



Analysis of Costs Using Patient Level Data from Randomized Trials

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Outline



- Background
- Literature Review Objectives and Methods
- General Findings
- Analysis of Costs
- Comparison of Costs and Effects with Assessment of Stochastic Uncertainty
- Handling of Incomplete Cost Data

Background



- The number of randomized-trial based economic evaluations has increased considerably over the past few years
- However, serious issues with methodology and reporting have been identified in such studies (Barber and Thompson 1997)

Background



- In the past decade, the field has matured, methods have advanced, and consensus regarding appropriate statistical methods has emerged in several areas
- ISPOR RCT-CEA Taskforce (2005)
 - “GOOD RESEARCH PRACTICES FOR COST-EFFECTIVENESS ANALYSIS ALONGSIDE CLINICAL TRIALS: THE ISPOR RCT-CEA TASK FORCE REPORT”
- Use of good research practices will enhance credibility and usefulness of these studies to decision-makers

Literature Review: Objective



- Our objective was to assess the use of good research practices in published randomized trial-based economic evaluations
- Practice areas assessed were:
 - (1) Analysis of costs
 - (2) Comparison of costs and effects with assessment of sampling uncertainty
 - (3) Handling of incomplete cost data

Literature Review: Methods



- Medline search (Sep 2004) for all studies which included terms in the title, abstract, or MeSH headings related to
 - costs (e.g. “cost(s)”, “economic evaluation(s)”, or “health economic(s)”)
 - clinical trials (e.g. “trial(s)” or “randomized controlled trials”)
- Search was limited to publications in English, involving human subjects, and published during 2003
- Exclusion criteria
 - Study was not a randomized trial
 - Study did not collect or analyze patient specific costs
 - Study applied clinical trial data in a decision analytic model
- 115 studies met selection criteria for review



Literature Review: Findings

General Study Information

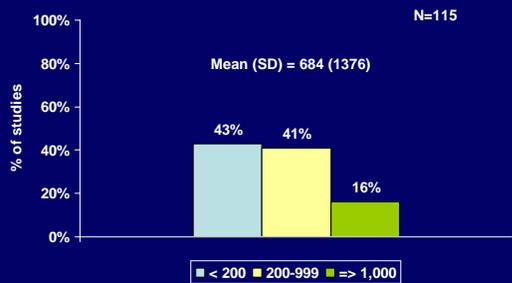


General Findings

- Studies covered a variety of clinical areas such as cardiovascular disease, musculoskeletal conditions, cancer, and psychiatry
- 85% of the studies were published in general medical, surgical, or subspecialty clinical journals and the remainder were in methods or policy journals
- The trials in which these economic analyses were performed were conducted in either the United States (24%), the UK (24%), multinationally (21%), or in other countries (31%)



Sample Size





Analysis of Costs

Preferred Analytic Approaches
&
Findings on Common Mistakes
Identified in Review

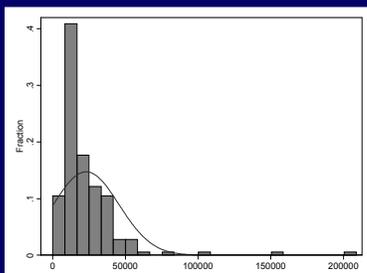


Cost Data 101

- Common feature of cost data is right-skewness (i.e., long, heavy, right tails)
- Cost data tend to be skewed because:
 - Can not have negative costs
 - More severe cases require substantially more services than less severe cases (“long heavy right tails”)
 - Catastrophes can yield small numbers of patients with astronomical costs (“Outliers”)



Typical Distribution Of Cost Data



| Sample | Mean | Median |
|---------|--------|--------|
| All | 23,019 | 16,052 |
| <75,000 | 20,430 | 15,960 |

Which Statistic Should be Used to Summarize Cost Data?

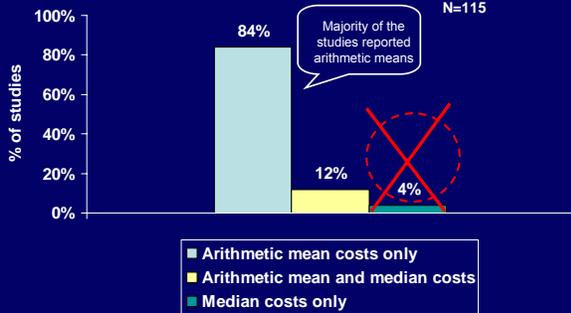


- What statistical formulation best characterizes the policy or decision problem of interest?
- For cost-effectiveness analysis: **ΔC (arithmetic mean)**
 - Social perspective: In economic theory, arithmetic mean costs and differences in arithmetic mean costs yield social efficiency
 - Budgetary perspective: arithmetic mean costs are a better summary of budgetary impact than median costs or log of costs (because $n \times \text{mean} = \text{total}$)
- Cost-effectiveness ratios ($\Delta C/\Delta E$) require an estimate of ΔC where:

$$\Delta C = C_t - C_s$$

$$\Delta E = E_t - E_s$$

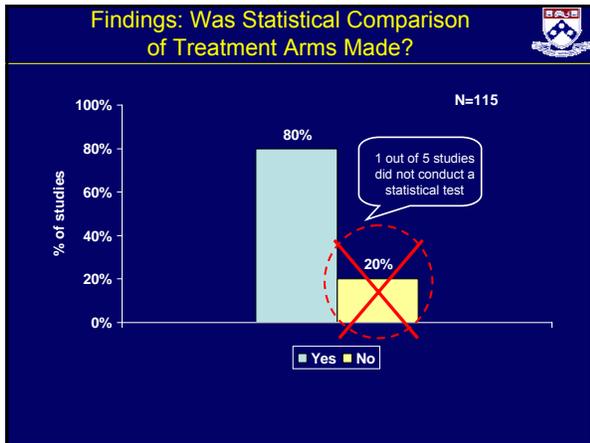
Findings: Cost Statistic Reported Across Treatment Arms



How Should Cost Data be Summarized?



- Arithmetic means and their difference
- Measures of variability and precision (e.g. std deviation)
- Quantiles such as 5%, 10%, 50% (median),...75%.....
- An indication of whether or not the difference in arithmetic means occurred by chance



Univariate Statistical Tests

- Usual starting point for comparing arithmetic means: T-tests and one way ANOVA
 - Makes assumption that the costs are normally distributed
 - While the normality assumption is routinely violated for cost data, in large samples these tests have been shown to be robust to violations of this assumption
- Because of distributional problems related to evaluating the arithmetic mean, there has been a growing use of alternative tests

Common Mistakes (I): Non-parametric tests

- Adoption of nonparametric tests of other characteristics of the distribution that are not as affected by the nonnormality of the distribution
 - Wilcoxon rank-sum or Mann-Whitney U test for difference in medians
 - Kolmogorov-Smirnov test for difference in cumulative distribution function

Problems With Non-parametric Tests



- Tests don't provide an estimate of the difference in arithmetic mean cost
- Tests don't yield inferences about the difference in arithmetic means
- BOTTOM LINE: tests may tell you some measure of the cost distributions differs between the treatment groups, but they DON'T tell you whether the parameter of interest – the arithmetic mean -- is different

Common Mistakes (II): Log Transformation



- Attempt to make the distribution more normal by taking the log transformation of cost
 - Estimate and draw inferences about the difference in log cost with the goal of applying these estimates and inferences to the arithmetic mean of cost
- If distribution of log cost is normal, t-test of log cost may be more efficient than t-test of nonnormally distributed cost

Problems With Log Transformations



- Transformation does not always yield normal distribution
- For the log transformation, one is making estimates and inferences about the ratio of the treatment group means or differences in geometric means
- For economic analysis, the outcome of interest is the difference in untransformed costs (e.g., "Congress does not appropriate log dollars")
 - Need to retransform log costs to original scale
 - Retransformation issues: Simple exponentiation of log costs results in geometric mean (not arithmetic mean). Need to apply appropriate smearing factors to obtain unbiased estimates

Problems With Log Transformations

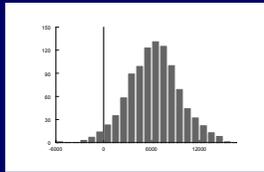


- “There is a very real danger that the log scale results may provide a very misleading, incomplete, and biased estimate.....on the untransformed scale, which is usually the scale of ultimate interest” (Manning, 1998)
- “This issue of retransformation...is not unique to the case of a logged dependent variable. Any power transformation of y will raise this issue” (Manning, 1998)

Better Statistical Approach: Non-Parametric Bootstrap



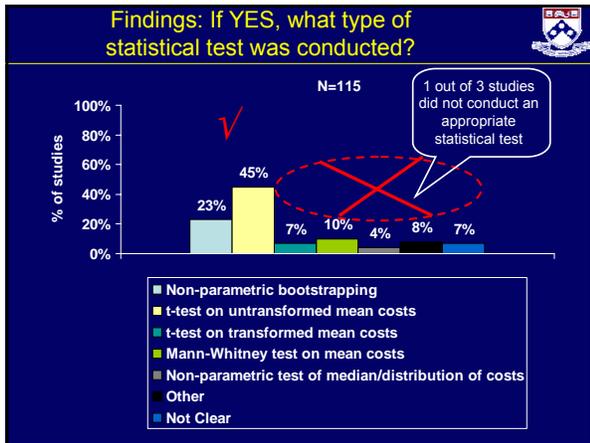
- Provides direct test of arithmetic mean of cost that avoids parametric assumptions
 - Estimates distribution of the observed difference in arithmetic mean cost using N bootstrap replicates
 - Yields a test of how likely it is that 0 is included in this distribution (by evaluating the probability that the observed difference in means is significantly different from 0)



Summary of Univariate Statistical Approach



- If arithmetic means are the most meaningful summary statistic of costs, one should test for significant differences in arithmetic mean costs
 - Parametric test of arithmetic means
 - T-test on untransformed costs
 - Non-parametric test of arithmetic means
 - Bootstrap methods



Illustrative Example 1

| | <u>Placebo</u> | <u>Treatment</u> |
|--------------|----------------|------------------|
| Mean (\$) | 20,287 | 25,185 |
| SD | 22,542 | 22,619 |
| Distribution | | |
| 5% | 4,506 | 10,490 |
| 25% | 9,691 | 13,765 |
| 50% | 13,773 | 18,834 |
| 75% | 23,044 | 31,069 |
| 95% | 53,728 | 51,771 |

Results from Different Statistical Tests Applied to Same Dataset

| <u>Test</u> | <u>P-value</u> |
|----------------------------------|----------------|
| T-test of mean difference | 0.16 |
| Non-parametric Bootstrap | 0.09 |
| T-test, log of cost difference | 0.001 |
| Wilcoxon rank-sum (Mann-Whitney) | 0.0002 |
| Kolmogorov-Smirnov | 0.001 |

Why Would Different Statistical Tests Lead To Different Inferences?



- The tests are evaluating differences in different statistics
 - T-test of untransformed costs indicates one cannot infer that the arithmetic means are different
 - Bootstrap leads to same inference as t-test and does not make the normality assumption
 - T-test of log costs indicates one can infer that the mean of the logs are different, and thus the geometric means of cost are different
 - Wilcoxon rank-sum test indicates one can infer that the medians are different
 - Kolmogorov-Smirnov test indicates one can infer that the distributions are different

Illustrative Example 2

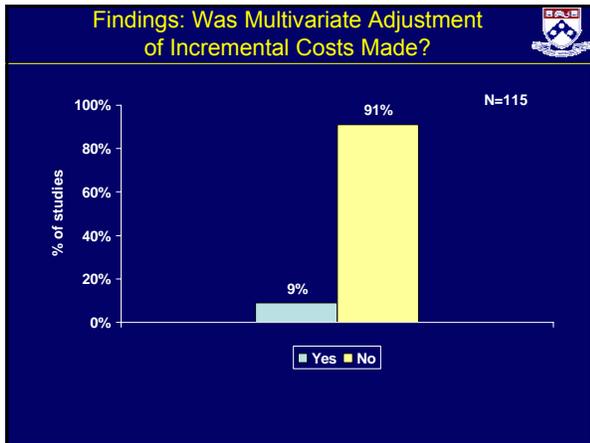


| | Mean | SD | Skewness | Kurtosis | Diff. | P-value |
|-------------------|-------|-------|----------|----------|-------|---------|
| Costs (\$) | | | | | | |
| Group 0 | 20000 | 10263 | 1.60 | 8.06 | 0 | 1.00 |
| Group 1 | 20000 | 3123 | 0.58 | 3.24 | | |
| Log Costs | | | | | | |
| Group 0 | 9.78 | 0.49 | -0.02 | 2.77 | 0.107 | 0.0000 |
| Group 1 | 9.89 | 0.15 | 0.16 | 2.86 | | |

Multivariable Analysis of Costs

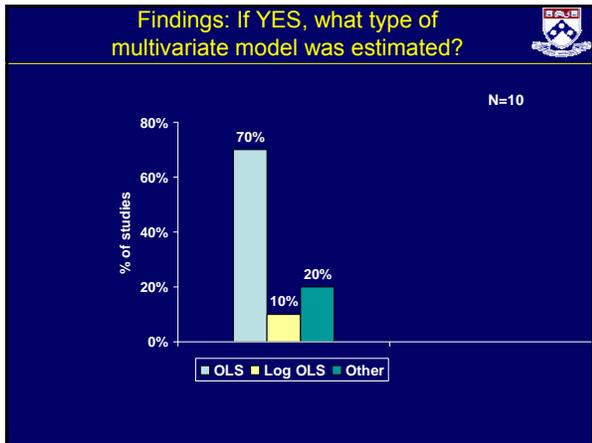


- Even if treatment is randomly assigned, multivariable analysis may be superior to univariate analysis because:
 - Improves the power for tests of differences
 - Facilitates subgroup analyses for cost-effectiveness (e.g., more and less severe; different countries; etc.)
 - Accounts for potential variations in economic conditions and practice pattern (by provider, center, or country) that may influence costs and that may not be accounted for by randomization
 - Helps explain what is observed (e.g., coefficients for other variables should make sense economically)



- ### Multivariable Techniques Used for the Analysis Of Costs
- Most common techniques
 - Ordinary least squares regression (OLS)
 - Ordinary least squares regression predicting the log transformation of costs (log OLS)
 - Generalized Linear Models (GLM)

- ### Multivariable Analysis
- Different multivariable models make different assumptions
 - When assumptions are met, coefficient estimates will have many desirable properties
 - With cost analysis, assumptions are often violated, which may produce misleading or problematic coefficient estimates
 - Bias (consistency)
 - Efficiency (precision)
 - The underlying distribution of costs should be carefully assessed to determine the most appropriate approach to conduct statistical inference on the costs between treatment groups



- ### Analysis of Costs: Summary
- Most studies presented arithmetic mean costs; however more than 1 in 3 studies either did not conduct a statistical test or used an inappropriate test
 - About 1 in 10 studies estimated incremental costs in a multivariate framework and most used OLS
 - Most studies did not report/assess distributional assumptions
 - No studies tested sensitivity of results to alternative multivariate techniques
 - No study used the GLM technique

Comparison of Costs and Effects and Assessing Sampling Uncertainty

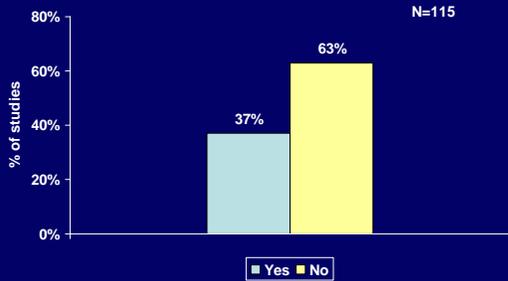
Preferred Analytic Approaches
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Findings on Common Mistakes
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Joint Comparison Of Costs And Effects

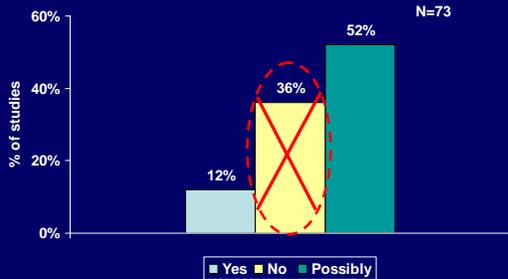


- The incremental cost-effectiveness ratio (ICER) is a useful decision tool to help determine whether the new therapy offers good value to the alternative
- Lack of joint comparison justified
 - **YES**: One therapy is unambiguously dominant over its alternative (i.e. significantly more effective and significantly less costly)
 - Joint comparison may not be necessary
 - **NO**: Tradeoff between costs and effects
 - Joint comparison necessary
 - **POSSIBLY**: No significant difference in effect
 - Need for a joint comparison still remains under most circumstances

Findings: Was Comparison of Costs and Effects Made?



Findings: If NOT, was the lack of joint comparison justified?

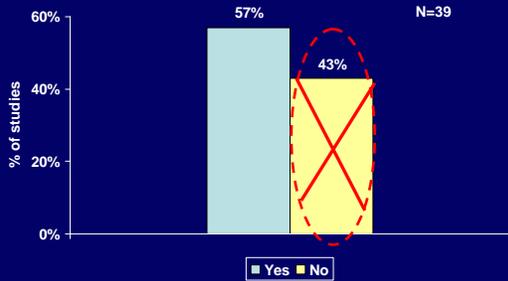


Sampling Uncertainty

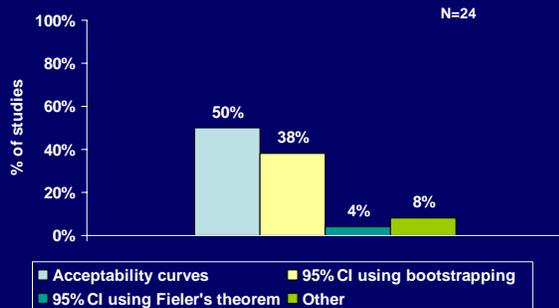


- Because cost-effectiveness ratios estimated from trial data are the result of samples drawn from the population, one should report the uncertainty in this outcome that derives from such sampling.
 - Confidence intervals for cost-effectiveness ratios
 - Confidence intervals for net monetary benefit curves
 - Cost-effectiveness acceptability curves

Findings: If joint comparison conducted, was sampling uncertainty measured?



Findings: If YES, how was sampling uncertainty measured?



* Other includes studies such as those that calculated 95% CI but did not specify how these were estimated (based on t-statistic, bootstrapping, etc.) or studies that calculated 95% CI for ICER based on 95% CI values for only the numerator (i.e. costs)

**Joint Comparison and Uncertainty:
Summary** 

- Only 37% of the studies conducted a joint comparison of costs and effects
- Depending on the strictness of the criteria, 23% to 56% of the 115 studies should have estimated costs and effects jointly, but failed to do so
- Among the studies that compared costs and effects, only half reported sampling uncertainty

Handling of Incomplete Cost Data 

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Censored Data 101 

- As economic data are increasingly collected alongside clinical trials the accommodation of censoring is becoming increasingly important within this context
 - Only recently the attention has turned to the issue of censored cost data
- Right censoring occurs whenever some individuals are not observed for the full duration of interest which results in information being incomplete for these patients
- Incomplete cost data can also be due to item-level missingness
 - Multiple-imputation approach preferred method

Degree and Mechanism of Missingness



- No clear rule of thumb on what degree of missing data is problematic and requires adjustment
 - “Ignoring small amounts of missing data is acceptable if a reasonable case can be made that doing so is unlikely to bias treatment group comparisons” – ISPOR RCT CEA Taskforce
- Need to diagnose mechanism of missingness
 - Missing completely at random (MCAR)
 - Missing at random (MAR)
 - Not missing at random (NMAR) or informatively (nonignorably) missing

Common Mistakes

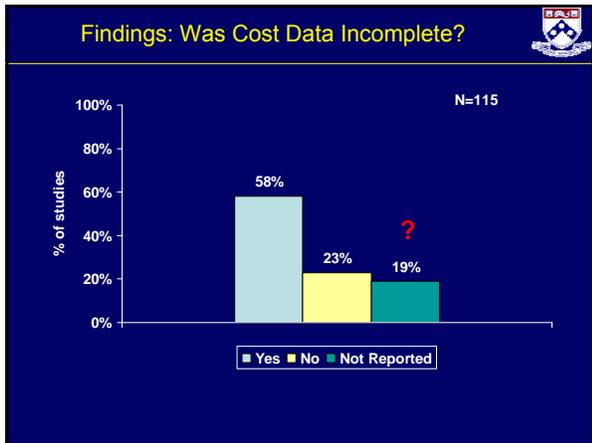


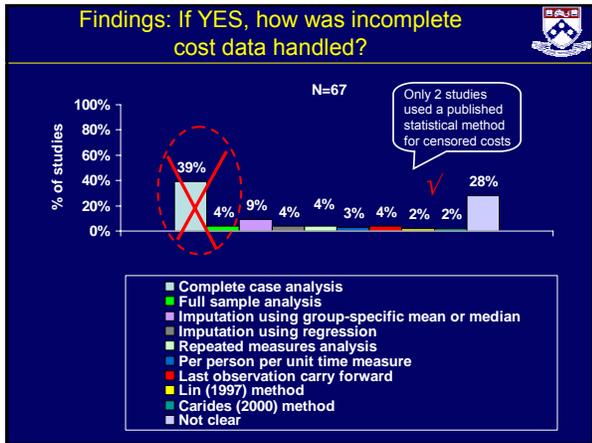
- Prevalent use of two “naive” estimators in the literature
 - Uncensored-cases estimator (Complete-case analysis)
 - Full-sample estimator (Average over all sample patients)
- Uncensored-cases estimator only uses the uncensored cases in the estimation of mean cost
 - Biased toward the costs of the patients with shorter survival times because larger survival times are more likely to be censored
 - Reduces power to test hypotheses
- Full-sample estimator uses all cases but does not differentiate between censored and uncensored observations
 - Always biased downward because the costs incurred after censoring times are not accounted for

Techniques to Handle Censored Costs



- Lin et al. 1997
- Carides et al. 2000
- Bang and Tsiatis 2000
- Lin 2000a & Lin 2000b
- Zhao and Tian 2001
- Jain and Strawderman 2002
- Relative advantages of some of these methods have been evaluated in
 - Raikou and McGuire 2004
 - O'Hagan and Stevens 2004
- These methods have been shown to perform better than “naive” methods





Handling of Incomplete Cost Data: Summary

- 1 in 5 studies did not even report whether cost data were complete or not
- Of those reporting, almost three-quarters had incomplete cost data
- Most studies used "naïve" methods to handle incomplete cost data and may have resulted in biased or inefficient estimates

Conclusion



- Our review finds a substantial number of clinical trial-based economic studies using statistical methods of poor quality
- Efforts are needed from different stakeholders to ensure that future clinical trial-based cost-effectiveness analyses address these issues to enhance the validity of their findings and ensure their usefulness in health-care decision making

Comments or Questions?