The value of value of information: Improving research design to impact on decision making

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Overview

• Health economics and decision analytic principles for robust decision making
• Designing research to make a difference – the value of information to decision making
• Taking Occams Razor to VOI methods - How can the VoI toolkit best be used to improve research design and prioritization?
• A robust framework for optimal decision making and efficient trial design within and across jurisdictions, allowing for decision contexts
• Conclusions, Policy and Research Implications

Economic evaluation and HTA

• Public health systems face scarcity of resources in attempting to satisfy health needs of defined populations over time
• Processes of Health Technology Assessment (HTA) attempt to inform choices between alternative strategies in treating defined patient populations based on ‘value’
  – expected incremental cost relative to expected incremental effects of alternative treatment strategies

VALUE

Incremental Cost

Incremental Health Outcome
Capturing incremental outcomes and resource use (costs) of alternatives

New therapy

Target Patient Group

Treatment pathways for therapies and associated outcomes

Health Outcomes - survival, events & health related utility over time -QALYS

Resource use and Cost

Direct cost
Follow up costs
Hospital, GP, specialist medications
Nursing home etc.

Decision model – PBAC perspective

Epidemiological Evidence – Risk factor
Prognostic model

Relative Treatment Effect

Absolute risk (Control Rx) \times \text{Treatment effect} = \text{Absolute effect difference}

Associated Resource use, cost and utility

Policy decisions

Net clinical benefit

Size of benefits and harms

The incremental cost-effectiveness plane

NW New treatment more costly
NE Maximum acceptable ICER

Existing treatment dominates

New treatment more effective
by/more costly

C

New treatment less effective

SW New treatment less costly

SE

New treatment dominates

New treatment less costly but less effective

Decision analytic principles in CE analysis

Robust cost effectiveness analysis requires:

- Unbiased estimation of treatment effect on health effects / resource use relative to an appropriate comparator (Comparability)

- Sufficient length of follow up and scope of resource use and health outcomes to capture incremental costs and effects (Coverage)

- Consideration of decision making uncertainty
Health economics and Decision Making

Decision makers with information on expected cost and effects of alternative treatment strategies can identify the preferred treatment strategy at a threshold value ($\lambda$) for the incremental cost effectiveness ratio (ICER)

$$ICER = \frac{\Delta C}{\Delta E} < \lambda$$

But.. uncertainty in relative costs and effects translates to decision uncertainty

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Potential value of research

- A decision analytic model summarising prior evidence allows identification of key uncertainties remaining e.g. IBIS

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Principles for robust decision making in HTA

- Decision making in HTA focuses on value for money across alternative treatment strategies in defined populations
- Economic and decision analytic principles support RCTs with appropriate comparators, adequate follow-up and coverage of incremental resource use and effects
- Patient level data is important in allowing for the joint distribution of costs and effects in modelling uncertainty – Bootstrapping or Fieller Method
- Net benefit (NB) allows ‘cost effectiveness’ evidence to be presented relative to ‘value for money’ DM thresholds
- Modelling may be required to generalise from RCT evidence - synthesise evidence, extrapolate beyond study follow-up, generalise to other settings (practice, populations)
Efficient research design and grant proposals
In general – illustrate
1. Uncertainty faced in policy/decision making
2. How research is expected to reduce uncertainty
Specifically
1. Use robust & policy relevant endpoints
2. Collect patient level data – effect and resource use (event) data to inform DM uncertainty
3. Model the expected value of information from planned research…

Designing research to make a difference – the expected value of information to decision making

Expected Value of Information
• Research has expected value in reducing decision making uncertainty …. further information is expected to reduce the likelihood of, and negative payoffs from bad decisions
- need a framework to quantify payoffs (under uncertainty) from bad decisions

Incremental Net Benefit (INB)
\[
\Delta C / \Delta E < \lambda \quad \Rightarrow \quad INB = \lambda \times \Delta E - \Delta C > 0
\]
Therefore, preferring a new therapy is equivalent to incremental net benefit being greater than 0
AND… the expected value of avoiding bad decisions can be estimated by integrating across the distribution of incremental net benefit below 0
The Expected Value of Sample Information

- The expected value of sample information (EVSI) estimates the expected value of avoiding bad decisions from reducing decision uncertainty.
- EVSI is the difference between the value of (avoiding) bad decisions given initial uncertainty (EVPI\textsubscript{0}) and the expected value of (avoiding) bad decisions at time $t$ with more evidence (EVPI\textsubscript{t}).

Decisions VoI measures can inform

1. Is further research for a specific HTA potentially worthwhile?
2. Is a given research design worthwhile?
3. What is the optimal research design?
4. How can funding best be prioritised across alternative research proposals?
What Vol measures are available to potentially inform decisions?

- The expected value of perfect information (EVPI) with current information
- Expected value of sample information (EVSI)
- Expected net gain (ENG) as EVSI less expected cost

In taking Occam’s razor to Vol methods we consider:
- First, which of these measures are necessary and sufficient to inform decisions 1-4 (their usefulness); and
- Second, the simplicity (complexity) with which they can be applied with current Vol methods.

Eckermann, Karnon & Willan (2010)

EVPI informing research decisions?

- Population EVPI - EVPI per patient multiplied by the patient population over the time horizon for which information is useful has been suggested as providing
  - an upper bound for the value of prospective research
  - a ‘necessary condition’ for further research where EVPI is ‘large enough’ to justify potential future research

However …

Limitations of current EVPI

- Whether EVPI is ‘large enough’ or not requires consideration of expected cost and value of research, which can vary from negligible to those of a large RCT
- Hence, the size of current EVPI does not provide a necessary condition to inform the decision of whether further research is worth

What is required to inform decisions?

- The expected value, expected cost and ENG (value less cost) of research are conditional on the extent of proposed research.
- Consideration of expected value, costs and ENG of actual trial designs are necessary to inform:
  1. Whether any further research is worthwhile;
  2. Whether a specific research design is worthwhile;
  3. Optimal research design; and
  4. Optimal prioritisation of research across HTAs
Illustrating the need to move beyond current EVPI

<table>
<thead>
<tr>
<th>HTA</th>
<th>EVPI</th>
<th>EVSI</th>
<th>Direct research cost</th>
<th>Oppor. cost of delay</th>
<th>Total cost US$</th>
<th>ENG US$</th>
<th>Return on direct investment</th>
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<td>A</td>
<td>50M</td>
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<td>E</td>
<td>25M</td>
<td>9.8M</td>
<td>2M</td>
<td>6M</td>
<td>10M</td>
<td>-0.2M</td>
<td>-17%*</td>
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<td>F</td>
<td>6M</td>
<td>3M</td>
<td>3M</td>
<td>0.5M</td>
<td>3.5M</td>
<td>-0.5M</td>
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Eckermann, 1 October 2010

e.g. Prioritising $12M to research

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Prioritise $12M based on
Max EVPI – support D, A, E & F Total ENG $4.4 M
Max ENG – support A, B & C Total ENG $31.0 M
Eckermann, 1 October 2010

What Vol methods allow optimisation of ENG?

- Use of the Central Limit Theorem (CLT) under an assumption of bivariate normal distribution:
  - Outperforms bootstrapping with small samples and skewed data (Nixon et al 2009)

Bootstrapping

Computationally expensive in estimating expected posterior EVPI for EVSI & prohibitive in optimising ENG across designs (Ades, Lu and Claxton 2004)

Eckermann, 1 October 2010
Expected value of perfect information with CLT

\[
L(b) = -b
\]

\[
\int_{-\infty}^{0} f(b) \, db = \pi - \Phi(-1) \quad \text{(Willan & Pinto 2005)}
\]

\[
\int_{0}^{\infty} f(b) \, db = 1 - \Phi(1) \quad \text{(Eckermann & Willan 2007)}
\]

If \( b > 0 \): \( L(b) = NBT(b) - NBT(b) = 0 \)

If \( b < 0 \): \( L(b) = NBS(b) - NBT(b) = -INB = -b \)

**Occam’s Razor - best use of VoI toolkit**

- Use of the CLT is both simpler and enables estimation of EVSI and optimal overall trial design - allows better informed decisions than alternate methods
- Bootstrapping can still be potentially useful in estimating partial EVPI, BUT high complexity and does not extend to EVSI with associated limitations – hence, Occam’s razor should be seriously considered in application of such methods
- VoI toolkit best used with CLT for overall trial design and decision making, focusing alternate methods where they may be most useful

CLT methods also allow for real decision contexts

- Use of the CLT has been shown to allow for critical decision contexts, including:
  - Opportunity costs and option value of delay (Eckermann & Willan 2007, 2008a)
  - Time (Eckermann & Willan 2008b)
  - Value of information across jurisdictions (Eckermann & Willan 2009)
  - Imperfect Implementation (Willan & Eckermann 2010)
- Establish that optimal research and reimbursement decisions are joint, not separable – require ENG for:
  - \( DT \) vs \( AN \): opportunity costs of delay; and
  - \( AT \) vs \( AN \): cost reversal (global trials where \( AT \) is feasible)

Joint research and reimbursement decisions

- Decision makers in the usual case of interest with evidence of positive but uncertain net benefit of a new therapy can choose between:
  1. delay & trial (DT)
  2. adopt and trial (AT)
  3. adopt with no trial (AN)
- How can VoI methods inform this choice?
Framework for optimal local decision making

- Optimal DM requires joint consideration of research and reimbursement, comparing ENG of designs for:
  1. **DT vs. AN** conditional on opportunity costs of delay and
  2. **AT vs. AN** conditional on cost of reversal (where AT feasible)

**AN** is preferred if ENG is not positive for any feasible trial.

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**e.g. Early vs. late External Cephalic Version (ECV)**

- Pilot RCT of 232 pregnant women presenting in breech position
  - 41/116 (35.2%) had non-Caesarian delivery in early (37 week) arm
  - 33/116 (28.4%) had non-Caesarian delivery in late arm
  - If avoiding Caesarian delivery is valued at $1,000 then

\[
\Delta = 41/116 \cdot 1000 - 33/116 \cdot 1000 = 68.97
\]

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Efficient trial design with early (34 weeks) vs. late (37 weeks) ECV

In North America, the optimal decision given pilot evidence, 0 cost of adoption and expected cost of reversal of US$2M is:

- **AT** with n=284 per arm, expected net gain of US$361,422

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Infeasibility of AT within jurisdiction

- Within jurisdiction - AT infeasible (unethical) where the new therapy has positive, while uncertain net clinical benefit – informed patients prefer certainty of treatment outside trial to chance of new therapy in a trial setting
- Hence, ‘within jurisdiction’ feasible options will often be restricted to **DT vs. AN**
- Note **DT vs. AN** is still a joint reimbursement / research decision
- Trials can be undertaken elsewhere – AT therefore remains a valuable option moving beyond ‘within jurisdiction’
The assumption of “prospective value only within jurisdiction”

- VoI methods applied to efficient trial design within jurisdiction assume evidence arising external to jurisdiction has retrospective value
- But only evidence arising within jurisdiction has prospective value
- However, publicly available evidence arising from trials is non-rival
- Hence, provided evidence can be translated, new evidence arising in one jurisdiction is expected to have value in each jurisdiction

Relaxing the within jurisdiction assumption

- Where prospective VoI from trials in other jurisdictions is considered, an additional viable option is for a side payment to influence trial design in another jurisdiction
- Avoids fixed trial costs and increases homogeneity of evidence
- Hence, a combined optimal trial across two jurisdictions improves on separate trials within each jurisdiction
- Extending this principle across all jurisdictions raises the question: what is the globally optimal trial design?

EVSI and costs across jurisdictions

- Each jurisdiction has:
  - a distribution for prior INB, cost of reversal; and, hence
  - EVSI conditional on Cr for AT and EVSI less opportunity costs for DT (local ‘VoI’)
- Hence, VoI for optimal decisions in each jurisdiction (j) can be summed across jurisdictions (given information is non-rival) to estimate global VoI at any trial size
- Global costs can be minimised (ENG maximised) in allocating trial sample across jurisdictions (nj,kj) for locally optimal decisions at any given trial size

Optimal trial design across jurisdictions

- The globally optimal trial design | optimal local decision making is given by the set of nj,kj that maximises

\[
\sum_{j=1}^{J} \max \left( \text{oENG}_{ij}(n_j, n_j), \text{oENG}_{ij}(n_j, n_j) \right) - \sum_{j=1}^{J} (C_j + 2n_j C_{ij})
\]

where the decision to delay or adopt is chosen by each jurisdiction to maximise local ENG (excluding direct trial costs)
- Direct costs of trial are shared globally
## ECV variables for decision making by jurisdiction

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<th>UK</th>
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<tbody>
<tr>
<td>Annual incidence $k_j$</td>
<td>50,000</td>
<td>10,000</td>
<td>3,000</td>
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<tr>
<td>Patient horizon at baseline $N$</td>
<td>1,000,000</td>
<td>200,000</td>
<td>60,000</td>
</tr>
<tr>
<td>Annual accrual rate $a_j$</td>
<td>1/100 = 500</td>
<td>1/20 = 500</td>
<td>1/6 = 500</td>
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<tr>
<td>Fixed cost* $C_{Fj}$</td>
<td>500,000</td>
<td>500,000</td>
<td>375,000</td>
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<tr>
<td>Variable cost* $C_{Vj}$</td>
<td>1000</td>
<td>1500</td>
<td>1200</td>
</tr>
<tr>
<td>Cost of reversal* $C_{Rj}$</td>
<td>2,000,000</td>
<td>1,000,000</td>
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* assuming a 20-year time frame  
* in US dollars

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### Advantages of global vs. locally optimal

- Recognises higher global value of information in optimal trial design
- Costs of sampling (fixed, variable and opportunity costs) can be minimised in allocating sample across jurisdictions
- Reduces heterogeneity of evidence across multiple trials, ‘Frankenstein’s Monster’ and increases expected homogeneity of practice (implementation) within & across jurisdictions
- Can identify how sub-optimal ‘locally sized’ optimal trials are: overcomes market failure from free rider effects (small trials) and sub-optimal spreading of fixed costs (too many trials)

Evidence required by companies is standardised across jurisdictions  
Higher quality evidence to inform regulators

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### Optimal trial design:

#### N. America, UK, Australia

#### Total EVSI

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* all figures in US dollars  
§ by negotiation

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**Optimal trial design for ECV across Australia, UK and North America**

**Optimal trial design**

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**Eckernann, 1 October 2010**
What if AT is infeasible within jurisdiction?

If AT is infeasible within a jurisdiction, then:

- the “Locally optimal” solution is:
  - no trial in North America, UK, Australia,
  - ENG=0

- the “Globally optimal” solution is to:
  - adopt in UK, North America and
  - delay with a trial of 339 patients per arm in Australia
  - ENG=$920,590

Hence ENG increases by:
- $418,276 if AT is feasible within jurisdiction;
- $920,590 if AT within jurisdiction is infeasible.

Translatability of evidence between jurisdictions

- Degree of translatability across jurisdictions depends on the extent to which local populations, practice and relative prices differ
- “The USA is different to the rest of the world” hence, a locally optimal trial in the USA may have limited value for the ROW (and vice versa)

Optimal trial design with imperfect translation

Typical case – imperfect translation between USA-ROW

- **Locally optimal**: trial in USA, no trial elsewhere – limited VOI to DM outside USA given imperfect translation
- **Globally optimal**: trial with patients in USA and ROW

Hence, imperfect translation increases the scope for gains in ENG from globally vs. locally optimal trial design

General principle: globally optimal trial has greater ENG than local trials unless no translatability anywhere – in which case locally optimal is globally optimal

Bottom line - globally

Optimal global trial design provides a first best solution, increasing ENG c.f. local trials by:

1. recognising global VOI
2. minimising trial cost and heterogeneity of evidence
3. overcoming market failure and technical infeasibility with AT

Globally optimal trial design for local decision making
Conclusions - research design

• Research has expected value to policy makers in reducing decision making uncertainty
• Efficient trial design and grant proposals should attempt to maximise the expected value relative to the expected cost of research – value of information methods can be used to estimate this explicitly
• VoI methods applying the CLT are simply, feasibly and robustly applied to optimise ENG in overall trial design given prior evidence and allow for important decision contexts - joint research & reimbursement decisions, time, OC & option value of delay, Vol across jurisdictions

Eckermann, 1 October 2010

Policy implications

• Funding bodies such as the NHMRC have a directive to “fund research which provides evidence to inform policy and practice”
• To best inform decision making research should be efficiently as well as robustly designed – consider the value of research to the decision maker in reducing DM uncertainty, relative to the cost of research
• Optimal design and decision making can be explicitly and systematically identified applying value of information methods, allowing for decision contexts
• Research efficiently designed to make a difference has the best chance of being funded, provide relevant information to inform decision making in policy and practice and hence make a difference.

Eckermann, 1 October 2010

Relevance to UOW research

• The UOW has the expertise to provide:
  – Robust evidence-based research to inform health care policy
  – Efficient research design, reflecting decision-making uncertainty
  – Comparison of performance in practice consistent with evidence based medicine

Eckermann 1 October 2010

Linking research, reimbursement and regulation of practice

Optimal research design – locally, globally, allowing for imperfect implementation

Translating evidence
(Eckermann, Coory & Willan 2009, 2010)

Multiple strategy comparison and ENL curves
(Eckermann, Briggs & Willan 2008, Eckermann 2009)

Comparison and efficiency measures in practice consistent with Maximising NB
(Eckermann 2004, Eckermann and Coelli 2008)

Eckermann, 1 October 2010


References – Value of information


References – Linking research, reimbursement and practice

Comparing multiple strategies and providers in practice – the net benefit correspondence theorem, C-DU plane and ENL curves and frontiers


Translating evidence – relative risk fallacies and odds ratios solutions


Eckermann, 1 October 2010