracy when applied correctly	Depends on normally distributed net benefits. Cannot be used when net benefits are non-normal or nonparametrically distributed.
Non-Parametric, Probabilistic Decision Model Approach to EVPI	Accuracy, ease of implementation after a probabilistic decision model is developed	Requires a probabilistic decision model
Non-Parametric, Probabilistic Decision Model Approach to EVPPI	Accuracy	Requires a probabilistic decision model, computationally intensive and time-consuming to implement
Bounding EVPI and EVPPI based on burden of disease and possible benefit of intervention (Maximum value of research)	Simplicity, speed of implementation	Requires disease burden information and plausible assumptions about benefit, imprecise
No modeling approach to EVPI and EVPPI	Speed of implementation, accuracy when conditions	Require experimental evidence on costs and QALYs from

	allow them to be applied	intervention initiation until disease resolution or death
Minimal (limited) modeling approach to EVPI and EVPPI	Speed of implementation, accuracy when conditions allow them to be applied	Require experimental evidence on costs and QALYs, not applicable to chronic conditions
Abbreviated models	Faster to implement than full decision models, can accommodate chronic conditions	Questions of structural validity, additional time required to construct
Model decomposition	Simplifies complicated decision models and may speed their creation, allows for stock model components to be combined	Methodological complexity, decomposed units must be independent, time required to develop individual decision models
Quadrature approach to EVPPI	Faster to implement than full estimation of EVPPI	Requires probabilistic decision model, still fairly time consuming especially in cases where φ is multidimensional
1-level shortcut to estimate EVPPI	Saves substantial computational time compared to non-parametric, probabilistic decision model approach to EVPPI	Requires probabilistic decision model, applicable only when φ is not correlated with ψ.

TABLE 2. Topics to Consider in Standardizing VOI Research for Research Prioritization

Issue of Standardization	**Importance**	**Challenges**
Durability, the likelihood that research continues to deliver benefits over time	Health technologies may be may be supplanted limiting the VOI. Alternatively, changes in other technologies may increase VOI.	Durability requires speculation about the future. Conservative or optimistic assumptions about durability will affect VOI estimates.
Implementation, the extent to which and the time entailed in adopting a new technology	Changes in policy take time to implement and not all individuals can be expected to participate.	While prior evidence can direct assumptions about implementation, without guidance choices about the level of implementation to assume will vary across studies.
Incidence, the occurrence of future cases of disease that will also benefit from the information to be collected	Information that informs a policy decision today will also influence that policy when it is applied to new instances of the disease in the future. Analyses that exclude future incidence will undercount VOI.	Estimating incidence requires additional modeling to forecast future population, and disease incidence, treatment, and outcomes. This proliferates the number of possible Markov states in the model
Population, the size of the	VOI rises with the population	Lack of consensus and

group to which the per person VOI estimates are applied	to which is it is applied. Different assumptions about the population of interest will lead to dramatically different conclusions about VOI.	potential political disagreements over the inclusion of international populations.
Time Horizon, the number of years over which benefits and costs are collected from the model	Time horizon affects the quantity of benefits and costs that result from or are averted by an intervention. Analyses with shorter time horizons ignore benefits that occur beyond the time horizon.	Decision models may not be easily modified to accommodate differences in time horizons. Very difficult or impossible to adjust publish results to account for differences in time horizons.
Discount rate, the time-preference for benefits that occur today in comparison to benefits that occur in the future.	The discount rate in part determines the value placed on benefits and costs that occur in the future.	Difficult to adjust published results to account for unpublished variation in discount rate.

References

1. United States Congress. PUBLIC LAW 111–148, 124 STAT. 727,. Washington, DC; 2010.
2. PCORI. *Draft National Priorities For Research and Research Agenda, Version 1.* Washington, DC 2012.
3. Cannon MF. The Moment It Produces Useful CER, PCORI Is Toast. http://www.cato-at-liberty.org/the-moment-it-produces-useful-cer-pcori-is-toast/. Accessed 1/31, 2012.
4. Meltzer DO, Hoomans T, Chung JW, Basu A. Minimal modeling approaches to value of information analysis for health research. *Med Decis Making.* Nov-Dec 2011;31(6):E1-E22.
5. Howard RA. Information Value Theory *IEEE Transactions on Systems Science and Cybernetics.* 1966;2(1):22-26.
6. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res.* Apr 2008;8(2):165-178.
7. Briggs A, Claxton K, Sculpher M. Section 6. Decision making, uncertainty, and the value of information. *Decision Modelling for Health Economic Evaluation*. New York: Oxford University Press; 2006.
8. Claxton KP, Sculpher MJ. Using value of information analysis to prioritise health research: some lessons from recent UK experience. *Pharmacoeconomics.* 2006;24(11):1055-1068.
9. Rein DB, Wittenborn JS, Zhang X, Song M, Saaddine JB. The Potential Cost-Effectiveness of Amblyopia Screening Programs. *J Pediatr Ophthalmol Strabismus.* Aug 30 2011:1-10.

10. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ.* Nov-Dec 1996;5(6):513-524.

11. Thompson SG, Nixon RM. How sensitive are cost-effectiveness analyses to choice of parametric distributions? *Med Decis Making.* Jul-Aug 2005;25(4):416-423.

12. 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. *J Health Econ.* Jan 2001;20(1):109-129.

13. Hazen G, Li Z. Cohort decomposition for Markov cost-effectiveness models. *Med Decis Making.* Jan-Feb 2011;31(1):19-34.

14. Brennan A, Kharroubi S, O'Hagan A, Chilcott J. Calculating partial expected value of perfect information via Monte Carlo sampling algorithms. *Med Decis Making.* Jul-Aug 2007;27(4):448-470.

15. O'Hagan A, Stevenson M, Madan J. Monte Carlo probabilistic sensitivity analysis for patient level simulation models: efficient estimation of mean and variance using ANOVA. *Health Econ.* Oct 2007;16(10):1009-1023.

16. Nixon J, Stoykova B, Glanville J, Christie J, Drummond M, Kleijnen J. The U.K. NHS economic evaluation database. Economic issues in evaluations of health technology. *Int J Technol Assess Health Care.* Summer 2000;16(3):731-742.

17. Gold MR, Siegel JA, Russell LB, Weinstein MC. *Cost-effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

18. Wennberg J, Gittelsohn. Small area variations in health care delivery. *Science.* Dec 14 1973;182(4117):1102-1108.

19. P. Bitler M, Schmidt L. Utilization of infertility treatments: the effects of insurance mandates. *Demography.* Feb 2012;49(1):125-149.

20. Neumann PJ, Weinstein MC. Legislating against use of cost-effectiveness information. *N Engl J Med.* Oct 14 2010;363(16):1495-1497.

21. Chambers JD, Neumann PJ. US healthcare reform: implications for health economics and outcomes research. *Expert Rev Pharmacoecon Outcomes Res.* Jun 2010;10(3):215-216.

22. Dolan P, Edlin R. Is it really possible to build a bridge between cost-benefit analysis and cost-effectiveness analysis? *J Health Econ.* Sep 2002;21(5):827-843.

23. Schlander M. Measures of efficiency in healthcare: QALMs about QALYs? *Z Evid Fortbild Qual Gesundhwes.* 2010;104(3):214-226.

24. Hammerschmidt T, Zeitler HP, Leidl R. A utility-theoretic approach to the aggregation of willingness to pay measured in decomposed scenarios: development and empirical test. *Health Econ.* Apr 2004;13(4):345-361.

25. Meehl PE. *Clinical versus statistical prediction : a theoretical analysis and a review of the evidence*. 1st Softcover Edition ed. Northvale, NJ: Jason Aronson; 1996.

26. Hoomans T, Seidenfeld J, Basu A, Meltzer DO**.** Systematizing the Use of Value of Information Analysis for the Prioritizing Systematic Reviews. Society for Medical Decision Making. Chicago; 2011.