Comparative Effectiveness Research:  
Focus on Pragmatic Trials

Jodi B. Segal, MD, MPH  
Johns Hopkins University School of Medicine  
Bloomberg School of Public Health  
May 24, 2010

“...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.”

---Institute of Medicine, 2009

"Comparative effectiveness research is designed to inform health care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options. The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care."

---Agency for Healthcare Research and Quality

• Any of these can be comparative effectiveness research but don’t have to be.  
• CER needs to compare alternatives and stakeholders are vitally important.

Late 1980’s: Early Appreciation of Medical Evidence

To ensure high-quality medical care:
1. Analyze evidence of the effectiveness, risks and costs of various medical practices
2. Monitor existing practices and compare them against accepted standards
3. Change the behavior of practitioners to ensure that care delivered meets the standards


The U.S. Preventive Services Task Force (USPSTF)

• The U.S. Preventive Services Task Force (USPSTF) convened by the U.S. Public Health Service in 1984
• Leading independent panel of private-sector experts in prevention and primary care.
• Conducts assessments of the scientific evidence for the effectiveness of a broad range of clinical preventive services
Cochrane Collaboration est. 1993

- An international, non-profit, independent organization, established to ensure that up-to-date, accurate information about the effects of healthcare interventions is readily available worldwide.
- Produces and disseminates systematic reviews of healthcare interventions, and promotes the search for evidence in the form of clinical trials and other studies of the effects of interventions.
- Named after the epidemiologist, Archie Cochrane (1909-1988), a British medical researcher who contributed greatly to the development of epidemiology as a science.

Gains in Health Services Research
(circa late 1980’s)

- Concerns on Capitol Hill about health care costs and viability of Medicare
- William Roper was head of Health Care Financing Administration (HCFA, now CMS) got effectiveness research as in item in proposed FY 1990 budget
- Later as White House health policy advisor advocated for “effectiveness research”


Agency for Health Care Policy and Research (AHCPR)

- Precursor had been National Center for Health Services Research, a program under the assistant secretary for HHS
- Promoted by legislation to be a PHS agency (1989)
- Remarkable change in funding for health services research with this move

AHRQ’s Current Mission

To improve the quality, safety, efficiency, and effectiveness of health care for all Americans. Information from AHRQ’s research helps people make more informed decisions and improve the quality of health care services.

Carolyn M. Clancy, M.D.,
Director, AHRQ

- June 2007, Testimony before U.S. House of Representatives Committee on Ways and Means, Subcommittee on Health
- “While this brave new world of health care presents wonderful opportunities, it also creates challenges. Chief among them is how to evaluate these innovations and determine which represent added value, which offer minimal enhancements to current choices, which fail to reach their potential, and which work for some patients and not for others.”

Report from the Congressional Budget Office in 2007
Research on the Comparative Effectiveness of Medical Treatments

Premise: it is possible to constrain health care costs both in the public programs and in the rest of the health system without adverse health consequences.

Perhaps the most compelling evidence is substantial geographic differences in spending on health care, which do not translate into higher life expectancy or measured improvements in other health statistics in the higher spending regions.
The American Reinvestment and Recovery Act (ARRA)  
February 17, 2009

- ARRA contains $1.1 billion for comparative effectiveness research.
  - $300 million is for AHRQ
  - $400 million is for the National Institutes of Health (NIH)
  - $400 million is at the discretion of the HHS Secretary

- Federal Coordinating Council for Comparative Effectiveness Research was created to offer guidance and coordination on the use of these funds.  
  http://www.hhs.gov/recovery/programs/os/cerbios.html

- AHRQ is using ARRA funds to expand and broaden comparative effectiveness research activities -- to increase the availability of research that will inform the real-world decisions facing patients and clinicians.

- The legislation called on the Institute of Medicine to recommend research priorities for the Secretary's funds

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- Locally involved --- Drs. Neil Powe, Kay Dickersin, Sean Tunis
- The Committee on Comparative Effectiveness Research Prioritization issued its final report June 30, 2009

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Initial National Priorities for Comparative Effectiveness Research  
Institute of Medicine -- June 30, 2009

Prioritized 100 research questions into 4 quartiles

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CER in the Health Reform Legislation

- Sec. 6301 Patient-Center Outcomes Research
  - Non-profit corporation (PCORI) to conduct comparative clinical effectiveness research
  - Board of Governors to include Director of AHRQ, Director of NIH, patients, providers, payers, health services researchers
  - Mandatory funding stream from a Research Trust Fund
  - Will include a Methodology Committee
  - Dissemination of results with assistance from AHRQ
  - Does not explicitly prohibit comparative cost effectiveness research
Key Methods for Comparative Effectiveness Research

- Review and synthesis of existing evidence
- Retrospective observational studies using secondary data
- Patient registries
- Pragmatic clinical trials

Why are we talking about this?

Pragmatic trials can (potentially) meet the needs of many decision makers

Regulators (Food and Drug Administration)

- A demonstration that the drug is likely to be safe in much of the population
- Information about the dose-response relationship between the clinical outcome and the drug dose
- Information about a drug’s efficacy
- Long-term safety information

Pharmaceutical or biotechnology companies

- To demonstrate efficacy of their product—prior to approval to get approval, and after approval to increase sales
- Need pharmacoeconomic information for product development
- Safety evaluation post-approval
- Data on efficacy and effectiveness to demonstrate superiority over competitors for marketing purposes

Clinicians and Patients

- Whether a medication should be used in a given individual

Payors

- Information for initial coverage decisions
- Information on effectiveness in usual care settings, as well as safety and costs in these settings
Pragmatic Clinical Trials: Definitions


“Should one prefer the goal of immediate applicability with a sacrifice of true understanding, or the more distant goal which may lead to greater enlightenment and which may prove more fertile for the future?”

Selection of outcomes to be evaluated in trials
- If outcome is relevant to patients, evaluate in a pragmatic trial
- If outcome has little biological information, evaluate in a pragmatic trial
- They used as an example the outcome of “returning to work”
- Explanatory approach: a strict patient selection criterion may be used in order to render the population homogenous and to reduce the withdrawal rate
- Pragmatic approach: a heterogeneous population with more withdrawals is acceptable

Pragmatic trials vs. Explanatory trials
- Pragmatic trials require trials that incorporate heterogeneity and ambiguity, and other “messy” aspects of clinical practice
- Opposing view is that these trials yield “messy” answers
- Used “pragmatic” and “fastidious” to differentiate
- “… a trial designed or analyzed with one viewpoint will often be unable to satisfy people who hold the opposite viewpoint, and vice versa.”

Other Names
- By the mid-1990’s, “mega-trial” was being used to describe large, simple randomized trials analyzed as intent to treat
- One of the first uses was to describe the GUSTO trial, which enrolled 41,021 patients and randomized them to 1 of 4 thrombolytic regimens for myocardial infarction (N Engl J Med 1993)
- Early proponents of these “large simple” trials were Peto and colleagues at the University of Oxford
- Detractors argue that the between-subject variation, within each treatment group in large simple trials, makes the results of these trials difficult to apply to an individual patient.

In the next decade, additional terms emerged: “naturalistic trials” and “effectiveness trials”
- Efficacy studies are closest Schwartz and Lellouch’s explanatory trials: aim to investigate whether an intervention works under optimal circumstances “can it work?”
- Effectiveness studies are closer in their goals to those of pragmatic studies: aim to evaluate whether an intervention works under usual circumstances “does it work?”
### Efficacy versus Effectiveness Trials

**Ann Rheum Dis 1999**

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<td>Comprehensive (for example, QoL, utilities); Weak link to mechanism of action; Short- and long-term horizon</td>
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### PRECIS

- Next advance grew out of discussion among investigators involved in the PRACTHC project, a Canadian and European Union initiative to promote pragmatic trials in low and middle-income countries.


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### Domains for the PRECIS Graphic

- The eligibility criteria for trial participants.
- The flexibility with which the experimental intervention is applied.
- The degree of practitioner expertise in applying and monitoring the experimental intervention.
- The flexibility with which the comparison intervention is applied.
- The degree of practitioner expertise in applying and monitoring the comparison intervention.
- The intensity of follow-up of trial participants.
- The nature of the trial’s primary outcome.
- The intensity of measuring participants’ compliance with the prescribed interventions, and whether compliance-improving strategies are employed.
- The specification and scope of the analysis of the primary outcome.

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### One Example

- **Effectiveness of Antipsychotic Drugs in patients with Chronic Schizophrenia** (Stroup, Schizophr Bull 2003)

- This trial is from the Clinical Antipsychotic Trials of Intervention Effectiveness Investigators (CATIE).

- To determine the comparative effectiveness of a representative antipsychotic (perphenazine) and several atypical antipsychotic medications for a representative sample of patients seeking treatment for chronic schizophrenia.

- The primary outcome was time to all-cause treatment failure, marked by the discontinuation of the study medication.
• Few exclusion criteria (safety and treatment refractory individuals)
• Patients and clinicians were masked to the treatment drug
• Aimed to enrolled 1,500 individuals from 50 clinical sites and follow them for 18 months.
• The treating physicians were allowed to titrate the medications to effectiveness.
• All patient participants were offered psychosocial interventions as well as an educational plan.

Controversies
• Concern that the design of a pragmatic trial exclusively answers questions from a public health perspective, and provides little information that is relevant to clinicians caring for individual patients
• Uncertainties about what should guide the choice of a trial design: the question being asked or who needs information from the trial
• A weakness of pragmatic trials is that with ‘negative’ results it is unclear whether the intervention is ‘worthless’ or whether it might, in fact, be worthwhile under some (more optimal) circumstances or for a subgroup of patients

Summary
• New era of comparative effectiveness research
• Needs new tools
• Focus needs to remain on who needs the information