Value of Information analysis for research decisions: Emerging good practice recommendations from the ISPOR VOI task force

W7 – Monday 6th November, 5:00 – 6:00pm
ISPOR 20th Annual European Congress
Scottish Event Campus
Glasgow, Scotland
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MODERATOR

Elisabeth Fenwick, PhD
Senior Principal,
Health Economics,
ICON plc
Abingdon, UK
Recent examples from the literature:
An unsystematic review of PubMed

“An expected value of perfect information of $4,195 per patient at societal willingness to pay of $50,000/QALY. The estimated value of partial perfect information regarding the HR was $3,702 per patient.”
Havrilesky, Chino, Myers. Gynecol Oncol. 2013

“EVPI per patient would be €204 at a €20,000 threshold value of society’s willingness to pay for one quality-adjusted life-year. Given a future population of 30,400 individuals, total EVPI would be €6.19 million.”
Bartha, Davidson, Brodkorn, Carlsson, Kalman. Trials. 2013

“The value of perfect information to reduce uncertainty was €291.6M at its lowest.”
Ramos, van Asselt, Kuiper, Severens, Maas, Dompeling, Knotterus, van Schayck. Eur J Health Econ. 2013

The expected value of perfect information is £43.1 million.

The expected value of perfect information (EVPI) associated with this decision is substantial (6.9 million pounds for the 20/40 model and 14.5 million pounds for the 20/80 model), with a sizeable EVPI associated with the effect of PDT on quality of life.
Trends in application of VOI

Reproduced from:
What is VOI?

- Difference in the payoffs associated with a decision made with and without additional information
- Decisions made on the basis of current level of information are uncertain
  - Non-zero probability decision is wrong
  - Costs associated with wrong decision
- Compare improved payoffs to additional cost of additional information
- EVPI - expected cost of uncertainty
- EVSI - expected reduction in uncertainty
ISPOR VOI Task Force Members (1)

- **Claire Rothery, PhD, Co-Chair**, Senior Research Fellow, University of York, York, England, UK
- **Elisabeth Fenwick, PhD, Co-Chair**, Senior Principal, Health Economics, ICON plc, Abingdon, UK
- **Anirban Basu, PhD**, Professor, Department of Pharmacy, University of Washington, Seattle, Washington, DC, USA
- **Salah Ghabri, MD, PhD**, Health Economist, Department of Economic and Public Health Evaluation, Haute Autorité de Santé, Paris, France
- **Saskia Knies, PhD**, Senior advisor pharmacoeconomics at National Health Care Institute (Zorginstituut Nederland), Diemen, the Netherlands
ISPOR VOI Task Force Members (2)

- Erik Koffijberg, PhD, Associate Professor of Health Economics, University of Twente, Enschede, The Netherlands

- James F. Murray, PhD, Research Fellow, Global Health Outcomes and Real World Evidence, Center of Expertise, Eli Lilly and Company, Indianapolis, USA

- Gillian D. Sanders Schmidler, PhD, Associate Professor of Medicine and of Biostatistics and Bioinformatics, Duke Clinical Research Institute, Duke University, Durham, NC, USA

- Lotte M.G. Steuten, PhD, Associate Member / Professor, Fred Hutch – HICOR / University of Washington – School of Pharmacy, Seattle, WA, USA

- Mark Strong, PhD, Section Director, Public Health, University of Sheffield, Sheffield, England, UK
Objectives of Task Force

Develop good practice guidance for VOI analysis methods to:

- Characterize uncertainty and perform VOI
- Aid in presentation and interpretation of VOI results
- Reduce barriers to VOI implementation
- Improve patient and health system performance outcomes

The task force will follow directly on from the ISPOR-SMDM Modelling Good Research Practices Task Force on Model Parameter Estimation and Uncertainty (Briggs et al., 2012) and the methods used to address recommendations in the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force Report (Garrison et al., 2013).
Specific aims

- Explain the importance of quantifying uncertainty and the value of further research for research prioritization decisions
- Develop recommendations to assess when additional evidence is required to reduce uncertainty in decision making
- Identify key steps and recommendations for good practices of performing, reporting, presenting and interpreting results of VOI analysis
- Provide clarity on how results of VOI analysis can be embedded into decision making processes
- Develop recommendations for use of VOI in jurisdictions that do not use cost-effectiveness information
- Identify areas where continued methodological development in VOI techniques is warranted
Paper 1

- **Audience:**
  - decision makers / health care payers considering comparative or cost-effectiveness analysis to inform their decisions
  - stakeholder groups making research prioritization decisions across a range of priority areas

- **Content:**
  - Decision making under uncertainty and the role of VOI analysis
  - Definition of VOI concepts and terminology
  - Overview of the steps to conduct a VOI analysis
  - Types of healthcare decisions supported by VOI analysis
  - Implications for research and policy decisions
    - with discussion of/references to examples
Paper II

- **Audience:** methodologists or analysts charged with undertaking VOI analysis to inform decision making

- **Content:**
  - Characterizing the sources of uncertainty for VOI
  - Key concepts, definitions and notation of VOI
  - Methods for computing EVPI, EVPPI and EVSI
  - Reporting of VOI results
  - Other considerations
    - minimal modelling describe how to monetize the value of further research
    - relevance of VOI in different contexts
  - Resources, skills and software

“greek”
## Timelines for Task Force

<table>
<thead>
<tr>
<th>Event</th>
<th>Revised Timeline</th>
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<tbody>
<tr>
<td>Reports out for 1st round review</td>
<td>August, 2017</td>
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<tr>
<td>Revisions based on comments received</td>
<td>September – November, 2017</td>
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<tr>
<td>Presentation at ISPOR Glasgow</td>
<td>November 6, 2017 (ongoing)</td>
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<tr>
<td>Task Force meeting at ISPOR Glasgow</td>
<td>November 7, 2017</td>
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<tr>
<td>Review round 2</td>
<td>January, 2018</td>
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<tr>
<td>Revisions based on membership review</td>
<td>January – March, 2018</td>
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<tr>
<td>Finalize reports</td>
<td>March – May, 2018</td>
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Objectives for workshop

- Introduce the ISPOR VOI Task Force and set out timelines for papers etc.
- Introduce the concept of VOI
- Describe the role of VOI in conditional reimbursement decisions
- Describe the use of VOI with different decision criteria (i.e. in absence of cost/QALY threshold)
- Discuss potential barriers for using VOI
- Present and get feedback regarding possible future research directions for VOI
Speakers

Saskia Knies, PhD
Senior Advisor
Pharmacoeconomics,
National Health Care Institute (Zorginstituut Nederland),
Diemen, the Netherlands

Claire Rotherapy, PhD
Senior Researcher,
TEEHTA
Centre for Health Economics,
University of York,
York, UK

Erik Koffijberg, PhD
Associate Professor,
Health Technology & Services Research Department,
MIRA institute for Biomedical Technology & Technical Medicine,
University of Twente
Enschede, The Netherlands
VOI and (conditional) reimbursement decisions

Saskia Knies PhD
**TASK FORCE PAPER 1**

**Audience:**
- decision makers / health care payers considering comparative or cost-effectiveness analysis to inform their decisions
- stakeholder groups making research prioritization decisions across a range of priority areas

**Content:**
- Decision making under uncertainty and the role of VOI analysis
- Definition of VOI concepts and terminology
- Overview of the steps to conduct a VOI analysis
- Types of healthcare decisions supported by VOI analysis
- Implications for research and policy decisions
  - with discussion of/references to examples
Types of healthcare decisions supported

1. Research prioritization decisions
2. Reimbursement of technology, incl. conditional reimbursement
3. Early technology/drug development decisions

Other types of decisions, e.g.:
- Value of subgroup information
- Outcomes based contracting
- Portfolio balance-risk
- Prioritizing update of systematic reviews
VOI for conditional reimbursement decisions

- EMA’s Adaptive pathways: early market authorisation new drugs
- Problem HTA organisations: premature evidence base

- VOI analysis of help beyond yes/no reimbursement decisions
- Decision additional evidence worthwhile:
  - Uncertainty about expected benefits
  - Does the uncertainty matter & how much?
  - Type of evidence most valuable
  - Value of additional research vs costs of research

- Value of delaying adoption vs value of providing early access
Coverage decisions with evidence development

Coverage with evidence development: overcomes the problems associated with making coverage decisions under uncertainty

- **Approve**: Could impact on the prospects of acquiring further evidence
- **Reject**: Could restrict patient access to promising new technologies

Approval with research (AWR)

- ‘Yes’ decision until further research is completed and guidance is established

Only in research (OIR)

- ‘No’ decision until further evidence establishes value
  - Only approved for use within the context of suitable research study
## Framework for characterising uncertainty

<table>
<thead>
<tr>
<th>Category</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Value of technology</strong></td>
<td>• Expected cost-effectiveness</td>
</tr>
<tr>
<td></td>
<td>• Assessment of health opportunity costs</td>
</tr>
<tr>
<td><strong>Irrecoverable costs</strong></td>
<td>• Sunk investment costs (e.g. capital costs)</td>
</tr>
<tr>
<td></td>
<td>• Learning curve profile</td>
</tr>
<tr>
<td><strong>Evidential uncertainty</strong></td>
<td>• Assessment of uncertainty in evidence base</td>
</tr>
<tr>
<td></td>
<td>• Is additional research needed?</td>
</tr>
<tr>
<td><strong>Decision uncertainty</strong></td>
<td>• Health consequences of uncertainty</td>
</tr>
<tr>
<td></td>
<td>• What type of research is needed?</td>
</tr>
<tr>
<td><strong>Future changes</strong></td>
<td>• Anticipated future changes</td>
</tr>
<tr>
<td></td>
<td>• Price, additional evidence, new technology</td>
</tr>
<tr>
<td><strong>Value of early access</strong></td>
<td>• Early access vs. costs of reversing decisions</td>
</tr>
<tr>
<td></td>
<td>• Value of research forgone by early access</td>
</tr>
</tbody>
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Combined assessment establishes the most appropriate policy choice:
- Approve,
- Reject,
- OIR,
- AWR
Case study: EECP for chronic stable angina

- Enhanced external counterpulsation (EECP) is a non-invasive procedure used to treat chronic stable angina
- Primary outcome is the symptomatic relief of angina symptoms
- EECP has large initial upfront costs of treatment (£4,347 per patient), which are irrecoverable once treated
- EECP as adjunct to standard therapy vs. standard therapy alone
- One RCT showed evidence of improved HRQoL at 12 months
- Uncertain whether HRQoL benefits are sustained beyond 12 months
Does more research seem worthwhile?

i. How uncertain is a decision to approve or reject the technology?

ii. Do the likely consequences of uncertainty justify further research?
   • NHB that could be gained if it could be resolved immediately
   • Upper bound on potential benefits of more research
   • ‘No’ decision can lead directly to guidance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost-effectiveness threshold at £20,000 per QALY</th>
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<tbody>
<tr>
<td></td>
<td>Incremental NHB QALY (£m)</td>
</tr>
<tr>
<td>EECP</td>
<td>1,405 (28.1)</td>
</tr>
<tr>
<td>Standard care</td>
<td>-</td>
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</tbody>
</table>
Is research possible with approval?

i. Type of evidence needed?

ii. Can the research be conducted while technology is approved?
   - Importance of parameters (values that change the decision)
   - Uncertainty in possible values (how likely to change)
   - NHB that are to be gained (expected consequences)
   - Determines whether AWR or OIR are possibilities

(1) Incremental HRQoL benefits in first year
(2) Probability of sustaining HRQoL benefits in subsequent years (group of elicited parameters)
(3) 2-year probability of repeat EECP sessions

Overall decision uncertainty (EVPI)

Expected consequences (QALYs)

- 8,127
- 3,860
- 0
- 9,287

0 1,000 2,000 3,000 4,000 5,000 6,000 7,000 8,000 9,000 10,000
Comparing decision options for EECP

<table>
<thead>
<tr>
<th>EECP</th>
<th>Approve</th>
<th>OIR</th>
<th>AWR</th>
<th>Reject</th>
<th>Value of AWR</th>
<th>Uncertainty resolved at launch</th>
<th>Value of evidence at launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressed in QALYs</td>
<td>Research reports in 3 years</td>
<td>1,391,001</td>
<td>1,397,192</td>
<td>1,393,578</td>
<td>1,389,596</td>
<td>-3,614</td>
<td>1,400,288</td>
</tr>
</tbody>
</table>

- AWR not valuable due to significant irrecoverable costs associated with EECP
- Values depend on time taken for research to report
Are the benefits of research greater than the costs?

i. Will the research be conducted?

ii. When will the results become available?

iii. How much uncertainty will be resolved?

iv. Costs of research

v. Impact of other sources of uncertainty
Conclusions

• Value of information analysis allows us to assess the value of research and policies most suitable to result in removing the health consequences of uncertainty

• Policy analysis based on value of information analysis can be used to consider the trade-off between the expected benefits to current patients from early access and the benefits to future patients from more research
Applications of VOI in different contexts

- VOI is relevant to a wide range of different types of health care systems and decision-making contexts.

- VOI theory can be expressed in terms of a generic utility function that does not impose a specific metric of value on the decision-maker.

- VOI can be applied using different objective functions that align with different perspectives:
  - Net health or monetary benefit (Payer/Societal perspective/different decision maker constraints)
  - Clinical perspective (PCORI, SWOG)
  - Revenue (manufacturer’s perspective)
Expected value of perfect information (EVPI):

$$EVPI(\theta) = E_\theta \{ \max_{d \in D} U(d, \theta) \} - \max_{d \in D} E_\theta \{ U(d, \theta) \}$$

Expected value of perfect parameter information (EVPPI):

$$EVPPI(\theta_i) = E_{\theta_i} \left[ \max_{d \in D} E_{\theta_c|\theta_i} \{ U(d, \theta_i, \theta_c) \} \right] - \max_{d \in D} E_\theta \{ U(d, \theta) \}$$

Expected value of sample information (EVSI):

$$EVSI = E_X \left[ \max_{d \in D} E_{\theta|X} \{ U(d, \theta) \} \right] - \max_{d \in D} E_\theta \{ U(d, \theta) \}$$
Step-by-step guide for the estimation of VOI

+ Good practice recommendations
  (Report 2 of ISPOR Task Force)
Research prioritization

- Topic generation
- Research questions requiring prioritization

- Value of Information
- Research proposals prioritized
- Proposals selected for funding

- Bookshelf of value
- Funding available

- Expenditure
- Value
Clinical perspective

- Use standard methods of systematic review and meta-analysis (or prior clinical study if only one study is available)
- Report uncertainty in the endpoint of interest
  - Range of plausible values that the outcome can take (e.g. 95% CI)
- Identify the consequences that can result from this uncertainty and the likelihood of these consequences occurring
  - VOI aggregates the probability-weighted consequences to yield a net health impact of uncertainty for each alternative intervention
- Specify a minimum clinical difference in outcomes required
  - To account for other aspects of outcome not captured in endpoint
  - Clinical practice unlikely to change without it
Effect of corticosteroids (CS) on mortality following significant head injury

Baseline event rate (control arms of the trials) = 0.378 (95% CI, 0.248 - 0.469)
Incidence in the UK = 8,800 per annum
Uncertainty in the health effects of CS following significant head injury

Additional deaths of using CS (per annum)
Potential benefits of additional research

Corticosteroids increase mortality
Corticosteroids reduce mortality

28% chance that mortality is higher
72% chance that mortality is reduced

Number of additional deaths with corticosteroids per annum

Potential health benefits of additional evidence = 51 deaths per annum

72% chance of no excess deaths
0.72

10% chance of 100 excess deaths
0.10

0.00 0.06 0.08 0.10 0.02 0.01
0 100 200 300 400 500 600 700 800 900 1000 >1000

Number of additional deaths with corticosteroids per annum

Probability of additional deaths with corticosteroids

Corticosteroids reduce mortality
Corticosteroids increase mortality

Probability of additional deaths with corticosteroids
0.06 0.02 0.01

0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00

Probability of additional deaths with corticosteroids

Number of additional deaths with corticosteroids per annum

Number of additional deaths with corticosteroids per annum

Potential health benefits of additional evidence = 51 deaths per annum
Assessing whether proposed research is worthwhile

- Was CRASH potentially worthwhile?
  - CRASH cost £2.2m and expected to avoid 1,371 deaths
  - CRASH offered £1,605 per death averted

- Should CRASH have been prioritised and commissioned?
  - Not based on hindsight
  - Comparison (based on similar analysis) with those proposals competing for limited research resources

- Other aspects of outcome?
  - Combining effects on mortality and disability
    - Expected benefits of 8,946 QALYs
    - £246 per QALY gained

- Are sufficient resource being devoted to research?
  - If unable to fund proposed research that is potentially worthwhile (compared to other use of the resources) then could improve health by allocating more resources to research
Recommendations for minimal modelling approach

- Minimal modelling approaches may be used as a substitute for full modelling in certain circumstances:

  - Clinical study should be sufficient to capture all important differences between interventions
  - Endpoints need to occur within the timeframe of the study
  - No competing causes of death or other events that occur outside study
  - Extrapolate endpoints to a meaningful measure of health benefit with relatively simple model


  Good practice recommendation

  Where VOI is applied without constructing a full disease and/or decision-analytic model, the underlying structural assumptions should be made as explicit as possible.

  Consideration should be given to the likely impact that these assumptions might have on the findings.
Manufacturer perspective

- VOI in product development lifecycle
- Used to assess which developments are potentially worthwhile
- Prioritise those that are potentially worthwhile
  - Difference between value and R+D costs (NPV) or % of R+D costs (ROI)
- Explore different specifications
  - More effective, benefits larger populations, reduce health care costs
- Update assessment during development
  - Inform stop/go and disinvestment decisions
Conclusions

- VOI is relevant to a wide range of different types of health care systems and decision-making contexts

- VOI should not be regarded as restricted to situations where full decision modelling or estimates of cost-effectiveness are available

- Types of health care decisions supported by VOI include:
  - Research prioritization decisions
  - Reimbursement decisions in HTA
  - Early drug/technology development decisions
  - Other types of decisions e.g., value of subgroup information, portfolio balance-risk over many projects, prioritizing the update of systematic literature reviews
Value of Information

Barriers

Future research

Erik Koffijberg, PhD
VOI in practice

- VOI has large potential
- Which has not been fully realized yet...
  - Outside of the UK, it is unclear to what degree the priorities identified by CEA and VOI methods were translated into actual research funding (Myers et al., 2011)
  - While VOI is increasingly part of health economic evaluations ... its uptake in real world decision-making remains limited (Steuten et al., 2013).
  - Large theoretical literature surrounding these techniques but currently there is little evidence of their application in decision making (Kent, et al., 2013)
  - Rarely used to inform funding decisions (Carlson et al., 2013)
  - Although VOI is described as best practice for handling decision uncertainty, its application remains limited (Bindels et al., 2015)
VOI in practice – Known barriers

Listed in literature
Bindels, et al. (2016)
Adronis (2015)
Carlson, et al. (2013)
Myers, et al. (2011)
Claxton, et al. (2005)

1. WHY PERFORM VOI?
2. HOW TO PERFORM VOI?
3. WHAT IS THE IMPACT OF VOI?
1. WHY PERFORM VOI?

- Policy makers do not think VOI is useful
- Unclear when performing VOI analysis if useful and what complexity is required
- VOI does not capture all of the uncertainties
VOI in practice – Known barriers

2. HOW TO PERFORM VOI?

- Practical guidelines on how to perform VOI are lacking
- Performing VOI is time-consuming
- Performing VOI is complex and requires technical expertise
- VOI requires a WTP to be defined for the relevant outcome
VOI in practice – Known barriers

3. WHAT IS THE IMPACT OF VOI

- Unclear how VOI outcomes are actually used in practice
- Policy makers find it difficult to interpret VOI outcomes unless engaged early on and helped to understand VOI methodology
- Not all optimal research designs, indicated by VOI, are feasible in practice
- Unclear who should pay for additional research
What do you see as the main Practical Barriers to conducting a VOI analysis?
What do you see as the main Practical Barriers to conducting a VOI analysis?

- **Access to VOI tools**: 10
- **Complexity of methods**: 11
- **Lack of VOI expertise**: 8
- **Lack of necessary data**: 12
- **Time required to conduct VOI**: 5
- **VOI does not incorporate all uncertainties**: 5
- **No accepted WTP threshold for outcome**: 6
- **Other barriers**: 7

@ISPOR 22nd Int meeting (Boston) VOI-TF survey
VOI in practice – Your barriers

@ISPOR 22nd Int meeting (Boston) VOI-TF survey
What do you see as the main barriers for Acceptance of VOI?
VOI in practice – Your barriers

@ISPOR 22nd Int meeting (Boston) VOI-TF survey
What do you see as the main barriers for Acceptance of VOI?

- Lack of uniform VOI guidelines (9)
- Decision makers do not think it’s useful (8)
- Optimal VOI designs may not be feasible (8)
- No clear criteria when VOI should be performed (8)
- Decision makers do not understand VOI (8)
- No accepted WTP threshold for outcome (8)
- Unsolved methodological issues (7)
- Unclear who would/should pay for research (7)
- Other acceptance barriers (9)
VOI TF – REPORTS 1 & 2

Report 1 - Gentle introduction to VOI
Addresses the **WHY** question, describes potential **IMPACT** by indicating how to use VOI outcomes in different types of health care decision problems

Report 2 - Technical details on performing VOI
Addresses the **HOW** question
Describes practical and efficient methods and tools
Support for taking away practical barriers to conducting VOI analysis

- Detailed description of all VOI steps
- Examples of publicly available VOI tools
- Discussion on the context in which
  a) simplified VOI calculations / minimal modelling
  b) efficient approximation of VOI outcomes

... can be applied to reduce the required time for VOI analysis and its complexity (e.g. SAVI, BCEAweb)
Future research on VOI

Methodological issues and evidence challenges
Future research on VOI

1. Developing VOI methods for complex situations
   - EVSI for multidimensional design space may be computationally challenging.
     - Explore methods to reduce this computational load
   - When evidence from a new study informs functions of model parameters multi-parameter evidence synthesis may be required to preserve the parameter correlation.
     - Compare different synthesis methods such as network meta-analysis (Welton et al. 2015)
   - RCTs for rare diseases are hard to implement due to limited sample size.
     - Explore how evidence from multi-national studies may inform the value of evidence and optimal resource allocation across jurisdictions
Future research on VOI

2. Optimizing the value of research to reduce structural uncertainties

- VOI measures are sensitive to uncertainty related to model structure. The credibility of VOI outcomes depends on the sources of uncertainty that have been reflected in the underlying model or analysis.
  - The value of reducing structural uncertainty (the “expected value of model improvement”) has been explored (Strong & Oakley, 2014), but methods in this area are, in general under developed.
Future research on VOI

3. Identifying appropriate time horizons for research decisions and future changes

- The time horizon for research decisions is unknown since it is a proxy for uncertain future changes. However, some assessment is required for estimating VOI outcomes.
  - Identifying the appropriate time horizon for research decisions and incorporating uncertainty in the time horizon is an area that has received little attention to date.
  - Identifying expected relevant changes over this time horizon (price changes of interventions, changes in clinical practice, introduction of new technologies) all impact VOI outcomes (Claxton et al. 2012).
Future research on VOI

4. Describing the relationship between evidence from a new study and implementation

- Often it may be relevant to model the relationship between strength of evidence from a new study and implementation speed of the considered intervention.
- Currently, evidence to inform the shape of such a function is limited (Kent et al. 2013)
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WiFi: ISPORGlasgow
Password: IQVIA2017
Poll: What do you think is the most relevant future research direction regarding methodological challenges?
Poll: What other future research direction regarding methodological challenges can you think of?
Poll: What do you think is most valuable next step in VOI research/implementation in general?
Questions