PARTNERSHIP IN APPLIED COMPARATIVE EFFECTIVENESS RESEARCH SCIENCE (PACES)

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Objectives

To understand the role of comparative effectiveness research and outcomes research in improving health.

To learn how Hopkins is working with the FDA to advance their use of comparative effectiveness research methods.
What is CER?

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.

- Institute of Medicine, 2009
The Problem

“I think there’s a general recognition that the system we have in America is fundamentally broken. We spend more than any country on Earth. Our health results look like we’re a developing nation.”

• Secretary Kathleen Sebelius, HHS
Two Big Forces Led U.S. to CER

- Desire to deliver clinical care based on evidence
- Desire to improve effectiveness of care while containing costs
A Drive for Evidence
Early Appreciation of Medical Evidence (late 1980’s)

To ensure high-quality medical care:

• Analyze evidence of the effectiveness, risks and costs of various medical practices (and define appropriateness of these practices)

• Monitor existing practices and compare them against accepted standards

• Change the behavior of practitioners to ensure that care delivered meets the standards

Weak Evidence in Guidelines: Recommendations Based on Randomized Trials

- Atrial fibrillation: 11.7%
- Heart failure: 26.4%
- Peripheral arterial disease: 15.3%
- ST-Elevation-MI: 13.5%
- Perioperative beta-blockers: 12.0%
- Secondary prevention: 22.9%
- Stable angina: 6.4%
- Supraventricular arrhythmias: 6.1%
- Unstable angina: 23.6%
- Valvular disease: 0.3%
- Ventricular arrhythmia: 9.7%
- Percutaneous angioplasty: 11.0%
- Bypass surgery: 19.0%
- Pacemaker: 3.5%
- Radionuclide imaging: 4.8%

Tricoci P et al. JAMA 2009
The U.S. Preventive Services Task Force

- First convened by the U.S. Public Health Service in 1984
- Independent panel of private-sector experts in prevention and primary care.
- Conducts rigorous, impartial assessments of the scientific evidence for the effectiveness of a broad range of clinical preventive services

**Mission** is to evaluate the benefits of individual services based on age, gender, and risk factors for disease; make recommendations about which preventive services should be incorporated routinely into primary medical care and for which populations; and identify a research agenda for clinical preventive care.
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.
Others Leaders in Systematic Reviews of Evidence

- Evidence Based Practice Centers of the Agency for Healthcare Research and Quality (since 1996)

- National Institute for Health and Clinical Effectiveness (U.K., National Health Service) (since 1999)
A Drive for Improving Efficiency of Care Delivery
• Prompted by John Wennberg’s research on practice variations and Robert Brook’s research at RAND
AGE-ADJUSTED DEATH RATES BY HSA, 1988-92

Heart disease
White male

Age-adjusted

(U.S. rate = 205.0)
Rate per
100,000
population
Comparative
mortality ratio
(HSA to U.S.)
253.8 – 328.6
1.24 – 1.60
236.8 – 253.7
1.16 – 1.24
215.2 – 236.7
1.05 – 1.16
199.9 – 215.1
0.98 – 1.05
179.5 – 199.8
0.88 – 0.98
166.7 – 179.4
0.81 – 0.88
112.4 – 166.6
0.56 – 0.81

ICD-9 Categories 390-398, 402, 404-429

Distribution of HSA rates per 100,000 population

Proportion
0.0
0.005
0.01
0.015

SOURCE: CDC/NCHS
Unsustainable Spending on Healthcare

Projected Spending on Health Care as a Percentage of Gross Domestic Product

(Percent)

Source: Congressional Budget Office.
Note: Amounts for Medicare are net of beneficiaries’ premiums. Amounts for Medicaid are federal spending only.
Gains in Health Services Research (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 an item in proposed FY 1990 budget
• Later as White House health policy advisor advocated for “effectiveness research”

Agency for Healthcare Research and Quality (AHRQ) – 1989 (formerly 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
2000-2010

• Political environment favoring modernization of health care delivery

• Recognition of the need for *effectiveness* in health care

• Health professionals being trained with increased focus on genomics and informatics (personalization)

• Health research with a focus on balancing effectiveness and safety
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.”
And yet …

Hard evidence is often unavailable about which treatments work best for which patients and whether the added benefits of more-effective but more expensive services are sufficient to warrant their added expense.

Goal of comparative effectiveness research is to generate better information about the risks and benefits and costs of different treatment options — which could eventually alter the way in which medicine is practiced and yield lower health care spending without having adverse effects on health.
The American Reinvestment and Recovery Act (ARRA) of 2009

Effective February 17, 2009
The American Reinvestment and Recovery Act (ARRA)

- ARRA contained **$1.1 billion** for comparative effectiveness research.
  - $300 million for the Agency for Healthcare Research and Quality (AHRQ)
  - $400 million for the National Institutes of Health (NIH)
  - $400 million at the discretion of the HHS Secretary

- The legislation called on the **Institute of Medicine** to recommend research priorities for the Secretary's funds
Patient Protection and Affordable Care Act
March 23, 2010

Included: Sec. 6301 Patient Centered Outcomes Research
Key Items in Sec. 6301

• Establishment of PCORI: Patient-Centered Outcomes Research Institute
• NOT an agency of the government

• Mission: The Patient-Centered Outcomes Research Institute (PCORI) helps people make informed health care decisions – and improves health care delivery and outcomes – by producing and promoting high integrity, evidence-based information – that comes from research guided by patients, caregivers and the broader health care community.
Is comparative effectiveness research the same as patient-centered outcomes research?
Overview

The Patient-Centered Outcomes Research Institute (PCORI) is an independent organization created to help people make informed health care decisions and improve health care delivery. PCORI will commission research that is guided by patients, caregivers and the broader health care community and will produce high integrity, evidence-based information.

PCORI is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI will use a variety of forums and public comment periods to obtain public input throughout its work.

Provide Input

The Patient-Centered Outcomes Research Institute solicits and receives input from the public about its work, as part of its commitment to transparency, credibility and access.

Funding Opportunities

PCORI Announces $26 Million Pilot Projects Grant Program, seeks Patient, Stakeholder and Scientific Reviewers.
Duties of PCORI

- Identifying research priorities
- Defining research agenda
- Carrying out research project agenda (largely through contracts)
- Research will take into account differences between patients
- Research will take into account differences in treatments
PCORI - Funding

• Supported by a trust fund

• Up to 20% of the Fund will support research capacity building and dissemination of results
SEC. 3311. PATIENT-CENTERED OUTCOMES RESEARCH TRUST FUND.

(a) CREATION OF TRUST FUND.—There is established in the Treasury of the United States a trust fund to be known as the ‘Patient-Centered Outcomes Research Trust Fund’ (hereafter in this section referred to as the ‘PCORTF’), consisting of such amounts as may be appropriated or credited to such Trust Fund as provided in this section and section 9602(b).

(b) TRANSFERS TO FUND.—

(1) APPROPRIATION.—There are hereby appropriated to the Trust Fund the following:

(A) For fiscal year 2010, $10,000,000.
(B) For fiscal year 2011, $50,000,000.
(C) For fiscal year 2012, $150,000,000.
(D) For fiscal year 2013—

(i) an amount equivalent to the net revenues received in the Treasury from the fees imposed under subchapter B of chapter 34 (relating to fees on health insurance and self-insured plans) for such fiscal year; and

(ii) $150,000,000.

(E) For each of fiscal years 2014, 2015, 2016, 2017, 2018, and 2019—

(i) an amount equivalent to the net revenues received in the Treasury from the fees imposed under subchapter B of chapter 34 (relating to fees on health insurance and self-insured plans) for such fiscal year; and

(ii) $150,000,000.

The amounts appropriated under subparagraphs (A), (B), (C), (D)(ii), and (E)(ii) shall be transferred from the general fund of the Treasury, from funds not otherwise appropriated.

(2) TRUST FUND TRANSFERS.—In addition to the amounts appropriated under paragraph (1), such amounts as may be appropriated from time to time for purposes relating to the quality, safety, and efficacy of health care and the outcomes of health care shall be transferred to the Trust Fund.
Key Methodologies of CER/PCOR
Types of questions

- Comparative
- Effectiveness
- Patient-centered/patient-relevant
- Stakeholders
Evidence review

- Skills of systematic review of the literature
- Skill of meta-analysis
- Skills to disseminate results of research through clinical practice guidelines/consumer guides/publications in the lay literature
Observational Research

- Difference between efficacy and effectiveness
- Large dataset research to understand effectiveness of therapies in a usual care setting
  - Administrative claims
  - Electronic medical records
  - Registries
  - “Repurposed” trial data
Experimental Research

Pragmatic clinical trials
Trials conducted in a usual care setting without tight inclusion and exclusion criteria
Stakeholder Engagement

• Learning better methods for engaging stakeholders in the process of designing research
• Methods for engaging community (clinicians and patients) in participating in research in their usual care setting
Modeling

• Decision-analysis
• Cost analysis (perhaps)
Partnership in Applied Comparative Effectiveness Science Initiative
Our Understanding (from the start)

• FDA has a unique role in the development of the scientific framework for CER ---FDA is interested in the safety and effectiveness of drugs across the drug’s lifecycle

• FDA also may have a role in providing clinical data for CER studies that would not be available from any other source.

• Our goal was to help advance the field of personalized medicine, aiming to better tailor treatments to individuals for whom the benefits are greatest and the risks lowest.
Puzzling …

Does FDA do comparative effectiveness research?

- FDA does not mandate comparative trials (almost always placebo controlled for registration)
- FDA does not typically mandate effectiveness trials (after approval)
- Yes – FDA is interested in drug safety through a drug’s life cycle
- Yes – FDA is very interested in benefit – harm balance in making post-approval decisions about labeling or withdrawal
- Yes – FDA is interested in personalized medicine – targeting therapy to patients who can most benefit
Investigators

Biostatisticians
Ravi Varadhan, PhD
Gary Rosner, PhD
Michael Rosenblum, PhD
Scott Zeger, PhD
Thomas Louis, PhD

Internists
Jodi Segal, MD, MPH
Carlos Weiss, MD, MHS (geriatrician)
Sonal Singh, MD, MPH
Nisa Maruthur, MD, MPH
Saman Nazarian, MD (cardiologist)

Economist
John Bridges, PhD
Decision Making

Population

Subgroup

Individual

Regulatory decisions

CER/PCOR

Clinical decisions
<table>
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<th>Project</th>
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<td>Understanding Role of Adaptive Designs in Phase III trials</td>
<td>Rosenblum and Zeger</td>
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<td>Methods for exploring heterogeneity of treatment effect in trial subgroups</td>
<td>Varadhan, Weiss, and Louis</td>
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<td>Advancing Bayesian methods to integrate historical trial data with newer trial data</td>
<td>Rosner and Nazarian</td>
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<td>Understanding the role of preference-based approaches to decision-making</td>
<td>Singh, Bridges, Maruthur</td>
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PACES: Proposed Four Projects

Understanding Role of Adaptive Designs in Phase III trials

Methods for exploring heterogeneity of treatment effect in trial subgroups

Advancing Bayesian methods to integrate historical trial data with newer trial data

Understanding the role of preference-based approaches to decision-making

Workshop 1: Meet the FDA and the Data
Workshop 1 – Winter 2011

Data Options Presented to Hopkins Investigators

- HIV
- Diabetes
- HPV
- Rotavirus
- Cardiac resynchronization devices
- Continuous glucose monitoring
- Osteoporosis
- Cervical discs
Projects Matched to Trials

Understanding Role of Adaptive Designs

Methods for exploring heterogeneity of treatment effect in subgroups

Advancing Bayesian methods to integrate historical data

Understanding the role of preference-based approaches to decision-making

HIV – 5 trials (3 drugs)

Osteoporosis – 2 trials (2 drugs)

Cardiac resynchronization devices – 3 trials

Diabetes – no data needed
Activated Buccaneer in Winter 2011

Initial Plan
Build a secure platform and workbench by which Hopkins could securely access the FDA data

Revised Plan
Put all of Buccaneer’s support into personnel dedicated to preparing the data for the Hopkins investigators
Projects Evolution

- Understanding Role of Adaptive Designs
- Methods for exploring heterogeneity of treatment effect in subgroups
- Advancing Bayesian methods to integrate historical data
- Understanding the role of preference-based approaches to decision-making
Model of PACES Success

**Input**
- ARRA funding
- Johns Hopkins Buccaneer CMTP
- Lewin FDA colleagues and staff
- Limited involvement of other stakeholders

**Intermediate outcomes**
- Demonstration of ability to access data securely
- Demonstration of ability to use data
- Completion of 4 proposed projects
- Delivery of methodological tools

**Long-term outcomes**
- Incorporation of new methods/tools into FDA’s regulatory processes
- Efficient delivery of safe and effective drugs/devices/biologics to individuals who can benefit
Thanks…

- All of the PACES coinvestigators
- Terrific collaborators at CMTP, Buccaneer, and Lewin
- Collaborators at FDA
- Project manager: Emily Little