Outcomes Research

- Evaluates outcomes of medical therapies (potentially including costs) and their impacts on people, organizations, and society
- Therapies can include drugs, devices, procedures, or broader programmatic or system interventions
- Outcomes can include mortality, morbidity, functional status, mental well-being, other aspects of health-related quality of life, cost, etc.
Pharmacoconomics

• Outcomes research specifically focused on economic outcomes of pharmaceuticals
• Multidisciplinary methods
  – Medicine
  – Pharmacy
  – Economics
  – Decision sciences
  – Operations research
  – Statistics / biostatistics
  – Other social sciences

Pharmacoeconomic Messages

• Therapy is good/bad value
• Budget impact
• Burden of illness
  – Often flag waving: “This disease is important…”
• Specific messages addressed depend in part on:
  – Disease and therapy under evaluation
  – Other therapies available to treat condition
  – Interest of regulatory bodies, providers, payers, and patients
Pharmacoeconomic Study Designs

- Clinical trials
  - Economic evaluation in clinical trials widespread
  - Little to no selection bias, but potential issues of generalizability
- Observational studies
  - Often more generalizable, but problems with selection bias
- Decision models
  - Often used to address pressing questions for which direct data are not available
  - Shares strengths and weaknesses of source data
  - Added uncertainties related to combining data from multiple sources and projection beyond the data

Decision Models

- Most frequent pharmacoeconomic study design
- While a number of different model structures can be used, two most common are:
  - Decision trees
  - Markov models

Decision Trees

- "Models" that use a tree-like structure to organize thoughts and data about problems (e.g., treatment decisions) and their consequences
- Characterized by decisions, chances, and outcomes
- Results based on probabilities and "rewards" for outcomes
- Time usually not directly modeled in decision trees
Prophylaxis for Chlamydia Trachomatis Infection

Markov Models
- Repetitive decision trees used for modeling conditions that have events that may occur repeatedly over time or for modeling predictable events that occur over time (e.g., screening for disease at fixed intervals) – e.g., Cycling among heart failure classes or screening for colorectal cancer
- Use of Markov models simplifies presentation of tree structure
- Markov models explicitly account for timing of events

Markov Model, NYHA Class and Death

Heart Failure Model
Pharmacoeconomics Methods Overview

Economic Evaluation Methods Overview
- Types of analyses
- Types of outcomes
- Perspective
- Steps in economic evaluation

Types of Analysis
Types of Analysis

• Cost identification
• Cost-effectiveness / cost-utility
• Cost-benefit

Generally distinguished by:
  – Outcomes included: e.g., costs alone vs costs and effects
  – How outcomes are quantified: e.g., as money alone or as health and money

Cost-Identification / Cost-minimization

• Estimates difference in costs between therapies, but not difference in other outcomes
• Commonly conducted when no difference observed in effectiveness
  – “As no statistical significant difference among the mean QALYs gained with the different hormonal therapies was detected (p = 0.12), CUA was replaced by a cost minimization analysis.”
  

• Appropriate solely when two therapies of equal efficacy are compared

Death of Cost-Identification?

• Old version: If two therapies' effects are identical, adopt cheaper of two therapies
  – Effect maximization corollary: If two therapies' costs are identical, adopt more effective of two
• New version: Because we generally can't conclude two therapies are identical (at most we fail to reject null hypothesis), cost-minimization analysis is unlikely to ever be appropriate
  – Substitute cost-effectiveness or cost-benefit analysis
**Cost-Effectiveness Analysis**

- Estimates differences in costs and differences in outcomes between interventions
  - Costs and outcomes measured in different units
- Incremental cost-effectiveness ratio
  
  \[
  \frac{\text{Costs}_1 - \text{Costs}_2}{\text{Effects}_1 - \text{Effects}_2}
  \]

- Results meaningful in comparison with:
  - Predetermined threshold/cut-off for willingness to pay
    - e.g., $50k-$100k / QALY or £20k-£30k / QALY
  - Other accepted and rejected interventions (league tables)

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**Cost-Utility Analysis**

- Costs and Outcomes measured in different units AND outcomes expressed in units of utility (e.g., QALYs)
- Referred to either as a fourth type of analysis or as a subset of cost-effectiveness analysis

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**Cost-Benefit Analysis**

- Estimates differences in costs and differences in benefits in same (usually monetary) units
- As with cost-effectiveness, requires a set of alternatives
- Net benefit is preferred expression cost-benefit result
  
  \[
  \text{(Benefit}_1 - \text{Benefit}_2) - (\text{Cost}_1 - \text{Cost}_2)
  \]
Review

- Investigators compared 2 treatments, “LessCost” and “MoreCure”
- They found that “LessCost” was less expensive and recommended its adoption by physicians
  - 100,000 vs 300,000

- What type of economic analysis are the investigators carrying out?
- Do you agree with their conclusion?

Example 2

- Investigators compared 2 treatments, “LessCost” and “MoreCure.” They observed the following:

<table>
<thead>
<tr>
<th></th>
<th>LessCost</th>
<th>MoreCure</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>100,000</td>
<td>300,000</td>
<td>-200,000</td>
</tr>
<tr>
<td>Benefit</td>
<td>100,000</td>
<td>500,000</td>
<td>400,000</td>
</tr>
</tbody>
</table>

- The authors concluded that MoreCure is net beneficial.

- What type of economic analysis are the investigators carrying out?
- Do you agree with their conclusion?

Example 3

- Investigators compared 2 treatments, “LessCost” and “MoreCure.” They observed that MoreCure cost 200,000 more than LessCost and provided 8 additional QALYs, i.e., 25,000 per QALY

- The authors recommended that MoreCure was good value for the cost

- What type of economic analysis are the investigators carrying out?
- Do you agree with their conclusion?
Types of Costs

- Direct: medical or nonmedical
- Time costs: Lost due to illness or to treatment
- Intangible costs

Types of costs included in an analysis depend on:
- What is affected by illness and its treatment
- What is of interest to decision makers
  - e.g., a number of countries’ decision makers have indicated they are not interested in time costs

What Effectiveness Measure?
What Effectiveness Measure?

- Can calculate a ratio for any outcome
  - Cost per toe nail fungus day averted
- For cost-effectiveness ratios to be an informative, must know willingness to pay for outcome
  - In many jurisdictions, quality-adjusted life year (QALY) is recommended outcome of cost-effectiveness analysis
- Some resistance to this outcome, particularly from U.S. Congress
  - [PCORI] “shall not develop or employ a dollars per quality adjusted life year (or similar measure that discounts the value of a life because of an individual’s disability) as a threshold to establish what type of health care is cost effective or recommended”

QALYs

- Economic outcome that combines preferences for both length of survival and quality into a single measure
- Help us decide how much to pay for therapies that:
  - Save fully functional lives/life years
    VS
  - Save less than fully functional lives/life years
    • e.g., heart failure drug that extends survival, but extra time spent in NYHA class III
    VS
  - Don’t save lives/life years but improve functioning
    • e.g., heart failure patients spend most of their remaining years in class I instead of class III

QALY Scores

- QALY or preference scores generally range between 0 (death) and 1 (perfect health)
  - E.g., health state with preference score of 0.8 indicates that year in that state is worth 0.8 of year with perfect health
  - There can be states worse than death with preference scores less than 0
Prescored Health State Classification Instruments

- Dominant approach for QALY measurement uses prescored health state classification instruments (indirect utility assessment)
- Participants' report their functional status across a variety of domains
- Preference scores derived from scoring rules that have usually been developed by use of samples from the general public

Prescored Instruments

- A number of prescored instruments are currently available for measuring preference scores for current health
  - EuroQol instrument (EQ-5D), 3 and 5 level
  - Health Utilities Index Mark 2 (HUI2)
  - Health Utilities Index Mark 3 (HUI3)
  - SF-6D
  - etc.
- Most instruments ask participants or their proxies to report on the health status of the patient

EQ-5D, HUI2, HUI3, and SF-6D

- EQ-5D, HUI2, HUI3, and SF-6D are 4 most commonly used prescored preference assessment instruments
- All 4 share features of ease of use
  - e.g., high completion rates and the ability to be filled out in 5 min or less
- All used to assess preferences for wide variety of diseases
- Extensive evidence that their scores differ, but little evidence that one is better than another
Perspective

Study Perspective
- Economic studies should adopt 1 or more “perspectives”
  - Societal
  - Payer (often insurer)
  - Provider
  - Patient
- Perspective helps identify services that should be included in analysis and how services should be cost out
  - e.g., patient out-of-pocket expenses may be excluded from insurer perspective
  - Not all payments may represent costs from societal perspective

Willingness to Pay
Willingness to Pay and Identification of an Appropriate Outcome Measure

- Can calculate a cost-effectiveness ratio for any outcome (e.g., cost/case detected; cost/abstinence day)
- To be informative, outcome must be one for which we have recognized benchmarks of cost-effectiveness
- In many countries, no general agreement on willingness to pay for commonly accepted outcomes such as quality-adjusted life years
- Greater uncertainty for disease-specific outcomes
- Argues against use of too disease-specific an outcome for economic assessment

Steps in Economic Evaluation

1. Quantify costs of care
2. Quantify outcomes
3. Assess whether and by how much average costs and outcomes differ among treatment groups
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 probability that ratio is acceptable
   - Potential hypothesis: Cost per quality-adjusted life year saved significantly less than $75,000
5. Perform sensitivity analysis
Sample Results Table

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Point Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental Cost</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>
<tr>
<td>Cost-Effectiveness Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Principal Analysis</td>
<td>Dominates</td>
<td>Dom to 6650</td>
</tr>
<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>Drug Cost</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>
</tr>
</tbody>
</table>

What Data / When?

- Phases I and II
  - Incidence and prevalence-based burden of illness
    - Incidence-based - lifetime costs of the disease for a cohort with incident disease
    - Prevalence-based - costs of disease during a given time period for prevalent cases
  - Natural history modeling
  - Preplanning for phase III economic studies
Phase III

- Cost / Efficacy studies in clinical trials
  - Provides economic data for registration, pricing, and early use
- Decision modeling of impacts of intervention
- Budget impact studies

Phase IV

- Cost / Effectiveness studies in usual care
  - Comparisons made in more realistic settings with more realistic protocols against comparators of interest to individual decision makers
  - Allow decision makers to assess whether economic results from phase III trials are generalizable to usual care
- Decision modeling of impacts of intervention
- Post marketing surveillance studies
  - Observational data to evaluate costs, effectiveness, and adverse experiences related to the drug

Who is Listening?
Who is Listening

- PE Recommendations/Guidelines (Partial list)
  - Australia
  - Austria
  - Baltic countries
  - Belgium
  - Brazil
  - China
  - Columbia
  - Cuba
  - Egypt
  - Finland
  - France
  - Hungary
  - Italy
  - Mexico
  - Netherlands
  - Norway
  - Poland
  - Russia
  - South Korea
  - Spain
  - Sweden
  - Taiwan
  - Thailand
  - U.K.

Use in US

- Common Belief: “Pharmacoeconomic data not used in US”
  - NIH expert guideline panels and Environmental Protection Agency can and do use
  - Chambers et al.: Lack of an estimate of cost-effectiveness associated with a decreased likelihood of Medicare coverage
  - Aspinall et al.: Veterans Health Administration “has emphasized use of cost-effectiveness data, especially for newer, costly drugs.”
  - Neuman and Bliss: 12% of FDA DDMAC warning letters between 2002 and 2011 cite health economic violations
  - Academy of Managed Care Pharmacy guidelines for pharmacoeconomic submissions to formularies

INFLUENCE OF ECONOMIC EVALUATIONS

- Number of studies reporting the influence of economic evaluations on healthcare decision making

<table>
<thead>
<tr>
<th>Degree of influence</th>
<th>&quot;Micro&quot; Physicians</th>
<th>&quot;Micro&quot; MCOs, P&amp;T committees, etc.</th>
<th>&quot;Macro&quot; Nat. deciders, HHS auth. Central formulary, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>2</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Major</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>N, studies</td>
<td>8</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>N, respondents</td>
<td>3766</td>
<td>1436+</td>
<td>1159+</td>
</tr>
</tbody>
</table>

Sources of Pharmacoeconomic Data

• Self generation by local experts
  – ISPOR chapters
• Multinational trials
• International collaborations between local scientists and scientists in other countries
  – NICE International
• Data borrowed from elsewhere
  – Transferability

Pichon-Riviere: Latin America Transferability Survey

<table>
<thead>
<tr>
<th></th>
<th>Researchers</th>
<th>Decision Makers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferability of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic Evaluation</td>
<td>6.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Budget Impact</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Barriers to Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare cost differences</td>
<td>6.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Epidemiology differences</td>
<td>6.1</td>
<td>7.5</td>
</tr>
<tr>
<td>Health care system diff</td>
<td>6.5</td>
<td>7.8</td>
</tr>
</tbody>
</table>

1 = not useful/less transferable; 10 = very useful/more transferable

Summary

- International use of pharmacoeconomic data growing
  - Improve value of healthcare
  - Manage healthcare budgets
- Multidisciplinary science: medicine, pharmacy, economics, decision sciences
- General methods well developed, but some areas – such as how best to transfer data across settings – still undergoing development
- Opportunities for data collection available throughout the drug development process
- International need for education of researchers, decision makers, and the general public