Guidelines and Standards for Observational Studies: 
Are We Headed for Discourse or Harmony?

Robert W. Dubois MD PhD, National Pharmaceutical Council,
Sally Morton PhD, University of Pittsburgh,
Rachael Fleurence PhD, Patient-Centered Outcomes Research Research
Institute
Jean Slutsky, PA, MSPH, Patient-Centered Outcomes Research Institute
Considerations for Today

1. Real-World Evidence is Here To Stay
2. Standards are Needed to Ensure Real-World Evidence is Useful
3. Lack of Clarity on Which Standards to Follow
4. End-Users Look to Experts for Agreement on Good Real-World Evidence
1. Real World Data Is Increasing

Nearly 8 out of 10 Providers use EHRs

CDC/NCHS Electronic Health Records Survey. Jan 2014

Medicare to Publish Trove of Data on Doctors
Information on 880,000 Physicians to Offer Look at Issues Including Billing, Number of Procedures and Patients Treated

By LOUISE RADNOFSKY | CONNECT
Updated April 2, 2014 9:01 p.m. ET

The Obama administration said it would publish as early as next week data on what Medicare paid individual doctors in 2012, aiming to boost transparency and help root out fraud.

The move, which faced force resistance from doctors' groups, would end a decadeslong block on making the information public.

pcornet The National Patient-Centered Clinical Research Network

The Washington Post

The Wall Street Journal | U.S.
2. Standards are Needed to Ensure Real-World Evidence is Useful

How a Family Tragedy Landed on a Retailer’s Mailing, Wall Street Journal, January 29, 2014
3. Proliferation of Guidelines... consensus?

Green = Reporting Standards
Orange = Research Standards

- 2000-2002: MOOSE
- 2003: ISPOR – Checklist
- 2007: ISPOR Good Research Practices (Multiple Publications / Standards)
- 2009: AHRQ Registry Handbook (v1)
- 2010: AHRQ EPC Grading for CER
- 2011: STROBE
- 2013-2014: PRISMA-P
- 2010: AHRQ Registry Handbook (v2)
- 2014: AHRQ Registry Handbook (v3)
- 2009-2014: GRACE 1.0
- 2011-2013: AMCP/ISPOR/NPC
- 2010-2012: RECORD
- 2009-2010: PCORI
- 2008-2009: GRACE 2.0
Is There a Rosetta Stone For Observational Studies?
4. Decision-Makers are Looking For Guidance

- **Managed care:** 54% sought greater clarity on RWE requirements
- **Clinical Guideline Groups:** Perceive Lack of Maturity and Agreement in the Field
- **Reviewers:** Which studies to fund
Discussion and Audience Participation

1. Are a common and agreed upon set of standards needed?
2. Is one set or multiple sets of standards and guidelines desirable?
3. How could the process be harmonized?
4. What are the potential implications for innovation?
Discourse or Harmony?

Sally Morton, PhD
Professor and Chair, Department of Biostatistics
University of Pittsburgh

Rachael Fleurence, PhD
Program Director, CER Methods and Infrastructure
Patient-Centered Outcomes Research Institute

Jean Slutsky, PA, MSPH
Chief Engagement and Dissemination Officer
Patient-Centered Outcomes Research Institute
Guidelines and Standards for Observational Studies: Are We Headed for Discourse or Harmony?

Sally C. Morton (scmorton@pitt.edu)
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh
ISPOR, June 2014
Has the Field of Observational Studies Matured?

- Do funders know which studies are credible enough to fund?
- Do researchers know which methods to use?
- Do the decision-makers know which studies were conducted in a credible manner and which ones to trust?
- Is there agreement on the methods?
Project Goal and Strategy

Goal: Compare and contrast *standards* for doing, and *guidelines* for reporting, observational studies

Strategy:

1. Create an evidentiary foundation through a limited systematic review and input from six experts
2. Develop a comparative table, a summary table, and policy recommendations
Citations identified through database searching (n = 177)

Additional citations identified through other sources (n = 4)

Citations after duplicates removed (n = 181)

Abstracts screened for relevance (n = 181)

Abstracts excluded (n = 138)

Full-text articles assessed for eligibility (n = 43)

Articles excluded (n = 32)

Standards/Guidelines included (n = 11)

Standards/guidelines after 3 ISPOR combined (n = 9)
Methods – Data Collection

Primary content table

• Established each standard/guideline as a column
• Selected observational study elements as row topics (influenced by GRACE)
• Populated cells
• Recorded duplicates across rows
• Condensed information (combined 3 ISPOR guidelines)
<table>
<thead>
<tr>
<th>Study Element</th>
<th>Guideline/Standard</th>
<th>GRACE Principles</th>
<th>AHRQ CER</th>
<th>PCORI Standards</th>
<th>... etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philosophy and Audience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research Plan Developed A Priori</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of Prior Research</td>
<td>empty</td>
<td>text</td>
<td></td>
<td></td>
<td>empty or text</td>
</tr>
<tr>
<td>Study Objectives and Research Questions</td>
<td>.... etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discussion and Conclusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RQ-1 Identify Gaps in Evidence:** Gap analysis and systematic reviews should be used to support the need for a proposed study.; (DUP) DR-1.E. Consistent Data Collection- Clear, operational definitions of data elements should be provided. Create and distribute standard instructions to data collectors. Use standardized data element definitions and/or data dictionaries whenever possible. When creating a new registry, published literature should be reviewed to identify existing, widely used definitions before drafting new definitions. CHOICE: If a systematic review is not available, a systematic review should be performed using accepted standards in the field (see standard SR-1), or a strong rationale should be presented for proceeding without a systematic review. In the case where a systematic review is not possible, the methods used to review the literature should be explained and justified.
Methods – Data Analysis

• What % of the guidelines/standards include the element?
• Across the element:
  • Do the guidelines/standards agree?
  • Where do they disagree?
• Is the level of detail sufficient to make the element actionable?
• How flexible are the elements to innovation?
Methods – Data Summarization

Summarized each row taking into consideration the number of entries addressing the issue, similarities, differences and choices:

- 7-9 guidelines/standards addressed
  - Content agreement (green)
  - Content disagreement (blue)
- 4-6 guidelines/standards addressed (yellow)
- 1-3 guidelines/standards addressed (red)
<table>
<thead>
<tr>
<th>Philosophy and Audience</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Plan Developed A Priori</td>
<td></td>
</tr>
<tr>
<td>Review of Prior Research</td>
<td></td>
</tr>
<tr>
<td>Study Objectives and Research Questions</td>
<td>NC</td>
</tr>
<tr>
<td>Hypotheses</td>
<td></td>
</tr>
<tr>
<td>Communication With Stakeholders</td>
<td></td>
</tr>
<tr>
<td>Study Protocol</td>
<td></td>
</tr>
<tr>
<td>Study Design</td>
<td></td>
</tr>
<tr>
<td>Study Limitations and Confounders</td>
<td></td>
</tr>
<tr>
<td>Population (target, source, study), including inclusion/exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Comparators</td>
<td></td>
</tr>
<tr>
<td>Sample Size &amp; Statistical Power</td>
<td></td>
</tr>
<tr>
<td>Measures, Endpoints and Outcomes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Sources (Collection, Coding, Capture &amp; Storage)</td>
</tr>
<tr>
<td>Data Linkage</td>
</tr>
<tr>
<td>Data Quality, Validity, and Privacy Assurance</td>
</tr>
<tr>
<td>Missing Data</td>
</tr>
<tr>
<td>Analysis</td>
</tr>
<tr>
<td>Descriptive Analysis, Inferential Analysis and/or Modeling</td>
</tr>
<tr>
<td>Confounders and Modifiers</td>
</tr>
<tr>
<td>Heterogeneity of Treatment Effect</td>
</tr>
<tr>
<td>Sensitivity Analysis</td>
</tr>
<tr>
<td>Discussion and Conclusions</td>
</tr>
<tr>
<td>Bias</td>
</tr>
<tr>
<td>Ethics Committee, IRB Approval or Other Ethical Considerations</td>
</tr>
<tr>
<td>Interpretation</td>
</tr>
<tr>
<td>Dissemination</td>
</tr>
</tbody>
</table>
• Example: Study Objectives and Research Questions

• 8 out of 9 guidelines/standards include reference to research questions and or objectives of the study being defined prior to the study being conducted

• 2 guidelines/standards specifically include PICOTS/PICO
But Sometimes Guidance Was In Conflict

• Example: Missing Data
• 7 out of 9 guidelines/standards mention missing data
• 6 guidelines/standards want information on the management of missing data
• Conflicts in guidance:
  – Mean value substitution
  – Substitution of predicted value from a regression model
  – Hotdeck imputation
  – Bayesian methods
  – Multiple imputation
Limitations

- Absence of information may represent lack of agreement or lack of prioritization
- Differences may be due to:
  - Audience (e.g., researchers vs. end-users)
  - Questions (e.g., pharmacovigilance vs. CER)
  - Philosophy (e.g., best practice vs. minimum standard)
  - Format (e.g., manual vs. yes/no questions)
Minimum Standards Versus Aspirational Practices

• Should there be a minimum set of standards?
• Should there be multiple standards (low, medium, high)?
• Will acknowledgment of choice allow for further innovation enhancement?
• As our methods evolve, how will standards be updated?
Future Opportunities

• Consensus development
  – Overall
  – Specific: E.g. missing data
• Areas ripe for new methods development
• Education and training
List of Included Standards/Guidelines

1. AHRQ: Developing a Protocol for Observational Comparative Effectiveness Research
2. CER Collaborative: Observational Study Assessment Questionnaire
3. ENCePP Checklist for Study Protocols
4. ENCePP Guide on Methodological Standards in Pharmacoepidemiology
5. FDA: Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
6. GRACE Checklist
7. GRACE Principles
9. PCORI Methodology Standards
Thank You

Sally C. Morton
scmorton@pitt.edu
Discourse or Harmony?

Sally Morton, PhD
Professor and Chair, Department of Biostatistics
University of Pittsburgh

Rachael Fleurence, PhD
Program Director, CER Methods and Infrastructure
Patient-Centered Outcomes Research Institute

Jean Slutsky, PA, MSPH
Chief Engagement and Dissemination Officer
Patient-Centered Outcomes Research Institute
Discussion and Audience Participation

1. Are a common and agreed upon set of standards needed?
2. Is one set or multiple sets of standards and guidelines desirable?
3. How could the process be harmonized?
4. What are the potential implications for innovation?
Thank you