Methods & Tools for Comparative Effectiveness Research

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Foreground
The Demise of US Health Policy Agencies

- OTA’s health program, 1975
- National Center for HC Technologies, 1978
- IOM’s Council on HC Tech Assessment, 1984
- AHCP, 1989

All dead by 2009
déjà vu?
US Health Policy Agency in 2009?

- American Recovery and Reinvestment Act
- $1.1 billion
- Conrad – Baucus Senate Bill
- HC Comparative Effectiveness Research Institute
- How can it / will the CER work?
- (Re)Inspired by a paper by Gail Wilensky (2006)

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CER Well-established in Other Countries

- **UK: NICE**  (National Institute for Health and Clinical Excellence)
- **France: HAS**  (Haute Autorite de Sante)
- **Germany: IQWiG**  (Institute für Qualitat und Wirtschaftlichkeit im Gesundheitswesen)
- **Australia:**  (Pharmaceutical Benefits Scheme)
- **Some Canadian provinces**
Innovation

ACCESS TO MARKET

EMEA  FDA  PMDA

HEALTH TECHNOLOGY ASSESSMENT (CER)

HAS  NICE  IQWIG

DECISION-REIMBURSEMENT-PRICING

$  €  £

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France: Comparative Effectiveness

1. Efficacy to effectiveness
   - Phase 2 to 3

2. Good enough to be reimbursed?

3. Better than other treatments?

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A Hot Potato

- Free markets do not apply to health care
  - “Let market forces work” objection to US CER
  - The guy who orders it does not pay for it
- “If medical care had been any other industry it would have failed years ago.”
- Health care lacks transparency
- Medical system uncertainty
- Health care system structure is highly resistant to change
  - Even though US medical innovation is so renowned for innovation

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A Hotter Potato

- Valuing human life in $
  - QALY & cost/QALY

- Rule of rescue

- Americans not coping well with mortality

- Forgotten meaning / purpose of insurance
  - History of health / life insurance

- Blending of risk with disease (Aronoff)
Purpose of CER

- To tell us what works, when, and for whom? (well… maybe)
- To aid in making informed clinical and health policy decisions
## Map of Presentation

<table>
<thead>
<tr>
<th>Question &gt;</th>
<th>Evidence Synthesis &gt;</th>
<th>Comparison &amp; Decide &gt;</th>
<th>Implement or Clean-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIV</td>
<td>Smoking cessation</td>
<td>Bayesian mixtures</td>
<td>EVPI</td>
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<tr>
<td></td>
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<td>TreeAge decision modeling</td>
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<td>Low back pain</td>
<td>Effect size to probability</td>
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<td>Different kinds of distributions</td>
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<td>Measurement</td>
<td>CEA – units</td>
<td>Economics</td>
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<td>CUA – QALY’s</td>
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</table>
Innovative Systems and System Innovations to Improve Lives

- Must evaluate
  - Perform as intended
  - Are they worth the cost?

- Evaluators need to capture data to
  - Inform policy
  - Inform service-level decision-making

- Continue or terminate (summative evaluation)
- Steer (formative evaluation)

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An Innovation may Work in a Complex Manner

- Some helped some not
- Some helped and some hurt
- Which ones patients?
  - Does an innovation cost more – or less?
  - Too often, the comparison is to its previous state or to a control state.
A Standard of Comparison

- Effect sizes comparing treatments to control are insufficient to decide among treatments.
- A new treatment must be compared to something.
  - Progression of science.
  - Perhaps every intervention does better than nothing.
- For health care innovation, the best comparison is the current standard of care.

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Questions Remaining after Evaluation

- Has the uncertainty been reduced enough to make a decision after evaluation?
- Or do we need to know more for policy implementation?
- Can we help clinical decision making?
- Will a specific particular client benefit?

Health technology assessment methods can help answer these questions

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Evaluating Medical Innovations
The Challenge for Alternative Medicine

The effect size of alternative medicine per a single condition, within the larger health care system
The Challenge for Alternative Medicine: How Big Is the Margin?

The effect size of alternative medicine

Is the margin worth paying for?

The effect size of non-specific factors

The therapeutic alliance

Regression to the mean

Natural history

Stereotype threat

Patient by provider stuff

Fear arousal

Cognitive biases

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The Challenge for Alternative Medicine: How Big Is the Margin?

The effect size of alternative medicine

Is the margin worth paying for?

The effect size of non-specific factors

Therapeutic alliance
Stereotype threat
Fear arousal
Cognitive biases

DISSONANCE
Regression to the mean
Natural history
Patient by provider stuff

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How Much Does the Margin Cost?

The effect size of alternative medicine

$66,000 / QALY?

The effect size of non-specific factors

Therapeutic alliance

Regression to the mean

Stereotype threat

Natural history

Fear arousal

Patient by provider stuff

Cognitive biases

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But

- Reducing demand for expensive medical care is a win!
- But still, a “winner” can be
  - More directed,
  - More wisely referred to,
  - Improved, and
  - Replaced with better, cheaper alternatives
Risks are Becoming Diseases

- High blood pressure
- Cancer survivors
- Practitioner provided prevention
  - “Not so fast!”
  - Unaffordable, even when cheap
# CER Guiding Principles

<table>
<thead>
<tr>
<th>UK / NICE</th>
<th>US – imputed cynically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robust (for what?)</td>
<td>Yep, for efficacy, but not for informing policy and clinical decision-making</td>
</tr>
<tr>
<td>Inclusive</td>
<td>Divisive</td>
</tr>
<tr>
<td>Transparent</td>
<td>Opaque</td>
</tr>
<tr>
<td>Independent of financial interests</td>
<td>Industry sponsored</td>
</tr>
<tr>
<td>Timely</td>
<td>Working on it! C-Path for fast-tracking</td>
</tr>
</tbody>
</table>

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CER Steps

1. PIV
2. Evidence synthesis
3. Compare
4. Decide
5. EVPI

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STEP 1. Prior Information Value, ex ante Valuation

- Is the problem important enough to warrant reimbursement in by a public or semi-public scheme?
  - A guaranteed treatment for athlete’s foot.
  - Cost: $1 million per patient

- What is the PIV (prior information value)?

- How valuable is the solution a particular health problem?
STEP 2. Evidence Synthesis

- Synthesized evidence must be usable
- The result must assist & not delay and obfuscate decision-making
- In effect, the evidence should reduce system uncertainty
Synthesizing Research By

- Meta-analyses
- Systematic reviews
- Cochrane collaboration
- Bayesian mixture-method
Cochrane Collaboration

- Archie Cochrane's call for systematic, up-to-date reviews of all relevant RCTs of health care
- Originally for reviews of controlled trials in pregnancy and childbirth
- To support the UK National Health Service
- Cochrane Centre’ opened in Oxford, England in October 1992
- October 1993 – first Cochrane Colloquium - 77 people from eleven countries co-founded 'The Cochrane Collaboration'
- Currently > 5,000 health care researchers, providers, policy makers, managers, consumers and educators

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Cochrane Collaboration

- Meta-analyses & systematic reviews
- Based on synthesized NHST research, so has many of the weaknesses of NHST
  - Avoids Type I error
  - More likely to make Type II error
    - (more likely to rule out an effective program or treatment)
  - Comparison groups vary (WLC, placebo, no-tx)
- Conclusions are often not informative, or do not address which innovation is better.

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Cochrane Sample Summaries

Telephone: “Our review of trials found telephone counseling to be effective; multiple sessions are likely to be most helpful.”

Physician: “when doctors provide brief simple advice about quitting smoking this increases the likelihood that someone who smokes will successfully quit and remain a nonsmoker 12 months later. More intensive advice may result in slightly higher rates of quitting.” [p. 2]

Individual counseling: “The review found that individual counseling could help smokers quit, but there was not enough evidence about whether more intensive counseling was better.”

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Figure 2. Forest plot of comparison: 1 Individual counselling compared to minimal contact control, outcome: 1.1 Smoking cessation at longest follow-up.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
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<tr>
<td>1.1.1 Counselling versus control (no systematic pharmacotherapy)</td>
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<tr>
<td>Vincis et al. 1988</td>
<td>27</td>
<td>188</td>
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<td>Bronson 1989</td>
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<td>77</td>
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<tr>
<td>Pederson 1991</td>
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<td>35</td>
<td>6</td>
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<tr>
<td>Cekene 1992</td>
<td>44</td>
<td>133</td>
<td>28</td>
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<tr>
<td>Stevens 1993</td>
<td>81</td>
<td>453</td>
<td>61</td>
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<tr>
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<td>25</td>
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<td>578</td>
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<td>Burling 2001</td>
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<td>91</td>
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<tr>
<td>Pedersen 2005</td>
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<td>Henriksen 2005</td>
<td>68</td>
<td>666</td>
<td>68</td>
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<tr>
<td>Kim 2005</td>
<td>28</td>
<td>200</td>
<td>18</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>3933</strong></td>
<td><strong>3922</strong></td>
<td><strong>78.6%</strong></td>
</tr>
</tbody>
</table>

Total events 431 306
Heterogeneity: p = 0.09; p < 0.0001
Test for overall effect: Z = 5.20 (p < 0.0001)

1.1.2 Counselling plus NRT versus NRT alone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
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<tr>
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<td>Total</td>
<td>Events</td>
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<tr>
<td>Fiore 2004</td>
<td>29</td>
<td>274</td>
<td>47</td>
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<tr>
<td>Jorenby 1995</td>
<td>53</td>
<td>168</td>
<td>44</td>
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<tr>
<td>Simon 2003</td>
<td>13</td>
<td>102</td>
<td>10</td>
</tr>
<tr>
<td>Wiggars 2006</td>
<td>35</td>
<td>180</td>
<td>27</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>732</strong></td>
<td><strong>1000</strong></td>
<td><strong>27.4%</strong></td>
</tr>
</tbody>
</table>

Total events 133 128
Heterogeneity: p = 0.08; p = 0.00; p = 0%
Test for overall effect: Z = 2.12 (p = 0.03)

Total (95% CI) 4665 4922 100.0% 1.39 [1.24, 1.57]

Total events 564 433
Heterogeneity: p = 25.19; df = 20 (p = 0.20); p = 20%
Test for overall effect: Z = 1.57 (p = 0.0001)
Weaknesses of Cochrane

- Products are health care related research only
- Depends on lots of published research
- Resource intensive
  - Experts and time required
- Not amenable to cross-comparing systems
  - Outcomes are usually against a control group
  - Great science, but not for decision-making
- Uncertainty not managed well
Cochrane: But Which Smoking Cessation Intervention is Best?

- Telephone Counseling
- Physician Advice
- Individual Behavioral Counseling

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Cochrane: But Which Smoking Cessation Intervention is Best?

Telephone

Physician

Therapist

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Cochrane is no help in comparing systems!
Bayesian Evidence Synthesis

- Decision-oriented
- Robust to deviations from normal distributions
- May track effects as compared to groups
- Gives relative effect sizes in comparison to a standard
- Can rank treatments – which include the various comparisons, including control groups.

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Choosing Outcomes
QALYs as Effects

- Morbidity
- Mortality
- Exchangeable in Cost Effectiveness Analysis and Cost Benefit Analysis
- Willingness to pay (WTP)
Cost (per QALY)

- A year of life adjusted for its quality or its value. A year in perfect health is considered equal to 1.0 QALY. The value of a year in ill health would be discounted. For example, a year bedridden might have a value equal to 0.5 QALY. [medicineNet.com]
### QALY Example: CRC

#### Search Results (Back) Article/Ratios

Your search returned 60 results

**Pick Columns to Display (Sort by)**

<table>
<thead>
<tr>
<th>Article ID</th>
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<th>Health State</th>
<th>Publication Year</th>
<th>Reference</th>
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<td>2007-01-03047</td>
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<td>Colorectal cancer patient with following disease progression</td>
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<td>Tappenden 2007 Eur J Cancer</td>
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<td>Colorectal cancer patient prior to disease progression</td>
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</tbody>
</table>
Problems with Effect Size

- A 20% effect size means?
- 20% get all better?
- Everyone gets 20% better?
- Some combination?
- 40% get better, 20% die

Milton Friedman: “Who wants to wade across a river which averages 4 feet deep?”
We Need Some Estimate of the Demand on Resources

- Full evaluations require some sense of cost.
- Costs are determined by perspective:
  - Payer (reduce payments)
  - Society (improve productivity)
  - Patient (pain relief)
- Opportunity costs
- Indirect costs
- Externalities

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A One-slide Course in Health Economics

- Strictly comparative to a current standard (no placebos, please!)
- Welfare economic theory
  - Pareto optimization
    - At least one helped, no one hurt
  - Cost-benefit analysis (consequences)
  - Willingness to pay, contingent valuation
- Operations research and management science
  - Constraint maximization
  - Social decision-making under finite resources
  - Cost-effectiveness method

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CEA versus CBA

- Cost benefit analysis (CBA) born out of social welfare theory.
  - Need measure combining morbidity and mortality
  - QALY

- Cost effectiveness analysis (CEA) born out of management science and operations research
  - Original units

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Analytic Perspective

- Depending on perspective ~
  - Patient / consumer
    - Costs of care
    - Externalities / indirect costs
    - Opportunity costs
  - Health care system
  - Payers
  - Societal – includes loss of life and productivity

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Conceptual Structure for Bayesian Indirect Comparisons

<table>
<thead>
<tr>
<th>Study #</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Control A</th>
<th>Control B</th>
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</table>

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## Weight by Study Quality

<table>
<thead>
<tr>
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<th>Treatment B</th>
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<th>Control B</th>
<th>Study Quality</th>
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</table>

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## Compare Treatments B to C

<table>
<thead>
<tr>
<th>Study #</th>
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<th>Treatment B</th>
<th>Treatment C</th>
<th>Control</th>
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</table>

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Bayesian Evidence Synthesis Demonstration

- [Run Demo]
- Show organization of studies
- Code
- Data
- Trace
- Convergence
- Distributions

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Random effects model for Smoking Cessation data

49 trials (47 + two 3-arm-trials),
96 data points,
5 treatments (var = tx)
   1 = baseline - control
   2 = quitline
   3 = physician minimal
   4 = physician intensive
   5 = individual counselling

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After 50,000 samples, Relative Effectiveness is…

<table>
<thead>
<tr>
<th>label</th>
<th>Mean rank</th>
<th>SD</th>
<th>Error (X 10^{-3})</th>
<th>2.5%</th>
<th>median</th>
<th>97.5%</th>
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<tbody>
<tr>
<td>Baseline/control</td>
<td>4.4</td>
<td>0.55</td>
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<td>3</td>
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<td>0.95</td>
<td>7.2</td>
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<td>9.3</td>
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<td>5</td>
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</tr>
</tbody>
</table>

Distribution of Rankings

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Effectiveness or Cost Effectiveness?

- WinBUGS can take different outcomes
Step 3. Decision Analysis

“A systematic approach to decision making under conditions of imperfect knowledge; a practical application of probability theory. Used to calculate the optimal strategy from among a series of alternative strategies.”
Incremental Cost Effectiveness Ratio (ICER)

- Plain cost-effectiveness can mislead
- Something cheap and ineffective can be cost effective
- Also, the ICER method does exactly what we want in Comparative Effectiveness Research: it compares a novel system to a current standard.
The cost effectiveness plane
Cost effectiveness plane

Plotting new treatment CE on this plot

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Cost effectiveness plane

Dominated

Tradeoffs

SW

Tradeoffs

NW

Tradeoffs

SE

Dominant

incremental cost ($) vs. incremental effect (QALYs)

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Incremental CE Ratio plot
Multiple ICER’s

From: Barton, Briggs, and Fenwick, 2005

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Incremental cost effectiveness Ratio

Figure 1. Incremental costs ($\Delta C$) and effects ($\Delta E$) of a new technology over an old one and the maximum acceptable incremental cost-effectiveness ratio without a kink (solid line) and with a kink (dotted line).
ICER strength

- Shows CE relative to a current standard of therapy or care
  - A direct comparison of two programs or interventions
  - CE’s then compare-able
  - Whereas CE ratios are not directly compare-able
- That which is barely effective and cheap could be just as cost effective as something very effective and very expensive

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STEP 4. *Ex post* VOI

- Cleaning up the analysis - what just happened?
  - Is there enough of an effect to continue looking for evidence?

- Value of information (VOI) analysis
  - Estimates degree of uncertainty
  - Affixes monetary value of reducing uncertainty
Expected value of perfect information
Expected value of perfect information

“The expected costs of uncertainty can be interpreted as the expected value of perfect information.”

Claxton 2006
Expected Value of Perfect Information (EVPI)

- Assume you could “buy” information that perfectly predicts a future outcome.

- The expected value of perfect information (EVPI) is the difference between expectation of the maximum benefit and expected net benefit:
Personalized Example

- The US economy
  - Credit uncertainty
  - Stock market volatility

- How much would you pay to reduce uncertainty?
  - There would be an upper limit.
  - Probably not more than what you are “worth”
The expected cost of uncertainty is determined jointly by the probability that

1) a decision based on existing information will be wrong, probability of error, and

2) the consequences of a wrong decision (expected opportunity loss)

This is variously called “expected cost of uncertainty” or “expected opportunity loss surrounding decisions”
EVPI: Three core tasks

1. Decision analytic model to represent the problem
2. Probabilistic analysis (PSA)
3. Establish the value of additional information

*EVPI estimates are for the individual patient or client!*
Calculation of EVPI – An example

Source: Tree Age Pro 2009 Users Manual  menke@email.arizona.edu
Calculation of EVPI – Rollback of Stock Tree

Source: Tree Age Pro 2009 Users Manual  menke@email.arizona.edu
Rearranging the Tree for Best Possible Outcome

Source: Tree Age Pro 2009 Users Manual  menke@email.arizona.edu
Rollback of Best Possible Outcome

Source: Tree Age Pro 2009 Users Manual  menke@email.arizona.edu
EVPI for Stock Investment

- $205 - $50 = $155
- It makes sense to pay *up to* $155 for market information that would allow you to predict the outcome

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## EVPI Conceptually

<table>
<thead>
<tr>
<th></th>
<th>Drug A</th>
<th>Drug B</th>
<th>Optimal choice</th>
<th>Maximum net benefit</th>
<th>Opportunity loss if choose “B”</th>
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<td></td>
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</table>

Current Information: 13  
Perfect Information: 13.8  
EVPI = 13.8 – 13 = 0.8

Source: Claxton, K – University of York  
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EVPI

- EVPI (Expected Value of Perfect Information) – the theoretical maximum worth to the decision maker of additional information about uncertain states of nature that is absolutely unerring.
What EVPI Means

- If EVPI > Decision threshold then collecting more information is worthwhile
- Reflects the amount of uncertainty in the data that is present
- One should delay adoption of technologies when the EVPI is large
Situations where EVPI may be useful

- Expensive technologies that have marginal benefits
- Concerns about TX safety – it may be worthwhile to delay adoption because the value of additional information exceeds the value gained from immediate adoption
- Setting research priorities for:
  - Health insurance plans
  - Pharmaceutical manufacturers
  - NIH and other government agencies

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Comparative effectiveness research can be accomplished in 4 general steps:
- Establishing prior information value
- Evidence synthesis
- Decision analysis
- Value of information analysis

There is absolutely no reason why CER cannot be carried out to improve health care policy and decisions.