How Might PCORI Change Clinical Trials Methodology?

David Meltzer MD, PhD
University of Chicago
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.

PCORI is an independent, non-profit organization authorized by Congress committed to continuously seeking input from patients and a broad range of stakeholders to guide its work.
Helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options. This research answers patient-centered questions such as:

**Expectations**

"Given my personal characteristics, conditions and preferences, what should I expect will happen to me?"

**Options**

"What are my options and what are the potential benefits and harms of those options?"

**Outcomes**

"What can I do to improve the outcomes that are most important to me?"

**Decisions**

"How can clinicians and the care delivery systems help me make the best decisions about my health and healthcare?"
Board of Governors Composition

The 21 member Board of Governors spans a diverse array of fields and areas of expertise within the Health Care arena.
The 17 member Methodology Committee brings varied scientific backgrounds, experiences, and areas of expertise to PCORI.
In order to answer these patient-focused questions, PCOR:

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, palliative, or health delivery system interventions to inform decision making, highlighting comparisons and outcomes that matter to people;

- Is inclusive of an individual's preferences, autonomy and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life;

- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination; and

- Investigates (or may investigate) optimizing outcomes while addressing burden to individuals, resource availability, and other stakeholder perspectives.
PCORI’s Core Duties

• Establish national *research priorities*

• Establish and carry out a *research agenda*

• Develop and update *methodological standards*

• **Disseminate** research findings
### Criteria for Research Outlined by Law

<table>
<thead>
<tr>
<th>Impact on Health of Individuals and Populations</th>
<th>Addresses Current Gaps in Knowledge/Variation in Care</th>
<th>Patient-Centeredness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvability through Research</td>
<td>Impact on Health Care System Performance</td>
<td>Rigorous Research Methods</td>
</tr>
<tr>
<td>Inclusiveness of Different Populations</td>
<td>Potential to Influence Decision-Making</td>
<td>Efficient Use of Research Resources</td>
</tr>
<tr>
<td>National Priorities for Research and Research Agenda</td>
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<td>---------------------------------------------------</td>
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<tr>
<td><strong>Assessment of Options for Prevention, Diagnosis, and Treatment</strong></td>
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<tr>
<td>• Comparisons of alternative clinical options to support personalized decision-making and self-care</td>
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<tr>
<td>• Identifying patient differences in response to therapy</td>
<td></td>
<td></td>
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<tr>
<td>• Studies of patient preferences for various outcomes</td>
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<td>✔</td>
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<td></td>
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<tr>
<td><strong>Improving Healthcare Systems</strong></td>
<td></td>
<td></td>
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<tr>
<td>• Improving support of patient self-management</td>
<td></td>
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<tr>
<td>• Focusing on coordination of care for complex conditions and improving access to care</td>
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<tr>
<td>• Comparing alternative strategies for workforce deployment</td>
<td></td>
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<tr>
<td><strong>Communication &amp; Dissemination Research</strong></td>
<td></td>
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<tr>
<td>• Understanding and enhancing shared decision-making</td>
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<tr>
<td>• Alternative strategies for dissemination of evidence</td>
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<tr>
<td>• Exploring opportunities to improve patient health literacy</td>
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<tr>
<td><strong>Addressing Disparities</strong></td>
<td></td>
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<tr>
<td>• Understanding differences in effectiveness across groups</td>
<td></td>
<td></td>
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<tr>
<td>• Understanding differences in preferences across groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reducing disparities through use of findings from PCOR</td>
<td></td>
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<tr>
<td>✔</td>
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<tr>
<td><strong>Accelerating PCOR and Methodological Research</strong></td>
<td></td>
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<tr>
<td>• Improving study designs and analytic methods of PCOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Building and improving clinical data networks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Methods for training researchers, patients to participate in PCOR</td>
<td></td>
<td></td>
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<tr>
<td>• Establishing methodology for the study of rare diseases</td>
<td></td>
<td></td>
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</tbody>
</table>
Figure 1: Traditional Process

**Investigator-Generated Research Just One Part of the Process**

- PCORI issues broad funding announcements
- Researchers partner with stakeholders to generate questions
- Researchers, stakeholders apply review criteria in their applications
- Peer review prioritizes applications by level of alignment with criteria

Diverse Research Portfolio answering key questions for patients and clinicians
Figure 2: Unique Process

**Patient/Stakeholder-Led Approach**

- PCORI and stakeholders generate and prioritize questions based on review criteria
- PCORI issues specific, funding announcements for highest priority topics
- Researchers and stakeholders develop responsive proposals
- Peer review prioritizes applications by level of alignment with criteria

**Diverse Research Portfolio answering key questions for patients and clinicians**
PCORI’s Process Transparent, Rigorous

Topic Generation *(Through Multiple Modes)*

Gap Confirmation

Research Prioritization

Final Selection for Specific PFAs (PCORI Board)

Patients & Stakeholders:
- Web Page
- Social Media
- Workshops
- Continuous Portfolio Review

PCORI
- AHRQ gaps
- NIH gaps

Other agencies:
- AHRQ gaps
- NIH gaps

Research Opportunities
## Quantitative VOI Estimates

<table>
<thead>
<tr>
<th>Topic Area</th>
<th>VOI Estimate ($ Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR in Knee Trauma</td>
<td>8</td>
</tr>
<tr>
<td>LVAD as Destination Therapy</td>
<td>8</td>
</tr>
<tr>
<td>Azithromycin vs. Augmentin in Sinusitis (ignoring costs)</td>
<td>40</td>
</tr>
<tr>
<td>Pegylated Liposomal Doxurubicin in Ovarian CA</td>
<td>206</td>
</tr>
<tr>
<td>Azithromycin vs. Augmentin in Sinusitis (including costs)</td>
<td>250</td>
</tr>
<tr>
<td>Treatment of Intermittent Claudication</td>
<td>573</td>
</tr>
<tr>
<td>Cognitive Behavioral Therapy for Post-partum Depression</td>
<td>603</td>
</tr>
<tr>
<td>Typical/Atypical Antipsychotics in Schizophrenia</td>
<td>124,658</td>
</tr>
</tbody>
</table>
Stakeholder Engagement in PCORI-funded Research

- Key stakeholders are engaged early and throughout the research process.
- PCORI will score applications on how meaningfully patients and stakeholders are engaged.
- Key stakeholders include those for whom the results of the research will be relevant:
  - Patients
  - Nonprofessional Caregivers
  - Clinicians (e.g. Physicians, Nurses, Pharmacists, Counselors, and other providers of care and support services)
  - Patient-Advocacy Groups
  - Community Groups
  - Researchers
  - Health-Related Associations
  - Policy Makers
  - Institutions, Including Organizational Providers, Purchasers, Payers, and Industry
What roles should patients and stakeholders play in research teams?

The engagement of patients and stakeholders should include:

• Participation in formulation of research questions;
• Defining essential characteristics of study participants, comparators, and outcomes;
• Monitoring of study conduct and progress; and
• Dissemination of research results.

Source: PCORI PFA Application Guidelines (Sec. 3.1.3.4) http://www.pcori.org/assets/PFAguidelines.pdf
The PCORI Methodology Committee
The Methodology Committee is charged with making **recommendations** regarding methods for patient-centered outcomes, which includes:

- **guidance** about the **appropriate use of methods** in such research
- **establishing priorities to address gaps** in research methods or their application
Patient-Centered Outcomes Research Institute


PCORI Methodology Committee

Mark Helfand, Alfred Berg, David Flum, Sherine Gabriel, and Sharon-Lise Normand, Editors

Published for Public Comment July 23, 2012
The mandate for PCORI’s Methodology Committee is to define methodological standards, recommended actions and a translation table to guide health care stakeholders towards the best methods for patient-centered outcomes research (PCOR).

Rigorous methods are essential to building trust in research findings.

The report is the necessary catalyst for scientifically rigorous, patient-centered outcomes research that can inform decision-making.

Once Report is revised and accepted by the PCORI Board of Governors, future PCORI funding applicants will be expected to reference the Standards in their applications and use the Standards in their PCORI funded research.
Formulating Research Questions

General and Crosscutting Research Prioritization

Causal Inference

Data Networks

General and Crosscutting

Adaptive Trials

Heterogeneity of Treatment Effects

Data Registries

Missing Data

Diagnostic Testing

Eg. Assess Instrumental Variable Assumptions (Std # 7.2.6)

Eg: Engage Patient Informants, Persons Representative of the Population of Interest, in All Phases of PCOR (Std # 4.1.1)
Heterogeneity of Treatment Effects

- People react differently to treatment
- Problems with summarizing/ averages
  - Answers across lots of types of people are not useful for decisions
  - Do not answer “what will happen to people like me”
- Challenges in dividing patients in ‘right’ groups
Heterogeneity (HTE) Standards

7.3.1 **State the Goals** of HTE Analyses

7.3.2 For Confirmatory and Descriptive HTE Analyses, Pre-specify Subgroups and Outcomes; for Confirmatory HTE Analyses, **Pre-specify Hypotheses** for Each Subgroup Effect

7.3.3 For Confirmatory HTE Analyses, **Report apriori Statistical Power**

7.3.4 For Any HTE Analysis, **Perform an Interaction Test** and Report Sufficient Information on Treatment Effect Estimates

7.3.5 For Exploratory HTE Analyses, **Discuss Findings in the Context of** Study Design and Prior Evidence

7.3.6 For Any HTE Analysis, **Report All** Pre-specified Analyses and, at Minimum, the Number of Post-hoc Analyses, Including Number of Subgroups and Outcomes Analyzed
How will PCORI Change Clinical Trials Methods?

• Through their use in PCORI trials
• Through establishment and dissemination of standards that may be used in other contexts
  – But will people use them?
  – If they know about them and know how to use them? If they want to? If they matter?
• Through methods research
  – New methods
    • Critical, though not all methodological problems can be solved
  – Research on whether/when methods change findings/outcomes
    • Self-selection as example
Background: Self-selection

- CEA often used to assess benefits of medical care relative to costs
  - QALYs reflect effectiveness of health in length and quality of life $= \sum \beta^t S_i Q_i$
  - Calculate cost/QALY and compare to some threshold (e.g. $\$100K/QALY$)
- Traditional CEA models use preferences (utilities) that average across individuals
- However, utilities may vary across individuals or populations and influence expected benefits of treatment
  - Implies effectiveness/cost-effectiveness can vary for individuals or populations that differ in preferences
- Preferences can also affect treatment choice
  - Specifically, patients whose preferences favor an option may be more likely to choose it
- This “self-selection” will tend to improve effectiveness and cost-effectiveness compared to traditional models that neglect self-selection
Standard CEA with Heterogeneous Individuals

Blue Dots = Treated Patients
Perfect Self-Selection

Blue Dots=Pts gain from Tx; Orange Dots=Pts lose from Tx
Effect of Perfect Self-Selection on CEA

Blue Dots=Pts gain from Tx; Orange Dots=Pts lose from Tx (reject)
Empirical Self-Selection

Blue Dots=Pts choose Tx; Orange Dots=Pts reject Tx
Empirical Self-Selection

Blue Dots=Pts choose Tx; Orange Dots=Pts reject Tx
## Results: Intensive Glucose Control vs. Conventional Control

<table>
<thead>
<tr>
<th>CE Approach</th>
<th>Group</th>
<th>N</th>
<th>Change in Costs ($)</th>
<th>Change in QALYs</th>
<th>CE Ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>Full Population</td>
<td>643</td>
<td>8072</td>
<td>-0.52</td>
<td>--</td>
</tr>
</tbody>
</table>
Blue dots--the cost-effectiveness values of individuals with an expected benefit from intensive therapy. Orange dots-- the cost-effectiveness values of individuals with a decrement in expected benefits with intensive therapy. M-- CE ratio for whole population. M’—CE ratio after self-selection.
### Results: Intensive Glucose Control vs. Conventional Control

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</tr>
<tr>
<td>Perfect Self-Selection</td>
<td>ΔQALY&gt;0</td>
<td>483</td>
<td>8155</td>
<td>0.40</td>
<td>20K</td>
</tr>
<tr>
<td></td>
<td>ΔQALY&lt;0</td>
<td>151</td>
<td>7893</td>
<td>-3.50</td>
<td>--</td>
</tr>
</tbody>
</table>
Empirical Self-Selection Effect for Intensive Therapy

Blue dots-- cost-effectiveness values for individuals who identify their care as intensive therapy with insulin. Orange dots-- cost-effectiveness values for all other individuals. M-- CE ratio for orange dot individuals. M'-- CE ratio for blue dot individuals.
## Results: Intensive Glucose Control vs. Conventional Control

<table>
<thead>
<tr>
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<th>Group</th>
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<td>7893</td>
<td>-3.50</td>
<td>--</td>
</tr>
<tr>
<td>Empirical Self-Selection</td>
<td>Self-identified intensive therapy</td>
<td>189</td>
<td>7951</td>
<td>0.19</td>
<td>42K</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>416</td>
<td>8138</td>
<td>-0.89</td>
<td>--</td>
</tr>
</tbody>
</table>
Cost-effectiveness of Intensive Therapy for Diabetes and Self-selection by Education

<table>
<thead>
<tr>
<th>CE Approach</th>
<th>Group</th>
<th>Less than HS Education</th>
<th>High School Graduate</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Δ COST</td>
<td>Δ QALY</td>
</tr>
<tr>
<td>Std. Full</td>
<td>188</td>
<td>7,928</td>
<td>-0.53</td>
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<tr>
<td>Perf. Exp.</td>
<td>139</td>
<td>7,886</td>
<td>0.37</td>
</tr>
<tr>
<td>Self-Sel.</td>
<td>Exp Ben</td>
<td>49 (26%)</td>
<td>8,048</td>
</tr>
<tr>
<td></td>
<td>Exp Harm</td>
<td>53 (28%)</td>
<td>7,696</td>
</tr>
<tr>
<td>Emp. Exp.</td>
<td>Exp Ben</td>
<td>135 (72%)</td>
<td>8,020</td>
</tr>
<tr>
<td>Self-Sel.</td>
<td>Exp Harm</td>
<td>135 (72%)</td>
<td>8,020</td>
</tr>
</tbody>
</table>
Thank You
Limitations

- Limitations of the diabetes simulation model
  - Model only compares HbA1c of 7.9% and 7%
- Other definitions of intensive therapy
  - E.g., actual treatments used, HbA1c
- Unclear if utilities are valid or stable over time
  - Cognitive dissonance might undermine predictive validity / welfare interpretation
- Assumes patient utilities relevant for CEA
- Describes cost-effectiveness of intensive therapy in this context
  - Would differ if intensive therapy used differently (e.g. decision aids)
Conclusions

• Accounting for self-selection can change cost-effectiveness of preference sensitive conditions
  – Intensive therapy changes from harmful to cost-effective at all ages
  – Effect mediated by increasing selectivity by age
• Cost-effectiveness analyses based on models need to measure choices and account for self-selection
• Policies to improve medical decision making may be highly valuable
  – Decision Aids
  – Copayments
• Education can be an important contributor to disparities in effectiveness and cost-effectiveness
  – Policies to improve decision making may vary in their effects by educational status
Questions and Future Work

• Is self-selection of medical treatments common and does it often vary by education or other patient-level factors, and is it an important cause of health disparities?

• If yes, what are the mechanisms that cause this?
  – Patient communication, understanding, assertiveness
    • Might decision aids especially help the less educated?
  – Physician responsiveness
  – Insurance coverage, freedom from cost concerns
    • Might copayments especially hurt the less educated?

• If yes, what is the right policy response?
  – Patient empowerment
  – Physician training/monitoring/incentives
  – Improve insurance coverage
  – Should coverage altered based on effectiveness of use?
Adaptive Trials

• Flexible not fixed
  – Adjust based on results that are monitored during study period

• Advantages
  – More relevant
  – Faster results
  – Less expensive (sometimes)

• Challenges
  – Complex to conduct
  – Need to be careful not to introduce bias into the study
8.1.1 **Specify** Planned Adaptations and Primary Analysis

8.1.2 **Evaluate Statistical Properties** of Adaptive Design

8.1.3 Specify Structure and Analysis Plan for Bayesian Adaptive Randomized Clinical Trial Designs

8.1.4 Ensure Clinical Trial **Infrastructure Is Adequate** to Support Planned Adaptation(s)

8.1.5 Use the **CONSORT** Statement, with Modifications, to Report Adaptive Randomized Clinical Trials
END
Effects of Decision Aids

• Accounting for self-selection provides a framework to value guidelines, decision-aids, or improved patient-doctor communication that can make care more consistent with patient preferences
Motivation for Decision Aids

Blue Dots=Pts getting Tx; Orange Dots=Pts not getting Tx
Aim of Decision Aids

Blue Dots = Pts getting Tx; Orange Dots = Pts not getting Tx
Value of Decision Aids

Blue Dots=Pts getting Tx; Orange Dots=Pts not getting Tx
Value of Decision Aid

• Effectiveness = \( \sum_{\text{Pts} \Delta} \Delta e \)
• Costs = \( \sum_{\text{Pts} \Delta} \Delta c \)
• Total Benefit
  Cost-Benefit = \( (1/\lambda) \sum_{\text{Pts} \Delta} \Delta e + \sum_{\text{Pts} \Delta} \Delta c \)
  Net Health Benefit = \( \sum_{\text{Pts} \Delta} \Delta e + \lambda \sum_{\text{Pts} \Delta} \Delta c \)
Per Capita Value of Identifying Best Population-level and Individual-level Care in Prostate Cancer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Population-level Therapy</td>
<td>$29</td>
</tr>
<tr>
<td>Best Individual-level Therapy</td>
<td>$2958</td>
</tr>
</tbody>
</table>
Copayments

• Self-selection suggests a framework to design co-payment systems to enhance the cost-effectiveness of therapies
Motivation for Copayment

Blue Dots = Pts getting Tx; Orange Dots = Pts not getting Tx
Motivation for Copayment ($\pi_c$)

Blue Dots=Pts getting Tx; Orange Dots=Pts not getting Tx
Per Capita Value of Identifying Best Population-level and Individual-level Care in Prostate Cancer with Full Insurance

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Population-level Therapy</td>
<td>$29</td>
</tr>
<tr>
<td>Best Individual-level Therapy</td>
<td>$2958</td>
</tr>
<tr>
<td>Best Individual-level Therapy with Full Insurance</td>
<td>$41</td>
</tr>
</tbody>
</table>
Conclusions

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  – Intensive therapy changes from harmful to cost-effective at all ages
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  – Decision Aids
  – Copayments

• Education can be an important contributor to disparities in effectiveness and cost-effectiveness
  – Policies to improve decision making may vary in their effects by educational status
Chapter 1. Introduction
Chapter 2. How the Methodology Committee Developed the Recommended Standards
Chapter 3. Overview of the Standards
Chapter 4. Methodological Standards for Patient-Centeredness of Research Proposals and Protocols
Chapter 5. Methods for Prioritizing Patient-Centered Outcomes Research
Chapter 6. Choosing Data Sources, Research Design, and Analysis Plan: Translation Framework and Development of a Translation Table
Chapter 7. General and Cross-Cutting Research Methods
Chapter 8. Design-Specific Methods
Chapter 9. Next Steps
3.1.3 Identify and Assess Participant Subgroups

3.1.4 Select Appropriate Interventions and Comparators

7.1.1 Assess Data Source Adequacy

7.1.2 A Priori, Specify Plans for Data Analysis that correspond to Major Aims

7.1.3 Document Validated Scales and Tests

7.1.4 Use Sensitivity Analyses to Determine the Impact of Key Assumptions

7.1.5 Provide Sufficient Information to Allow for Assessment of Internal and External Validity
7.2.1 Define Analysis Population Using Information Available at Study Entry

7.2.2 Describe Population that Gave Rise to the Effect Estimate(s)

7.2.3 Precisely Define the Timing of the Outcome Assessment Relative to the Initiation and Duration of Intervention

7.2.4 Measure Confounders before Start of Exposure

7.2.5 Assess Propensity Score Balance

7.2.6 Assess Instrumental Variable Assumptions
7.4.1 Describe Methods to **Prevent and Monitor** Missing Data

7.4.2 Describe **Statistical Methods** to Handle Missing Data

7.4.3 **Use Validated Methods** to Deal with Missing Data that Properly Account for Statistical Uncertainty due to Missingness, Such as Multiple Imputation. All Forms of Single Imputation Are Discouraged

7.4.4 Record and Report All **Reasons for Dropout** and Missing Data, and Account for All Patients in Reports

7.4.5 **Examine Sensitivity** of Inferences to Missing Data Methods and Assumptions, and Incorporate into Interpretation.
Data Networks

• Explosion of new data
  – Electronic Medical Records (EMRs)
  – Linking data sets
  – New data collection technology

• Need to assure
  – Patient Privacy
  – Data quality
  – Consistency
7.5.1 Data Integration Strategy
7.5.2 Risk Assessment Strategy
7.5.3 Identity Management and Authentication of Individual Researchers
7.5.4 Intellectual Property Policies
7.5.5 Standardized Terminology Encoding of Data Content
7.5.6 Metadata Annotation of Data Content
7.5.7 Common Data Model
Registries

• Database
  – Information generated during normal care
  – Focused on a disease or treatment
  – Data from multiple sources

• Challenges
  – Privacy
  – Data Quality and Consistency
  – Sorting out cause and effect
8.2.1 Describe **Data Linkage Plans**, if Applicable
8.2.2 **Plan Follow-up** Based on the Registry Objective(s)
8.2.3 Describe **Data Safety and Security**
8.2.4 Take Appropriate Steps to Ensure **Data Quality**
8.2.5 Document and **Explain Any Modifications** to Protocol
8.2.6 Collect Data **Consistently**
8.2.7 Enroll and Follow Patients **Systematically**
8.2.8 Monitor and Take Actions to **keep Loss to Follow-up to an Acceptable Minimum**
8.2.9 Use Appropriate Statistical Techniques to **Address Confounding**
8.3.1 Specify Clinical Context and Key Elements of Diagnostic Test Study Design

8.3.2 Study Design Should Be Informed by Investigations of the Clinical Context of Testing

8.3.3 Assess the Effect of Factors Known to Affect Diagnostic Performance and Outcomes

8.3.4 Structured Reporting of Diagnostic Comparative Effectiveness Study Results

8.3.5 Give Preference to Randomized Designs of Studies of Test Outcomes
Translation Table maps research methods to specific research questions

**Research Question**
- Prioritized research questions
- Formulated patient-centered research question

**Interface**
- Defines relative importance of *Evidence Characteristics*
- Identify *intrinsic and extrinsic study characteristics*
- Facilitates choices/tradeoffs on a set of dimensions

**Translation Framework**
- Matches research question to study design, data source, analytic strategy
- Separate *Frameworks* for different *Research Dimensions*, e.g. therapeutics, diagnostics, evidence synthesis, etc.
What it means for you?

• Recommended standards are known to this audience

• Useful as training tools

• Useful to identify and prioritize gaps in methodological knowledge

• Serve as a mechanism to engage the broader community – in workshops, advisory boards, public comment periods etc.

• Guide the future of PCORI
A Special Thank You to...

Editing Team/ Interim Researchers

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Heidi D. Nelson, MD, MPH
Ed Reid, MS, MAT
Annette Totten, PhD
Tim Carey, MD, MPH
Howard Balshem
Justine Siedenfeld
Crystal Smith-Spangler, MD

Workshop External Attendees

Kate Bent, PhD
Karl Claxton, PhD
Christine Laine, MD, MPH, FACP
Richard Nakamura, PhD
Evelyn Whitlock, MD, MPH
Tanisha Carino, PhD
Steve Phurrough, MD, MPA
Cynthia Chauhan, M.S.W.
Pat Deverka, M.D.
Kay Dickersin, M.A., Ph.D
Lorraine Johnson, J.D., M.B.A
David Osoba, B.Sc., M.D., F.R.C.P.C
Dennis Revicki, Ph.D.
John Santa, M.D., M.P.H.
Albert Wu, M.D., M.P.H

Principal Investigators and Research Team Members

- University of Maryland, Pharmaceutical Health Services Research Department (Daniel Mullins, Ph.D.)
- Mayo Clinic, Knowledge and Evaluation Research Unit (M. Hassan Murad, M.D., MPH)
- Oregon Health & Science University, The Center for Evidence-Based Policy (Pam Curtis, M.S.)
- Oxford Outcomes, Ltd., Patient Reported Outcomes (Andrew Lloyd, Ph.D.)
- Northwestern University/UNC Chapel Hill (Zeeshan Butt, Ph.D./Bryce Reeve, Ph.D.)
- Johns Hopkins University (Tianjing Li, MD, MHS, PhD)
- Johns Hopkins University – School of Medicine (Ravi Varadhan, PhD)
- Berry Consultants (Scott Berry)
- Brown University (Constantine Gatsonis, PhD)
- Brigham and Women’s hospital and Harvard Medical School (Josh Gagne, PharmD, ScD)
- Outcome Sciences, Inc. (A Quintiles Company) (Richard Giklich, MD)
- University of California San Diego (UCSD) (Lucila Ohno-Machado, MD, PhD)
- Hayes, Inc. (Petra Nass, PhD)
- NORC at the University of Chicago (David Rein, PhD)
- Duke Evidence-Based Practice Center (Evan Myers, MD, MPH)
- Medical College of Wisconsin (Theodore Kotchen, MD)

Electronic Data Systems Interviewees

*57 interviewees from:
- Government
- Associations
- Academia
- Commercial
- Health Care Providers

Respondents to RFI — Input Draft Translation Table Framework

*Over 15 submissions received

PCORI Staff

Interim Consultants
Methodology Report

- Submitted to the PCORI Board of Governors on May 10, 2012
- Accepted by the PCORI Board of Governors on May 21, 2012
- **A public comment period on the draft report:** Through September 14 2012
- Revisions go to the Board of Governors November 2012 for final approval
Thank You!
What Makes PCORI Funding Different?

• Special features include:
  – Patient & Stakeholder Engagement Plan
  – Dissemination and Implementation Assessment
  – Reproducible and Transparent Research Plan
  – PCORI Criteria Outlined by Statute
  – Complies with Methodology Standards
  – User-friendly announcements to encourage broader range of applicants

Key 2012 Accomplishments

- First National Patient and Stakeholder Dialogue Event (Feb. 27)
- Adopted Revised Definition of Patient-Centered Outcomes Research in Response to Public Comment (Mar. 5)
- Completed 53-day Public Comment Period on National Priorities and Research Agenda (Mar. 15)
- **First Draft Methodology Report delivered to Board (May 10)**
- Adopted Revised National Priorities and Research Agenda in Response to Public Comment (May 21)
- **Issued First Funding Applications for Primary Research (May 22)**
- Launched online registration system to receive applications; issued call for reviewers (June 1)
Support

• Disparities
  – National Pharmaceutical Council

• Self-selection
  – American Association of Medical Colleges
  – Centers for Disease Control
  – Pharmaceutical Health Outcomes Group

• Aging
  • National Institute of Aging
Heterogeneity and Health Disparities

• Heterogeneity
  – People differ in many ways that produce variation in treatment effects
  – Personal (e.g., genes, educ.) and social factors (e.g., health care quality) may contribute
  – Choices they make – disadvantageous and advantageous
    • Advantageous choices (self-selection) often neglected

• Health Disparities
  – Disadvantage due to race, ethnicity, socioeconomic factors (e.g., education)
  – Personal (e.g., genes, educ.) and social factors (e.g., health care quality) may contribute
  – Choices they make – disadvantageous and advantageous

• How might these interact?
  – Could inadequate responsiveness to heterogeneity contribute to health disparities?
  – Could disadvantaged individuals/groups be less likely to have
    • Economic resources needed to access care specific to their individual needs?
    • Attentive clinicians who will identify and respond to their individual needs?
    • Make decisions consistent with their preferences?
Overall Aims

• To examine whether self-selection in the presence of heterogeneity affects the effectiveness and cost-effectiveness of intensive therapy for diabetes
• To test whether education affects self-selection

Outline
– Theory/Background
  • Theory of self-selection
  • Rationale for studying self-selection in cost-effectiveness analysis (CEA) of intensive therapy for diabetes
    – Self-selection by age
  • Rationale for studying effects of education
– Methods
– Results
– Conclusions
– Implications
Effects of Education on the Cost-Effectiveness of Treatment

- Complex associations between education and health
  - Education increases return to health
  - Health increases return to education
  - Both may be affected by third variable (ability)
- Education improves efficiency of health production
  - Becker (1965), Michael (1972), Grossman (1972)
  - Self-management/adherence -- Goldman and Smith (2002)
- Might selection of treatments vary by education?
  - Better patient communication, understanding, assertiveness
  - More physician responsiveness
  - Greater insurance coverage, freedom from financial concerns
  - Tend to suggest effectiveness, and perhaps cost-effectiveness should improve, ceteris paribus
Background: Diabetes in the Elderly

- Diabetes care guidelines call for intensive lowering of glucose among younger patients.
- However, unclear if this should apply to older patients:
  - Gains in life expectancy smaller
  - Side effects of treatment may dominate
  - CE models of intensive therapy in older patients:
    - Minimal or even negative effects on QALYs
    - Not cost-effective
  - Know many older patients refuse intensive therapy
- Suggests self-selection may have important effects on CEA in diabetes treatment by age
Methods: Interviews

- Interviewed 678 diabetes patients attending University of Chicago and an affiliated community hospital in English or Spanish
  - Age > 18
  - Excluded if dementia or Folstein mini-mental status <17
- Preferences (utilities) obtained by time trade-off questions
- Utilities obtained for
  - Conventional and intensive glucose lowering (using insulin or oral medications)
  - Blindness, end-stage renal disease, lower extremity amputation
- Data on treatment choices and patient characteristics (including education) collected by medical records review
Methods: Modeling

- CDC simulation model of intensive therapy for type 2 diabetes
  - HbA1c 7.9% vs. 7%

- Used patient-specific data to calculate predicted patient-level effects on costs, QALYs
  - Age, sex, race, duration of diabetes
  - Utilities for intensive/conventional therapy, diabetic complications

- Analyses of effectiveness and cost-effectiveness of:
  - Intensive vs. conventional therapy
  - Contrast all patients vs. perfect self-selection vs. empirical self-selection
  - Study effects age <40, 40-70, >70
## Patient Characteristics (N=678)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years (SD)</td>
<td>62 (14)</td>
</tr>
<tr>
<td>Female, %</td>
<td>58</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>African American, %</td>
<td>39</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>34</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>24</td>
</tr>
<tr>
<td>Education &lt; High School Graduate, %</td>
<td>57</td>
</tr>
<tr>
<td>Mean Duration of Diabetes, years (SD)</td>
<td>9.9 (8.5)</td>
</tr>
</tbody>
</table>
## Age Groups

<table>
<thead>
<tr>
<th>Age groups</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>45 (7)</td>
</tr>
<tr>
<td>40-70</td>
<td>405 (60)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>228 (34)</td>
</tr>
</tbody>
</table>
# Complication Utilities

<table>
<thead>
<tr>
<th>Complication</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>0.65 (0.63, 0.67)</td>
</tr>
<tr>
<td>Mild Stroke</td>
<td>0.71 (0.68, 0.73)</td>
</tr>
<tr>
<td>Severe Stroke</td>
<td>0.32 (0.29, 0.34)</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>0.67 (0.65, 0.70)</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.56 (0.53, 0.59)</td>
</tr>
<tr>
<td>Diabetic Retinopathy</td>
<td>0.54 (0.51, 0.57)</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.40 (0.37, 0.42)</td>
</tr>
<tr>
<td>Mild Kidney Disease</td>
<td>0.66 (0.63, 0.69)</td>
</tr>
<tr>
<td>Kidney Failure</td>
<td>0.36 (0.34, 0.39)</td>
</tr>
</tbody>
</table>
## Treatment Utilities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Glucose Control</td>
<td>0.77 (0.75, 0.80)</td>
</tr>
<tr>
<td>Intensive Glucose Control</td>
<td>0.69 (0.66, 0.71)</td>
</tr>
<tr>
<td>Complication</td>
<td>Mean, Persons on Intensive Therapy</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Angina</td>
<td>0.67</td>
</tr>
<tr>
<td>Mild Stroke</td>
<td>0.71</td>
</tr>
<tr>
<td>Severe Stroke</td>
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</tr>
<tr>
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<td>0.42</td>
</tr>
<tr>
<td>Mild Kidney Disease</td>
<td>0.66</td>
</tr>
<tr>
<td>Kidney Failure</td>
<td>0.38</td>
</tr>
</tbody>
</table>
## Treatment Utilities by Treatment Status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean, Persons on Intensive Therapy</th>
<th>Mean, Persons not on Intensive Therapy</th>
<th>Difference, Intensive – Not Intensive (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Glucose Control</td>
<td>0.78</td>
<td>0.77</td>
<td>-0.01 (-0.06, 0.04)</td>
</tr>
<tr>
<td>Intensive Glucose Control</td>
<td>0.76</td>
<td>0.65</td>
<td>-0.11 (-0.16, -0.05)</td>
</tr>
</tbody>
</table>
# Results: Intensive Glucose Control vs. Conventional Control

<table>
<thead>
<tr>
<th>CE Approach</th>
<th>Group</th>
<th>N</th>
<th>Change in Costs ($)</th>
<th>Change in QALYs</th>
<th>CE Ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>Full Population</td>
<td>643</td>
<td>8072</td>
<td>-0.52</td>
<td>--</td>
</tr>
</tbody>
</table>
Blue dots--the cost-effectiveness values of individuals with an expected benefit from intensive therapy. Orange dots-- the cost-effectiveness values of individuals with a decrement in expected benefits with intensive therapy. M-- CE ratio for whole population. M’—CE ratio after self-selection.
## Results: Intensive Glucose Control vs. Conventional Control

<table>
<thead>
<tr>
<th>CE Approach</th>
<th>Group</th>
<th>N</th>
<th>Change in Costs ($)</th>
<th>Change in QALYs</th>
<th>CE Ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard</strong></td>
<td>Full Population</td>
<td>643</td>
<td>8072</td>
<td>-0.52</td>
<td>--</td>
</tr>
<tr>
<td><strong>Perfect Self-Selection</strong></td>
<td>ΔQALY&gt;0</td>
<td>483</td>
<td>8155</td>
<td>0.40</td>
<td>20K</td>
</tr>
<tr>
<td></td>
<td>ΔQALY&lt;0</td>
<td>151</td>
<td>7893</td>
<td>-3.50</td>
<td>--</td>
</tr>
</tbody>
</table>
Empirical Self-Selection Effect for Intensive Therapy

Blue dots-- cost-effectiveness values for individuals who identify their care as intensive therapy with insulin. Orange dots-- cost-effectiveness values for all other individuals. M-- CE ratio for orange dot individuals. M'-- CE ratio for blue dot individuals.
## Treatment Effects by Age

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Change in Costs ($)</th>
<th>Change in QALYs</th>
<th>P-value for change in QALYs</th>
<th>CE Ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=40</td>
<td>44</td>
<td>5693</td>
<td>-1.48</td>
<td>0.26</td>
<td>---</td>
</tr>
<tr>
<td>41-70</td>
<td>390</td>
<td>8418</td>
<td>-0.50</td>
<td>&lt;0.01</td>
<td>---</td>
</tr>
<tr>
<td>&gt;70</td>
<td>209</td>
<td>7926</td>
<td>-0.36</td>
<td>&lt;0.01</td>
<td>---</td>
</tr>
</tbody>
</table>
## Empirical Self-Selection by Age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Self-Selection group</th>
<th>N</th>
<th>Change in Costs ($)</th>
<th>Change in QALYs</th>
<th>CE Ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>Self-identified intensive</td>
<td>14</td>
<td>4888</td>
<td>0.59</td>
<td>8K</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>28</td>
<td>6012</td>
<td>-2.63</td>
<td>--</td>
</tr>
<tr>
<td>40-70</td>
<td>Self-identified intensive</td>
<td>123</td>
<td>8178</td>
<td>0.18</td>
<td>45K</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>248</td>
<td>8543</td>
<td>-0.87</td>
<td>--</td>
</tr>
<tr>
<td>&gt;70</td>
<td>Self-identified intensive</td>
<td>52</td>
<td>8240</td>
<td>0.10</td>
<td>82K</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>140</td>
<td>7847</td>
<td>-0.59</td>
<td>--</td>
</tr>
</tbody>
</table>
### Self-reported Intensive Glucose Control by Age

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Self-reported intensive glucose control, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>33</td>
</tr>
<tr>
<td>&lt;40</td>
<td>39</td>
</tr>
<tr>
<td>40-70</td>
<td>34</td>
</tr>
<tr>
<td>&gt;70</td>
<td>27</td>
</tr>
</tbody>
</table>