Can value of information analysis help inform research priorities?

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Based on “Systematizing the Use of Value of Information Analysis for Prioritizing Systematic Reviews”
Methods Research on Future Research Needs, Agency for Healthcare Research and Quality (AHRQ) / BCBS Association TEC-EPC
Introduction

- With finite funds for health research, must prioritize among topics
- Systematic reviews inexpensive compared to primary data collection, but expensive enough that not all possible reviews may be funded
  - Guideline updating is similar
- Value of information (VOI) analysis can provide quantitative estimates of the value of research
- Can VOI help inform priorities for systematic reviews/guideline development?
  - VOI complex / costly compared to other prioritization approaches (e.g., subjective judgment) and even systematic reviews
  - Newer approaches to calculating VOI may reduce barriers to its practical use [Meltzer, Hoomans, Chung, Basu, 2011]
  - How might VOI practically be used to inform priorities for systematic reviews (and guideline development)?
Outline

• Review of VOI
  – Theory
  – Tools for practical application of VOI

• Prioritizing systematic reviews
  – Current approach
  – Possible VOI framework
  – Experience applying framework

• Conclusions
  – For use of VOI to inform priorities for systematic reviews
  – For use of VOI to inform research priorities
Cost-effectiveness analysis has long been used to assess the value of medical treatments and the information that comes from diagnostic tests

- Cost-effectiveness measured in Cost/QALY
- Net health benefits
  = gain in QALYs – opportunity cost of spending in QALYs
- Net monetary benefit
  =$ value of improved health - costs

Newer value of information techniques have extended these tools to assess the value of medical research
Research as Value of Information

\[
\begin{aligned}
\text{Test} & \quad S & U(T|S) & \\
& \quad H & pU(T|S)+(1-p)U(N|H) & U(N|H) \\
\text{Don’t Test} & \quad S & \text{Max}\{pU(T|S)+(1-p)U(T|H), \ pU(N|S)+(1-p)U(N|H)\} & \\
& \quad H & & \\
\end{aligned}
\]
Value of Information Approach to Value of Research

- **Without information**
  - Make best compromise choice not knowing true state of the world (e.g., don’t know if intervention is good, bad)
    - With probability p: get $V(\text{Compromise}|G)$
    - With probability 1-p: get $V(\text{Compromise}|B)$
- **With information**
  - Make best decision knowing true state
    - With probability p: get $V(\text{Best choice}|G)$
    - With probability 1-p: get $V(\text{Best choice}|B)$
- **Value of information**
  
  \[
  = \mathbb{E}(\text{outcome}) \text{ with information} - \mathbb{E}(\text{outcome}) \text{ w/o information} \\
  = \{p*V(\text{Best choice}|G) + (1-p)*V(\text{Best choice}|B)\} - \{p*V(\text{Compromise}|G) + (1-p)*V(\text{Compromise}|B)\} \\
  = p \cdot \{V(\text{Best choice}|G) - V(\text{Compromise}|G)\} + (1-p) \cdot \{V(\text{Best choice}|B) - V(\text{Compromise}|B)\} \\
  = \text{Probability Compromise Choice Wrong} \cdot \text{Value of Correcting Compromise} \\
  = \text{Value of Research}
  \]
### Information Requirements for Value of Information Calculations
(Meltzer. J Health Econ 2003)

<table>
<thead>
<tr>
<th>Conceptual Basis</th>
<th>Information Required</th>
<th>Missing Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Burden of Illness</td>
<td>Priors for Subject of Research</td>
</tr>
<tr>
<td>Expected Value of Information</td>
<td>Expected Gain in Welfare from Research</td>
<td>Yes</td>
</tr>
<tr>
<td>Expected Value of Perfect Information</td>
<td>Expected Gain from Perfectly Informative Specific Experiment</td>
<td>Yes</td>
</tr>
<tr>
<td>Maximum Value of Information</td>
<td>Maximum Possible Gain from Specific Experiment</td>
<td>Yes</td>
</tr>
<tr>
<td>Maximum Value of (Disease-Specific) Research</td>
<td>Maximum Possible Gain for Target Disease</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Practical Applications of Value of Information

- VOI requires modeling population value of information

\[ VOI = \sum_{t} \beta^t \times D(t) \times I(t) \times N_t \times IVOI \]

where

- \( \beta^t \) is time preference discount factor
- \( D(t) \) is depreciation of knowledge over time
- \( I(t) \) is extent of implementation
- \( N_t \) is number of eligible individuals in each cohort
- \( IVOI \) is individual VOI

- VOI based on decision models
  - IVOI modeled with decision model
  - UK (NICE): Alzheimer’s Disease Treatment

- Minimal modeling approaches to VOI
  - IVOI comes (nearly) directly from clinical trial
  - Limited modeling: CATIE Trial atypical antipsychotics,
  - No modeling: Erlotnib in Pancreatic CA, Azithromycin v. Augmentin in sinusitis

- Bound with more limited data (burden of illness)
Full Modeling:
“Bayesian Value of information analysis: An application to a policy model of Alzheimer's disease.”

Figure 1. A Markov model of disease progression.
Uncertainty in Incremental Net Benefits

Figure 2A. Prior distribution of incremental net benefit.
Value of Research by Value of Health

Figure 3B. EVPI for treatment choice (US population).
Contributors to Value of Research

Figure 4. EVPI for model inputs (210 weeks).
Practical Applications of Value of Information

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Limited Modeling: The Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE)

• $42.6 million, NIMH-funded randomized trial of Atypical Antipsychotic Drugs (A-APDs) and a Neuroleptic (Perphenazine) in patients with established schizophrenia

• Major findings
  o Discontinuation rates similar with A-APDs and Perphenazine
  o Perphenazine cost-effective first-line treatment

• Impact
  o Frequently discussed in coverage decisions
  o Some have argued results should be considered definitive
# CATIE Cost-Effectiveness Results

<table>
<thead>
<tr>
<th></th>
<th>Monthly Costs</th>
<th>QALY Mean</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (sd) ($)</td>
<td>(sd)</td>
<td>($/QALY)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>817 (728)</td>
<td>0.722 (0.0064)</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1619 (1442)</td>
<td>0.723 (0.0063)</td>
<td>9,624,000</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1635 (1457)</td>
<td>0.706 (0.0066)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1680 (1497)</td>
<td>0.721 (0.0065)</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

(Ref: Rosenheck et al., 2006; Private Communications with Dr. Rosenheck)

Only statistically significant difference:

\[ QALY_{\text{Perphenazine}} > QALY_{\text{Risperidone}} \quad (p-val < 0.001) \]
Simulated Distribution of Mean QALYS
(Based on uncertainty around CATIE results)

E(QALY)/per patient per year

- Olanzapine: 0.723 (0.0063)
- Quetiapine: 0.721 (0.0065)
- Risperidone: 0.706 (0.0066)
- Perphenazine: 0.722 (0.0064)
Simulated Distribution of Mean Costs
(Based on uncertainty around CATIE results)

E(QALY)/per patient per year

Olanzapine: $1606 (1421)
Quetiapine: $1685 (1485)
Risperidone: $1621 (1439)
Perphenazine: $810 (723)
Realizations of Value of Research Over Time

Value of Future Research to Prevalent and Incident Cohorts at $50k/QALY

Total Value to Each Incident Cohort: $6.6 billion
Total Value to Prevalent & Next 20 Incident Cohorts: $342 billion
Net Expected Value of Sample Information
(at $50K, $100K and $150K/QALY)

Cost of Research: $3 mill + (sample size*4)*($5000/month)*18 months

Optimal sample size for each arm = 22,500
No Modeling Approach: 
Azithromycin vs. Augmentin in Acute Sinusitis

- Azithromycin more costly but easier and more effective
- RCT (Marple et al 2010)
  - Primary outcome resolution of symptoms within 5 days
    - 70/236 patients (29.7%) in the azithromycin extended-release arm
    - 45/238 patients (18.9%) in the amoxicillin/clavulanate arm
    - Difference: 10.8%; 95% confidence interval [CI]: 3.1–18.4%
  - By day 28:
    - 26/236 patients (11.0%) in the azithromycin extended release arm
    - 27/238 patients (11.3%) in the amoxicillin/clavulanate arm
    - Difference: -0.4%; 95% CI: -6.1% to 5.3%
  - Completion of trial to equal resolution key to avoid building model
Appendix B. Curves for symptom resolution in azithromycin extended release versus amoxicillin/clavulanate in acute sinusitis

Estimated Hazard ratio = 1.13 (95% CI: 0.91-1.42)

Difference:
Azithromycin 7.55 (SE 0.260) days

vs.
Amoxicillin/Clavulanate 8.12 (SE 0.210) days
VOI Estimation

- Cost-Effectiveness Results and Decisions Based on Current Information
  - Azithromycin mean time to resolution of 7.55 days (SE=0.260) vs. 8.12 days (SE=0.210) for amoxicillin/clavulanate (p value for difference 0.077).
  - WTP $73.2/day (SE=6.66) in 2010 U.S. dollars (Tolley et al.)
  - Cost (AWP Drug Topics Red Book, 2010)
    - 10 days oral amoxicillin/clavulanate 875/125 mg every 12 hours: $31.99
    - Single oral dose of azithromycin extended release (2 g): $55.68
  - Net benefit = WTP – Costs
  - Current treatment decision is azithromycin (Net Benefit= (8.12 - 7.55)*$73.2 - ($55.68-$31.99) = $18.2).

- Estimate IVOI by bootstrap sampling out of distribution of average benefits and costs and averaging the net benefit of over amoxicillin/clavulanate over azithromycin/clavulanate whenever amoxicillin had a positive net benefit.

- Incidence, Time Horizon and Discounting
  - 10 million cases/year.
  - 10-year horizon based on patent expiration for azithromycin
  - Discount rate of 3%.
VOI Results

- EVPI Benefits alone: $40 million (range $13 million - $109 million over WTP $25 to $200/day of avoided sinus congestion).
  - Chance information change current decision of using azithromycin based on effectiveness results only about 4%.
- EVPI with costs: $250 million at baseline threshold of $73/day
- Max VOI: $400 million at threshold value of $50/day avoided symptoms where the probability of current decision azithromycin cost-effective 50%.
No Modeling: Gemcitabine + Erlotnib vs. Gemcatabine in Pancreatic CA

Conceptual Value of Information

- VOI requires modeling population value of information

\[ VOI = \sum_{t} \beta^{t} \times D(t) \times I(t) \times N_{t} \times IVOI \]

where
- \( \beta^{t} \) is time preference discount factor
- \( D(t) \) is depreciation of knowledge over time
- \( I(t) \) is extent of implementation
- \( N_{t} \) is number of eligible individuals in each cohort
- \( IVOI \) is individual VOI

- I VOI
  - \( p(\text{change decision}) \times \) Expected value of change if change desirable
  - IVOI low if either of these small enough unless other very large
  - In principle, all items above
# Quantitative VOI Estimates

<table>
<thead>
<tr>
<th>Topic Area</th>
<th>VOI Estimate ($ Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR in Knee Trauma</td>
<td>8</td>
</tr>
<tr>
<td>LVAD as Destination Therapy</td>
<td>8</td>
</tr>
<tr>
<td>Azithromycin vs. Augmentin in Sinusitis (ignoring costs)</td>
<td>40</td>
</tr>
<tr>
<td>Pegylated Liposomal Doxycyclin in Ovarian CA</td>
<td>206</td>
</tr>
<tr>
<td>Azithromycin vs. Augmentin in Sinusitis (including costs)</td>
<td>250</td>
</tr>
<tr>
<td>Treatment of Intermittent Claudication</td>
<td>573</td>
</tr>
<tr>
<td>Cognitive Behavioral Therapy for Post-partum Depression</td>
<td>603</td>
</tr>
<tr>
<td>Typical/Atypical Antipsychotics in Schizophrenia</td>
<td>124,658</td>
</tr>
</tbody>
</table>
# AHRQ EPC Methods Paper: Minimal Modeling Approaches to VOI (Medical Decision Making)

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Definitions*</th>
<th>VOI Calculations</th>
<th>Data Requirements</th>
<th>Clinical Application(s)</th>
<th>Advantages (+) and Disadvantages (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Modeling</td>
<td>Full characterization of the disease/ treatment using a decision model or other simulation model of relevant health state</td>
<td>Simulation/ bootstrapping, parametric and/or nonparametric</td>
<td>Data on all model parameters</td>
<td>Chronic conditions, complex diseases</td>
<td>- Complex and time-consuming modeling exercises</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Equation-based computation, parametric</td>
<td></td>
<td></td>
<td>+ Detailed uncertainty analysis and VOI estimates, including calculation of EVPPI</td>
</tr>
<tr>
<td>Limited Modeling</td>
<td>Any modeling necessary (e.g., modeling of patient survival, mapping of treatment effect to utilities or aggregate approximation of costs) without using a decision model or other simulation model of relevant health states</td>
<td>Simulation/ bootstrapping, parametric and/or nonparametric</td>
<td>Intermediate measures for health outcomes or QALYs, costs and/or NBs; Survival data</td>
<td>Acute conditions, end of life treatments</td>
<td>+ Reduced need for complex and time-consuming modeling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Equation-based computation, parametric</td>
<td></td>
<td></td>
<td>+ Complementary to adaptive clinical trial design</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Requires clinical trial that can requires only modeling of survival or other limited modeling to generate comprehensive measure of net benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ No comprehensive uncertainty analysis and VOI estimates (EVPPI)</td>
</tr>
<tr>
<td>No Modeling</td>
<td>Direct replication or direct calculation of (incremental) effects on comprehensive health outcomes (e.g. QALYs, and/or net benefits)</td>
<td>Simulation/ bootstrapping, parametric and/or nonparametric</td>
<td>Distributions of comprehensive health outcomes or, QALYs and/or net benefits</td>
<td>Acute conditions, end of life treatments Direct measurement of final health outcomes</td>
<td>+ No need for complex and time-consuming modeling</td>
</tr>
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<td>Equation-based computation, parametric</td>
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<td>+ Complementary to adaptive clinical trial design</td>
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<td></td>
<td>- Requires clinical trial that can provide comprehensive measure of net benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- No comprehensive uncertainty analysis and VOI estimates (EVPPI)</td>
</tr>
</tbody>
</table>

* All approaches seek to address specific treatment or coverage decisions, to characterize decision uncertainty and to establish VOI estimates  
EVPPI: expected value of partial perfect information
VOI to Prioritize Systematic Reviews

To explore **whether and how VOI** might be effectively and efficiently used to inform priorities for systematic reviews

**Algorithm:** To develop an algorithm for selecting approaches to use VOI to inform priorities for systematic review

**Review:** To review priority setting processes for systematic reviews in health care organizations and the published literature with a focus on the use of VOI

**Application:** To assess the potential utility of the algorithm in prioritizing 41 topics nominated to AHRQ’s EPCs for systematic review in 2009
Algorithm: Principles of VOI

\[ \text{VOI} = \sum_{t} \beta^{t} \cdot \text{Dur}_{t} \cdot \text{Pop}_{t} \cdot \left( \sum_{j} \text{Imp}_{j|\theta} \cdot E_{\theta|\theta} \text{NB}(j, \theta) \right) - \sum_{j} \text{Imp}_{j|\theta} \cdot E_{\theta} \text{NB}(j, \theta) \) - C_{lt} - C_{\text{VOI}} \]

Future research \hspace{2cm} Current information

Conceptual

\( E_{\theta} \text{NB}(j, \theta) \): Reduction in uncertainty about benefits of intervention \( j \)

Elements of VOI:

\( \text{Imp}_{j|\theta} \): Likelihood of implementation of \( j \)

\( \text{Dur}_{t} \): Durability of evidence from future research

\( \text{Pop}_{t} \): Size of patient population targeted

\( C_{it} \): Costs of information through future research

\( C_{\text{VOI}} \): Costs of VOI assessment
## Algorithm: Approaches to Calculating VOI

<table>
<thead>
<tr>
<th>Conceptual VOI</th>
<th>Bounding exercise using information on $E_0\text{NB}(j,\theta)$, Imp$_j$, Dur$_j$, Pop$_j$</th>
<th>Quantitative estimates of VOI elements (useful if $1+ \approx 0$)</th>
<th>Rare diseases, controversial treatment, active R&amp;D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal Modeling</strong></td>
<td>Direct replication of data, or modeling that is limited to survival or quality of life</td>
<td>Comprehensive outcomes, e.g., QALYs, life expectancy, and/or costs</td>
<td>Acute conditions, end-of-life treatment</td>
</tr>
<tr>
<td><strong>Full Modeling</strong></td>
<td>Full characterization of disease and treatment, incl. health states</td>
<td>Structuring of model, data input for each parameter</td>
<td>EVPPI, (additional) primary data collection</td>
</tr>
<tr>
<td><strong>Maximal Modeling</strong></td>
<td>Comprehensive modeling organized around clusters of topics</td>
<td>Clustering of topics in clinical domain(s)</td>
<td>Chronic conditions, complex diseases, integrated care</td>
</tr>
</tbody>
</table>

| Least complex / costly              | Most complex / costly                                                                  |
Maximal modeling VOI: Coronary Heart Disease Model [Weinstein et al., 1987]
Maximal Modeling VOI: CDC Diabetes Model
Algorithm for selecting approach to VOI

Potential Topic for Research

- Conceptual VOI = Low
  - No VOI

- Conceptual VOI ≠ Low
  - Topic Does Not Clusters with Others in Domain
    - Comprehensive Outcomes Available
      - Minimal Modeling
      - Data Collection = Costly
        - Full Modeling
    - No Comprehensive Outcomes Available
      - Maximal Modeling
        - No VOI

(If not chosen)
Review of Literature and Priority Setting Processes

• Most organizations use expert judgment to prioritize systematic reviews

• None use VOI
  – Not surprising as most VOI applications use full modeling

• Some use criteria that relate to elements of VOI:
  • Reduction in uncertainty about benefits: 92%
  • Likelihood of implementation of technology: 54%
  • Durability of evidence from systematic review: 31%
  • Size of patient population targeted: 46%
Application:
Prioritizing 41 topics nominated to AHRQ’s EPCs for systematic review

- Conceptual VOI = Low
  - No VOI
    - 21 topics; $E_{\theta}NB(j,\theta) \approx 0$ (86% of topics)

- Conceptual VOI ≠ Low
  - Topic Does Not Cluster with Others in Domain
    - Comprehensive Outcomes Available
      - Minimal Modeling
        - 6 topics
    - No Comprehensive Outcomes Available
      - No VOI
        - Full Modeling
          - 7 topics
      - Maximal Modeling
        - 5 topics
      - Data collection ≠ Costly
        - No VOI
          - 2 topics
Conceptual VOI: limited value in further modeling, with VOI = 0 based on information for elements

\[
VOI = \sum_{t} \beta^{t} \cdot Dur_{t} \cdot Pop_{t} \cdot \left( \sum_{j} Imp_{j|\theta} - \sum_{j} Imp_{j|\theta} \cdot \mathbb{E}_{\theta} \cdot NB(j, \theta) \right) - C_{lt} - C_{VOI}
\]

Future research

Current information

Ketogenic Diet in Children with Intractable Epilepsy: No Studies Available to Reduce Uncertainty about Benefits Compared with Pharmacotherapy  \(\Rightarrow\)  \(E_{\theta|\theta} \cdot NB(j, \theta) = E_{\theta} \cdot NB(j, \theta)\)

Practice Structuring in Community-Based Psychiatric Care: Coverage / Payment Policies Drive Implementation of 15-Min Med-Checks as Standard Practice  \(\Rightarrow\)  \(Imp_{j|\theta} = Imp_{j|\theta} = 0\)

Hormone Therapy for Menopausal Symptoms: 29 New Comparative Effectiveness Studies To Be Completed within 1-3 Years Make Review Nondurable  \(\Rightarrow\)  \(Dur_{t} = 0\)

Phenylalanine-Restricted Diet in Phenylketonuria: 2000 Incident Patients per Year Comprise Relative Small Patient Population  \(\Rightarrow\)  \(Pop_{t} \downarrow 0\)
Discussion and Limitations

- As efforts to generate more topics for systematic reviews increase and guidelines accumulate that could be reviewed, need for tools to inform priorities may increase.
- VOI principles and methods may be useful as part of process of informing priorities.
- Algorithm may be used to identify practical approaches to using VOI:
  - Conceptual VOI aligns well with current triage process:
    - Formal use of VOI concepts may make conceptual process more explicit and quantifiable (e.g., durability, net benefit (costs)) – used by PCORI.
    - Not to replace judgment, but to complement to it.
  - Possible two-stage triage/prioritization process: 1) conceptual VOI, and 2) practical quantitative VOI calculations:
    - VOI often only provides upper bound (e.g., EVPI) on VOI.
    - VOI does not capture the value of other reasons for reviewing nominated topics, e.g., selecting technical briefs, topic refinement.
Future Directions

• Test use of VOI in priority-setting process for systematic reviews and research more generally
  – Assess whether VOI perceived as useful by researchers
  – Assess whether adding VOI to standard approach changes decisions
  – Assess value/impact of research where VOI might change decisions
    • Health/monetary impact, impression of stakeholders

• May use VOI to look for important topics within topics (e.g., medication switching in schizophrenia) and value of research in the context linked factors (e.g., linked nutritional factors)