ICER vs. INB: The Statistical Issues

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What is Cost-Effectiveness Analysis?

The process of combining cost and effectiveness data in a rational resource-allocation scheme.
The Statistical Issues

- What to estimate?
- How to summarize uncertainty?
Example: The Sepsis Data

- RCT comparing IL1ra with placebo in sepsis.
- Cost: Dfl.
- Effectiveness: 28-day survival probability.
### The Data

<table>
<thead>
<tr>
<th></th>
<th>IL1ra</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Cost</td>
<td>35,100</td>
<td>33,720</td>
</tr>
<tr>
<td>Var(Mean Cost)</td>
<td>4,000</td>
<td>4,000</td>
</tr>
<tr>
<td>Survival Rate</td>
<td>0.84</td>
<td>0.56</td>
</tr>
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<td>Var(Survival Rate)</td>
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<td>Corr(Survival,Cost)</td>
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Simplified Analysis of the Sepsis Data

- Cost: $p = .81$ (favors placebo).
- Effect: $p = .023$ (favors IL1ra).

Assumptions and Notation

- Two-arm study (experimental vs. control).
- $\epsilon_1$: Average effectiveness of test (e.g., survival or QALYs).
- $\epsilon_0$: Average effectiveness of control.
- $\gamma_1$: Average cost of test (US$).
- $\gamma_0$: Average cost of control.

Treatment effect on effectiveness: $\epsilon_1 - \epsilon_0$

Treatment effect on cost: $\gamma_1 - \gamma_0$
Figure 1: Treatment effects in cost-effectiveness analysis.
Concept 1: Incremental Cost-Effectiveness Ratio (ICER)

Ratio of Rx effect on cost to Rx effect on effectiveness:

\[ \text{ICER} = \frac{\gamma_1 - \gamma_0}{\epsilon_1 - \epsilon_0}. \]

ICER = slope of ray from origin to the treatment effects.

- If test is more effective (and expensive) than standard, ICER is cost per additional unit of health purchased.
- If test is less effective (and expensive) than standard, ICER is savings per unit of health forgone.
Using the ICER in Resource Allocation

Idealization of the insurer’s problem:

• Fixed amount of money.

• Several populations of insureds (e.g., heart disease, breast cancer, etc.).

• Array of mutually exclusive treatments for each population.
Using the ICER in Resource Allocation

Optimal allocation strategy:

- Rank treatments, least → most effective, within each disease.
- Calculate ICERs; eliminate dominated.
- Recompute ICERs and re-rank by ICER (lowest to highest).
- Starting with lowest ICER, keep buying until money is gone.
- Highest ICER you can afford is the *shadow price*.

Alternatively:

- Calculate ICERs; eliminate dominated; recalculate.
- Purchase all treatments with ICER less than threshold.
- More exclusive, efficient insurers have higher thresholds.
Problems with ICER

- Negative values are meaningless.
- Ordering ICER: Direction of increasing ICER is opposite in quadrants NE & SW.
- ICER is a discontinuous function of effectiveness.

Interpretation of point and interval estimates is problematic!
Figure 2: Ranking of ICERs in quadrants NE and SW.
Figure 3: ICER as a function of cost and effectiveness effects.
Consequences for Inference

• Fieller’s method CIs work OK.

• Other approaches (Taylor series, resampling) fail when significance of effectiveness is modest.

• The question is not how but whether to make inferences about ICER …

• … and the answer is No!
Can This Parameter Be Saved?

Using a Bayesian approach:

- Estimate posterior probability for each quadrant.
- For each quadrant, compute interval estimate for ICER given that the effect estimates are in that quadrant.
Concept 2: Net Benefit

Define threshold price $\lambda > 0$: The max (min) an insurer is willing to pay (receive) to obtain (forgo) a unit of effectiveness.

Measure differences by incremental net monetary benefit ($INMB$):

$$INMB(\lambda) = \lambda(\epsilon_1 - \epsilon_0) - (\gamma_1 - \gamma_0)$$

$INMB =$ gain (in dollars) from adopting the test therapy.

Figure 4: Incremental net monetary benefit.
C/E Analysis by Estimating INMB

Advantages:

• Units are dollars; direct interpretation.
• Statistical inference is easy (linear combination of cost and effect estimates).
• No ambiguity about quadrants.

Problem: What is the “correct” $\lambda$?
Data Analysis with INMB

Plot interval estimates of INMB for a range of \( \lambda \).

Alternatively, plot \( \Pr[\text{INMB} > 0 \mid \text{data}] \) against \( \lambda \) (\( C/E \) acceptability curve; van Hout et al. 1994).
A Unifying Property

Let $CS = \{\lambda : \text{CI for INMB}(\lambda) \text{ covers 0}\}$.

Then $CS = \text{Fieller’s method confidence set for ICER}$.

(See Heitjan 2000.)

Consequence: Test dominates control at $\lambda_A$ does not imply that it dominates at $\lambda_B > \lambda_A$. 
**Example: Sepsis Data (Again)**

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Cost: \( p = .81 \); effectiveness: \( p = .023 \).

Fieller confidence sets for ICER:

- 95%: \((-108,400; 55,900)\).
- 98%: \((-\infty; 135,200) \cup (324,600; \infty)\).
Figure 5: 95% confidence limits for ICER.
Figure 6: 98% confidence limits for ICER.
Figure 7: Approximate posterior density of treatment effects in the sepsis study.
Example: Sepsis Data

QUADRANT PROBABILITIES

<table>
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<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE (Cost-increasing tradeoff)</td>
<td>.594</td>
</tr>
<tr>
<td>NW (Placebo dominates)</td>
<td>.003</td>
</tr>
<tr>
<td>SW (Cost-reducing tradeoff)</td>
<td>.009</td>
</tr>
<tr>
<td>SE (IL1ra dominates)</td>
<td>.395</td>
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Example: Sepsis Data

INTERVAL ESTIMATES FOR ICER

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<th>Interval (Dfl/life saved)</th>
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<tbody>
<tr>
<td>Bayesian (NE)</td>
<td>(791; 63,400)</td>
</tr>
<tr>
<td>Bayesian (SW)</td>
<td>(8,400; 4,580,000)</td>
</tr>
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<td>Fieller (95%)</td>
<td>(−108,400; 55,900)</td>
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<tr>
<td>Fieller (98%)</td>
<td>(−∞; 135,200) ∪ (324,600; ∞)</td>
</tr>
<tr>
<td>Bonferroni</td>
<td>(−3,390,000; 4,050,000)</td>
</tr>
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Figure 4

Figure 8: C/E acceptability curve for the sepsis trial.
Summary

• Usefulness of ICER is limited to cases where treatment and cost effects are known to both be positive (negative).

• INMB solves these problems but requires specification of a range of threshold prices.

• Statistical analysis is straightforward with INMB and has been extended to modeling of censored cost and effectiveness data.

• Bayesian, classical nonparametric approaches are feasible.
REFERENCES

Sepsis example:


ICER, NMB and Fieller’s method:


Bayesian analysis of cost-effectiveness:


Nonparametric approaches to estimating cost-effectiveness:


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