Patient-Centered Outcomes Research Institute

Methodology Committee Update
May 16, 2011
(6) ESTABLISHING THE METHODOLOGY COMMITTEE

(A) IN GENERAL. The Institute shall establish..

(B) APPOINTMENT AND COMPOSITION....

(C) FUNCTIONS. - Subject to subparagraph (D), the methodology committee shall work to develop and improve the science and methods of comparative clinical effectiveness research by, **not later than 18 months** after the establishment of the Institute, directly or through subcontract, developing and periodically updating the following:

(i) Methodological Standards for research
(ii) A Translation Table
(i) Methodological standards for research (a report).

... shall provide specific criteria for **internal validity**, **generalizability**, **feasibility** and **timeliness of research** and for **health outcomes measures**, **risk adjustment** and other relevant aspects of research and assessment with respect to the design of the research. .... shall be **scientifically based** and include methods by which **new information, data or advances in technology** are considered and incorporated into ongoing research projects by the Institute, as appropriate. ... **input from relevant experts, stakeholders and decision makers** and shall provide opportunities for **public comment**... shall include methods by which **patient subpopulations** can be accounted for and evaluated in different types of research... build on existing work on methodological standards for **defined categories** of health interventions and for each of the major categories of CER (determined as of the date of enactment of the Patient Protection and Affordable care Act).
(ii) A Translation Table

...designed to provide guidance and act as a reference for the Board to determine research methods that are most likely to address each specific research question.

(D) CONSULTATION AND CONDUCTION OF EXAMINATIONS

....MC may consult and contract with IOM and academic nonprofit or other private and governmental entities with relevant expertise to carry out activities described in subparagraph (C) and may consult with relevant stakeholders to carry out such activities.

(E) REPORTS....submit reports to the Board on committee performance of the functions described in subparagraph (C). Reports shall contain recommendations for the Institute to adopt methodological standards developed and updated by the MC as well as other actions deemed necessary to comply with such methodological standards.
Progress to date & Future Directions:

1. Foundational Tasks
   - Charter – Approval
   - Working Definition - Approval of Next Steps
   - Work-Plan

2. Core Tasks
   - Methodological Standards for PCOR
   - A Translation Table

3. Evaluating and Updating Core Tasks

4. Provide Methodological Expertise
Methodology Work Cycle

Foundational Tasks:
- Working Definition of PCOR
- Establish Operating Principles & Guidelines: Charter; WorkPlan
Foundational Tasks
Team:
Robin Newhouse, PhD, RN
Michael Lauer, MD
Naomi Aronson, PhD
Alfred Berg, MD, MPH
Steven Goodman, MD, PhD
## Tactics and Timeline

<table>
<thead>
<tr>
<th>Task</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Draft Charter</td>
<td>3/23/11</td>
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<tr>
<td>Charter Subgroup Meetings</td>
<td>3/23-4/18/11</td>
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<tr>
<td>Draft Charter to Committee Chairs</td>
<td>4/22/11</td>
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<tr>
<td>Revisions to Draft Charter</td>
<td>4/25/11</td>
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<tr>
<td>MC approval of Charter</td>
<td>4/26/11</td>
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<tr>
<td>PCORI Board Conf. Call</td>
<td>5/10/11</td>
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<tr>
<td>Submit for Board review and approval</td>
<td>5/16/11</td>
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Purpose

The Methodology Committee ("Committee") shall make recommendations to the Board of Governors ("Board") regarding methods for patient-centered outcomes research......

Membership:

The Committee shall consist of up to 15 members who are appointed by the Comptroller General of the United States......

Committee Operations

The Committee shall meet upon the call of the Committee Chair, upon the call of a majority of its members, or upon the call of the Board Chair .......

Responsibilities

The Committee shall have the responsibility of making recommendations to the Board of Governors on the following matters .......
Request Approval
Team:

David Flum, MD, MPH
Mary Tinetti, MD
Mark Helfand, MD, MS, MPH
Jean Slutsky, PA, MSPH
Sebastian Schneeweiss, MD, ScD
Patient Centered Outcomes Research (PCOR) helps people make informed healthcare decisions and allows their voice to be heard in assessing the value of healthcare options. It answers questions like, “Given my personal characteristics, conditions and preferences, what should I expect will happen to me?”, “What are my options and what are the benefits and harms of those options?” and “What can I do to improve the outcomes that are most important to me?”

The characteristics of PCOR:

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, 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

PCOR may also focus on optimizing outcomes while addressing burden to individuals, resource availability, and other stakeholder perspectives.
Next Steps

1. Methodology Committee to adopt as a working definition to guide its work

2. Invite detailed input from Board, gather input from stakeholders and the public

3. Synthesize input and revise accordingly

4. Bring revised Definition for final Board consideration
Request Approval of Next Steps
Team:
Brian Mittman, PhD
Michael Lauer, MD
Robin Newhouse, PhD, RN
Gail Shearer, MPP
Jane Van Dervoort, BS
Consolidated Work Plan

Combines individual plans to provide an overall “roadmap” for MC work.

1. Foundational tasks (Objectives 1-4)
2. Core tasks to develop MC’s key deliverables (Objectives 5-10)
3. Continuing tasks to implement and maintain the deliverables and facilitate their effective use.
4. Supplementary tasks such as providing additional input and guidance to the Board.

Resources required for each MC activity include:

1. MC and BoG members
2. PCORI staff (existing and to-be-hired, eg. researchers)
3. Existing contractors (e.g., communications) and new contractors, including entities such as the Institute of Medicine (IoM)
4. Meetings, workshops etc. (including external input)
<table>
<thead>
<tr>
<th>Deadline</th>
<th>Deliverable</th>
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<tbody>
<tr>
<td>July 18, 2011</td>
<td>Review of Existing Standards/Guidance &amp; Evidence Map</td>
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<td>Advisory Groups/External Stake-holder Engagement Strategy</td>
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<td></td>
<td>Methodological Gaps</td>
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<td></td>
<td>Tier One Methodological Research Projects</td>
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<td></td>
<td>Criteria to Classify Proposed Standards</td>
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<td></td>
<td>Final Work Plan and Budget</td>
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<tr>
<td>Sept. 19, 2011</td>
<td>Methods Workshops</td>
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<tr>
<td></td>
<td>Advisory Groups Meetings</td>
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<tr>
<td></td>
<td>Detailed Outline of Methodology Report and Translation Table</td>
</tr>
<tr>
<td>Nov. 1, 2011</td>
<td>Methodology Report and Translation Table Draft</td>
</tr>
<tr>
<td>Nov. 14, 2011</td>
<td>Internal Review of Methodology Report and Translation Table</td>
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<tr>
<td>Feb. 2012</td>
<td>Gather stakeholder &amp; public input for Methodology Report and Translation Table</td>
</tr>
<tr>
<td>May 10, 2012</td>
<td>Final Submission of Methodology Report 1.0 and Translation Table 1.0</td>
</tr>
<tr>
<td></td>
<td>Strategy for annual review and update for 2.0</td>
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</tbody>
</table>
Core Tasks

Methodological Guidance for PCOR
Methodology addresses the ‘how’ of PCOR, e.g.

**Patient centered outcomes:**
- How to elicit patient values
- How to operationalize as valid reliable & usable instruments
- How these outcomes triangulate with conventional outcomes/measures
- How to quantify clinically meaningful increment of change

**Patients like me:**
- How to measure patient differences from average study results
- How to identify characteristics that predict differences
- How to incorporate complexities of care delivery settings

**Randomized vs observation studies:**
- How to minimize bias in observational data
- How to assess trade-offs
Methodology Cmt Work Cycle

- Identify critical Gaps in Knowledge and/or Implementation
- Review (Update) Landscape: Methodological Standards & Translation Table
- Advance Methodological Research and Innovation to address Gaps

Foundational Tasks → → → Staff
Proposed Approach

1. Review and understand intent
2. Conduct landscape review
   - Obtain expert, stake-holder, and public input: methods workshops
   - Review existing standards and guidance
   - Summarize other literature & commissioned white papers/reports/reviews
   - Method exists, strong evidence, wide implementation = best practice
   - Method exists, strong evidence – implementation gap
   - No method – true gap
4. Propose 1st set of Standards based on best practices
5. Propose Methodological Research Projects based on gaps
6. Create the translation table incorporating best practices and gaps as a guidance tool
Comparative effectiveness research: Policy context, methods development and research

(1) Meaningful involvement of patients, consumers, clinicians, payers, and policy makers in key phases of CER study design and implementation; (2) Development of methodological ‘best practices’ for the design of CER studies that reflect decision-maker needs and balance internal validity with relevance, feasibility and timeliness; and (3) Improvements in research infrastructure to enhance the validity and efficiency with which CER studies are implemented. The approach to addressing each of these issues should be informed by the understanding that the primary purpose of CER is to help health care decision makers make informed clinical and health policy decisions.
Developing methodological guidance for CER

“A crucial requirement of effective CER will be to employ the best analytical methods and data in studies of Clinical and Health Policy Questions.”

Matching CER research questions to appropriate CER methods

“The range of potential CER questions and the methods most suitable for answering them suggests that a goal of this next phase of CER research should include developing more systematic evidence on best practices that could be applied to the entire portfolio of CER methods….

Eventually, it will be useful to be able to complete a ‘translation table’ similar to the basic draft provided in Table II, which includes a few proposed uses for some categories of CER trials

… a clearer understanding of appropriate methods for non-experimental effectiveness research is essential. More specifically, methodological guidance can improve the rigor and internal validity of non-experimental studies….”
2. Conduct landscape review

Obtain expert, stake-holder, and public input:

- **AHRQ Community Forum**: The Community Forum initiative is funded under the American Recovery and Reinvestment Act of 2009 (ARRA). Its purpose is to improve and expand public and stake holder engagement in the Patient-Centered Outcomes Research (PCOR), or Comparative Effectiveness Research (CER), supported by the Agency for Healthcare Research and Quality (AHRQ).

- **Methods Workshops**: MC members have identified 22 organizations and 53 individuals to consider inviting to provide expertise.
2. Conduct landscape review

- Review existing standards and guidance
- Summarize other literature & commissioned white papers/reports/reviews.

- Method exists – best practice
- Method exists – implementation gap
- No method – true gap

- *MC members identified a total of 64 gaps*
4. Propose 1st set of standards based on best practices

5. Propose Tier 1 Methodological Research Projects based on gaps

6. Create the translation table incorporating best practices and gaps as a guidance tool
6. Create the translation table incorporating best practices and gaps as a guidance tool

But……….  

*We must imagine/visualize it first ......*
Examples of Translation Tables from the literature
<table>
<thead>
<tr>
<th>Description</th>
<th>Example</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pragmatic clinical trials</td>
<td>These RCTs are designed to demonstrate how a medical intervention works in a typical, real-world setting. Features of these trials can include all or a combination of the following: relaxed inclusion/exclusion criteria, relaxed protocol, longer term endpoints, active comparators, and outcome measures of relevance to patients, payers, and physicians [22]</td>
<td>Are newer types of antihypertensive agents, which are currently more costly to purchase on average, as good or better than diuretics in reducing coronary heart disease incidence and progression? [23] The ALLHAT study used patient relevant outcomes, had minimal inclusion criteria, and there was some flexibility in the dosing of the therapies. Because these trials are designed to meet the needs of decision-makers, the results tend to be more generalizable, the outcomes are useful to patients and physicians making tough clinical choices, and the trial maintains all or much of the scientific rigor of traditional RCTs.</td>
</tr>
<tr>
<td>Cluster RCTs</td>
<td>Groups of people are randomized to an intervention instead of randomizing individuals. These groups can be, for example, communities, regional payers, purchasers, delivery systems, clinics, etc. Individuals within a cluster will tend to resemble each other, which needs to be taken into account in the statistical analysis.</td>
<td>What is the comparative effectiveness of the American Cancer Society smoking cessation program versus the American Lung Association smoking cessation program? [24] In this study, different clinics adopted different smoking cessation programs. This approach is ideal for comparing alternative, established therapies with true equipoise, rather than new therapies, and common therapies rather than novel or high-profile therapies. Cluster RCTs can also provide a rigorous evaluation of the effectiveness of therapies in real-world settings, especially when consent by cluster is acceptable.</td>
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<tr>
<td>Bayesian / Adaptive trials</td>
<td>Unlike traditional RCTs, the Bayesian approach makes use of prior information on a medical intervention to estimate a priori distribution. This prior information is then combined with trial data to create a posterior distribution. Trial data can be analyzed frequently and compared with the prior information to inform the direction of the study.</td>
<td>What is the most effective treatment method for patients with a given biomarker profile? [25] The authors propose to adaptively randomize patients to one of four treatment groups with allocation based on prior accumulated data. The Bayesian approach incorporates prior information into the data analysis, which can lead to mid-course modifications to the trial design, and potentially avoid the need to start new separate trials to reflect knowledge gained during the course of the trial.</td>
</tr>
<tr>
<td>N-of-1 trials</td>
<td>N-of-1 trials are single event case studies to look at the effect of an intervention in an individual. Generally, there are two or more periods, alternating when the participant receives the therapy and one where he does not. This allows physicians to look for clinically meaningful differences in outcomes. [26] Multiple N-of-1 trials can be combined to estimate population effects.</td>
<td>What is the optimal drug x in patient y that effectively balances drug’s efficacy with its side effects? A number of other study questions are described in a manuscript by Guyatt et al., 1990 [27]. In general, this design is best for chronic and relatively stable conditions. There is an emphasis on optimizing effectiveness for the individual rather than for a population of patients. This design allows researchers to obtain information on individual treatment response. This approach is useful for chronic conditions with readily assessable primary therapeutic effect.</td>
</tr>
<tr>
<td>Delayed-design or ‘advance coverage’ trials</td>
<td>Many variations exist. The most common version for this design is that participants are randomized either to receive the intervention from the start of the trial, or to have the intervention withheld for a pre-specified amount of time. By the end of the trial, both study groups have received the study intervention [28]</td>
<td>This trial design has been employed for several studies of neuroprotective treatments for Parkinson disease [29]. For example, what is the comparative effectiveness of early versus later initiation of rasagiline on progression of disability in patients with Parkinson disease? [30] All participants are eventually given the potentially beneficial medical intervention, which overcomes some of the ethical concerns raised by traditional RCTs, while maintaining a control group. This approach may be particularly useful for CER when applied to cluster RCTs.</td>
</tr>
</tbody>
</table>
The Translation Table

September, 2010

Taxonomy for monitoring methods within a medical product safety surveillance system:

Report of the Mini-Sentinel Taxonomy Project Work Group

Joshua J. Gagne, Bruce Fireman, Patrick Ryan, Malcolm Maclure, Tobias Gerhard, Darren Toh, Jeremy A. Rassen, Jennifer Nelson, Sebastian Schneeweiss for the Taxonomy Project Writing Group
## Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

<table>
<thead>
<tr>
<th>Monitoring scenario characteristics with implication for design choicea</th>
<th>Characteristics of the (potential) exposure-HOI link</th>
<th>Monitoring scenario characteristics with implication for analytic choicea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure persistence</strong> (transient, sustained)</td>
<td><strong>Onset of exposure risk window</strong> (Immediate, delayed)</td>
<td><strong>Within-person (negligible, needs to be addressed)</strong></td>
</tr>
<tr>
<td><strong>Duration of exposure risk window</strong> (short, long)</td>
<td><strong>Between-person (negligible, needs to be addressed)</strong></td>
<td><strong>Design choiceb</strong> (self-controlled, cohort)</td>
</tr>
<tr>
<td><strong>HOI onset</strong> (abrupt, insidious)</td>
<td><strong>Background frequency of exposure</strong> (infrequent, rare)</td>
<td><strong>Background frequency of HOI</strong> (infrequent, rare)</td>
</tr>
<tr>
<td><strong>Analytic choice</strong></td>
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<tr>
<td><strong>Transient</strong> (e.g. vaccine, initiation of a drug; including episodic drug use [e.g. triptans] to the extent that the question pertains to its transient nature)</td>
<td>Immediate</td>
<td>Abrupt</td>
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<tr>
<td></td>
<td>Short</td>
<td>Negligible</td>
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<td></td>
<td></td>
<td>Needs to be addressed</td>
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<td>Infrequent</td>
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<td></td>
<td>Rare</td>
<td>Rare</td>
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<td><strong>Insidious</strong></td>
<td>Infrequent</td>
<td>Insidious</td>
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<td>cohort (self-controlled)</td>
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<td>Rare</td>
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<td><strong>Abrupt</strong></td>
<td>Infrequent</td>
<td>Abrupt</td>
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<td>self-controlled (or cohort)</td>
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<td>Infrequent</td>
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<td>Rare</td>
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<td>3</td>
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<td><strong>Insidious</strong></td>
<td>Infrequent</td>
<td>Insidious</td>
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<td>self-controlled or cohort</td>
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<tr>
<td><strong>Needs to be addressed</strong></td>
<td>Infrequent</td>
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<td>Rare</td>
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</tbody>
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*a* Characteristics of the (potential) exposure-HOI link

*b* Design choice based on analytic choice and background frequency of exposure.
Visualize the Translation Table

In order to determine optimal model and enable next steps we proposed and discussed several models for the translation table (straw men) considering

- Organizing principle (eg. method, clinical question, cross-cutting-question)
- Architecture (eg. table, decision tree, other)

Next Steps: Assemble experts/ stakeholders to react to/improve upon our proposals, eg. methodology workshops
Consult and Contract as needed to complete the work
Summary and Next Steps

- Methodology committee is off and running!
- Established operating principles and completed key foundational tasks
- Created an organizational framework to guide the work comprising our core function:

  Providing methodological guidance and promoting methodological innovation for Patient Centered Outcomes Research
Methodology Committee

Naomi Aronson
Ethan Basche
Alfred Berg
Jean Slutsky
Dave Flum
Sherine Gabriel
Mark Helfand
Steven Goodman
John Ioannidis

Mike Lauer
David Meltzer
Brian Mittman
Robin Newhouse
Sharon-Lise Normand
Sebastian Schneeweiss
Mary Tinetti
Clyde Yancy

Committee Support:
Gail Shearer, Jane Van Dervoort, Lauren Greco
THANK YOU!