Good Value for the Cost

• Economic data collected as primary or secondary endpoints in randomized trials are commonly used in the evaluation of the value for the cost of medical therapies
  – Short-term economic impacts directly observed; 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

Outline

• Steps in economic evaluation
• Strategic issues
  – What medical service use should one collect?
  – How naturalistic should the study design be?
  – What is the appropriate sample size?
  – What is the likelihood that the cost-effectiveness ratio observed in the trial describes longer term therapy?
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 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: Perform sensitivity analysis

Ideal Economic Evaluation Within a Trial

- 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

Issue #1: What Medical Service Use Should One Collect?

- 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
  - Minimizing unmeasured services reduces the likelihood that differences among them will lead to biased estimates
  - Provides a measure of overall variability
Measure as Much as Possible

• The best approach is to measure as many services as possible
• General Strategy: Identify a set of medical services one will collect, and assess them any time they are used, independent of the reason for their use
• There are no a priori guidelines about how much data are enough, nor are there data on the incremental value of specific items in the economic case report form
• Decisions about the services to measure should take into account the expense of collecting particular data items

Document Likely Service Use During Trial Design

• 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
• Guard against possibility that new therapy will induce medical service use that differs from current medical service use

Other Types of Costs?

• Other types of costs that sometimes are documented within economic evaluations include:
  – Time costs: Lost due to illness or to treatment
  – Intangible costs
• Types of costs that should be included in an analysis depend on what is affected by illness and its treatment and what is of interest to decision makers
  – e.g., the National Institute for Clinical Excellence (U.K.) and the Australian Pharmaceutical Benefits Scheme has indicated they are not interested in time costs
Specific Recommendations, Which Services?

- Identify common patterns of medical service use in centers/countries that will participate in the trials
  - Speak with experts in multiple centers
  - Focus groups, etc.
- Design case report forms to collect important, common medical service use
- Collect the services independent of the reason for their use
- Pilot test the forms
- Consider collecting costs other than medical service use

Issue #2. How Naturalistic Should The Study Design Be?

- The primary purpose of cost-effectiveness analysis is to inform real-world decision-makers about how to respond to real-world health care needs
- Thus, the more naturalistic the trial, in terms of participants, analysis based on the intention to treat, and limitation of loss to follow-up, the more likely the data developed within the trial will speak directly to the decision question

Naturalism: Intention-To-Treat Analysis

- Economic questions relate to treatment decisions (e.g., whether to prescribe a therapy), not whether the patient received the drug prescribed nor whether, once they started the prescribed drug, they were switched to other drugs
  - Implication: costs and effects associated with these later decisions should be attributed to the initial treatment decision
- Thus, trial-based cost-effectiveness analyses should adopt an intention-to-treat design
Naturalism: Loss to Follow-up

• Trials should be designed in such a way that they minimize the occurrence of missing data
  – For example, study designs should include plans to aggressively pursue subjects and data throughout the trial
  – One recent long-term study of treatment for bipolar disorder was designed from the outset to respond to missed interviews by:
    1) intensive outreach to reschedule the assessment, followed by
    2) telephone assessment, followed by
    3) interview of a proxy who had been identified and consented at the time of randomization

• Investigators should also ensure that:
  – Follow-up continues until the end of the study period
  – Data collection should not be discontinued simply because a subject reaches a clinical or treatment stage such as failure to respond (as, for example, happens in some antibiotic, cancer chemotherapy, and psychiatric drug trials)
  • Given that failure often is associated with a change in the pattern of costs, discontinuation of these patients from the economic study is likely to bias the results of an economic evaluation that is conducted as part of the trial

Specific Recommendations, Naturalism

• Use the intention to treat sample for the economic analysis
• Be aggressive in maintaining follow-up, including continuing to collect data on those who fail or switch therapy
• Use appropriate analytic to address missing data if and when they occur
• To the extent possible in a registration trial, minimize the effect of the protocol on patient care
Issue #3. What is the Appropriate Sample Size to Address Economic Questions?

- Economic sample size calculations are based on the number of study subjects needed to rule out that the therapy is unacceptable (equivalently, to ruling out that the net monetary benefits of the intervention are less than 0)

\[ n = \frac{(\alpha + \beta)^2 \left[ 2 \, sd^2 + 2 \, W^2 \, sd^2 - 2 \, W \, (2sd)^{1.5} \times (2sd)^{1.5} \right]}{(W \, Q - \Delta C)^2} \]

where \( n \) equals n/group; \( sd \) = the standard deviation for costs (c) and effects (q); \( W \) equals the maximum willingness to pay one wishes to rule out; and \( \rho \) equals the correlation of the difference in cost and effect.

Correlation Between Costs and Effects

- All else equal, the required sample size is less when the therapies have a Win/Lose (positive) correlation
  - As the effectiveness increases, the cost increases (e.g., stroke care)
- All else equal, the required sample size is greater when the therapies have a Win/Win (negative) correlation
  - As the effectiveness increases, the cost decreases (e.g., asthma care)
- Extreme values of correlation between costs and effects can have dramatic effects on the confidence interval for the cost effectiveness ratio/NMB and thus on the sample size required to demonstrate value for the cost.

Maximum Willingness to Pay and Identification of an Appropriate Outcome Measure

- The sample size calculations described above assume that we have an idea about what we would like to pay to obtain a unit of outcome
- In many medical specialties, researchers use disease specific outcomes
- While one can calculate a cost-effectiveness ratio for any outcome one wants (e.g., cost/case detected or cost/additional abstinence day), to be convincing that a new, more costly and more effective therapy is good value, the outcome must be one for which we have recognized benchmarks of cost effectiveness
  - Argues against use of too disease-specific an outcome for economic assessment.
Specific Recommendations, Sample Size

- If home testing is both clinically equivalent to and less expensive than in lab testing, a “disease-specific” outcome such as cases detected may be sufficient (depending on “how equivalent” it is)
- If home testing is less effective and less expensive, one needs to know the value of the lost effectiveness so that it can be compared with the cost savings
  - Requires that we either know what it is worth to detect a case or that we use a more general health outcome such as QALYs
- Sleep apnea research at a disadvantage because the cost-effectiveness of diagnosis of sleep apnea has not been well established experimentally (i.e., no event trials)

Issue #4. What Is The Likelihood That The Cost-effectiveness Ratio Observed In The Trial Describes Longer Term Therapy?

- When the trial observes cost-effectiveness for a time-limited period (e.g., 2 or 3 years), but the therapy will be taken for lifetime, one should consider the likelihood that the cost-effectiveness ratio observed in the trial will describe longer term therapy
  - Referred to as a time by treatment interaction

Likelihood of a Time By Treatment Interaction

- Time by treatment interaction less likely to be substantial when the intervention’s cost and outcome begin at approximately the same time and continue to be incurred together over time (e.g., drug therapy for heart failure)
- Interaction more likely to be substantial when:
  - Treatment cost and outcome incurred over time, but outcome delayed for a number of years (e.g., risk reduction from cholesterol-modifying therapy) OR increasing with time
  - Treatment cost incurred initially (e.g., surgical removal of tumor) and outcome (e.g., survival) accrued over time
Addressing a Time By Treatment Interaction

- Evaluate what was observed during the trial (within-trial analysis)
- Develop decision analytic models to make projections beyond the period of observation (projection)

Specific Recommendations, Treatment by Time Interaction

- Evaluate whether a strong treatment by time interaction is expected
- If yes, consider development of a decision model to assess the potential magnitude of the interaction
  - Substantial amounts of the data used for the decision model should be derived from the trial
  - Where necessary, augment data from the trial with epidemiologic data on long term outcomes, etc.

Summary

- Clinical trials may provide one of the best opportunities for developing information about a medical therapy’s value for the cost
- 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
Further reading: