CEA: NEW METHODOLOGIC APPROACHES

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RECENT HISTORY: “IS THE THERAPY GOOD VALUE FOR THE COST?”

10-15 years ago, generally would have supported message about value for cost by use of decision analytic models such as decision tree or Markov models

- Little or none of the economic results would have been directly observed
  * e.g., the clinical evidence about the therapy might be that it reduced blood pressure
  * These data often would be combined with epidemiologic data relating blood pressure to death and disability to project the likely economic impact of therapy

- Reported results would have included:
  * Point estimates of incremental costs, outcomes, and comparison of costs and effects from a “principal” or “base-case”
  * Results of sensitivity analysis

RECENT HISTORY, VALUE FOR COST (II)

In the mid-90's, for a cutting edge evaluation, the message would have been supported by use of data from randomized trials that included economic outcomes as primary or secondary endpoints of the trials

- Short-term economic impacts of the therapy would be directly observed; longer term impacts potentially would be projected by use of decision analysis

- Reported results would have included:
  * Point estimates and confidence intervals for estimates of incremental costs and outcomes
  * Point estimates and results of sensitivity analysis for the comparison of costs and effects
### Example of Typical Mid '90s Results

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Point Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental Costs</td>
<td>-713</td>
<td>-2123 to 783</td>
</tr>
<tr>
<td>Incremental QALYS</td>
<td>0.13</td>
<td>0.07 to 0.18</td>
</tr>
</tbody>
</table>

### Cost-Effectiveness Ratios

- **Principal Analysis**
  - Dominates
  - NA

- **Survival benefit**
  - -33%
  - Dominates
  - NA
  - +33%
  - Dominates
  - NA

- **Intervention costs**
  - -50%
  - Dominates
  - NA
  - +50%
  - Dominates
  - NA

- **Hospitalization costs**
  - -50%
  - Dominates
  - NA
  - +50%
  - Dominates
  - NA

- **Discount rate**
  - 0%
  - Dominates
  - NA
  - 7%
  - Dominates
  - NA

### Recent History, Primary Message (III)

By the end of the 90's, for a cutting edge evaluation, the message would still have been supported by use of an evaluation conducted as part of a randomized trial.

- Short- and long-term economic impacts of therapy would continue to be directly observed/projected.
- The primary difference in the reported results would be the inclusion of confidence intervals for estimates of the comparison of costs and effects.
- In addition, the impact of sensitivity analysis on the comparison of costs and effects would be judged by its impact on both the point estimates and the confidence intervals of the ratios.
### EXAMPLE OF TYPICAL LATE ’90’S RESULTS

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#### Cost-Effectiveness Ratios

<table>
<thead>
<tr>
<th>Principal Analysis</th>
<th>Dominates</th>
<th>Dom to 6650</th>
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<tr>
<td>Survival benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-33%</td>
<td>Dominates</td>
<td>Dom to 9050</td>
</tr>
<tr>
<td>+33%</td>
<td>Dominates</td>
<td>Dom to 5800</td>
</tr>
<tr>
<td>Hospitalization costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-50%</td>
<td>Dominates</td>
<td>Dom to 5300</td>
</tr>
<tr>
<td>+50%</td>
<td>Dominates</td>
<td>Dom to 8400</td>
</tr>
<tr>
<td>Drug costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-50%</td>
<td>Dominates</td>
<td>Dom to 4850</td>
</tr>
<tr>
<td>+50%</td>
<td>Dominates</td>
<td>Dom to 8750</td>
</tr>
<tr>
<td>Discount rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>Dominates</td>
<td>Dom to 6350</td>
</tr>
<tr>
<td>7%</td>
<td>Dominates</td>
<td>Dom to 7000</td>
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### RECENT DEVELOPMENTS

- Addressing stochastic uncertainty in the comparison of costs and effects
- Analyzing cost data for cost-effectiveness analysis
- Assessing the generalizability (i.e., homogeneity) of the comparison of costs and effects in different settings (e.g., different systems of care or different countries)

#### ADDRESSING STOCHASTIC UNCERTAINTY AND SAMPLE SIZE FOR ECONOMIC QUESTIONS

- Prior to early 1990’s, clinical economists did not have an answer to questions about stochastic uncertainty related to cost-effectiveness ratios
  - Could express this uncertainty for the numerators and denominators of the ratios separately
  - For the ratio, however, we usually said that we evaluated uncertainty using sensitivity analysis
- Since that time there has been rapid development of methods for assessing this uncertainty
  - Confidence intervals for cost-effectiveness ratios
    - Fieller’s theorem (potentially undefined)
    - Nonparametric bootstrap (potentially undefined)
  - Other approaches
    - Acceptability curves (evaluates the probability that the ratio is acceptable)
    - Net benefits (transforms the ratio in a way that its ratio is always defined)
CURRENT STATE OF THE ART

! Develop and test hypotheses about cost-effectiveness ratios

- E.g., the incremental ratio of therapy X compared with therapy Y will be lower than $Z per QALY (where Z represents one’s estimate of the acceptable upper limit for the confidence interval, referred to as the ceiling ratio)

! Test these hypotheses by determining whether the net monetary benefits (NMB) calculated using a ceiling ratio of Z are significantly greater than 0 (or whether the limits of the confidence interval around the cost effectiveness ratio are acceptable)

NET MONETARY BENEFITS

! A composite measure (part cost-effectiveness, part cost-benefit analysis), usually expressed in dollar terms, which is derived by rearranging the following decision rule:

\[
CR > \frac{(Costs_1 - Costs_2)}{(Outcomes_1 - Outcomes_2)}
\]

where \( CR = \) ceiling ratio (e.g., $60,000)

! Most commonly expressed as what may be called net monetary benefits

\[
(CR \times (Outcomes_1 - Outcomes_2)) - (Costs_1 - Costs_2) > 0
\]

! All else equal, one should adopt programs with net monetary benefits that are greater than 0 (i.e., programs with incremental cost effectiveness ratios that are less than the ceiling ratio)

ADVANTAGES OF USE OF NMB FOR EVALUATING STOCHASTIC UNCERTAINTY

! NMB a continuous variable like age, height, or weight, with a relatively normal distribution

! When each patient contributes an estimate of total costs and outcome to the analysis (e.g., when one is not using techniques to account for censored data), NMB can be calculated -- and tested statistically -- as a difference in per-patient means

! Variance (and thus the CI) of NMB is well defined

\[
VAR(NMB) = s_C^2 + s_E^2 - 2 R_C D s_C s_E
\]

where \( s_C \) and \( s_E \) equal the standard error of the mean difference in costs and effects, respectively; \( R_C \) equals the ceiling ratio (e.g., $40,000 per QALY); and \( D \) is the correlation between the difference in costs and effects

IMPLICATIONS FOR SAMPLE SIZE DETERMINATION

! The ability to develop and test hypotheses about economic value of new therapies has led to changes in methods for estimating sample size for such evaluations

! Prior to the development of the literature that described confidence intervals for cost-effectiveness ratios, a common approach was to base sample size on the larger of the sample sizes needed for estimating pre-specified cost and effect differences

- i.e., what sample size was required to identify a $1000 difference in costs, and what was required to identify a 10% reduction in mortality
SAMPLE SIZE FOR ECONOMIC QUESTIONS

Once the literature on confidence intervals developed, however, it became clear that the goal of economic evaluations in trials was to determine the likelihood that the therapy represented good value for the cost.

Current sample size methods base their calculations on the number of study subjects needed to rule out unacceptably high upper confidence limits for the cost-effectiveness ratio (equivalently, to rule out that the net monetary benefits of the intervention are less than 0).

E.g., sample size for NMB uses the standard formula for continuous variables

\[
n = \frac{2\sigma^2 (1 - R^2)(\frac{z_{\alpha/2} + z_{\beta/2}}{\Delta NMB})^2}{\Delta NMB^2}
\]

where \( \Delta NMB \) equals the difference in mean NMB between the therapies; \( F^2 \) equals the variance; and \( R^2 = \) variance explained by other covariates in OLS (assuming OLS is used to predict the difference).

INFORMATION REQUIRED TO ESTIMATE SAMPLE SIZE FOR ECONOMIC QUESTION

The newer methods generally require more information than is needed for estimating sample sizes for clinical outcomes or for cost differences alone.

Basic data for such calculations include the magnitude of the incremental costs and outcomes one expects to observe in the trial; the standard deviations for costs and outcomes in each of the treatment groups; and the correlation between costs and outcomes.

CORRELATION BETWEEN COSTS AND EFFECTS

Correlation between costs and effects can have dramatic effects on the confidence interval for the cost effectiveness ratio.