Introduction to Comparative Effectiveness Research

Greg Cooper, MD
Outline

• Overview/Why CER
• Methods/Examples
• CER at Case
Comparative Effectiveness Research

• IOM Definition

• CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.

• The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.
CER - ACA Definition

• Research evaluating and comparing health outcomes and the clinical effectiveness, risks and benefits of 2 or more medical treatments, services and items
Investing in CER

- 2008 AHRQ budget for Effective Healthcare Program = $30 million
- 2009 ARRA funding for AHRQ CER = $300 million
- NIH: $400 million
- DHHS: $400 million
- Total CER investment $1.2 billion in 2009 (62% for research, rest for infrastructure and dissemination)
CER Defining Characteristics

- Objective of directly informing clinical or health policy decision
- Compares at least 2 alternatives
- Results at population and subgroup level
- Measures outcomes important to patients
- Methods and data sources appropriate for the decision of interest
- Conducted in real world setting
IOM Distribution of Research Priorities

Graph showing the distribution of research priorities across various research areas. The y-axis represents the number of priority topics, and the x-axis lists different research areas. The graph uses bars to indicate the number of primary and secondary research areas for each topic.
Categories of CER Methods

- Systematic reviews of existing research
- Decision modeling, with or without cost information
- Retrospective analysis of existing clinical or administrative data
  - Medicare, Medicaid claims
- Prospective, non-experimental studies, including registries
- Experimental studies, including RCT’s
All Methods Have a Role

• Inevitable tradeoff between internal validity and feasibility, generalizability, cost, time
• Experimental studies will have a crucial role in CER, and there is need for improving design and implementation
• Non-experimental methods hold great promise, particularly as methods are refined and data infrastructure is improved
CRC Mortality Is Decreasing
NOTE: This graph shows the age-adjusted incidence rates (cases/100,000) averaged over the 3-year period 1993 to 1995. Primary care supply is defined as the percentage of all physicians who are in a primary care specialty.
Ecological fallacy

The graph shows the decline in the number of pairs of brooding storks and the number of millions of newborn babies from 1965 to 1980. The graph illustrates that the decrease in stork populations may not accurately reflect the decrease in human population growth, highlighting the ecological fallacy.
Systematic Review of the Evidence

• Comprehensive review of the evidence
• Evidence is rated by level
• Recommendations are made and graded
Meta-Analysis

- Combine results from multiple studies
- “Like” 1 really big study
- Analyze the combined data
- Great when lots of small trials
  - Each trial lacking sample size to prove significance
- Inexpensive, objective method for summarizing the collective experience
- Assumes identical patient populations
- Assumes identical protocols
  - Statistical methods for adjusting for heterogeneity
Endoscopic versus Surgical Management of Malignant Colon Polyps: A Community-Based Comparative Analysis

Gregory S Cooper, MD
Fang Xu, PhD
Mark D Schluchter, PhD
Jill Barnholtz Sloan, PhD
Siran Koroukian, PhD
Background

• Polyp with malignant cells
• Management either polypectomy or surgical resection
  – Polypectomy: Less morbidity and mortality
  – Surgical: Uncertain number with nodal metastases, more complete staging
• To date, only single institution studies
Goals

- Describe prevalence of endoscopic versus surgical management
- Identify predictors of endoscopic management strategy
- After adjusting for predictors, compare outcomes
  - Post-procedure complications
  - Receipt of surgery/reoperation
  - Second primary/recurrent cancer
  - Long term survival
SEER-Medicare Database

- Collaborative effort with NCI and CMS
  - patients ≥ 65 years linked by unique identifiers

- SEER population-based registries
  - Currently 25% of US population

- All Medicare files (inpatient + outpatient)

- Uses: pre and post-diagnosis measures (diagnoses + procedures), comorbid illnesses
Sample

- Stage T1N0M0 malignant colon polyp 1992-2005
- Exclusions: age <66, prior cancer diagnosis, non-adenocarcinoma, rectal cancers, receipt of neither polypectomy nor surgery, HMO enrollment, non Parts A and B
- 2077 patients
  - Surgery 1340 (64.5%)
  - Polypectomy 737 (35.5%)
Outcomes

• Complications within 30 days
  – Endoscopic: perforation or bleeding requiring hospitalization
  – Surgical: requiring postoperative interventions*
• Subsequent surgery after 6 months
• Second primary cancers (SEER)
• Recurrence: chemotherapy or metastatic diagnosis codes 6 months-2 years**
• Survival through 2007

** Earle, et al: Med Care 2002
HR 1.51 (95% CI 1.31-1.74; p<0.001)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Polypectomy</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>1.4%</td>
<td>8.8%*</td>
</tr>
<tr>
<td>Surgery &gt; 6 mos.</td>
<td>4.5%</td>
<td>7.2%+</td>
</tr>
<tr>
<td>Recurrence</td>
<td>13.2%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Second Cancers</td>
<td>3.7%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

*p<0.001; +p=0.01
Analysis

• Propensity score:
  – Adjusts for measured and unmeasured factors in treatment allocation
  – All potential predictors of endoscopic management in multivariate logistic model
  – Develop predicted probability in each patient
  – Divide into quintiles of probability and compare survival with endoscopic and surgical treatment in each subgroup
Polypectomy Frequency by Propensity Score Quintile

<table>
<thead>
<tr>
<th>Quintile</th>
<th>% of Patients</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>
Strengths and Limitations

**Strengths**
- Population-based, large-sample size
- Variety of practice settings and specialists
- Cancer related data validated

**Limitations**
- Medicare billing data
- No data on polypectomy margins, lymphatic invasion
- Patient preferences regarding management
Summary

• More than 1/3 of patients with malignant polyps treated with polypectomy
• Selection bias toward higher surgical risk
• Outcomes compared favorably to surgery
What is Economic Evaluation

• A tool to compare the costs and outcomes of different interventions
• Compare two treatment options for a specific problem (TIPS vs. Banding)
• Compare two different interventions for two different problems (BMT vs. Liver Xplant)
• Compare intervention to status quo (Antiviral therapy vs. conservative tx for HCV)
Why Perform Economic Analyses

• Resources are scarce
• Options about how to address health problems
• Findings used to help set priorities, determine which programs get funded
• Model: Ca – Cb / Oa – Ob
## Types of Analyses

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Denominator</th>
</tr>
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<tbody>
<tr>
<td>Cost-minimization</td>
<td>None</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Impact on survival (direct or intermediate outcome)</td>
</tr>
<tr>
<td>Cost-utility</td>
<td>Value of state produced (QALY)</td>
</tr>
<tr>
<td>Cost-benefit</td>
<td>Dollars</td>
</tr>
</tbody>
</table>
Cost Effectiveness Analysis

• Combines outcomes with costs
• Key is choice of outcome
  – Final: life years saved
  – Intermediate: mm Hg bp reduction
Measuring Utility

• Use if:
  – Quality is an important outcome
  – Mortality data are available
  – Difference in effectiveness between alternatives

• Methods of measuring
  – Ratings scale
  – Standard gamble
  – Time trade off
Cost Benefit Analysis

- Cost and outcomes measured in dollars
- Results expressed as ratio or net savings
- Attach dollar value to year of life or quality of life change
- Willingness to pay: estimate maximum would pay for intervention to reduce death or morbidity
Decision Analysis

• Systematic, quantitative approach to making decisions under conditions of uncertainty

• Steps:
  – Structure problem, including perspective
  – Develop decision tree
  – Add probabilities
  – Value consequences
  – Average out and fold back
Decision Tree

- Sequence of events flow from left to right
- Decision nodes represented by squares
- Chance nodes represented by circles
- Sensitivity analysis: set upper and lower bounds on possible range of estimates; see if choice is robust
- Data from literature, expert panels, patient surveys
Decision Trees

• Point estimates: probability of event fixed
• Monte Carlo simulation: develop CI around point estimate; random set of observations through model
• Markov model: allow cycling through disease states (i.e., disease state $\Rightarrow$ health $\Rightarrow$ disease; disease state $\Rightarrow$ new disease)
Add Utilities

- Health state utilities are used to measure how people value different states of health
- Quality-adjusted life year (QALY)
- A year of life is a year of life? No.
- QALY = 1 year of life in excellent health
- Health conditions cause utility to be <1
  - If a state of health is such that utility = 0.5, then 2 years of life in this state = 1 year of healthy life
<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug A</strong></td>
<td>$100</td>
<td>10.00 QALYs</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>$1,100</td>
<td>10.05 QALYs</td>
</tr>
</tbody>
</table>

**Incremental Cost-Effectiveness Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Δ Cost</th>
<th>Δ Effective.</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug A</strong></td>
<td>------</td>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>$1,000</td>
<td>0.05 QALYs</td>
<td>$20,000/QALY</td>
</tr>
</tbody>
</table>

*Is this intervention cost-effective?*
Decision Tree for Abdominal Aortic Aneurysm (AAA)
Decision Model for Abdominal Aortic Aneurysm (AAA)
Cost-Effectiveness of Low Dose Aspirin + Colonoscopy

- Lower effectiveness of colonoscopy for cancer prevention in the right colon
- Aspirin also protective, especially in right colon
- ? Combination
- Cost-effectiveness model: no screening vs. aspirin vs. colonoscopy (with surveillance) vs. combination

Hasan, Rex, Cooper; Gut in press
<table>
<thead>
<tr>
<th></th>
<th>No screening</th>
<th>Aspirin</th>
<th>Colonoscopy</th>
<th>Aspirin and colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC cases, n</td>
<td>5,903</td>
<td>3,858</td>
<td>1,759</td>
<td>1,105</td>
</tr>
<tr>
<td>%</td>
<td>-</td>
<td>35</td>
<td>68</td>
<td>78</td>
</tr>
<tr>
<td>CRC deaths, n</td>
<td>2,482</td>
<td>1,458</td>
<td>803</td>
<td>477</td>
</tr>
<tr>
<td>%</td>
<td>-</td>
<td>41</td>
<td>68</td>
<td>81</td>
</tr>
<tr>
<td>Life-years gained, n</td>
<td>-</td>
<td>6,232</td>
<td>13,922</td>
<td>15,108</td>
</tr>
<tr>
<td>Screening cost, ($M)</td>
<td>-</td>
<td>30</td>
<td>249</td>
<td>279</td>
</tr>
<tr>
<td>Total, $/person</td>
<td>2,227</td>
<td>1,791</td>
<td>3,105</td>
<td>3,169</td>
</tr>
<tr>
<td>ICER vs no screening,</td>
<td>-</td>
<td>Dominates $436/person</td>
<td>6,307</td>
<td>6,237</td>
</tr>
</tbody>
</table>
Sensitivity Analysis

• If increased colonoscopy effectiveness in right colon to 73% (baseline 53%), adding aspirin no longer cost-effective
• If incidence of stroke increase by 4.5x or GI bleeding increase by 2.6x, adding aspirin no longer cost-effective
Pragmatic Clinical Trials

• Compared to explanatory
• Decision maker viewpoint – should we provide intervention?
• Whether an intervention works in “real world” conditions
• Whether it works, not how or why
Pragmatic Clinical Trials

• Patient selection reflects routine practice
  – Exclude only if contraindicated
• Intervention to discretion of clinician
  – Dose adjustment
• Control routine practice (vs. placebo)
• Patient centered outcomes
• Always ITT analysis
Pragmatic Clinical Trials

- Identify prevalent condition
  - Often based on symptoms rather than explicit, verifiable diagnoses
- Evaluate common clinical dilemma in that condition
- Develop pragmatic study to understand health outcomes between competing management approaches
Primary Care Management of GERD

• Open label study of patients with symptomatic GERD despite H2RA or omeprazole
• Randomization at clinic level (n=226)
• Screened on basis of 5 item questionnaire
• Intervention esomeprazole at dose selected by clinician or continued care
• Measured HRQOL and utilities at 4 weeks

## Results

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
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<tbody>
<tr>
<td>None or minimal sx</td>
<td>58%</td>
<td>29%</td>
</tr>
<tr>
<td>PPI baseline</td>
<td>$1213 per QALM</td>
<td>---------</td>
</tr>
<tr>
<td>H2RA baseline</td>
<td>$648 per QALM</td>
<td>---------</td>
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CER and the CTSA

• Develop a CTSA Consortium-wide framework for community-engaged and CER that will support improvement in healthcare access, quality, efficiency and patient-centered outcomes and will improve the health of diverse communities and the public

• CER Key Function Committee (KFC)
CER at Case

- Pilot projects 2010
  - Paul Drawz
  - Morgan Jones
  - Siran Koroukian
- Research symposium 2010
- Office of Clinical Research
- Three focal areas
  - Large database
  - Economic analysis
  - EHR
Research Concierge

Primary CER

Assign to CER

Consultation as needed by other Cores

Secondary CER

Assign to: BERD, BRIM, PBRN

CER Consults
Educational Programs

- Seminars every other month
- June course (EPBI 467)
- Other activities based on feedback
Funding

- Pilot projects announced 9/30
- Collection of preliminary data for future PCORI research agenda
- Up to 40 awards (250K per year)
- Stakeholder involvement required
- New methods
- Development of multistakeholder research process
- Outcomes measurement tools
- Not specific interventions