OBSERVATIONAL STUDIES IN A LEARNING HEALTH SYSTEM

An Institute of Medicine Workshop
Sponsored by the Patient-Centered Outcomes Research Institute

A LEARNING HEALTH SYSTEM ACTIVITY
IOM ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE

APRIL 25-26, 2013

THE NATIONAL ACADEMY OF SCIENCES
2101 CONSTITUTION AVENUE, NW
WASHINGTON, DC

Meeting objectives
1. Explore the role of observational studies (OS) in the generation of evidence to guide clinical and health policy decisions, with a focus on individual patient care, in a learning health system;
2. Consider concepts of OS design and analysis, emerging statistical methods, use of OS’s to supplement evidence from experimental methods, identifying treatment heterogeneity, and providing effectiveness estimates tailored for individual patients;
3. Engage colleagues from disciplines typically underrepresented in clinical evidence discussions;
4. Identify strategies for accelerating progress in the appropriate use of OS for evidence generation.

Day 1: Thursday, April 25th

8:00 am        Coffee and light breakfast available

8:30 am        Welcome, introductions and overview
Welcome, framing of the meeting and agenda overview

Welcome from the IOM
Michael McGinnis, Institute of Medicine

Opening remarks and meeting overview
Joe Selby, Patient-Centered Outcomes Research Institute
Ralph Horwitz, GlaxoSmithKline
9:00 am | Workshop stage-setting

- Session format
  - Workshop overview and stage-setting
    Steve Goodman, Stanford University
  - Q&A and open discussion

- Session questions:
  - How do OS contribute to building valid evidence to support effective decision making by patients and clinicians? When are their findings useful, when are they not?
  - What are the major challenges (study design, methodological, data collection/management/analysis, cultural etc.) facing the field in the use of OS data for decision making? Please include consideration of the following issues: bias, methodological standards, publishing requirements.
  - What can workshop participants expect from the following sessions?

9:45 am | Engaging the issue of bias

Moderator: Michael Lauer, National Heart Lung and Blood Institute

- Session format
  - Introduction to issue
    Sebastian Schneeweiss, Harvard University
  - Presentations:
    - Instrumental variables and their sensitivity to unobserved biases
      Dylan Small, University of Pennsylvania
    - An empirical approach to measuring and calibrating for error in observational analyses
      Patrick Ryan, Johnson & Johnson
  - Respondents and panel discussion:
    - John Wong, Tufts University
    - Joel Greenhouse, Carnegie Mellon University
  - Q&A and open discussion

- Session questions:
  - What are the major bias-related concerns with the use of observational study methods? What are the sources of bias?
  - How many of these concerns relate to methods and how much to the quality and availability of suitable data? What barriers have these concerns created for the use of the results of observational studies to drive decision-making?
o What are the most promising approaches to reduction of bias through the use of statistical methods? Through study design (e.g. Dealing with issues of multiplicity)?
o What are the circumstances under which administrative (claims) data can be used to assess treatment benefits? What data are needed from EHRs to strengthen the value of administrative data?
o What methods are best to adjust for the changes in treatment and clinical conditions among patients followed longitudinally?
o What are the implications of these promising approaches for the use of observational study methods moving forward?

11:30 am | Lunch

Participants will be asked to identify among their lunch table, what they think the most critical questions are for PCOR in the topics covered by the workshop. These topics will them be circulated to the moderators of the proceeding sessions.

12:30 pm | Generalizing RCT results to broader populations

Moderator: Harold Sox, Dartmouth College

➢ Session format
  o Introduction to issue
    Robert Califf, Duke

  o Presentations:
    ▪ Generalizing the right question
      Miguel Hernan, Harvard University

    ▪ Using observational studies to determine RCT generalizability
      Eloise Kaizar, Ohio State

  o Respondents and panel discussion:
    ▪ William Weintraub, Christiana Medical Center
    ▪ Constantine Frangakis, Johns Hopkins University

Q&A and open discussion

➢ Session questions:
  o What are the most cogent methodological and clinical considerations in using observational study methods to test the external validity of findings from RCTs?
  o How do data collection, management, and analysis approaches impact generalizability?
  o What are the generalizability questions of greatest interest? Or, where does the greatest doubt arise? (Age, concomitant illness, concomitant treatment) What examples represent well established differences?
  o What statistical methods are needed to generalize RCT results?
Are the standards for causal inference from OS different when prior RCTs have been performed? How does statistical methodology vary in this case?

What are the implications when treatment results for patients not included in the RCT differ from the overall results reported in the original RCT?

What makes an observed difference in outcome credible? Finding the RCT-shown effect on the narrower population? Replication in >1 environment? Confidence interval of the result? Size of the effect in the RCT?

Can subset analyses in the RCT, even if underpowered, be used to support or rebut the OS finding?

2:15 pm  Break

2:30 pm  Detecting treatment-effect heterogeneity

Moderator: Richard Platt, Harvard Pilgrim Health Care Institute

➢ Session format
  o Introduction to issue
    David Kent, Tufts University

  o Presentations:
    ▪ Comparative effectiveness of coronary artery bypass grafting and percutaneous coronary intervention
      Mark Hlatky, Stanford University

    ▪ Identification of effect heterogeneity using instrumental variables
      Anirban Basu, University of Washington

  o Respondents and panel discussion:
    ▪ Mary Charlson, Cornell University
    ▪ Mark Cullen, Stanford University

Q&A and open discussion

➢ Session questions:
  o What is the potential for OS in assessing treatment response heterogeneity and individual patient decision-making?
  o What clinical and other data can be collected routinely to affect this potential?
  o How can longitudinal information on change in treatment categories and clinical condition be used to assess variation in treatment response and individual patient decision-making?
    ▪ What are the statistical methods for time varying changes in treatment (including co-therapies) and clinical condition?
What are the best methods to form distinctive patient subgroups in which to examine for heterogeneity of treatment response?
- What data elements are necessary to define these distinctive patient subgroups?

What are the best methods to assess heterogeneity in multi-dimensional outcomes?

How could further implementation of best practices in data collection, management, and analysis impact treatment response heterogeneity?

What is needed in order for information about treatment response heterogeneity to be validated and used in practice?

| 4:15 pm | Summary and preview of next day |
| 4:45 pm | Reception |
| 5:45 pm | Adjourn |

Day 2: Friday, April 26th

8:00 am Coffee and light breakfast available

8:30 am Welcome, brief agenda overview, summary of previous day

Welcome, framing of the meeting and agenda overview

9:00 am Predicting individual responses

Moderator: Ralph Horwitz, GSK

- Session format
  - Introduction to issue
    Burton Singer, University of Florida

  - Presentations:
    - Data-driven prediction models
      Nicholas Tatonetti, Columbia University

    - Individual prediction
      Michael Kattan, Cleveland Clinic
Respondents and panel discussion:
- Peter Bach, Sloan Kettering
- Mitchell Gail, National Cancer Institute

Q&A and open discussion

Session questions:
- How can patient-level observational data be used to create predictive models of treatment response in individual patients? What statistical methodologies are needed?
- How can predictive analytic methods be used to study the interactions of treatment with multiple patient characteristics?
- How should the clinical history (longitudinal information) for a given patient be utilized in the creation of prediction rules for responses of that patient to one or more candidate treatment regimens?
- What are effective methodologies for producing prediction rules to guide the management of an individual patient based on their comparability to results of RCTs, OS, and archived patient records?
- How can we blend predictive models, which can predict impact of treatment choices, and causal modeling, that compare predictions under different treatments?

10:45 am Break

11:00 am Conclusions and strategies going forward

Panel members will be charged with highlighting very specific next steps laid out in the course of workshop presentations and discussions and/or suggesting some of their own.

Panel:
- Cynthia Mulrow, University of Texas
- Jean Slutsky, Agency for Healthcare Quality and Research
- Steve Goodman, Stanford University

Session questions:
- What are the major themes and conclusions from the workshop’s presentations and discussions?
- How can these themes be translated into actionable strategies with designated stakeholders?
- What are the critical next steps in terms of advancing analytic methods?
- What are the critical next steps in developing data bases that will generate evidence to guide clinical decision making?
- What are critical next steps in disseminating information on new methods to increase their appropriate use?
12:15 pm  Summary and next steps

Comments from the Chairs
Joe Selby, Patient-Centered Outcomes Research Institute
Ralph Horwitz, GlaxoSmithKline

Comments and thanks from the IOM
Michael McGinnis, Institute of Medicine

12:45 pm  Adjourn

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Planning Committee

Co–Chairs
Ralph Horwitz, GlaxoSmithKline
Joe Selby, Patient-Centered Outcomes Research Institute

Members
Anirban Basu, University of Washington
Troy Brennan, CVS/Caremark
Louis Jacques, Centers for Medicare & Medicaid Services
Steve Goodman, Stanford University
Jerry Kassirer, Tuft University
Michael Lauer, National Heart Lung and Blood Institute
David Madigan, Columbia University
Sharon-Lise Normand, Harvard University
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