Analysing Resource Use and Cost from Randomized Controlled Trials

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DIA Economic Assessments Workshop - Feb. 16, 2001
Goal: Gain an appreciation of some issues in and approaches to analysing resource utilization (RU) and cost data
Scope of Problem

• General Research Question:
  – Do patients utilize fewer healthcare resources and incur lower costs with Trt A compared to Trt B?
    • Specify time horizon (trial period, fixed w/in trial, beyond trial)

• Ideal Clinical/Economic Trial
  – designed to also address *economic* research question
  – adequate sample size
  – no missing data; complete follow-up
  – includes patient-level data on RU and cost
Scope of Problem (continued)

- Actual Clinical Trial and Associated Analytic Issues
  - Usually designed to answer *clinical* research question
    - time horizon may be too short to answer health-economic question
    - sample size may be inadequate for precise estimation of health-economic endpoint(s)
  - Data often skewed, outlier-prone, highly variable
  - Potential for missing/ incomplete follow-up (censored) data
  - Total count/cost vs. history (timing of resource use/cost)
  - Cost data not captured ⇒ require external source
Example 1: Elevated Cholesterol (4S)

Estimate & compare CV hospitalizations

- RCT conducted in post-MI / angina patients with hypercholesterolemia
- Randomized to active treatment (simvastatin) or placebo
- Design: 4,444 pts, minimum of 5 year follow-up
- Clinical endpoints: all-cause mortality, incidence of major coronary events.

- Issues:
  - clinical vs. economic perspective
  - non-normality/skewness of total 5-year hospitalizations
Example 2: Heart Failure (ELITE II)

Estimate & compare outpatient visits

- RCT conducted in heart failure patients at least 60 years of age
- Randomized to losartan or captopril
- Design: 3,152 pts, minimum of 1 year follow-up
- Clinical endpoints: all-cause mortality, study discontinuation due to adverse effects

Issues:
- missing/censored data
- differential utilization depending on whether patient discontinued study
Example 3: Heart Failure (SOLVD)

Estimate & compare 3-year mean cost

• RCT conducted in symptomatic heart failure patients
• Randomized to active treatment (enalapril) or placebo
• Design: 2,569 pts, minimum of 2 year follow-up
• Clinical endpoints: mortality, hospitalization, incidence of MI

• Issues:
  – right-skewed/heteroscedastic cost data
  – censoring
Analysis of Resource Utilization (events)

- Events may represent resources utilized (e.g. hospitalizations, emergency room visits, outpatient visits) or clinical outcomes that lead to costs (e.g. opportunistic infections)

- Clinical vs. economic perspective
  - clinical perspective: ratios -- relative risk / risk reduction
  - economic perspective: means and differences -- average # of counts / difference in average number of counts
Analysis of RU: Complete Information

- Simplest analytic situation, but less common
  - may hold for a portion of the trial period
    (e.g., 4S with minimum of 5 years of follow-up)

- Most statistical tools to be discussed work here
  - Resampling (bootstrap) methods
  - For very large studies, normal theory based methods
    (Use with Caution!)
  - Wilcoxon rank sum (Caveat: for testing differences in distribution, not means)
Analysis of RU: Complete Information

4S: Distribution of Hospitalizations over 5 Years

Wilcoxon Rank Sum: p < .0001

Mean no. of hosp: simvastatin: 0.58 vs. placebo: 0.79 (Δ=0.22)
### Analysis of RU: Complete Information

<table>
<thead>
<tr>
<th>Method</th>
<th>$\Delta$</th>
<th>Standard Error</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Theory</td>
<td>-0.22</td>
<td>0.0418</td>
<td>(-0.300, -0.136)</td>
</tr>
<tr>
<td>Bootstrap Normal*</td>
<td>-0.22</td>
<td>0.0406</td>
<td>(-0.297, -0.138)</td>
</tr>
<tr>
<td>Bootstrap BCa*</td>
<td>-0.22</td>
<td>0.0406</td>
<td>(-0.299, -0.140)</td>
</tr>
</tbody>
</table>

*See Efron and Tibshirani (‘94)
Analysis of RU: Complete Information

4S: Bootstrap Replicates for 5-Year Mean Cost Difference
Analysis of RU: Incomplete Information

• **Goal:**
  
  Estimate and compare average utilization (events) per patient per time unit (eg. hospitalizations/year)

• **Key Question:**

  Does the utilization rate differ over time?
  – NO: only need to account for **time of follow-up**
  – YES: need to account for **timing of events** or
    
    • limit time horizon to minimum follow-up time observed
ELITE II Heart Failure Trial: Outpatient Visits

- 3,152 pts randomized to losartan or captopril
- Minimum of 1 year follow-up
- Outpatient visit information collected every 4 months
- Reporting period -- prior 30 days
- Patients dropping out of study tend to report greater numbers of outpatient visits (in the months prior to dropout) than those staying in study
Analysis of RU: Incomplete Information

ELITE II: Estimated* Mean Number of Outpatient Visits by Month

<table>
<thead>
<tr>
<th>Month</th>
<th>Losartan Completers</th>
<th>Losartan Discons.</th>
<th>Captopril Completers</th>
<th>Captopril Discons.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Locfit smoother based on local Poisson models
ELITE II Heart Failure Trial: Outpatient Visits --Estimation Method*

- For each treatment group, separate patients into 2 groups --
  - those not discontinuing due to adverse effects (‘completers’)
  - those discontinuing due to adverse effects
- Within each group --
  - estimate the mean number of outpatient visits by month *conditional on survival* by applying a local likelihood based smoother assuming a Poisson model (available from http://cm.bell-labs.com/stat/project/locfit)
  - weight (multiply) the estimated conditional mean outpatient visits by the Kaplan-Meier survival probabilities
  - sum the products over the full period of follow-up and annualize
- Combine the two group estimates to get overall estimate --
  - Losartan: 9.9  Captopril: 11.5  Difference (95% CI):  -1.7 (-4.2, 0.2)

*Variation of two-stage method proposed in Carides, Heyse, and Iglewicz (‘00)
Analysis of Cost

- May first wish to assess amount of resources used to determine if treatment differences exist
  - Treatments may reduce one type of resource, but increase another
- Cost provides a meaningful way to aggregate different types of resources
- Analytic issues similar to resource utilization, but
  - Variability even greater
  - Results may differ depending on whose costs are used.
- Interest in estimating cost for fixed time horizon, e.g.,
  - 3 yrs, 5 yrs, 10 yrs, or “lifetime”
Analysis of Cost: Complete Follow-up

• Variety of approaches available:
  – Wilcoxon rank sum
  – Parametric methods (i.e. ANOVA / t-test)
  – Resampling methods (bootstrap)/randomization test

• If high percentage of pts w/o cost, consider two compartment models (Diehr, et al., 1999)
**Analysis of Cost: Censoring**

- **Goal:** Estimate and compare mean cost per patient when information on cost for some patients is incomplete (censored) due to follow-up time less than chosen time horizon

- **Key Question:** Are patients lost to follow-up due to covariate-related (could be treatment) drop-out?
  - NO, administrative censoring only: many valid estimation methods exist (Lin, et al. ‘97; Carides, Heyse, Iglewicz ‘00; Bang and Tsiatis ‘00)
  - YES: can incorporate covariate-dependent censoring in stratified Cox proportional hazards model (Cox ‘72; Lin ‘00).
Analysis of Cost: Censoring

SOLVD: Average Monthly Cost by Month Post-Randomization Conditional on Survival

![Graph showing the average monthly cost ($US) by month post-randomization for Enalapril and Placebo with p-values indicating statistical significance.](image-url)
Analysis of Cost: Censoring

- Two general strategies:
  - Inverse probability weighting - weight costs more as more censoring occurs (Bang and Tsiatis, ‘00):
    \[
    \frac{1}{N} \sum_{i} wt \bullet (\text{total cost of patient } i)
    \]
    or
    \[
    \frac{1}{N} \sum_{j} \sum_{i} wt \bullet (\text{cost of patient } i \text{ in interval } j)
    \]
  - Conditional methods for censored cost data
    \[
    \sum P(s) \bullet E(\text{cost} \mid s) \quad \text{or} \quad \sum P(\text{dth}) \bullet E(\text{total cost} \mid \text{dth})
    \]
Analysis of Cost: Censoring

- Lin et. al. (1997) proposed conditional method depending on whether cost history or total cost is available --
  - Partition time into intervals
  - $E(C|s)$ and $E(C|dth)$ --: avg cost (during interval or total) among patients surviving or dying during interval
  - $P(s)$ and $P(dth)$ based on Kaplan-Meier
  - Assumes censoring/deaths only at interval cutpoints
Analysis of Cost: Censoring

- Carides (‘98) and Carides, Heyse, Iglewicz (‘00) proposed two-stage conditional method when total cost is available
  - Total cost is comprised of survival time and error
  - Mean cost is estimated in two stages
    - $E(C|dth)$ is based on estimated relationship between cost and time: parametric regression model or nonparametric smoother
    - $P(dth)$ based on Kaplan-Meier
  - Gains efficiency over Lin by exploiting relationship between total cost and survival time
  - Does not assume censoring only at interval cutpoints
  - Can extend to handle cost history and covariates
## Comparison of approaches: SOLVD cost estimates ($US)

<table>
<thead>
<tr>
<th>Method</th>
<th>Enalapril</th>
<th>Placebo</th>
<th>Δ</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted</td>
<td>11324</td>
<td>12898</td>
<td>-1574</td>
<td>(-3076, -263)</td>
</tr>
<tr>
<td>Weighted Partitioned</td>
<td>11346</td>
<td>12909</td>
<td>-1563</td>
<td>(-3242, 55)</td>
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<tr>
<td>Two Stage</td>
<td>11201</td>
<td>12931</td>
<td>-1736</td>
<td>(-3113, -317)</td>
</tr>
<tr>
<td>Two Stage – AS*</td>
<td>11184</td>
<td>12786</td>
<td>-1602</td>
<td>(-2920, -423)</td>
</tr>
</tbody>
</table>

*AS = ‘Average/Smooth’ -- Utilizes cost history
Summary

- Unlikely to have the ideal trial
- Methods useful for the analysis of RU and costs
  - Complete Information
    - bootstrap; normal theory (very large $n$)
  - Incomplete Information
    - ‘imputation’ methods
    - inverse probability weighting
    - conditional (on death or survival) methods
- Analytic approaches may not overcome all issues, but can give reasonable answers
References