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

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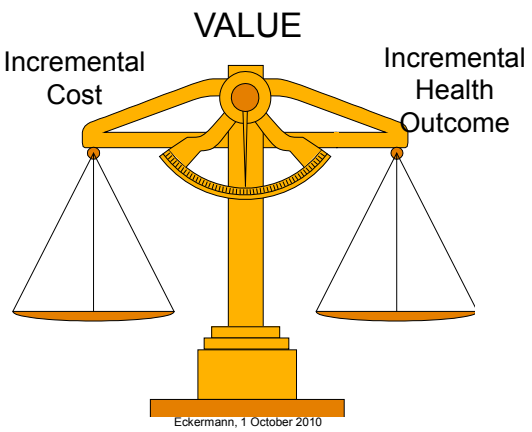
Overview

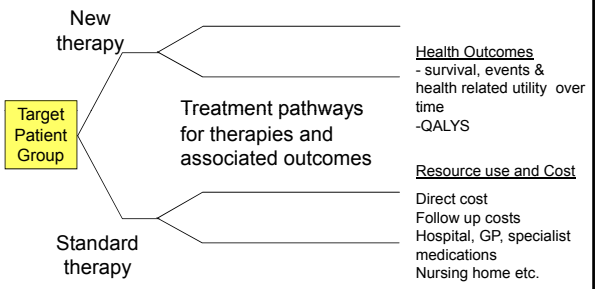
- Health economics and decision analytic principles for robust decision making
- Designing research to make a difference – the value of information to decision making
- Taking Occams Razor to VOI methods - How can the VoI toolkit best be used to improve research design and prioritization?
- A robust 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

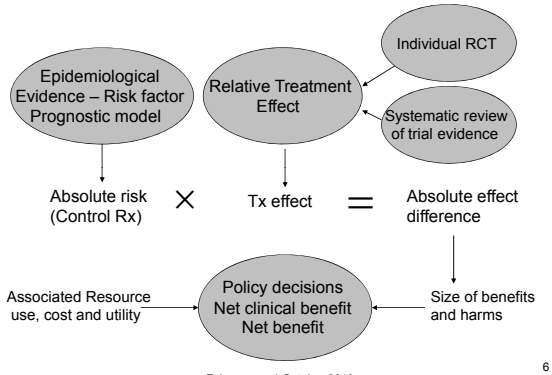
- Public health systems face scarcity of resources in attempting to satisfy health needs of defined populations over time
- Processes of Health Technology Assessment (HTA) attempt to inform choices between alternative strategies in treating defined patient populations based on 'value'
  - expected incremental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



Capturing incremental outcomes and resource use (costs) of alternatives



Decision model – PBAC perspective

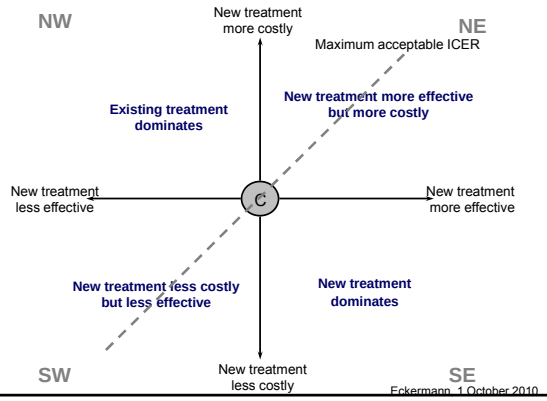


Decision analytic principles in CE analysis

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

The incremental cost-effectiveness plane



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 (λ) for the incremental cost effectiveness ratio (ICER)

$$ICER = \Delta C / \Delta E < \lambda$$

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

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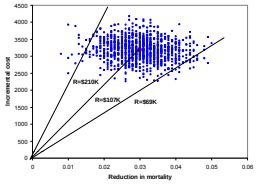
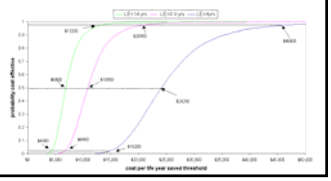
Modelling decision uncertainty

- Patient level data enables robust estimation of ICER uncertainty with bootstrapping of patients 'cost and effect' - allows for covariance structure
- Translating this to cost effectiveness acceptance curves allows policy makers to be informed of decision making uncertainty at any threshold





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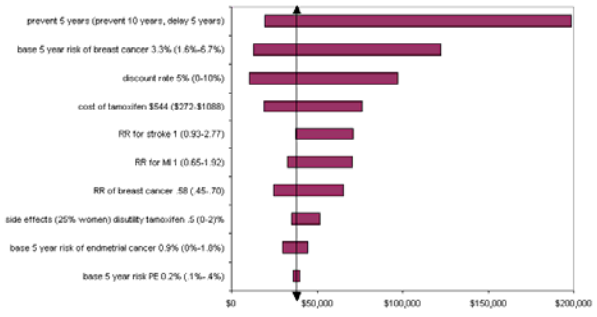
Potential value of research

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



Eckermann, Martin, Stockler and Simes (2003)

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)

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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)

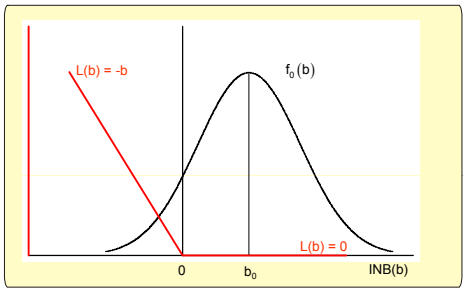
$$\Delta C / \Delta E < \lambda$$

$$\Leftrightarrow INB = \lambda \times \Delta E - \Delta C > 0$$

Therefore, preferring a new therapy is equivalent to incremental net benefit being greater than 0

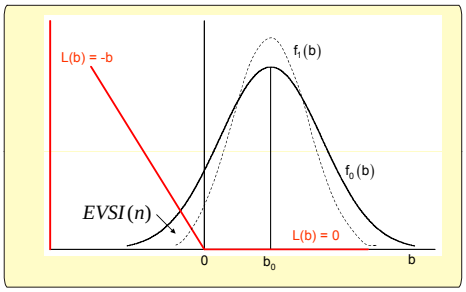
AND… the expected value of avoiding bad decisions can be estimated by integrating across the distribution of incremental net benefit below 0

Expected value of perfect information (EVPI) given current density for INB (b) Eckermann & Willan (2007)



EVPI – the expected value of losses avoided with perfect information can be estimated for current evidence between 2 strategies by integrating across the distribution of INB below 0

Expected value of sample information (EVSI) per patient is current EVPI less the expectation of future EVPI with research design **| prior density of INB**



Further information is expected to reduce the likelihood, and extent, of losses integrated across INB < 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 ($EVPI_0$) and the expected value of (avoiding) bad decisions at time t with more evidence ($EVPI_t$)

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 VoI 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 VoI 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 VoI 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

HTA	EVPI	EVSI	Direct research cost	Opport. cost of delay	Total cost US$	ENG US$	Return on direct investment
A	50M	10M	1M	4M	5M	5M	500%
B	100M	50M	10M	15M	25M	25M	250%
C	5M	2M	1M	0	1M	1M	100%
D	101M	10.1M	6M	4M	10M	0.1M	2%
E	25M	9.8M	2M	8M	10M	-0.2M	-10%*
F	6M	3M	3M	0.5M	3.5M	-0.5M	-17%*

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e.g. Prioritising $12M to research

HTA	EVPI	EVSI	Direct research cost	Opport. cost of delay	Total cost US$	ENG US$	Return on direct investment
A	50M	10M	1M	4M	5M	5M	500%
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E	25M	9.8M	2M	8M	10M	-0.2M	-10%*
F	6M	3M	3M	0.5M	3.5M	-0.5M	-17%*

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

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e.g. Prioritising $16M to research

HTA	EVPI	EVSI	Direct research cost	Opport. cost of delay	Total cost US$	ENG US$	Return on direct investment
A	50M	10M	1M	4M	5M	5M	500%
B	100M	50M	10M	15M	25M	25M	250%
C	5M	2M	1M	0	1M	1M	100%
D	101M	10.1M	6M	4M	10M	0.1M	2%
E	25M	9.8M	2M	8M	10M	-0.2M	-10%*
F	6M	3M	3M	0.5M	3.5M	-0.5M	-17%*

Prioritise $16M based on
Max EVPI – support D, B Total ENG $25.1 M
Max return – support A, B, C Total ENG $31.0 M **+ $4M for increased services or future research**

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What VoI 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)
  - Enables simple estimation of EVSI, ENG for optimal overall trial design (Eckermann, Karnon & Willan 2010, Eckermann & Willan 2007,2008,2009, Willan and Pinto 2005)

Bootstrapping

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

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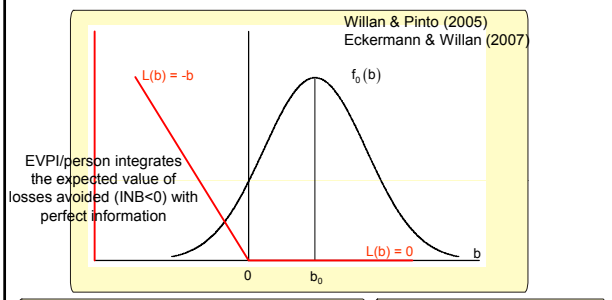
Expected value of perfect information with CLT



$L(b) = NB_{Best}(b) - NB_T(b)$

If b > 0: $L(b) = NB_T(b) - NB_T(b) = 0$

If b ≤ 0: $L(b) = NB_S(b) - NB_T(b) = -INB = -b$

$$E_0[L(b)] = \int_{-\infty}^{0} -b \cdot f_0(b)\,db$$

$$= e^{-b_0^2/(2v_0)}\sqrt{v_0/(2\pi)} - b_0\Phi\left(-b_0/v_0^{\frac{1}{2}}\right)$$

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

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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)

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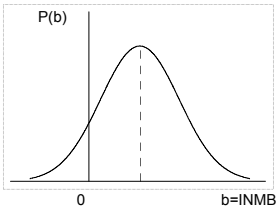
Joint research and reimbursement decisions

- 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?

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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

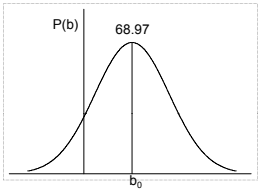
and

2. **AT vs. AN** conditional on cost of reversal (where AT feasible)

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

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

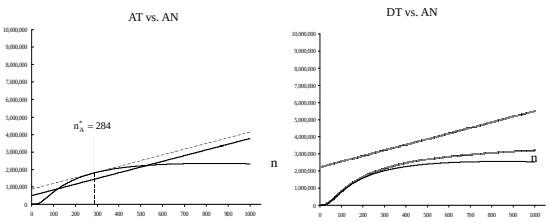
- Pilot RCT of 232 pregnant women presenting in breech position
- 41/116 (35.2%) had non-Caesarian delivery in early (37 week) arm
- 33/116 (28.4%) had non-Caesarian delivery in late arm
- If avoiding Caesarian delivery is valued at $1,000 then



$$b_0 = \lambda(\Delta_{0e} - \Delta_{0c}) = 1000\left(\frac{41}{116} - \frac{33}{116}\right) = 68.97$$

$$v_0 = 1000^2\left\{\frac{41/116(1-41/116)}{116} + \frac{33/116(1-3/116)}{116}\right\} = 3724.78$$

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

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 ($n_j s$) 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 $n_j s$ that maximises

$$\sum_{j=1}^{J} \max\left(\text{oENG}_{\text{D}j}(n, n_j), \text{oENG}_{\text{A}j}(n, n_j)\right) - \sum_{j=1}^{J} (C_{fj} + 2n_j C_{vj})$$

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

		US	UK	Australia
Annual incidence	k_j	50,000	10,000	3,000
Patient horizon at baseline§	N_0	1,000,000	200,000	60,000
Annual accrual rate	a_j	$k_j/100 = 500$	$k_j/20 = 500$	$k_j/6 = 500$
Fixed cost*	C_{fj}	500,000	500,000	375,000
Variable cost*	C_{vj}	1600	1600	1200
Cost of reversal*	C_{rj}	2,000,000	1,000,000	500,000

§ assuming a 20-year time frame
* in US dollars

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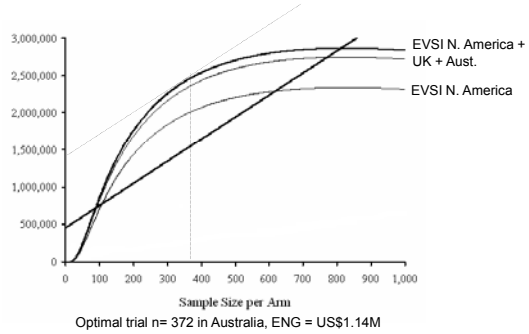
Optimal trial design: N. America, UK, Australia



Optimal trial n= 372 in Australia, ENG = US$1.14M

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

		Locally Optimal (n_1, n_2, n_3) = (284, 0, 0)	Global Optimal (n_1, n_2, n_3) = (0, 0, 372)
EVSI	N. America	1,789,828	2,018,030
	UK	310,941	352,199
	Australia	51,966	59,440
Total EVSI		**2,152,735**	**2,429,669**
Opportunity Cost	N. America	19,586	0
	UK	0	0
	Australia	0	19,244
	Total	19,586	19,244
Financial Cost	N. America	1,408,800	§
	UK	0	§
	Australia	0	§
	Total	1,408,800	1,267,800
Total Cost		**1,428,386**	**1,287,044**
ENG	N. America	361,442	§
	UK	310,941	§
	Australia	51,966	§
Total ENG		**724,349**	**1,142,625**

* all figures in US dollars
§ by negotiation

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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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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:

i. recognising global VOI
ii. minimising trial cost and heterogeneity of evidence
iii. 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, VoI across jurisdictions

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.

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

Linking research, reimbursement and regulation of practice

Optimal research design – locally, globally, allowing for imperfect implementation
(Eckermann, Karnon and Willan 2010; Eckermann & Willan 2007,2008,2009; Willan and Eckermann 2010)

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)

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