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

	IL1ra	Placebo
Mean Cost	35,100	33,720
Var(Mean Cost)	4,000	4,000
Survival Rate	0.84	0.56
Var(Survival Rate)	0.09	0.09
Corr(Survival,Cost)	0.34	0.34

Simplified Analysis of the Sepsis Data

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

Source: Gordon *et al.* (1992) & Fisher *et al.* (1994), discussed by van Hout *et al.* (1994), Laska, Meisner & Siegel (1997).

Assumptions and Notation

- Two-arm study (experimental vs. control).
- ϵ_1: Average effectiveness of test (e.g., survival or QALYs).
- ϵ_0: Average effectiveness of control.
- γ_1: Average cost of test (US$).
- γ_0: Average cost of control.

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

Treatment effect on cost: $\gamma_1 - \gamma_0$

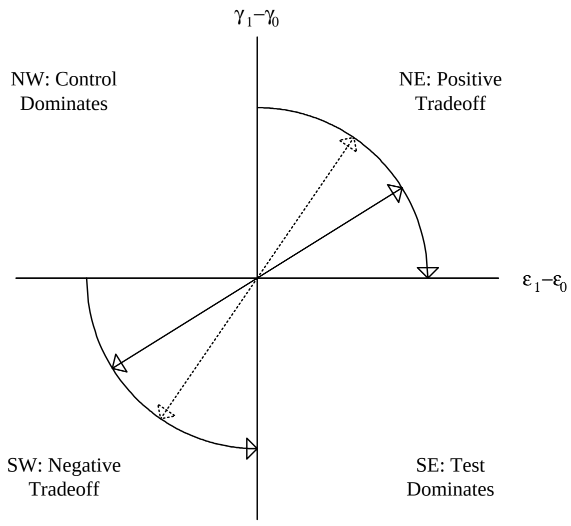

Figure 1: Treatment effects in cost-effectiveness analysis.

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 $\rightarrow$ 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!

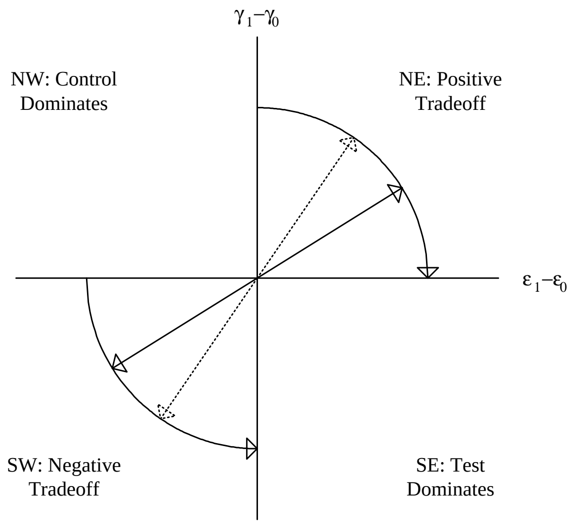

Figure 2: Ranking of ICERs in quadrants NE and SW.

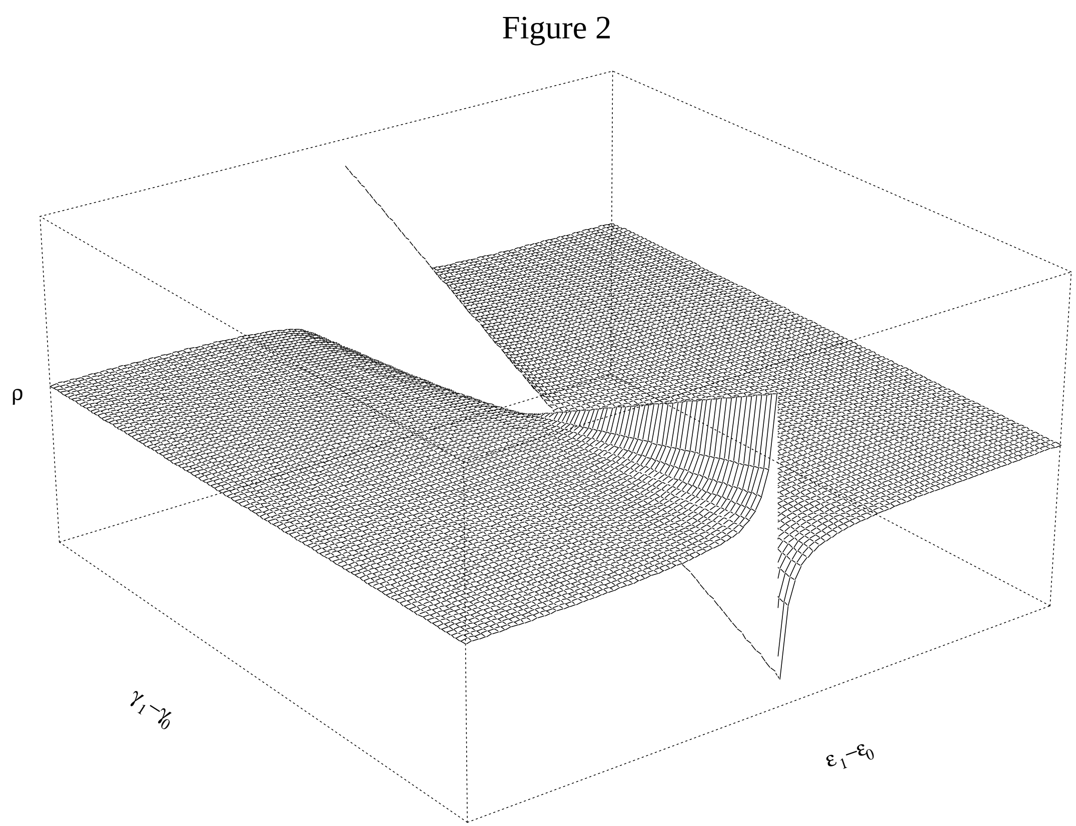

Figure 3: ICER as a function of cost and effectiveness effects.

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)*:

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

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

See Stinnett & Mullahy (1998).

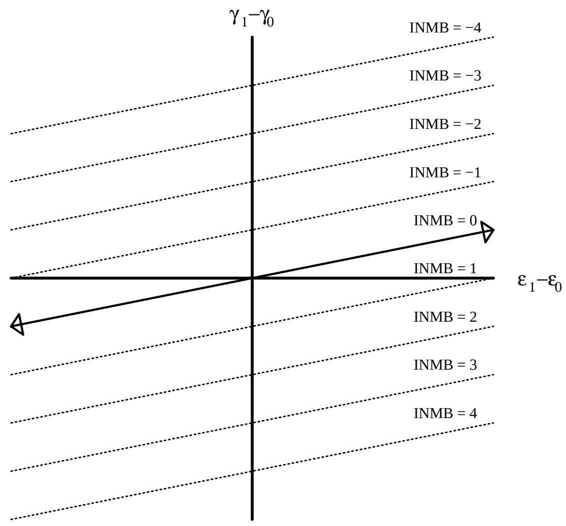

Figure 4: Incremental net monetary benefit.

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" λ?

Data Analysis with INMB

Plot interval estimates of INMB for a range of λ.

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

A Unifying Property

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

Then CS = Fieller's method confidence set for ICER.

(See Heitjan 2000.)

Consequence: Test dominates control at λ_A *does not imply* that it dominates at $\lambda_B > \lambda_A$.

Example: Sepsis Data (Again)

	IL1ra	Placebo
Mean Cost	35,100	33,720
Var(Mean Cost)	4,000	4,000
Survival Rate	0.84	0.56
Var(Survival Rate)	0.09	0.09
Corr(Survival,Cost)	0.34	0.34

Cost: $p = .81$; effectiveness: $p = .023$.

Fieller confidence sets for ICER:

- 95%: $(-108{,}400; 55{,}900)$.
- 98%: $(-\infty; 135{,}200) \cup (324{,}600; \infty)$.

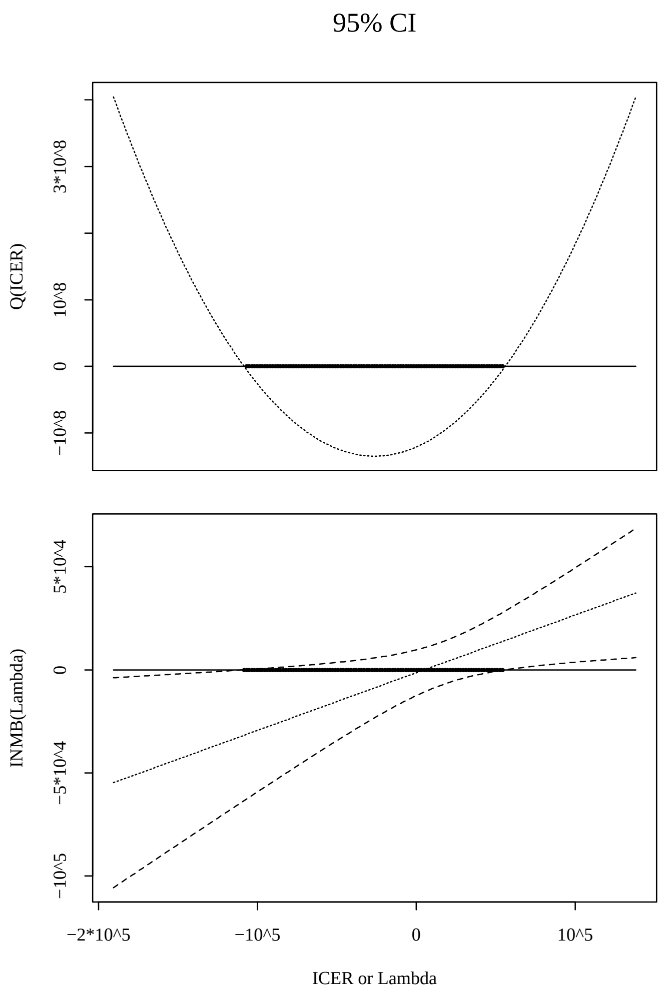

Figure 5: 95% confidence limits for ICER.

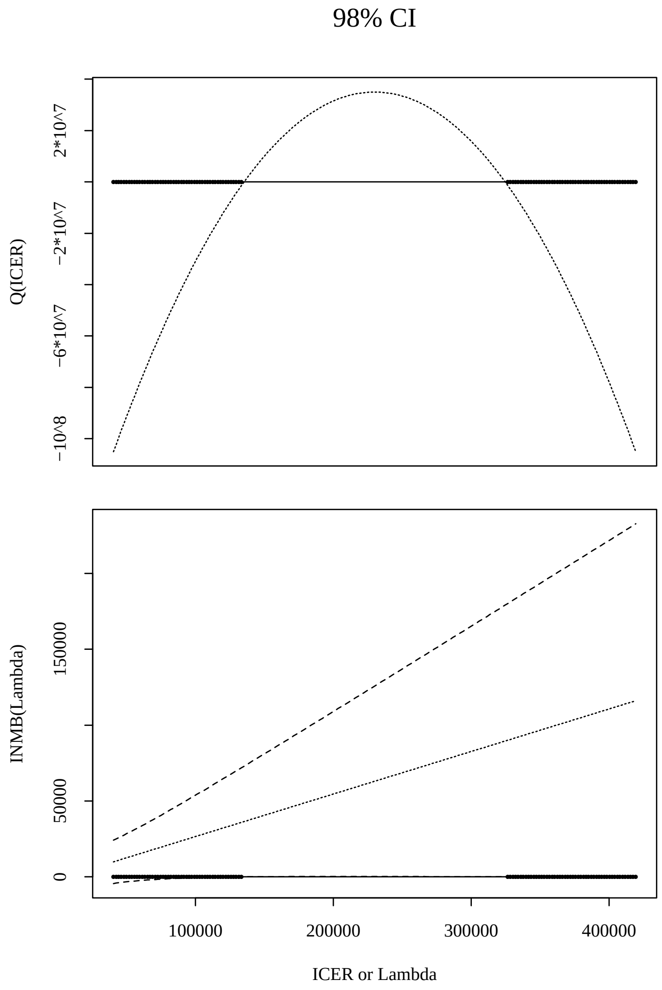

Figure 6: 98% confidence limits for ICER.

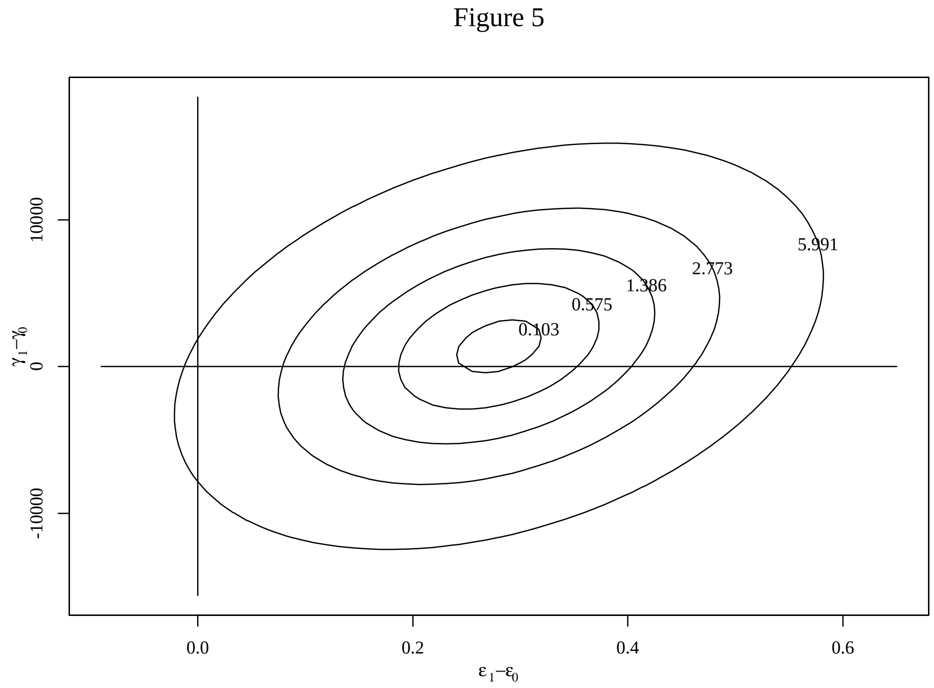

Figure 7: Approximate posterior density of treatment effects in the sepsis study.

Example: Sepsis Data

QUADRANT PROBABILITIES

Quadrant	Probability
NE (Cost-increasing tradeoff)	.594
NW (Placebo dominates)	.003
SW (Cost-reducing tradeoff)	.009
SE (IL1ra dominates)	.395

Example: Sepsis Data

INTERVAL ESTIMATES FOR ICER

Method	Interval (Dfl/life saved)
Bayesian (NE)	(791; 63,400)
Bayesian (SW)	(8,400; 4,580,000)
Fieller (95%)	$(-108{,}400; 55{,}900)$
Fieller (98%)	$(-\infty; 135{,}200) \cup (324{,}600; \infty)$
Bonferroni	$(-3{,}390{,}000; 4{,}050{,}000)$

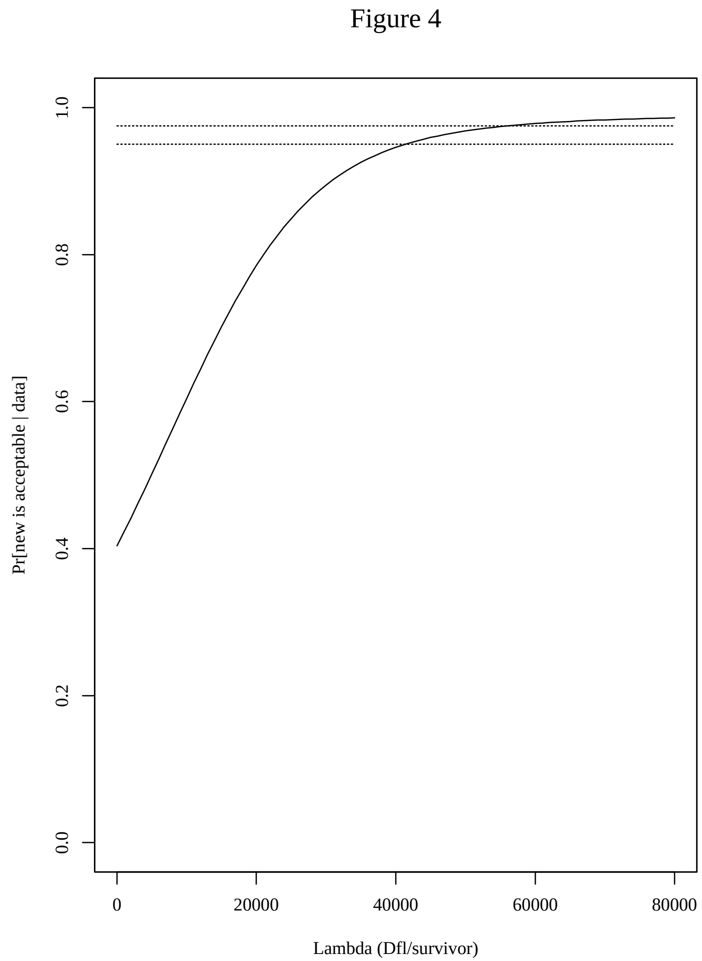

Figure 8: C/E acceptability curve for the sepsis trial.

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.

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