Methods of estimating confidence-intervals in cost-effectiveness analysis

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Outline

Introduction

- Economic evaluation of healthcare treatments, new therapies, and technologies is fundamentally concerned with decision making.
- In the context of **limited resources and budget-constraints** of health care, the effectiveness of a healthcare intervention is a necessary but not sufficient condition for provision of that intervention.
- The availibility of patient-specific cost and effect data from randomized clinical trials has driven rapid development of statistical methods for cost-effectiveness analysis.
- Several measures of cost-effectiveness have been proposed, for example the cost- effectiveness ratio, cost-effectiveness acceptibility curve, and net benefit ratio.
- The statistic of interest in most economic evaluation studies is the **incremental cost-effectiveness ratio (ICER)**.

Incremental Cost-Effectiveness Ratio (ICER)

Definition

- The **ICER** of a new health program/treatment is defined to be as the ratio of **difference of expected costs** and the **difference of expected effects**.

$$\text{ICER} = \frac{\text{expected cost of T1} - \text{expected cost of T2}}{\text{expected effect of T1} - \text{expected effect of T2}}$$

- Easy to interpret: *additional cost per unit of effectiveness gained by using treatment 1 instead of treatment 2.*
- Although very easy to interpret, deriving statistical properties of a **ratio parameter** is difficult.
  - To test the hypothesis regarding the sign and magnitude of ICER.
  - To allow decision maker to determine how much confidence should be placed on the results.
  - To guide decisions about further research.

Incremental cost-effectiveness ratios

General Theory of Ratio Distributions

- Let X, Y be R.V. with expected values $E(X)$ and $E(Y)$ and the **ratio of interest** $\rho := \frac{\mathrm{E}(X)}{\mathrm{E}(Y)}$.
- Unbiased estimators for the expected values are $\bar{x}$ and $\bar{y}$. Then $(\bar{X}, \bar{Y})$ is distributed (approximately or exact) as bivariate normal.
- An intuitive point estimate for the ratio of interest is

$$\bar{p} = \frac{\bar{x}}{\bar{y}}$$

- **Unusual Behaviour:**
  - Neither the expected value of nor variance exist.
  - The estimator is unbiased.
- In particular the ratio of two independent standard Gaussian random variables follows a **Cauchy distribution**.

Statistical Framework

The Main Question...

What methods exist for statistical inference for the cost-effectiveness ratio

$$\text{ICER} = \frac{\text{cost of treatment 1} - \text{cost of treatment 2}}{\text{effect of treatment 1} - \text{effect of treatment 2}}$$

Probabilistic Measures

- Consider a randomized trial with two treatment arms, T_1 and T_2. Let the cost (lower is better) and effectiveness (higher is better) for subject j who receives treatment i be C_{ij} and E_{ij}.
- Assume that (C_i, E_i) has a bivariate distribution with expected values (μ_i, ϵ_i), variance (σ_i^2, τ_i^2), and covariance γ. Also assume they are independently and identically distributed over all patients.

Treatment 1 is cost-effective if...

$$C_1 \leq C_2 \text{ and } E_1 \geq E_2$$

Thus decision maker is interested in the probability

$$\mathcal{P}(C_1 \leq C_2 + \delta_C \text{ and } E_1 \geq E_2 + \delta_E)$$

or alternatively,

$$\mathcal{P}(C_1 \leq C_2 + \delta_C \mid E_1 \geq E_2 + \delta_E)$$

Parametric Methods

The Normality Assumption

Assume

$$\begin{pmatrix} C_i \\ E_i \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \mu_i \\ \epsilon_i \end{pmatrix} , \begin{pmatrix} \sigma_i^2 \\ \tau_i^2 \end{pmatrix} \right) \tag{1}$$

Let $\hat{C}_i, \hat{E}_i$ be the unbiased estimators for μ_i, ϵ_i. It follows, the **difference of expected costs** and **difference of expected effects** also follows the normal distribution,

$$\Delta \hat{C} = (\hat{C}_1 - \hat{C}_2) \sim \mathcal{N}(\mu, \sigma)$$
$$\Delta \hat{E} = (\hat{E}_1 - \hat{E}_2) \sim \mathcal{N}(\epsilon, \tau)$$

where

$$\mu = \mu_1 - \mu_2 \qquad \epsilon = \epsilon_1 - \epsilon_2$$
$$\sigma = \sigma_1^2/N_1 + \sigma_2^2/N_2 \qquad \tau = \tau_1^2/N_1 + \tau_2^2/N_2$$

and covariance ω

Parametric Methods - ICER

Cost-Effectiveness Ratios

Using the **expected value** of the *difference in expected costs μ and effects ϵ*, define the **incremental cost-effectiveness ratio**,

$$\rho = \frac{\mu}{\epsilon} := \frac{\mu_1 - \mu_2}{\epsilon_1 - \epsilon_2}$$

which is **estimated** by

$$\hat{R} = \frac{\Delta \hat{C}}{\Delta \hat{E}} := \frac{(\hat{C}_1 - \hat{C}_2)}{(\hat{E}_1 - \hat{E}_2)}$$

- Recall, the *ICER* ρ is the incremental cost of obtaining one additional unit of effect by using treatment T_1 instead of treatment T_2.

Bonferroni (Box) Intervals

- Wakker and Klassenn described a method for producing confidence intervals for ρ based on Bonferroni's inequality.
- We are interested in inference about $\rho = \frac{\mu}{\epsilon}$. Since normality is assumed, obtain $(1 - plpha)\%$ and $1 - (1 - p)\alpha\%$ confidence limits for the parameters μ and ϵ, for $0 \leq p \leq 1$.
- Let the lower and upper confidence limits be denoted by L_C, U_C for costs and L_E, U_E for effects. **If all four are positive,**

Then by an application of Bonferroni's inequality...

$$\mathcal{P}\left[\frac{L_C}{U_E} < \rho < \frac{U_C}{L_E}\right] \geq 1 - \alpha$$

where the event $\frac{L_C}{U_E} < \rho < \frac{U_C}{L_E}$ is a conservative $(1 - \alpha)\%$ confidence interval of ρ.

Taylor's Method

- Since the ICER is a ratio of two random variables, its exact variance can not be derived in a closed form.
- O'Brien et al proposed a method to estimate variance by a Taylor series approximation

Approximation by Taylor's series...

$$\mathrm{Var}(\hat{R}) = \mathrm{Var}\left(\frac{\Delta\hat{C}}{\Delta\hat{E}}\right) \approx \left(\frac{\mu}{\epsilon}\right)^2 \left(\frac{\sigma^2}{\mu^2} + \frac{\tau^2}{\epsilon^2} - \frac{2\omega}{\mu\epsilon}\right)$$

The means and variances can be estimated by substituting the sample means and variances.

- The confidence interval can then be constructed assuming a normal distribution based on the central limit theorem.
- The $(1-\alpha)\%$ confidence interval is

$$\hat{R} \pm z_{1-\frac{\alpha}{2}} \sqrt{\mathrm{Var}(\hat{R})}$$

Fieller's Theorem

- Proposed by Fieller (1954), the method transforms the ratio into a linear function of two variables.
- Application of Fieller's theorem method does not restrict the distribution of the ratio to be normal or symmetric.
- The estimated correlation between costs and effects is included in the computation.

Define the Net Monetary Benefit...

For $\hat{\Delta C} \sim \mathcal{N}(\mu, \sigma^2)$ and $\hat{\Delta E} \sim \mathcal{N}(\epsilon, \tau^2)$ with covariance ω, define

$$\Delta P = \Delta\hat{C} - \rho\Delta\hat{E}$$

Then, observe

$$\frac{\Delta\hat{C} - \rho\Delta\hat{E}}{\sqrt{\sigma^2 + \rho^2\tau^2 - 2\rho\omega}} \sim \mathcal{N}(0, 1)$$

Fieller's Method

Fieller's Method, continued

At a signifance level of α, the confidence interval is obtained by solving the inequality

$$\left|\frac{\Delta\hat{C} - \rho\Delta\hat{E}}{\sqrt{\sigma^2 + \rho^2\tau^2 - 2\rho\omega}}\right| \leq z_{\frac{\alpha}{2}} \tag{2}$$

$$\implies \qquad s\rho^2 - 2t\rho + u \leq 0 \tag{3}$$

where $z_{\frac{\alpha}{2}}$ is the critical value from the standard normal distribution and,

$$s = \Delta\hat{E} - z_{\frac{\alpha}{2}}\tau^2$$
$$t = \Delta\hat{C}\Delta E - z_{\frac{\alpha}{2}}\omega$$
$$u = \Delta\hat{C}^2 - z_{\frac{\alpha}{2}}\sigma^2$$

Equation (3) is called the **Fieller quadratic**.

Nonparametric Methods

Bootstrap Method

- Most common used method for ICERs since it is free of model assumptions.
- Generally yield reliable results for data with moderate sample sizes.
- The computation requires resampling from the study (say K times) and computing cost-effectiveness ratios in each of the samples.
- Using the mean costs and mean effects of each of the K samples, obtain K ICERs $\hat{\mathbf{R}}^* = [\hat{R}_1^*, \hat{R}_2^*, \ldots, \hat{R}_K^*]$ which form an emperical distribution of $\hat{R}$.
- **Methods for inference:** Standard, t-, Percentiles, and Bias-corrected-and-accelerated.

Comparisons and Limitations of Methods

- Bonferroni and Taylor intervals that assume the normal sampling distribution have poor coverages. However they can be applied in more diverse settings and are easier to compute.
- In terms of the coverage accuracy, Chaudhary and Stearns (1996) recommended Fieller's and the bias-corrected bootstrap methods.
- Polsky et al. (1997) and Briggs et al. (1999) also found Fieller's method was best, while M.Y. Fan and X.H. Zhou (unpublished manuscript) recommended the bootstrap-t interval.
- Fieller's interval requires finding roots of a quadratic equation and these can be imaginary. In addition, if this quadratic equation has one root, the confidence interval is half open.

Agent Based Modelling

- Large number of Monte Carlo simulations.
- Can the above framework be modified to use time-series data instead of patient level data?

Alternative Methods

Alternative parametric and nonparametric methods

- Generalized Pivotal Quantity.
- Bayesian Methods.
- Edgeworth Expansions for the Incremental Cost-Effectiveness Ratio (ICER) .
- *Net Health Benefit Approach and Regression Framework.* Define the **incremental net benefit** as

$$\Delta E \cdot \lambda - \Delta C \tag{4}$$

  where λ is a *willingness to pay* parameter.
- The Cost-Effectiveness Acceptability Curve (CEAC).

See Paper

Thank you