Sampling Uncertainty and Patient-Level Cost-Effectiveness Analysis

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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:
  \[ \frac{1000}{0.01} = \frac{100,000}{\text{QALY saved}} \]

\[ \Delta C = 1000; \ SE_C = 325; \Delta Q = 0.01; \ SE_Q = 0.001925; \]
\[ p = -0.71; \text{DOF} = 498 \]
The Acceptability Curve

Review of Results for Experiment 1

"Pattern 1" Findings

Pattern 1 Findings (2)

Experiment 3

"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 can be confident the more effective therapy is not good value
One cannot be confident the two therapies differ from one another
One can be confident the more effective therapy is good value

- 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:
  \[ \frac{400}{0.02} = \frac{20,000}{QALY \ saved} \]
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 are 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.

What Just Happened?

<table>
<thead>
<tr>
<th>N / Group</th>
<th>Point Est P, QALYs</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>100,000 0.00000 28,200 to 245,200</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>100,000 0.02 -28,263 to 1,414,564</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>100,000 0.11 LL, -60,556 to UL, -1,137,190 to</td>
<td></td>
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</tbody>
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- As the sample size shrinks, the limits grow wider.
- When the limits grow wide enough to include the Y axis, 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 = 25/group, between -1,137190 and -60,556

Confidence Statements
- What confidence statements can we make about this experiment?
  - Because the entire upper right quadrant falls within the confidence interval, there is no WTP where we can be confident the therapies differ in their value

Same Confidence statements from NMB and Acceptability Curves

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

Conclusions
- For any given willingness to pay, an experiment ALWAYS allows us to draw one of three conclusions:
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