

Real World Evidence Joint STF



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Real World Evidence & Decision Makers

- RWD studies are:
 - Routinely used by decision makers to assess treatment associated adverse events
 - But used much less to assess effectiveness, though they could be very useful for studies of subpopulations, secondary indications, treatment regimens, etc.
- What's the problem?
 - Lack of randomization, of course
 - But also lack of trust and transparency related to data-dredging and reproducibility of results
- How can ISPOR help?
 - Good methodological practices for dealing with bias, confounding, etc; we have done multiple Good Practices Reports
 - **Needed: Good procedural practices to deal with trust and transparency concerns**

Current Procedural Practices – A Comparison



- Pre-Approval RCTs
 - Pre-registration on public website (ClinicalTrials.Gov)
 - Completion of an *a priori* protocol and data analysis plan
 - Transparent documentation for any changes in study procedures
 - Expectation that all RCT results will be made public
- Real World Data Studies
 - No well-accepted recommendations for good procedural practices
 - A few groups have begun to weigh in here; needs reinforcement
 - Must address data dredging, publication bias issues
 - Other concerns include internal validity, inaccurate recording of health events, opaque reporting
 - *Following/adapting RCT-like practices is a logical starting point*

Objectives of Joint ISPOR-ISPE Special Task Force



- To provide a clear set of good practices for enhancing the transparency and reproducibility, as well as the overall credibility, of real world database studies in health care, with the aim of improving the confidence of decision-makers, particularly regulatory decision-makers, in utilizing such evidence.
- The Transparency manuscript has been led by ISPOR and the Reproducibility manuscript has been led by ISPE; there has been cross-membership coordination of manuscripts across groups.
- We plan joint publication in *Value in Health* and ISPE's journal, *Pharmacoepidemiology and Drug Safety*, and perhaps a shorter "Viewpoint" article for a more policy-oriented journal.

Joint STF members

ISPOR

- **Marc Berger, MD**, (*co-chair*); Pfizer, New York, NY, USA
- **Daniel Mullins, PhD**, (*co-chair*); University of Maryland, Baltimore, MD, USA
- **Diana Brixner, RPh, PhD**, University of Utah, Salt Lake City, Utah, USA
- **Hans-Georg Eichler, MD**, European Medicines Agency, **London, UK**
- **Wim Goettsch, PhD**, EuNetHTA JA3, Diemen, The Netherlands
- **David Madigan, PhD**, Columbia University, New York, NY, USA
- **Harold Sox, MD**, PCORI, Washington, DC, USA
- **Rosanna Tarricone, MSc, PhD**, Bocconi University, Milan, IT
- **John Watkins, MPH, PharmD**, Premera Blue Cross, Mountlake Terrace, WA, USA
- **Richard Willke, PhD**, ISPOR, Lawrenceville, NJ

ISPE

- **Sebastian Schneeweiss, MD, ScD**, (*co-chair*)
Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA
- **Shirley V. Wang, PhD, ScM** (*co-chair*)
Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA
- **Jeffrey Brown, PhD**, Department of Population Medicine, Harvard Medical School, Boston MA, USA
- **Ian Douglas, PhD**, London School of Hygiene and Tropical Medicine, London, UK
- **Joshua J. Gagne, PharmD, ScD**, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA
- **Olaf Klungel, PhD**, Department of Pharmaceutical Sciences, University of Utrecht, Utrecht, Netherlands
- **Jeremy A. Rassen, ScD**, Aetion Inc., New York, NY, USA
- **Liam Smeeth MSc, PhD**, London School of Hygiene and Tropical Medicine, London, UK

Timeline

Nov-Dec 2016	Proposal initiation and initial HSPC review
January 2017	Preliminary BoD approval
Feb-March	In-person meeting of ISPOR group to work through key issues and begin assembly of first draft (NYC) Final HSPC & BoD approval
April	Manuscript draft completed
May	Primary review group review Two presentations at ISPOR Boston meeting.
June	Manuscript revision and ISPOR/ISPE membership review
July	Final manuscript submissions to ViH and P & DS
2 nd half of 2017	Presentation(s) at other conferences/meetings
Sept-Oct	Potential Washington DC conference

Transparency (ISPOR-led) Manuscript



Key Definition/Distinction: Categories of RWD Treatment Effect Studies

- **Exploratory Study**
 - Typically does not hypothesize the presence of a specific treatment effect and/or its magnitude
 - Primarily serves as first step to learn about possible treatment effects
 - Less pre-planned and allows for process-adjustments as investigators gain knowledge of the data
- **Confirmatory Study**
 - Evaluates the presence or absence of a pre-specified treatment effect and/or its magnitude
 - Tests a specific hypothesis in a specific data set
 - In conjunction with other evidence, may lead to treatment recommendations

Recommendations for Confirmatory Studies

(Good Procedural Practices = Good Study Hygiene)



- Pre-registration: post study protocol and analysis plan on public registration site prior to conducting the study analysis
 - e.g., clinicaltrials.gov, ENCEPP, HSRProj
- Publish study results with attestation to conformance and/or deviation from original analysis plan
 - Medical Journal, Web-site, Study Registry
- Provide opportunities to replicate findings
- Perform studies on a different data set than the one used to generate the hypotheses to be tested unless it is not feasible
- Authors should work with individuals to address methodologic criticisms of their study; publishing or posting on public websites the criticisms and responses would be useful
- Include key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA/payers, manufacturers) in designing, conducting, and disseminating the research

Reproducibility (ISPE-led) report

- This report focuses on enhancing existing reporting guidelines (RECORD) by identifying a minimum set of items necessary to report in detail in order to achieve fully reproducible evidence from large healthcare database cohort studies.
- The guidance document and checklist enhancement to RECORD guidelines developed by this work group addresses issues related to:
 - Specific operational decisions behind analytic data extraction from raw longitudinal data, with a focus on temporal anchors
 - The minimum reporting necessary for independent investigators to be able to reproduce a database cohort study, starting from analytic data extraction from a raw longitudinal data source
 - The minimum reporting on characteristics of the analytic cohort (before and after adjustment) necessary to assess whether a study has been reproduced

Related sessions in Boston

<p>Monday 11-12 (IP2)</p>	<p>Joint ISPOR-ISPE Special Task Force on Real World Experience in Regulatory Decision Making: Will Transparency Improve Acceptability?</p>
	<p>(Mullins, Berger, Marinac-Dabic, Jonsson)</p>
<p>Tuesday 11-12 (W10)</p>	<p>Improving Reproducibility and Robustness of Evidence from Large Health Care Databases with Specific Reporting Guidance</p>
	<p>(Wang, Schneeweiss, Berger)</p>
<p>Wednesday 8:45-9:45 (IP19)</p>	<p>Toward Open Science for Large Health Care Database Research: Improving Transparency and Reproducibility of Evidence</p>
	<p>(Willke, Antman, Shrank, Wang)</p>

Thank you !

Questions?