Cost-Effectiveness History

- Traditionally used decision analytic models – decision trees, Markov models -- to assess cost-effectiveness of medical interventions
- In past 20 years, has been a growth in evaluating cost-effectiveness as part of RCTs

Cost-Effectiveness History (II)

- Evaluation in RCTs has led to rapid improvements in statistical interpretation of cost-effectiveness
  - First report on methods for calculating confidence intervals for cost-effectiveness ratios published in 1994
  - “Modern” methods for calculating sample size and power introduced in late 1990’s
Good Value for the Cost

- Primary economic message often supported by use of an evaluation from a randomized trial that included economic outcomes as primary or secondary endpoints
  - Short-term economic impacts directly observed; for chronic conditions, longer term impacts potentially projected by use of decision analysis
  - Reported results: point estimates and confidence intervals for estimates of incremental costs, outcomes, and the comparison of costs and effects
  - Impact of sensitivity analysis on the comparison of costs and effects judged by its impact on both the point estimates and the confidence intervals of the ratios

Example

<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 Dom to 6650
- Survival benefit: -33% Dominates Dom to 9050
- +33% Dominates Dom to 5800
- Hospitalization costs: -50% Dominates Dom to 5300
- +50% Dominates Dom to 8400
- Drug costs: -50% Dominates Dom to 4850
- +50% Dominates Dom to 8750
- Discount rate: 0% Dominates Dom to 6350
- 7% Dominates Dom to 7000

Trials and Models

- Complementary, not in opposition
- Trials have advantages that:
  - Outcomes are directly observed
  - Document existing relationships in all their complexity, with fewer required simplifying assumptions
- Trials have disadvantages that:
  - Usually performed in specialized populations, specialized settings, with mandated care that need not reflect usual practice
  - Don’t always follow patients for full episode of care
Outline

- Steps in economic evaluation
- The gold standard and its tensions
- 3 strategic issues

Steps in Economic Evaluation

Step 1: Quantify the costs of care
Step 2: Quantify outcomes
Step 3: Assess whether and by how much average costs and outcomes differ among the treatment groups
Step 4: Compare magnitude of difference in costs and outcomes and evaluate “value for costs” (e.g. by reporting a cost effectiveness ratio, net monetary benefit, or the probability that the ratio is acceptable)
- A hypothesis that might be tested in such a study is that the ratio of the cost per quality-adjusted life year saved is significantly less than $60,000
Step 5: Evaluate stochastic uncertainty and perform sensitivity analysis

Ideal Economic Evaluation Within a Trial

- Is conducted in naturalistic settings, compares the therapy with other commonly used therapies, and studies the therapy as it would be used in usual care
- Performed with adequate power to assess the homogeneity of results in the wide range of clinical settings and among the wide range of clinical indications in which the therapy will be used
- Designed with an adequate length of follow-up to assess the full impact of the therapy
- Conducted within a time frame that allows the resulting information to inform important decisions in the adoption and dissemination of the therapy
Ideal Economic Evaluation Within a Trial (II)
• Measure all costs of all participants prior to randomization and for the duration of follow-up
  – Costs after randomization—cost outcome
  – Costs prior to randomization—potential predictor
• Independent of the reasons for the costs
• Most feasible when:
  – Easy to identify when services are provided
  – Service/cost data already being collected
  – Ready access to data

Difficulties Achieving an Ideal Evaluation
• Potential difficulties in meeting these goals within trials
  – Settings often controlled; comparator isn’t always the most commonly used therapy; investigators haven’t always learned fully how to use the new therapy under study
  – In some cases, sample size required to answer economic questions is greater than sample size required for clinical questions
  – In some cases, ideal length of follow-up required to answer economic questions is longer than follow-up necessary to answer clinical questions

Trade-off
• These trials may be the only source of information needed for important early decisions about the adoption and diffusion of the therapy
• TRADE-OFF: Ideal vs best feasible
Three Strategic Issues
1) What preplanning should be done in preparation for the trial?
2) What medical service use (also referred to as resource use) should one measure?
3) How naturalistic should the study design be?

What Preplanning?
• Estimate means, variances, and correlations for costs, health-related quality of life, and preferences
• Identify the types of medical services used by study participants
• Identify an appropriate length of follow-up for economic endpoints
• Pilot test data collection instruments and procedures
• Gauge levels of patient interest in the study

Estimating Means, Variances, and Correlation
• Used for sample size estimation
• Goal of sample size for economic evaluation:
  – Determine the likelihood that a therapy represents good value for the cost
  ► Number of study participants needed to rule out unacceptably high cost-effectiveness ratios or net monetary benefit less than 0
• Stata Programs:
  http://www.uphs.upenn.edu/dgimhsr/stat%20samps.htm
What information?

- Generally require more information than is needed for estimating sample sizes for clinical outcomes or for cost differences alone
  - Magnitude of the difference in costs and outcomes one expects to observe
  - Standard deviations for costs and outcomes in each treatment group
  - One's willingness to pay for health
  - Correlation between costs and outcomes

Correlation Between Costs and Effects

Correlation Between Costs and Effects

Power and the Joint Outcome of Cost and Effect

- What would your clinical colleagues conclude about this therapy's clinical effectiveness?
- Your economic colleagues about whether it saves costs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SE</th>
<th>T</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>20</td>
<td>776</td>
<td>0.26</td>
<td>0.98</td>
</tr>
<tr>
<td>QALY</td>
<td>.04</td>
<td>.0224</td>
<td>1.786</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Appropriate Length of Follow-up

Migraine Costs

Cost per day ($) vs. Days


What Medical Service Use?

- Real/perceived problems:
  1. Don’t have sufficient resources to track all medical service use
  2. In some cases, don’t expect to affect all medical service use, just that related to the disease in question
- Implication: given sample size in trial, collection of all medical services, independent of the reason for these services, may swamp the “signal” with “noise”

→ Why not limit data to disease-related services?

Limit Data to Disease-Related Services?

- Little if any evidence exists about the accuracy, reliability, or validity of such judgments
- Easy for judgments to be flawed
  - Investigators routinely attributes AEs to the intervention, even when participants received vehicle/placebo
  - In many cardiovascular trials both “related” hospitalizations (e.g., heart failure) and “unrelated” hospitalizations are affected by intervention
- Potential biases more of a problem in unblinded studies, but need not “balance out” in double-blinded studies
Measure As Many Services As Possible

- Measure services that make up a large portion of the difference in treatment between patients randomized to the different therapies under study
  - Provides an estimate of the cost impact of the therapy
- Measure services that make up a large portion of the total bill
  - Provides a measure of overall variability
  - Minimizing unmeasured services reduces the likelihood that differences in measured services will be biased

General Recommendations

- Identify a set of medical services one will collect, and assess them any time they are used, independent of the reason for their use
- If data collection is limited to a single page in the CRF:
  - Collect big-ticket items, (e.g., hospitalization, long term care, etc); don’t sweat smaller ticket items
    - Heart failure: hospitalization costs, number of outpatient visits
    - Hospitalized infections: ICU, stepdown, and routine care days; major procedures
    - Asthma: ED visits, Hospitalizations, comedications

Better Approach

- Decisions improved if one documents the types of services used by patients who are similar to ones who will be enrolled in the trial
  - Review medical charts or administrative data sets
  - Survey patients and experts about the kinds of care received
  - Have patients keep logs of their health care resource use
Decisions about the services to measure should take into account the expense of collecting particular data items

How Naturalistic
• Primary purpose of economic analysis is to inform real-world decision makers about how to respond to real-world health care needs
• Thus, the more naturalistic the trial, the more likely the results from the trial will speak to the decision question
  – Type of participants enrolled
  – Intention to treat
  – Limiting loss to follow-up
  – Limiting protocol-induced services

Protocol-Induced Services
• Common reaction is to exclude costs of these services
  – Rationale: Wouldn’t be done in usual care
• However:
  – In their simplest form, exclusion of protocol-induced services is not particularly important
  – In their most pernicious, exclusion is impossible
Simple Protocol-Induced Services

- Maneuver given to everyone that has little or no impact on clinical care of patient
  - Represents the simple addition of a constant
  - If maneuver would have been performed in some participants but not others, the fact that the services are mandated for everyone biases toward the null, because can no longer observe a difference that might have existed

Pernicious Protocol-Induced Services

- Active monitoring (e.g., for DVT) can lead to:
  - Earlier detection of outcomes at a less severe stage of outcome
    - Potentially with lower costs
    - Detection of more outcomes than would have been detected in usual care
      - With attendant increase in costs
  - Simply “excluding” these protocol-induced services and their impact on cost and outcome is impossible

Pernicious Protocol-Induced Services (II)

- Mandating treatment in excess of what would be provided in usual care
  - Leads to observation of costs in excess of what would be routinely incurred for the less effective therapy
  - Impact depends on whether “excess” services are cost-effective or not
    - If no, biased against the less effective therapy
    - If yes, biased toward this therapy
Discussion

- Clinical trials may provide the best opportunity for developing information about a medical therapy’s value for the cost early in its product life.
- When appropriate types of data are collected and when they are analyzed appropriately, these evaluations can provide data about uncertainties related to the assessment of the value for the cost of new therapies that may be used by policy makers, drug manufacturers, health care providers and patients when the therapy is first introduced in the market.

Additional Slides

Economic Messages

- Economic studies may convey a number of potential messages, which depend in part on the:
  - The disease and therapy under evaluation
  - The other therapies that are available to treat the condition
  - Interests of regulatory bodies, providers, payers, and patients
- Primary economic message
  - The therapy is “good value for the cost”
• Different study designs are available to support different messages
  – Clinical trials, decision analytic models, and observational studies can be used to support messages about value for the cost

Study Designs For Supporting Economic Messages

Design Issues Not Unique To Trials

• A number of design issues apply equally to economic evaluations that are incorporated within clinical trials and to other economic evaluations:
  – The type of analysis that will be conducted (e.g. cost-benefit, cost-effectiveness, or cost minimization analysis)
  – The types of costs that will be included (e.g. direct medical, direct nonmedical, productivity, and intangible)
  – The perspective from which the study will be conducted
• These issues have been well addressed in the literature