Overview

• CEA basics
• CEA alongside clinical trials
• Example
• Policy Context
CEA Basics
Cost-Effectiveness Analysis

• Standardized methodology for comparing benefits and costs of interventions designed to improve health*
• Compare alternative treatment strategies
  – Is the new treatment strategy “cost-effective” compared to standard care?
• Provide standard metric to compare value across therapies for different diseases
  – Where should we spend limited health dollars?

Cost-Effectiveness Analysis is a Comparison of Alternatives

Incremental Cost-Effectiveness Ratio (ICER)
Therapy A Vs. Therapy B

\[
\text{Cost (A) - Cost (B)} \div \text{Outcome (A) - Outcome (B)}
\]
THE COST-EFFECTIVENESS PLANE

NW

Existing treatment dominates

New treatment more costly

New treatment less effective

New treatment less costly but less effective

SE

New treatment less costly

New treatment dominates

NE

New treatment more effective but more costly

New treatment more effective

C
<table>
<thead>
<tr>
<th>Type of Economic Analysis</th>
<th>Description of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-minimization</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>(Least expensive way to treat a condition)</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Natural effects</td>
</tr>
<tr>
<td></td>
<td>(e.g. cases identified, life years gained)</td>
</tr>
<tr>
<td>Cost-utility</td>
<td>Quality adjusted life years</td>
</tr>
<tr>
<td></td>
<td>(quantity of life adjusted for quality 1 = ideal health, 0 = dead)</td>
</tr>
<tr>
<td>Cost-benefit</td>
<td>Monetary value of health and life</td>
</tr>
<tr>
<td></td>
<td>(willingness to pay for health effects)</td>
</tr>
</tbody>
</table>
CEA Alongside Clinical Trials
Economic Evaluation Alongside Clinical Trials: What are the Advantages?

• High internal validity of RCTs
  – RCT/CEA vs. synthetic CEA (i.e., via models)

• Efficiency
  – Lower costs of piggyback CEAs vs post hoc CEA

• Timing
  – Clinical and economic results presented together
Clinical Trial + CEA = Imperfect Marriage

• External Validity
  – clinical care which occurs in the trial is not representative of care that occurs in typical medical practice

• Study Objectives
  – Clinical trials and cost-effectiveness analyses are designed for different purposes and audiences
Methods are Standardized for CEA Alongside RCTs

Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report

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1Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 2Pfizer, Inc., Bridgewater, NJ, USA; 3University of Oxford, Oxford, UK; 4MEDIAP International, London, UK; 5Brunel University, Uxbridge, Middlesex, UK; 6Genentech, San Francisco, CA, USA; 7Merck & Co., Inc, Blue Bell, PA, USA; 8University of Pennsylvania, Philadelphia, PA, USA; 9AstraZeneca, Lund, Sweden; 10Kaiser Permanente, Pasadena, CA, USA; 11Duke Clinical Research Institute, Durham, NC, USA

ABSTRACT

Objectives: A growing number of prospective clinical trials include economic end points. Recognizing the variation in methodology and reporting of these studies, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) chartered the Task Force on Good Research Practices: Randomized Clinical Trials—Cost-Effectiveness Analysis. Its goal was to develop a guidance document for designing, conducting, and reporting cost-effectiveness analyses conducted as a part of clinical trials.

Methods: Task force cochairs were selected by the ISPOR Board of Directors. Cochairs invited panel members to evaluate, analysis, and reporting of results. Task force members agreed that trials should be designed to evaluate effectiveness (rather than efficacy), should include clinical outcome measures, and should obtain health resource use and health state utilities directly from study subjects. Collection of economic data should be fully integrated into the study. Analyses should be guided by an analysis plan and hypotheses. An incremental analysis should be conducted with an intention-to-treat approach. Uncertainty should be characterized. Manuscripts should adhere to established standards for reporting results of cost-effectiveness analyses.
Resourcing a Piggyback CEA*

• Consent form modifications

• Staff time
  – Design and collection
    • Health care use (e.g., insurance claims)
    • QOL surveys
  – Data entry

• Analyst time

*Not all clinical trials need a piggyback CEA!
RCT/CEA Example
SWOG 9509: PC vs VC

Untreated Patients with Stage IIIb and IV NSCLC

**RANDOMIZED**

Paclitaxel 225 mg/m² + q 3 wks

Carboplatin AUC 6

Vinorelbine 25 mg/m² + q 4 wks

Cisplatin 100 mg/m²
Economic Analysis Alongside SWOG 9509

• Research question:
  – Estimate the cost-effectiveness of vinorelbine + platinum vs. paclitaxel + carboplatin for patients with advanced non-small cell lung cancer
SWOG 9509: PC vs VC
Overall Survival

- **CBDCA+Pac**
  - N: 208
  - Deaths: 159
  - Median Survival (Months): 8
  - 1-Year Survival: 38%
  - 2-Year Survival: 15%

- **CDDP+Vin**
  - N: 202
  - Deaths: 156
  - Median Survival (Months): 8
  - 1-Year Survival: 36%
  - 2-Year Survival: 16%

P = .73
### SWOG 9509: PC vs VC

**Quality of Life Analysis at 25 weeks**

<table>
<thead>
<tr>
<th></th>
<th>VC</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>37%</td>
<td>28%</td>
</tr>
<tr>
<td>Stable</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td>Declined</td>
<td>40%</td>
<td>39%</td>
</tr>
</tbody>
</table>

*p=NS*
# Lifetime Average Costs

<table>
<thead>
<tr>
<th>Category</th>
<th>Cis + Vinorelbine (N=186)</th>
<th>Carbo + Paclitaxel (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Procedures</strong>*</td>
<td>$2,637</td>
<td>$3,161</td>
</tr>
<tr>
<td><strong>Blood Products</strong></td>
<td>$166</td>
<td>$182</td>
</tr>
<tr>
<td><strong>Supportive Care Medications</strong></td>
<td>$4,804</td>
<td>$4,339</td>
</tr>
<tr>
<td><strong>Prot Chemo Deliv</strong>*</td>
<td>$2,199</td>
<td>$1,007</td>
</tr>
<tr>
<td><strong>Prot Chemo Drug</strong>*</td>
<td>$5,069</td>
<td>$16,732</td>
</tr>
<tr>
<td><strong>Non-Protocol Therapy</strong></td>
<td>$8,372</td>
<td>$7,037</td>
</tr>
<tr>
<td><strong>Medical Care Days/Visits</strong></td>
<td>$9,964</td>
<td>$11,062</td>
</tr>
<tr>
<td><strong>Total</strong>*</td>
<td><strong>$33,209</strong></td>
<td><strong>$43,522</strong></td>
</tr>
</tbody>
</table>

* = Significant difference
How to Identify Cancer Clinical Trials for Piggyback CEA Studies?

• General issues
  – Disease burden
  – Cost of therapies (new and established)
  – Downstream impact on costs and outcomes
  – Likelihood of clinical impact of a positive study

• **Value of Information** analysis holds promise as a way to identify studies that warrant funding
Estimated Value of Information Provided by the National Emphysema Treatment Trial*

*Multicenter NHLBI-sponsored RCT of lung volume reduction surgery (LVRS) for persons with severe emphysema. Included a piggyback CEA.

Source: Medical Care 2008;46:542

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WTP = $50,000/ QALY</th>
<th>WTP = $100,000/ QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental cost-effectiveness ratio (ICER)</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>Expected value of perfect information</td>
<td>46</td>
<td>670</td>
</tr>
<tr>
<td>Expected value of sample information</td>
<td>41</td>
<td>660</td>
</tr>
<tr>
<td>Expected net benefit of sampling</td>
<td>−19</td>
<td>600</td>
</tr>
<tr>
<td>Probability of change in decision</td>
<td>0.04</td>
<td>0.24</td>
</tr>
</tbody>
</table>

TABLE 3. EVI Results for LVRS at WTP Thresholds of $50,000 and $100,000 per QALY Assuming 1250 Subjects per Arm in the NETT ( Millions of Dollars)
Policy Context
Oncology Spending

• Oncology spending is rising >15% percent annually, faster than total health care spending

• Much of the cost increase in oncology is driven by three factors
  – Replacement of less expensive with more expensive treatments
  – More aggressive use of treatment and treatment combinations
  – Prolongation of the period of treatment

• Cost is becoming an increasingly intrusive concern for patients, providers, and payers alike
Tier 4 plans typically have a 20-33% coinsurance rate.
Consequences of Financial Costs of Cancer

- Used up all or most of savings: 25%
- Borrowed money from relatives: 13%
- Contacted by a collection agency: 11%
- Unable to pay for food, heat, housing: 11%
- Aid from charity or public assistance: 7%
- Got a loan/another mortgage: 7%
- Declared bankruptcy: 3%

Source: Kaiser Family Foundation, 2006
Consequences of Financial Costs of Cancer

- Used up all or most of savings: 25% (Always Insured), 46% (Ever Uninsured)
- Borrowed money from relatives: 13% (Always Insured), 30% (Ever Uninsured)
- Contacted by a collection agency: 11% (Always Insured), 34% (Ever Uninsured)
- Unable to pay for food, heat, housing: 11% (Always Insured), 41% (Ever Uninsured)
- Aid from charity or public assistance: 7% (Always Insured), 35% (Ever Uninsured)
- Got a loan/another mortgage: 7% (Always Insured), 15% (Ever Uninsured)
- Declared bankruptcy: 3% (Always Insured), 6% (Ever Uninsured)

Source: Kaiser Family Foundation, 2006
Economic Evaluation Alongside Clinical Trials: Why Should They be Done?

• “If costs per enrollee in Medicare and Medicaid continued to grow at the same rate...federal spending on those two programs alone would increase from about 5% of GDP today to about 20% by 2050 — roughly the share of the economy now accounted for by the entire federal budget”

• “Relatively little rigorous evidence is available about which treatments work best for which patients or whether the benefits of more expensive therapies warrant their additional costs”

  – Peter Orszag, NEJM 2007;357:1885
Cost-Effectiveness Fallacies

• Cost ≠ cost-effectiveness
  – A costly cancer treatment can be highly cost-effective
  – An inexpensive cancer treatment can have poor cost-effectiveness

• Cost-effective ≠ inexpensive
  – Adopting a new cost-effective cancer treatment often increases overall health care spending
## Cost-Effectiveness

### Cancer Prevention and Control

<table>
<thead>
<tr>
<th>Indication</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically node-negative breast cancer</td>
<td>Intra-operative touch imprint cytology</td>
<td>Standard post-operative sentinel lymph node survey</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>ER+ breast cancer, (-) lymph nodes</td>
<td>Surgery + AC</td>
<td>Surgery alone</td>
<td>$12,000</td>
</tr>
<tr>
<td>Cervical cancer prevention, age 25</td>
<td>HPV vaccine</td>
<td>No vaccine</td>
<td>$20,000</td>
</tr>
<tr>
<td>ER+ breast cancer, age 64</td>
<td>Anastrozole</td>
<td>Tamoxifen</td>
<td>$87,000</td>
</tr>
<tr>
<td>Local stage prostate cancer, age 75</td>
<td>Radiation</td>
<td>Watchful waiting</td>
<td>$220,000</td>
</tr>
<tr>
<td>Hodgkin’s disease Stage III-IV complete remission</td>
<td>Annual computed tomography x 5 yrs</td>
<td>No computed tomography</td>
<td>$9.6 million</td>
</tr>
</tbody>
</table>

https://research.tufts-nemc.org/cear/Default.aspx
National Institute for Health and Clinical Excellence (NICE)

- Implemented in the United Kingdom in 1999
- A Special Authority within the National Health Service (NHS)
- Remit is to consider ‘clinical and cost-effectiveness’
  - Eliminate ineffective treatments
  - Concentrate the available budget on the cost-effective treatments
  - Ensure all patients have equal access to cost-effective care
PRESS RELEASE

NICE guidance recommends lenalidomide for multiple myeloma

The National Institute for Health and Clinical Excellence (NICE) has today (18 June) published final guidance on the use of lenalidomide for multiple myeloma in people who have received at least one prior therapy. The new NICE guidance recommends lenalidomide in combination with dexamethasone as a treatment option for people with multiple myeloma who have received two or more prior therapies. The cost of the drug beyond 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer, Celgene.
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Ideal Role of Cost-Effectiveness In Cancer Care

Develop and Evaluate New Cancer Treatment

Understanding the Clinical Context:
- Prevalence of disease
- Evidence of safety, efficacy and effectiveness
- Availability and efficacy of alternative therapies
- Disparities in access to care

Cost-Effectiveness Analysis

Professional Recommendations/Practice Guidelines

Clinical Practice
Actual Role of Cost-Effectiveness in Cancer Care

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- Prevalence of disease
- Evidence of safety, efficacy and effectiveness
- Availability and efficacy of alternative therapies
- Disparities in access to care

Cost-Effectiveness Analysis

Professional Recommendations/Practice Guidelines

Clinical Practice
Questions?
Reference and Backup Slides
Other examples when NICE was able to use CEA in pricing negotiations

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Disease area</th>
<th>Product(s)</th>
<th>Manufacturer</th>
<th>Payer</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>UK</td>
<td>Multiple myeloma</td>
<td>Velcade</td>
<td>Johnson and Johnson</td>
<td>NHS</td>
<td>J &amp; J agreed to reimburse the NHS in either cash or product for patients who do not respond (Response measure: 50% decrease in serum M protein) after 4 cycles of treatment with Velcade. Responding patients receive additional 4 cycles.</td>
</tr>
<tr>
<td>2008</td>
<td>UK</td>
<td>Colorectal cancer</td>
<td>Erbitux</td>
<td>Merck</td>
<td>Primary care trust</td>
<td>Rebate direct to primary care trust on the cost of any vials of Cetuximab used for patients who do not achieve a pre-agreed clinical outcome (‘nonresponders’) at up to 6 weeks (up to an agreed maximum of 3200 milligrams).</td>
</tr>
<tr>
<td>2008</td>
<td>UK</td>
<td>NSCLC</td>
<td>Erlotinib</td>
<td>Roche</td>
<td>Primary care trust (UK)</td>
<td>Roche will rebate the cost of erlotinib for NSCLC treatment to achieve drug acquisition cost parity compared to docetaxel for an average patient duration.</td>
</tr>
<tr>
<td>2008</td>
<td>UK</td>
<td>Mesothelioma and NSCLC</td>
<td>Pemetrexed</td>
<td>Ely Lilly</td>
<td>Primary care trust (UK)</td>
<td>Discounted price for drug after certain preagreed level of expenditure at full price has been reached.</td>
</tr>
<tr>
<td>2009</td>
<td>UK</td>
<td>Kidney cancer</td>
<td>Sutent</td>
<td>Pfizer</td>
<td>NHS</td>
<td>Pfizer agreed to provide a 5% discount on the unit price of Sutent and cover the cost of the first 6 weeks of treatment</td>
</tr>
</tbody>
</table>
Question: Will Cost-effectiveness Analysis Shut off the Cancer Treatment Pipeline?
FDA approvals for new cancer drug treatments, 1996-2005

- New Entity
- New indication (Existing Drug)
- TOTAL
Recent NICE Controversy

• In August 2008, NICE published its Appraisal Consultative Document on four new drugs for treating advanced renal carcinoma (bevacizumab, sorafenib, sunitinib, temsirolimus).

• It recommended that none of the four drugs should be used in the NHS on the grounds that they were not cost-effective.

• Oncologists and patient organizations were outraged, since these drugs are widely used in many other countries and offer benefit to patients for whom no other effective treatments are available.

• NICE has responded with a national survey to determine if the population wants higher thresholds for treatments at the end of life.