Good Value for the Cost

- A common goal of an economic analysis is to identify when we can be confident that one therapy is good value compared to another.
- A threat to such confidence arises because the economic result observed in an experiment may not truly reflect the result in the population.
  - Single sample drawn from a population.
- This form of uncertainty is referred to as sampling (or stochastic) uncertainty.
  - A commonly used approach for addressing this threat is to use the data from the experiment to identify when we can be confident about the value for the cost.

Outline

- Describe methods for identifying when we can and cannot be confident about a therapy’s value for the cost:
  - Confidence intervals
  - Decision threshold
- Goal is to demonstrate the quantification and interpretation of sampling certainty by use of CI for CER, CI for NMB, and acceptability curves. Don’t focus on the technical aspects of estimation.
  - Computer code is available on website: http://www.uphs.upenn.edu/dgimhsr/eeinct_cicer.htm
Sampling Uncertainty

• For clinical outcomes, we can be confident that a therapy is clinically effective when its confidence interval excludes our decision threshold; we can’t be confident when its interval includes our decision threshold
  – Decision threshold = 1 for RR and OR
  – Decision threshold = 0 for risk differences and changes in a continuous outcome

• For cost-effectiveness outcomes, we also can be confident that a therapy is cost-effective when the confidence interval excludes our decision threshold
  – Decision threshold = WTP for CER and acceptability curve
  – Decision threshold = 0 for NMB

Differences in Clinical and Economic SU

• While there are similarities between how we interpret sampling uncertainty for clinical and economic outcomes, there are also at least 2 differences
  – Less debate about the specific value of the decision thresholds for clinical outcomes than for economic
    • It is expected that the maximum willingness to pay can differ among decision makers, particularly in different decision making jurisdictions
  – Less debate about the level of confidence required to be confident of clinical effectiveness
    • Conclusions in this talk are independent of the level of confidence we are seeking (e.g., 95% confidence or even 1% confidence)

Conclusions

• For any given willingness to pay, an experiment ALWAYS allows us to draw one of three conclusions:
  – We can be confident that one therapy is good value compared to the alternative
  – We can be confident that the alternative therapy is good value compared to the first
  – We cannot be confident that the two therapies differ in their economic value

• If our goal is to identify which of these 3 statements holds for a given willingness to pay, confidence intervals for cost-effectiveness ratios, confidence intervals for NMB, and acceptability curves ALWAYS provide the same answer
Conclusions (2)

- Confidence intervals for cost-effectiveness ratios provide decision makers with concise information (i.e., 0, 1, or 2 numbers) that allows them to determine – based on their own WTP -- if they can be confident about a therapy's value.

- Acceptability curves have the added advantage of allowing decision makers to assess alternate confidence levels if such alternative levels are of interest.

Experiment 1

- Suppose you conducted an economic evaluation of two therapies and found that:
  - Therapy A on average cost 1000 more than therapy B, SE = 325, p=0.002
  - Therapy A on average yielded 0.01 QALYs more than therapy B, SE = 0.001925, p<0.0000
  - The correlation between the difference in cost and effect was -0.71; and there were 250 participants per group in the trial

- Point estimate CER:
  \[ \frac{1000}{0.01} = 100,000 \text{ / QALY saved} \]

\[ \Delta C = 1000; SE_{\Delta C} = 325; \Delta Q = 0.01; SE_{\Delta Q} = 0.001925; \\
p = -0.71; DOF = 498 \]
Constructing CI for NMB for Experiment 1

WTP: 50,000; NMB: -500; 95% CI: -1284 to 284

CI for NMB for Multiple WTP

Willingness to Pay

Net Monetary Benefit

Constructing the Acceptability Curve

4000 Replicates: 10% = 2.5%
Review of Results for Experiment 1

Confidence interval for CER
CER CI: (28,200 to 245,200)

Confidence frontier for NMB
CI intersect decision threshold (0) at 28,200 to 245,200

Acceptability curve
Acceptability curve intersects 0.025 and 0.975 at 28,200 and 245,200

"Pattern 1" Findings

• We refer to findings like those in experiment 1 as pattern 1 findings
• If all experiments had this type of finding, there’d be no debate about whether we should use CI for CER or CI for NMB
• They occur when the difference in effect is significant
• We know we are observing a pattern 1 finding when:
  – The confidence interval for the cost-effectiveness ratio excludes the Y axis (i.e., LL < PE < UL)
  – Both NMB confidence limits curves intersect the decision threshold (0) once
  – The acceptability curve intersects horizontal lines drawn at both 0.025 and 0.975 on the Y axis.
Pattern 1 Findings (2)

One cannot be confident the two therapies differ from one another.

One can be confident the more effective therapy is not good value.

Willingness to Pay

-∞ - 0  +∞

* In cases where some of the boundaries between the regions occur at negative willingnesses to pay, we may not always observe all 3 regions on an acceptability curve or NMB plot.

Experiment 3

- Suppose you conducted an economic evaluation of two therapies and found that:
  - Therapy A on average cost 400 more than therapy B, SE = 325, 𝑝=0.22
  - Therapy A on average yielded 0.02 QALYs more than therapy B, SE = 0.02, 𝑝<0.32
  - The correlation between the difference in cost and effect was 0.25; and there were 250 participants per group in the trial
- Point estimate CER:
  \[ \frac{400}{0.02} = 20,000 \text{ / QALY saved} \]

\[ \Delta C = 400, SE_C = 325 \text{ (p=0.22)}; \Delta Q = 0.02, SE_Q = 0.02 \text{ (p = 0.32)}; \rho = .25; \text{DOF} = 498 \]
Pattern 3 Findings

- We refer to findings like those in experiment 3 as pattern 3 findings.
- They occur only when the difference in effect is not significant.
- Has only one range of findings: can’t be confident that the therapies differ.
- We know we’re observing a pattern 3 finding when:
  - The confidence interval for the CER is undefined.
  - Neither NMB confidence limit curve intersects the decision threshold (0).
  - The acceptability curve never intersects horizontal lines drawn at either 0.025 and 0.975 on the Y axis.

Experiment 2

- Suppose you conducted a set of experiments all with the same means and SDs for cost and QALYs, with the only difference being in their sample sizes.
  - Therapy A on average cost 35 more than therapy B, SD for cost = 8692.7143 per group
  - Therapy A on average yielded 0.04 QALYs more than therapy B, SD for QALYs = 0.25043961 per group.
  - The correlation between the difference in cost and effect was 0.706.
- Point estimate CER:
  $\frac{35}{0.04} = 875 / \text{QALY saved}$
Experiment 2, N = 1,000 / Group

- SE cost = 388.75; SE QALYs = 0.0112

Same Experiment, But N = 500 / Group

- SE cost = 549.78; SE QALYs = 0.015839

Same Experiment, But N = 250 / Group

- SE cost = 777.5; SE QALYs = 0.0224
What Just Happened?

<table>
<thead>
<tr>
<th>N / Group</th>
<th>Point Est</th>
<th>P, QALYs</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>875</td>
<td>0.0004</td>
<td>-34,100 to 15,300</td>
</tr>
<tr>
<td>500</td>
<td>875</td>
<td>0.01</td>
<td>-91,000 to 20,300</td>
</tr>
<tr>
<td>250</td>
<td>875</td>
<td>0.07</td>
<td>LL, 245,200 to UL, -∞ to 28,200</td>
</tr>
</tbody>
</table>

- As the sample size shrinks, the limits grow wider
- When the limits grow wide enough to include the Y axis, \((-\infty/\infty)\) they develop what some consider “odd” properties
  - Occurs when p-value for effectiveness > 0.05

“Odd” Properties

- Lower limit represents a larger number than the upper limit
- Point estimate either a larger number than both the lower and upper limits OR a smaller number than both limits
- WTP excluded from the confidence interval include the ratios with values between the upper and lower limits
  - In the example where N = 250 / group, between 28,200 and -245,200

Confidence Statements

- What confidence statements can we make about this experiment?
  - So long as our WTP is between 28,200 and 245,200, we can be confident that the therapy is good value
Pattern 2 Findings

- We refer to findings like those in experiment 2 as pattern 2 findings.
- They occur only when the difference in effect is not significant.
- We know we are observing a pattern 2 finding when:
  - The confidence interval for the CER includes the Y axis (i.e., LL > UL < PE, or PE > LL > UL).
  - One NMB confidence limit curve intersects the decision threshold (0) twice; the other limit never intersects the decision threshold.
  - The acceptability curve intersects a horizontal line drawn at either 0.025 and 0.975 on the Y axis twice and never intersects the other line.

Pattern 2 Findings (2)

- One cannot be confident the two therapies differ from one another.
- One can be confident that one of the therapies is good value.
- One cannot be confident the two therapies differ from one another.

Willingness to Pay
Two Lines Through Origin, 3 Different Experiments

Experiment 1
CER CI: 28,200 to 245,200

Experiment 2(a)
CER CI: 245,200 to 28,200
$\Delta C = 35; \Delta Q = 0.04$

Experiment 2(b)
CER CI: 245,200 to 28,200
$\Delta C = 1985; \Delta Q = 0.0001$

Two Lines, 3 Different Experiments (II)

- 2 of the CI must include the Y axis, 1 must not
- In 2 experiments $\Delta Q$ is not significant, whereas in 1 it is
- 1 CI includes ratios between 28,200 and 245,200 and excludes all else; 2 CI exclude ratios between 28,200 and 245,200 and include all else
- In at least one of the experiments $\Delta C$ must be significant; in at least one it must not be
- W must fall within the interval defined for at least 1 of the experiments and fall outside the interval defined for at least 1 of the experiments
- Which of the experiments is which?

Overview of Patterns of Results

**PATTERN 1**
One cannot be confident the more effective therapy is not good value
One cannot be confident the two therapies differ from one another
Willingness to Pay

**PATTERN 2**
One cannot be confident the two therapies differ from one another
One can be confident one of the therapies is good value
Willingness to Pay

**PATTERN 3**
One cannot be confident the two therapies differ from one another
Willingness to Pay
Overview of Patterns of Results (II)

• The observed pattern is a function of $\Delta C$ and $\Delta E$, their SEs and correlation, the DOF, and the confidence level
  – All experiments will display all 3 patterns depending on the confidence level
    • Experiment 1: pattern 1, $t < 5.184$; pattern 2, $5.184 \leq t \leq 7.571$; pattern 3, $t > 7.571$
  • The observed pattern is independent of method used to express sampling uncertainty
  • When calculating NMB and acceptability curves, one may not recognize these patterns
    – Patterns are defined over $W$ values that range from $-\infty$ to $\infty$, but NMB and acceptability curves usually calculated for positive values of $W$ only

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