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

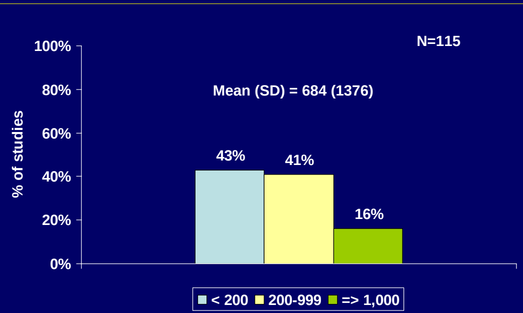
Literature Review: Findings

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



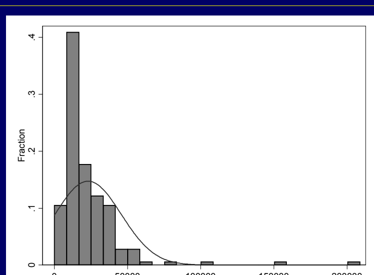
Analysis of Costs

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

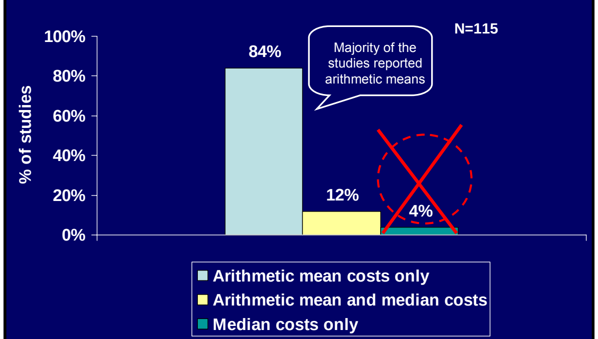
Which Statistic Should be Used to Summarize Cost Data?

- 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 x mean = total)
- Cost-effectiveness ratios (ΔC/ΔE) require an estimate of ΔC where:

  ΔC= Ct - Cs

  ΔE= Et - Es

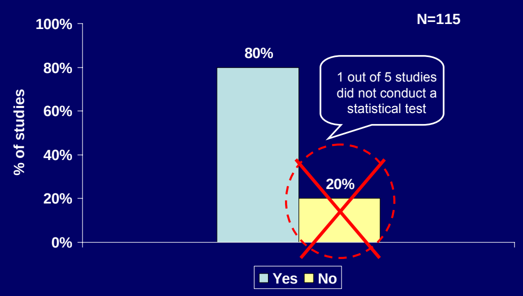
Findings: Cost Statistic Reported Across Treatment Arms



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

Findings: Was Statistical Comparison of Treatment Arms Made?



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

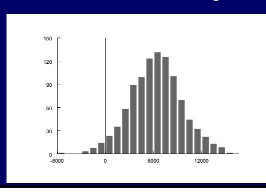
- Transformation does not always yield normal distribution
- For the log transformation, one is making estimates and inferences about the ratio of the treatment group means or differences in geometric means
- For economic analysis, the outcome of interest is the difference in untransformed costs (e.g., "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

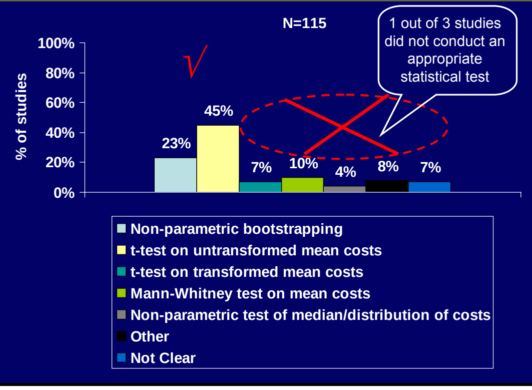
- Provides direct test of arithmetic mean of cost that avoids parametric assumptions
  - Estimates distribution of the observed difference in arithmetic mean cost using N bootstrap replicates
  - Yields a test of how likely it is that 0 is included in this distribution (by evaluating the probability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

Findings: If YES, what type of statistical test was conducted?



Illustrative Example 1

	Placebo	Treatment
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

Test	P-value
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

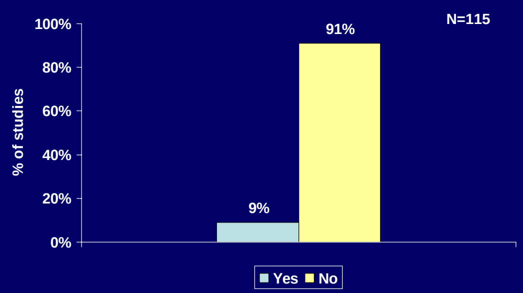
Illustrative Example 2

	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)

Findings: Was Multivariate Adjustment of Incremental Costs Made?



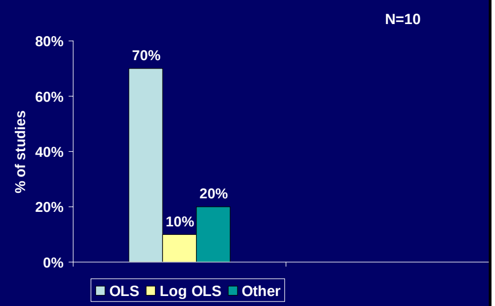
Multivariable Techniques Used for the Analysis Of Costs

- 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

Findings: If YES, what type of multivariate model was estimated?



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

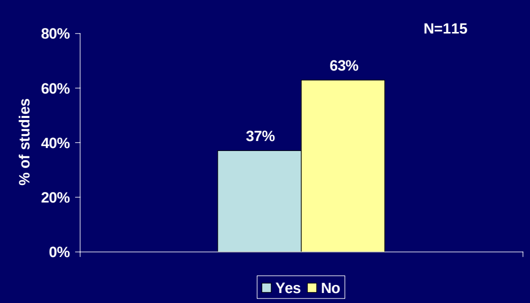
Comparison of Costs and Effects and Assessing Sampling Uncertainty

Preferred Analytic Approaches
&
Findings on Common Mistakes
Identified in Review

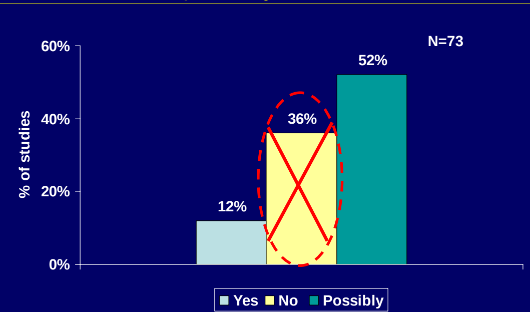
Joint Comparison Of Costs And Effects

- 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?



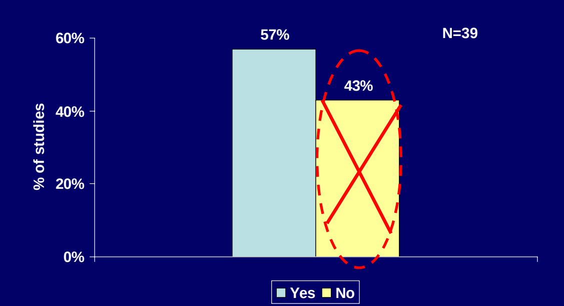
Findings: If NOT, was the lack of joint comparison justified?



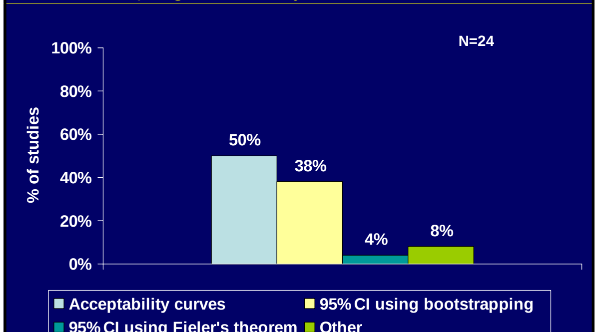
Sampling Uncertainty

- 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

Preferred Analytic Approaches
&
Findings on Common Mistakes
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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

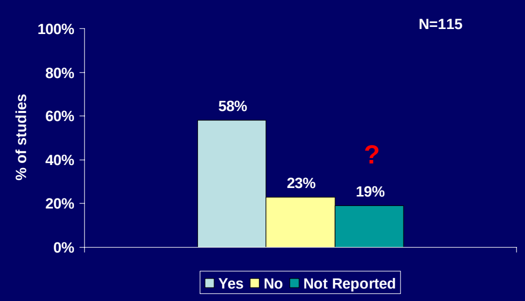
Common Mistakes

- 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

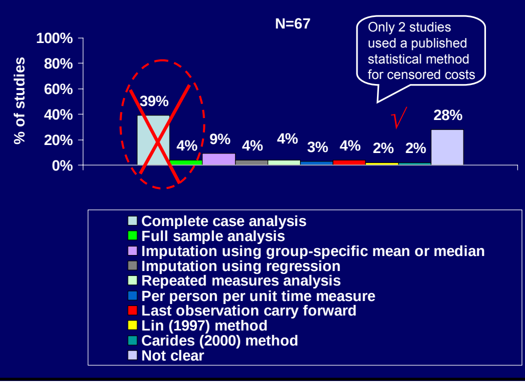
Techniques to Handle Censored Costs

- 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 "naïve" methods

Findings: Was Cost Data Incomplete?



Findings: If YES, how was incomplete cost data handled?



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?