Other Designs in Biomedical Research: An Introduction to Pharmacoconomics and Economic Evaluation

PHARM 309
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Objectives

• Introduce some of the basic concepts of economic evaluation.
• Illustrate how evidence is used in economic evaluation, and particularly the role of modelling.

Agenda

• Why are we doing more economic evaluation?
• Demystifying pharmacoconomics
• Role of evidence and modelling: GUSTO Case Study
• Users' Guide to Medical Literature
Percent of GDP Spent on Health, 2003

Source: OECD, 2005

Health Spending per Capita ($PPP), 2003

Source: OECD, 2005

Drugs as Percent of Total Health Spending, 2003

Source: OECD, 2005
Pharmaceutical (and Other Medical Nondurable) Spending per Capita ($PPP), 2000

Real Annual Growth in GDP (gray), Health Spending per Capita (yellow), and Drug Spending Growth (red), 1991-2001


- % GDP to health spending: US—15% in 2003 vs. 8.5% OECD
- Per capita spending: US—$5,267 vs. $2,193 OECD median
- Hospital beds per 1000: US—2.9 vs. 3.7 OECD median
- Physicians per 1000: US—2.4 vs. 3.1 OECD median
- Nurses per 1000: US—7.9 vs. 8.9 OECD median
- MRI units per 1000: US—8.2 vs. 5.5 OECD median
- CT scanner per mill: US—12.8 vs. 13.3 OECD median
Funding New Products: the Budget Constraint

Reimbursement of a new product must be compatible with:
- Planned growth rate for total budget
- Planned fund allocation for pre-existing products
- Planned funds allocation for other new products deemed reimbursable

There is always a trade-off between price and volumes.

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- Demystifying pharmacoeconomics
- Role of evidence and modelling: GUSTO Case Study
- Users’ Guide to Medical Literature

COST AND OUTCOMES EVALUATION

- Scarcity of resources
- Need to make choices: “opportunity cost”
- Decisions need to be based on comparisons of costs and benefits
- Efficiency is not the same as cost cutting
What is Pharmacoeconomic Research?
A branch of health economics primarily concerned with assessing the cost-effectiveness of drug therapies.
• Identifies and measures all costs and outcomes (clinical, health, quality-of-life, and survival).
  -- goes beyond the safety and efficacy information that has historically been collected for clinical trials
• Compares costs and outcomes of a new drug to those of a standard intervention (which ideally is the intervention most commonly used).
• Assesses the “value for money” of projected outcomes of therapy (e.g... - Go/No go Decisions, Pricing, Strategic Marketing)
Pharmacoeconomic Modelling of Drug Therapies:

Key Outcomes

Treatment Comparison:
- Clinical/Epidemiological
- Pharmacoeconomic

Efficacy

Drug Therapy A
- Efficacy
- Quality of Life

Drug Therapy B
- Safety
- Survival Benefit

Types of Pharmacoeconomic Analyses

<table>
<thead>
<tr>
<th>Method of Analysis</th>
<th>Cost Measurement</th>
<th>Outcome Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-Consequences</td>
<td>$</td>
<td>Multidimensional listing of outcomes</td>
</tr>
<tr>
<td>Cost-Minimization (CMA)</td>
<td>$</td>
<td>Equivalence demonstrated in comparative groups</td>
</tr>
<tr>
<td>Cost-Effectiveness (CEA)</td>
<td>$</td>
<td>“Natural” units (life-year gained, mg/dL blood glucose, mm Hg blood pressure, single outcome</td>
</tr>
<tr>
<td>Cost-Utility (CUA)</td>
<td>$</td>
<td>Life years adjusted for quality of life (QALY); multiple outcomes</td>
</tr>
<tr>
<td>Cost-Benefit (CBA)</td>
<td>$</td>
<td>$; multiple outcomes combined into one value.</td>
</tr>
</tbody>
</table>

Types of Economics / Outcomes Analyses

- **Descriptive**: Cost or Burden of Illness
- **Economic Evaluations**:
  - Cost-consequences analysis—Descriptive
  - Cost-minimization analysis—Equal outcomes
  - Cost-effectiveness analysis—Clinical outcomes
  - Cost-utility analysis—QALY outcomes
  - Cost-benefit analysis—Monetary outcomes
  - Budget impact analysis—Aggregate net cost impact
- **Patient-Reported Outcomes Assessments**
  - Health Profile—domains of quality of life
  - Preferences, satisfaction, compliance, convenience
Cost-Benefit Analysis or Cost-Effectiveness Analysis?

- Problem is measuring the benefits
  » Ideally benefits measured in same units as costs
  » But very difficult to reveal consumer valuations in terms of “Willingness to Pay”
- Cost-Effectiveness Analysis is the practical solution
  » Benefits made comparable in physical units and/or utility metric
  » Financial streams incorporated in monetary units
  » Allows comparison between alternative technologies

Cost-Effectiveness Analysis (CEA) and the Incremental CE Ratio (ICER)

- CEA in health care is about comparing two alternatives (1 & 2):
- The ICER = \( \frac{\text{Cost}_2 - \text{Cost}_1}{\text{Outcome}_2 - \text{Outcome}_1} \)
- Costs are measured in monetary units
- Outcomes can be measured in a variety of ways but must be in the same units.

Costs (in the Numerator)

- Direct medical
  » Resources involved in providing medical services to treat a condition and its side effects
  » E.g. days in hospital, surgical procedures, clinic or office visits to physician, drugs, laboratory tests, nursing home days, home health care
- Direct non-medical
  » Non-medical resources used directly in conjunction with medical care consumption
  » E.g. transportation, lodging, modifications to home
- Indirect costs
  » Resource costs associated with illness that indirectly affect societal output
  » E.g. lost productivity and earnings due to morbidity and mortality
Cost-Consequences Analysis: Example

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine</th>
<th>CellCept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rejection Treatment</td>
<td>$6,000</td>
<td>$4,000</td>
</tr>
<tr>
<td>Graft Survival/Dialysis</td>
<td>21,000</td>
<td>19,000</td>
</tr>
<tr>
<td>Drug Cost</td>
<td>1,000</td>
<td>6,000</td>
</tr>
<tr>
<td>CMV Disease</td>
<td>2,000</td>
<td>2,000</td>
</tr>
<tr>
<td>Total First Year Cost</td>
<td>$30,000</td>
<td>$31,000</td>
</tr>
<tr>
<td>Consequences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rejection Rate</td>
<td>48.0%</td>
<td>32%</td>
</tr>
<tr>
<td>1 Year Graft Survival</td>
<td>85.0%</td>
<td>89.0%</td>
</tr>
<tr>
<td>SF-36—Physical Function</td>
<td>71.8</td>
<td>73.8</td>
</tr>
</tbody>
</table>

Cost-Minimization Analysis

- When the treatment outcomes of two alternatives are "identical"?

Examples:
  » brand name drug vs. generic.
  » two drugs in same class

Cost-Effectiveness Analysis

Per 100 Patients

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine</th>
<th>CellCept</th>
</tr>
</thead>
<tbody>
<tr>
<td>total cost</td>
<td>$2,890,000</td>
<td>$2,930,000</td>
</tr>
<tr>
<td># of rejections</td>
<td>48</td>
<td>32</td>
</tr>
<tr>
<td>average ratio</td>
<td>$2,890,000</td>
<td>$2,930,000</td>
</tr>
<tr>
<td>per rejection</td>
<td>$60,000</td>
<td>$85,000</td>
</tr>
<tr>
<td>$1,760 per rej</td>
<td>$91,560</td>
<td>$2,500 per rejection avoided</td>
</tr>
</tbody>
</table>

incremental cost-effectiveness ratio:

```
cost drug A - cost drug B
outcome drug A - outcome drug B
```

```
= $2,890,000 - $2,930,000
= $40,000
= $2,500 per rejection avoided
```
### EXAMPLES OF EFFECTIVENESS MEASURES USED IN COST-EFFECTIVENESS ANALYSES

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Clinical Field</th>
<th>Effectiveness measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logan et al. (1981)</td>
<td>Treatment of hypertension</td>
<td>MmHg blood pressure reduction</td>
<td></td>
</tr>
<tr>
<td>Schulman et al. (1990)</td>
<td>Treatment of hypercholesterolaemia</td>
<td>% serum cholesterol reduction</td>
<td></td>
</tr>
<tr>
<td>Hull et al. (1981)</td>
<td>Diagnosis of deep vein thrombosis</td>
<td>Cases of DVT detected</td>
<td></td>
</tr>
<tr>
<td>Sculpher and Buxton (1993)</td>
<td></td>
<td>Asthma Episode-free days</td>
<td></td>
</tr>
<tr>
<td>Mark et al. (1995)</td>
<td>Thrombosis</td>
<td>Years of life gained</td>
<td></td>
</tr>
</tbody>
</table>

### Cost-Utility Analysis
- Expresses the outcomes in a common metric that can be used for comparing different drugs or technologies
- Benefits captured as “quality-adjusting” life years gained (QALYs).
- There are many theoretical controversies and measurement issues in this field, but QALYs are generally seen as a reasonable, practical measure of utility to the patient.

### Health Rating Scale for Measuring Utility

Two different health situations are described in the boxes below. They are hypothetical / imaginary situations - try to imagine how you would feel in those states. For each situation (A and B) draw a line to a single point on the scale that would reflect how you would rate the situation.

- **Possible/Imaginary Situation A:**
  - Your kidney transplant has been a success:
  - You have plenty of energy and are able to do all you would like in terms of work and leisure activities.
  - etc.

- **Possible/Imaginary Situation B:**
  - Your kidney has failed and you are on dialysis:
  - You often feel tired and sluggish.
  - etc.

- **Possible/Imaginary Situation C:**
  - Your blood sugar levels are well controlled:
  - You feel generally healthy and have no symptoms.
  - etc.

- **Possible/Imaginary Situation D:**
  - Your blood sugar levels are not well controlled:
  - You feel lethargic and have frequent symptoms.
  - etc.

Possible/Imaginary Situation E:
- Your lung function has improved significantly:
- You feel much more active and able to perform daily activities.
- etc.

Possible/Imaginary Situation F:
- Your lung function has not improved:
- You feel short of breath and have difficulty with daily activities.
- etc.
Outcome Measure: QALY
Quantity and Quality Of Life (Area Under The Curve (AUC))

The QALY concept simultaneously captures gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) - 1: full health - 0: death

The Technology Adoption Decision

<table>
<thead>
<tr>
<th>HEALTH OUTCOMES IMPACT</th>
<th>WORSENS</th>
<th>IMPROVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCREASES COST</td>
<td>DON'T ADOPT</td>
<td>?</td>
</tr>
<tr>
<td>DECREASES COST</td>
<td>?</td>
<td>ADOPT (&quot;Dominant&quot;)</td>
</tr>
<tr>
<td>COST IMPACT</td>
<td>Adoption depends on relative size of cost increase vs. the improvement</td>
<td></td>
</tr>
</tbody>
</table>

Adoption unlikely, should depend on relative size of cost savings

Adoption depends on relative size of cost increase vs. the improvement?

The Technology Adoption Decision
(Strategy A Versus Strategy O - Which One To Choose?)

Adapted from Black (1998)
Some Examples of ICER

- Intensive care for seriously ill patients with multiple trauma (460'000 USD / LYG)
- Home dialysis (vs. transplantation) for end-stage renal disease
- Cervical cancer screening every five years for women age 35+ with 3+ kids
- Lovastatin for men age 55-64 with heart disease and <250 mg/dl

Example: Cost per Quality-Adjusted Life Year—Hemodialysis (versus No Treatment)

<table>
<thead>
<tr>
<th>Costs, survival, and quality of life of treating patients with 2 alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs, survival, and quality of life of treating patients with 2 alternatives</td>
</tr>
<tr>
<td>Which treatment would you select?</td>
</tr>
<tr>
<td>Which outcome do you value most?</td>
</tr>
</tbody>
</table>

Applying cost and outcomes assessment to decision making

Cost per Year for Dialysis: $50,000
Quality Adjustment Factor for Dialysis: 0.60
Quality Adjustment Factor for Death: 0.0

C-E Ratio = Incremental Cost / Incremental Benefit

= $50,000 - 0
= 0.6 - 0
= $83,000/QALY
FRAMING THE PROBLEM: PERSPECTIVE AND TIME HORIZON

• Perspective: Viewpoint of study determines which data to collect:
  » Hospital
  » Health Care System
  » Payer
  » Society

• Time horizon of study should be long enough to capture main costs and effects

League Tables, Cost Per QALY Threshold, and (Economic) Value

• League Table
  » Ranking or listing of possible spending options based on cost-utility ratio (i.e., Cost per QALY)

• Cost Per QALY Threshold
  » Cost-Utility Ratio (e.g., £30,000 per QALY; or US$50,000-$173,000) below which most technologies are covered.

• Economic Value
  » Defined as willingness to pay: cost per QALY threshold has been interpreted as Societal WTP or Value

Growth in Published Cost-Utility Analyses, 1976-2001
(from the Harvard Center for Risk Analysis, CEA Registry)

www.hsph.harvard.edu/cearegistry/
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• Users’ Guide to Medical Literature

GUSTO—Clinical Trial Features

• 4 different regimens: t-PA; streptokinase+IV heparin; streptokinase+subcut. heparin;
t-PA+streptokinase.
• total sample=41,021; US sample=23,105; economic study U.S. subsample=2,600.
• Found absolute decrease of 1% in 30-day mortality from all causes to t-PA treated patients.

Clinical Results

<table>
<thead>
<tr>
<th></th>
<th>SK</th>
<th>t-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>mortality</td>
<td>7.3%</td>
<td>6.3%</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>hemorrhagic stroke</td>
<td>0.52%</td>
<td>0.72%</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.030</td>
</tr>
<tr>
<td>mortality/ nonfatal disabling stroke</td>
<td>7.8%</td>
<td>6.9%</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>
t-PA versus Streptokinase

The NNT is 110 and the CNT is $243,000 to save one life.

GUSTO--Economic Substudy Features

- US sample=23,105 (initial hospitalization); telephone follow-up survey subsample=2,600.
- Telephone follow-up at 30 days, 6 months, and 12 months for medical use and quality of life.
- Took “societal” perspective (for costs).
- Performed cost-effectiveness and cost-utility analysis.
- Survival and costs discounted at 5%.
- Medical care costs based on Duke cost accounting system and Medicare payments.
- Long-term survival (to 15 years) projected using Duke cardiovascular registry database.

CEA - Data Collection

- CEA was conducted in a subset of US patients (n=2,600)
- data collected via structured telephone interviews, followed up with source documentation
- time points - 30 days, 6 months, 1 year
- data collection focused on resource utilization and QoL variables
CEA - Modelling Survival

- composite modelling approach
  - one year survival collected directly
  - years 2-15 from Duke Cardiovascular Disease Database
  - period beyond 15 years estimated using survival analysis
  - age, sex, & infarct location used as covariates in survival analysis
- 5% discount rate used

CEA - Cost Analysis

- initial hospitalization costs via Duke cost-accounting system
- follow-up costs to one year via multiplication of average resource utilization and Medicare DRG reimbursement rates for each resource
- no cost differential after first year
- drug acquisition costs from Red Book
- expressed as 1993 US dollars

CEA - Quality of Life

- dual approach used, with battery and utility measurement
- battery included several questionnaires, focusing on different dimensions of QoL
- utility measurement by time tradeoff method
### CEA - Results

<table>
<thead>
<tr>
<th></th>
<th>Non-Drug Costs</th>
<th>Drug Costs</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$ 24,575</td>
<td>$ 320</td>
<td>$ 24,895</td>
</tr>
<tr>
<td></td>
<td>$ 24,990</td>
<td>$ 2,750</td>
<td>$ 27,740</td>
</tr>
<tr>
<td></td>
<td>$ 415</td>
<td>$ 2,430</td>
<td>$ 2,845</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Life Yrs (undis)</th>
<th>Life Yrs (dis)</th>
<th>Cost/LYG (dis)</th>
<th>Utility</th>
<th>QALY (dis)</th>
<th>Cost/QALYG (dis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15.27 yrs</td>
<td>9.50 yrs</td>
<td>$ 32,678</td>
<td>0.90</td>
<td>8.55 yrs</td>
<td>$ 36,402</td>
</tr>
<tr>
<td></td>
<td>15.41 yrs</td>
<td>9.58 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** numbers are rounded off, so CE ratios shown are not exact

### CEA - Sensitivity Analysis

- parameters varied included
  - one year survival
  - long-term survival
  - discount rate
  - cost differences in first year
  - cost differences after first year
  - utilities
  - risk of stroke

### CEA - Conclusion

- league table approach used in interpretation
- concluded that treatment with accelerated t-PA rather than SK “… compares favorably with other therapies whose added medical benefit for dollars spent is judged by society to be worthwhile.”

  - Mark et al. (1995)
t-PA versus Streptokinase: Cost-effectiveness differs by age and location of the infarction

- Inferior MI, age < 40: 0.03 $203,071
- Anterior MI, age < 40: 0.04 $123,609
- Inferior MI, age 40 - 60: 0.07 $74,816
- Anterior MI, age 40 - 60: 0.10 $49,877
- Inferior MI, age 61 - 75: 0.16 $27,873
- Anterior MI, age 61 - 75: 0.20 $20,601
- Inferior MI, age > 75: 0.26 $16,246
- Anterior MI, age > 75: 0.29 $13,410

CONCLUSION:
Some Points to Remember

- Real-world decision-making requires a synthesis of different kinds of evidence.
- Different stakeholders pay different roles in the “system”, have different incentives, and have different needs for evidence and information.
- Increasing demand for economic evaluation
- Payers focus on value for money
- Economics helps but it does not make decisions
- Evidence from trials and the need for models
- Emerging role of pragmatic trials with CE
- Patient-centered outcomes; QOL, utility
- Need for transparency of studies
- Need to educate consumers of studies

Agenda

- Why are we doing more economic evaluation?
- Demystifying pharmacoeconomics
- Role of evidence and modelling: GUSTO Case Study
- Users' Guide to Medical Literature
Clinicians often participate in making clinical policy decisions for large groups of patients. At this level, it’s reasonable to address resource allocation and cost.

Clinical scenario: clinician on hospital’s pharmacy and therapeutics (P&T) committee.

Key Questions for Clinicians about Economic Studies (Drummond et al., JAMA, 1997)

- Are the results valid?
  - Did the analysis provide a full economic comparison of health care strategies?
  - Were the costs and outcomes properly valued and measured?
  - Was appropriate allowance made for uncertainties?
  - Are estimates of costs and outcomes related to the baseline risk in the treatment population?

- What were the results?
  - What were the incremental costs and outcomes of each strategy?
  - Do incremental costs and outcomes differ between subgroups?
  - How much does allowance for uncertainty change the results?

- Will the results help in caring for my patients?
  - Are the treatment benefits worth the harms and costs?
  - Could my patients expect similar health outcomes?
  - Could I expect similar costs?

Table 2: Key Methodological Features (Drummond et al.)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mark et al.</th>
<th>Green et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study design</td>
<td>Cost-effectiveness and cost-utility analyses concurred with economic test</td>
<td>Cost-utility analyses using a decision-analytic model</td>
</tr>
<tr>
<td>Viewpoint for analysis</td>
<td>Societal</td>
<td>Not stated</td>
</tr>
<tr>
<td>Alternatives compared</td>
<td>IPA (improvement for patients)</td>
<td>IPA (improvement for patients)</td>
</tr>
<tr>
<td>Benefit measured</td>
<td>Life-years saved and quality-adjusted life-years (QALY)</td>
<td>Life-years saved and quality-adjusted life-years (QALY)</td>
</tr>
<tr>
<td>Source(s) of effectiveness data</td>
<td>QUESTO trial (1-year survival) and European Nervous Disease Database (long-term survival)</td>
<td>QUESTO trial (1-year survival) and European Nervous Disease Database (long-term survival)</td>
</tr>
<tr>
<td>Uncertainty of quality of life weightings</td>
<td>W2Q in 2000-210 years was included in the QALY; trial</td>
<td>W2Q in 21 years was included in the QALY; trial</td>
</tr>
<tr>
<td>Estimate of resource use</td>
<td>QALY (1) patients received at the QESTO trial (based on high probability of occurrence of resource use up to 1 y)</td>
<td>QALY (1) patients received at the QESTO trial (based on high probability of occurrence of resource use up to 1 y)</td>
</tr>
<tr>
<td>Discount(s) of cost data</td>
<td>QALY (1) discounting system and Medicare CPT codes</td>
<td>QALY (1) discounting system and Medicare CPT codes</td>
</tr>
<tr>
<td>Discounting</td>
<td>Life per year</td>
<td>Life per year</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Various estimates of survival and cost, also varied discount rate and assumed independence of baseline variables</td>
<td>Various estimates of survival and cost, also varied discount rate and assumed independence of baseline variables</td>
</tr>
</tbody>
</table>
B. What Are the Results and Will They Help Me in Caring for My Patients? (O’Brien et al., JAMA, 1997)—Comparing Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Mark et al.</th>
<th>Kalish et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental cost</td>
<td>$2760</td>
<td>$2535</td>
</tr>
<tr>
<td>Cost per QALY</td>
<td>$32,678</td>
<td>$30,300</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Most sensitive to mortality benefit</td>
<td>Most sensitive to mortality benefit</td>
</tr>
</tbody>
</table>

User’s Guides: Economic Analysis of Clinical Practice: B. What Are the Results and Will They Help Me in Caring for My Patients? (O’Brien et al., JAMA, 1997)

• “cost-effectiveness should focus on strategies, not drugs. The cost-effectiveness of t-PA depends on how the drug is administered and to whom it is given.” (Lee)
• “The ultimate criterion is one of local opportunity cost: what are the health benefits you will no longer realize if resources are expended on t-PA?”
• “For evidence to be relevant to policy decisions we would prefer evidence to be more related to effectiveness than efficacy.”
• How transferable are treatment patterns and costs across jurisdictions?
• Countries differ in the value they place on health benefits vs. other goods: acceptable cost-effectiveness threshold will vary.

Links to Important Information Sources

- International Society for Pharmacoeconomics and Outcomes Research (www.ispor.org)
- Center for Health System Change (www.hschange.org)
- Journal Health Affairs (www.healthaffairs.org)
- Academy of Managed Care Pharmacy (www.amcp.org)
- UK National Institute of Clinical Excellence (www.nice.org.uk)
- Harvard CEA Registry (www.hsph.harvard.edu/cearegistry/)
Thank you!

Questions?