www.ispor.org

ISPOR

Improving healthcare decisions

Real-World Evidence for Drug Effectiveness Evaluation: Addressing the Credibility Gap

Richard Willke, PhD, Chief Science Officer, ISPOR

NIH Collaboratory Grand Rounds, October 25, 2019

Disclosures

Richard Willke was employed by Pfizer and its legacy companies from 1991 to 2016

Acknowledgements

This presentation has benefited from my participation in several working groups and conferences in recent years.

ISPOR Stakeholders

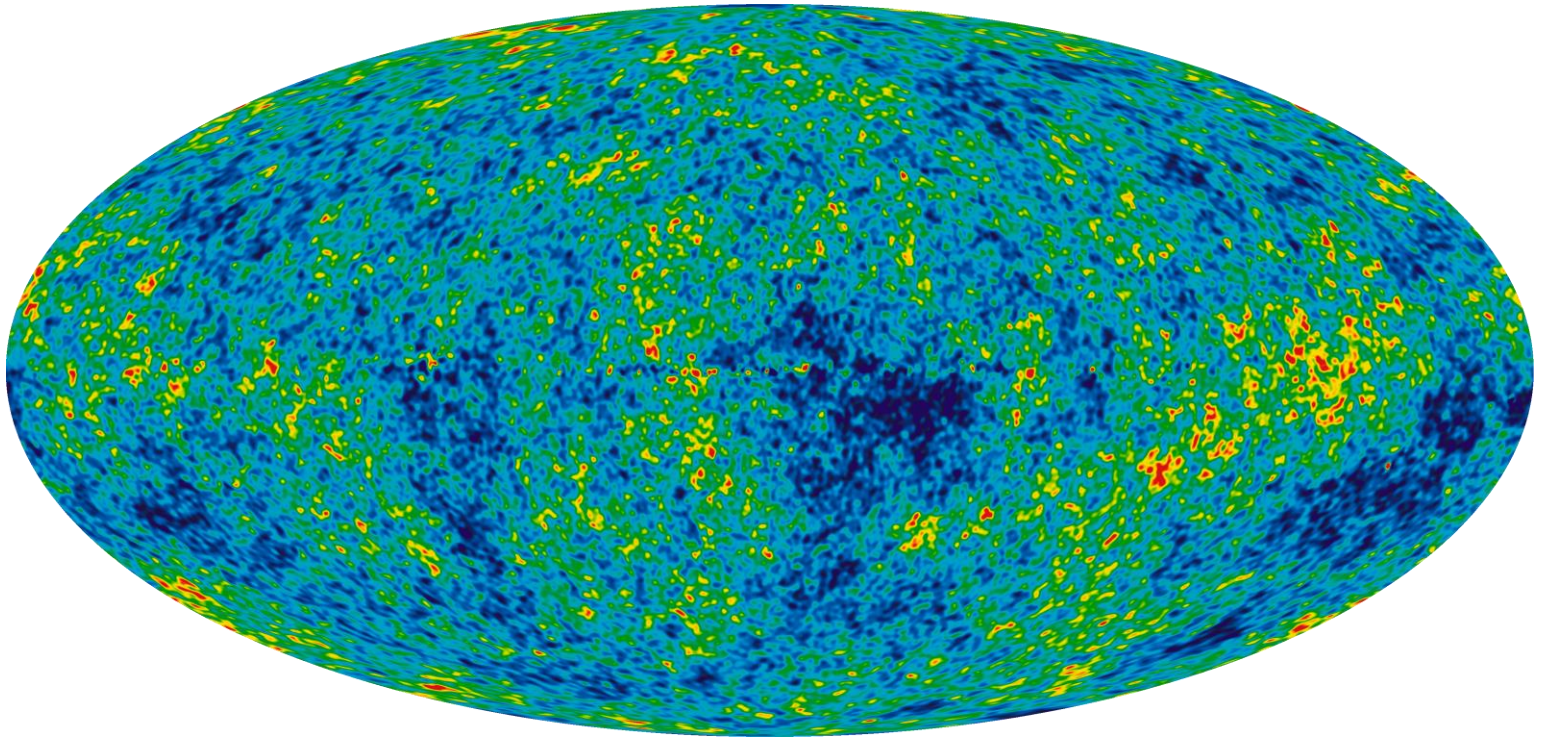
ISPOR is an international, multistakeholder nonprofit dedicated to advancing health economics and outcomes research excellence to improve decision making for health globally.

The Challenge of Real World Evidence

So much data, so much potential information

but is the evidence derived

reliable and trustworthy?



Framework for FDA's Real-World Evidence Program December 2018

"As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information."
Scott Gottlieb, FDA Commissioner National Academies of Science, Engineering, and Medicine, Examining the Impact of RWE on Medical Product Development, September 19, 2017

"FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval."
Janet Woodcock, M.D., Director, CDER

SOURCES OF REAL WORLD EVIDENCE

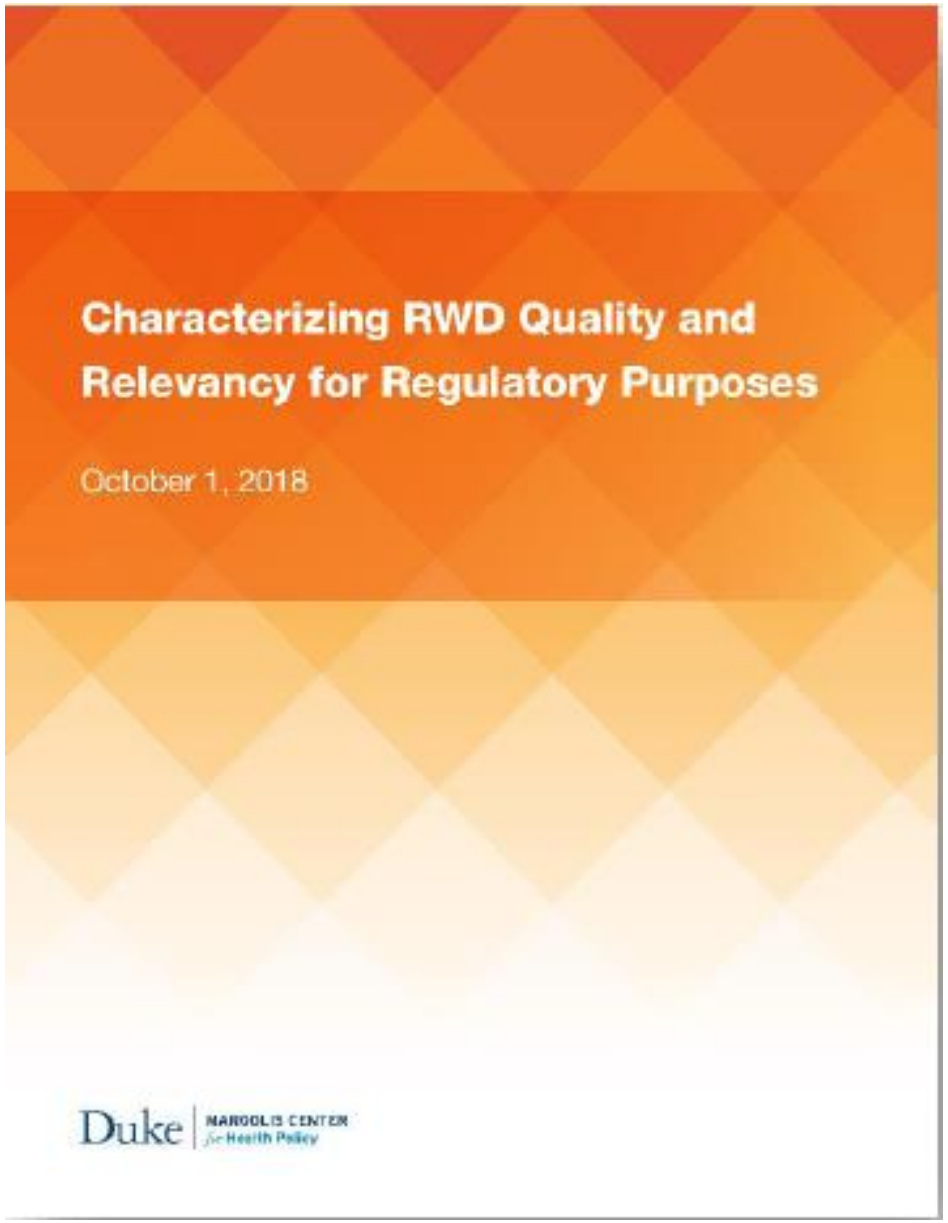
- PRAGMATIC CLINICAL TRIALS
- PROSPECTIVE OBSERVATIONAL STUDIES / REGISTRIES

- **SECONDARY USE OF EXISTING RWD**
  - **Retrospective Observational Studies of Existing Datasets**

Making RWE Useful Requires

- Quality Production
  - Careful data collection and/or curation
  - Appropriate analytic methods
  - Good procedural practices for transparent study process
  - Replicability/reproducibility
- Responsible Consumption
  - Informed interpretation
  - Fit-for-purpose application

Recent work on Data Quality from the Duke-Margolis RWE Collaborative

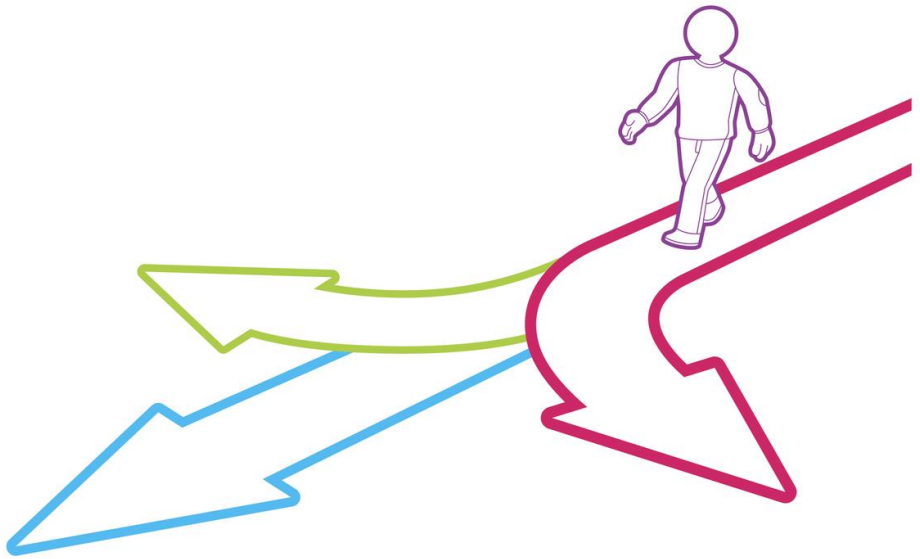


RWD analytical gremlins

- Non-representative populations
- Upcoding
- Missing data, especially when not at random
- Misclassification bias, other types
- Immortal time bias
- Ascertainment bias
- Protopathic bias
- Berkson's paradox
- Informative censoring
- Depletion of susceptibles
- Channeling bias/confounding by indication
- Healthy user effect
- Adjustment for causal intermediaries
- Reverse causality
- Time-varying confounding
- Selection bias or endogeneity by any other name
- And … p-hacking

And a variety of analytical pathways

- New user design
- Stratification
- Propensity score matching
- Regression analysis
- GLM/GEE
- Instrumental variable analysis
- Finite mixture modeling
- Classification trees
- Random forest
- Other machine learning approaches



"If you don't know where you're going, you'll end up someplace else."

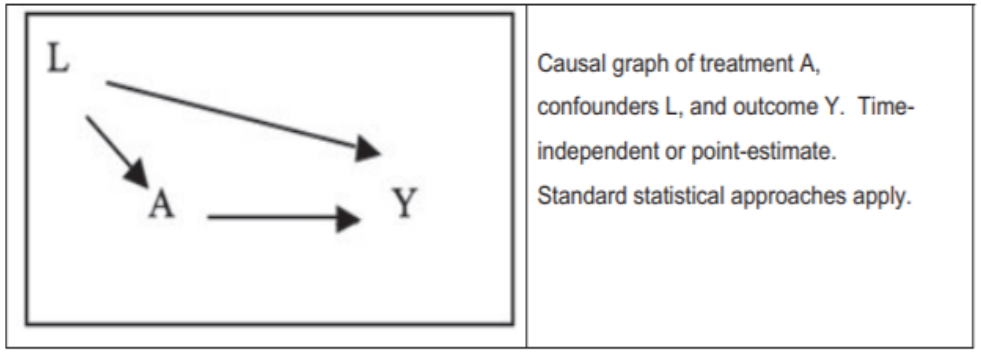
Dynamite with a laser beam?

Causal inference approaches, e.g.,

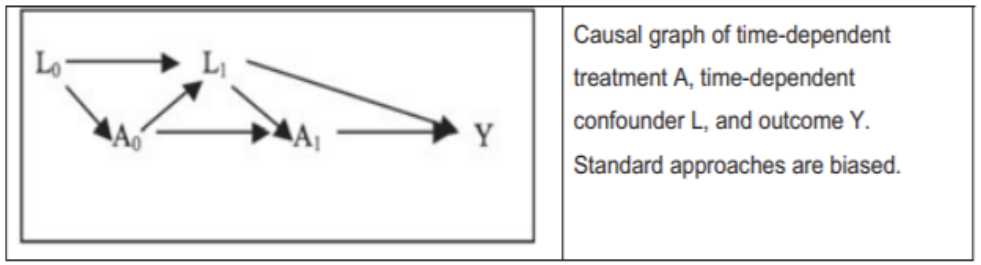
- Directed acyclic graphs
- Structural equation models
- Marginal structural models
- G-estimation of structural nested models
- Sequential approaches
  - Estimate prediction/classification models using machine learning techniques to select features
  - Estimate causal models with epidemiologic or econometric approaches using selected features in the model specifications
- Targeted maximum likelihood

As well as:

- Quasi-experimental designs, e.g., natural experiments and difference in difference analysis, nonequivalent group design, regression discontinuity designs
- Specification tests for residual confounding



b



From Johnson ML, Crown W, et al. Value in Health 2009; 12:1062-1073.

ISPOR Task Force Reports on RWD Methods for Comparative Effectiveness Analysis

(among many other sources)

Berger ML, Mamdani M, Atkins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: The ISPOR good research practices for retrospective database analysis task force report—Part I. Value Health 2009;12:1044-52.

Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML, Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of non-randomized studies of treatment effects using secondary data sources: The ISPOR good research practices for retrospective database analysis task force–Part II. Value Health 2009;12:1053-61.

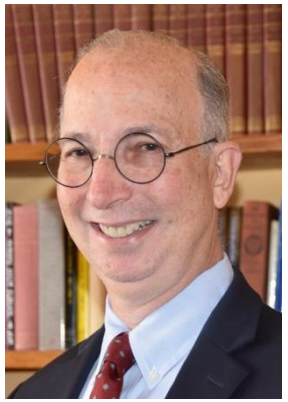
Johnson ML, Crown W, Martin BC, et al. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: The ISPOR good research practices for retrospective database analysis task force report—Part III. Value Health 2009;12:1062-73.

ISPOR/ISPE Joint Special Task Force on Real World Evidence in Health Care Decision Making

Objective: To provide a clear set of good practices for enhancing the transparency, credibility, and reproducibility of real world database studies in healthcare, with the aim of improving the confidence of decision-makers in utilizing such evidence.

STF work initiated late 2016, published Sept 2017

Transparency Paper Co-Chairs



Marc Berger, MD
New York, NY, USA

C. Daniel Mullins, PhD
University of Maryland, Baltimore, MD, USA

Reproducibility Paper Co-Chairs

Sebastian Schneeweiss, MD, ScD, FISPE
Harvard Medical School, Boston, MA, USA

Shirley Wang, PhD, MSc
Harvard Medical School, Boston, MA, USA

VALUE IN HEALTH 20 (2017) 1003–1008

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Original Report

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger[1,], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]*

Read the freely available
Good Practices Reports
ispor.org/RWEinHealthcareDecisions

PDS Pharmacoepidemiology & Drug Safety

Official Journal of the International Society for Pharmacoepidemiology

ORIGINAL REPORT

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2] | Sebastian Schneeweiss[1,2] | Marc L. Berger[3] | Jeffrey Brown[4] | Frank de Vries[5] | Ian Douglas[6] | Joshua J. Gagne[1,2] | Rosa Gini[7] | Olaf Klungel[8] | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |

on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

VALUE IN HEALTH 20 (2017) 1003–1008

Available online at www.sciencedirect.com

ScienceDirect

Transparency of study processes

Original Report

Good Practices for R … nd/or Comparative Effecti … int ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger[1,], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]*

PDS Pharmacoepidemiology & Drug Safety

Official Journal of the International Society for Pharmacoepidemiology

ORIGINAL REPORT

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2] | Sebastian Schneeweiss[1,2] | Marc L. Berger[3] | Jeffrey Brown[4] | Frank de Vries[5] | Ian Douglas[6] | Joshua J. Gagne[1,2] | Rosa Gini[7] | Olaf Klungel[8] | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |

on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

VALUE IN HEALTH 20 (2017) 1003–1008

Available online at www.sciencedirect.com

ScienceDirect

Transparency of study processes

Original Report

Good Practices for R … nd/or Comparative Effecti … int ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger[1,], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]*

PDS Pharmacoepidemiology & Drug Safety

Official Journal of the International Society for Pharmacoepidemiology

ORIGINAL REPORT

Reporting to Improve Repro … dity Assessment for Healthcare …

Reproducibility of study implementation

Shirley V. Wang[1,2] | Sebastian Schnee … [4] | Frank de Vries[5] | Ian Douglas[6] | Joshua … | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |

on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

Reproducibility - Good study procedures

- The importance of achieving consistently reproducible research is recognized in many reporting guidelines
  - STROBE, RECORD, PCORI Methodology Report, EnCePP
  - ISPE Guidelines for Good Pharmacoepidemiology Practice (GPP)
- While these guidelines certainly increase transparency, even strict adherence to existing guidance would not provide all the information necessary for full reproducibility.

What do we need?

Sharing Data	Would allow exact reproduction However: **Data use agreements usually do not allow sharing HIPAA-limited data with third parties**
Sharing programming code	Demonstrates good will However: **It is almost impossible for a third party to assess whether a study was implemented as intended**
Sharing all study implementation parameters and definitions	**Provides clarity on what was actually done and enables reproduction with confidence**

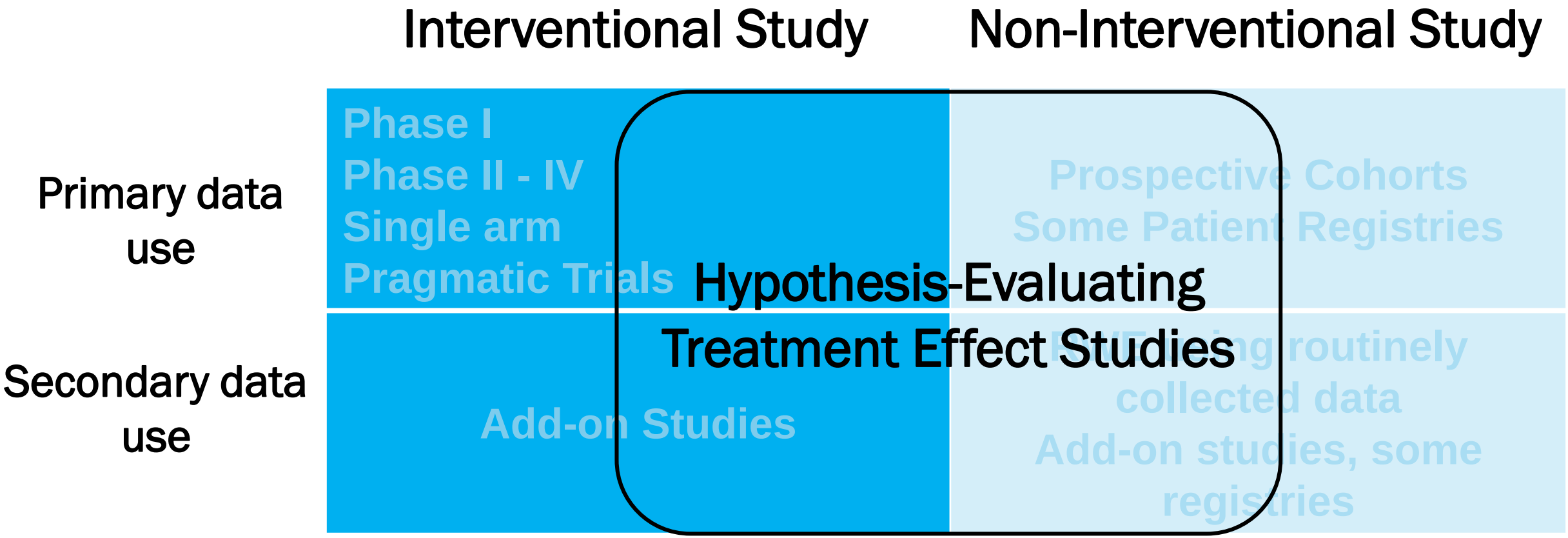
Transparency - Primary Recommendations

1. A priori, determine and declare that study is a “Hypothesis-Evaluating Treatment Effect” (HETE) or “exploratory” study
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/ or deviation from original analysis plan.
4. Enable opportunities for replication of HETE studies whenever feasible (ie, for other researchers to be able to reproduce the same findings using the same data set and analytic approach).
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested, unless it is not feasible.
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (eg, patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, and manufacturers) in designing, conducting, and disseminating the research.

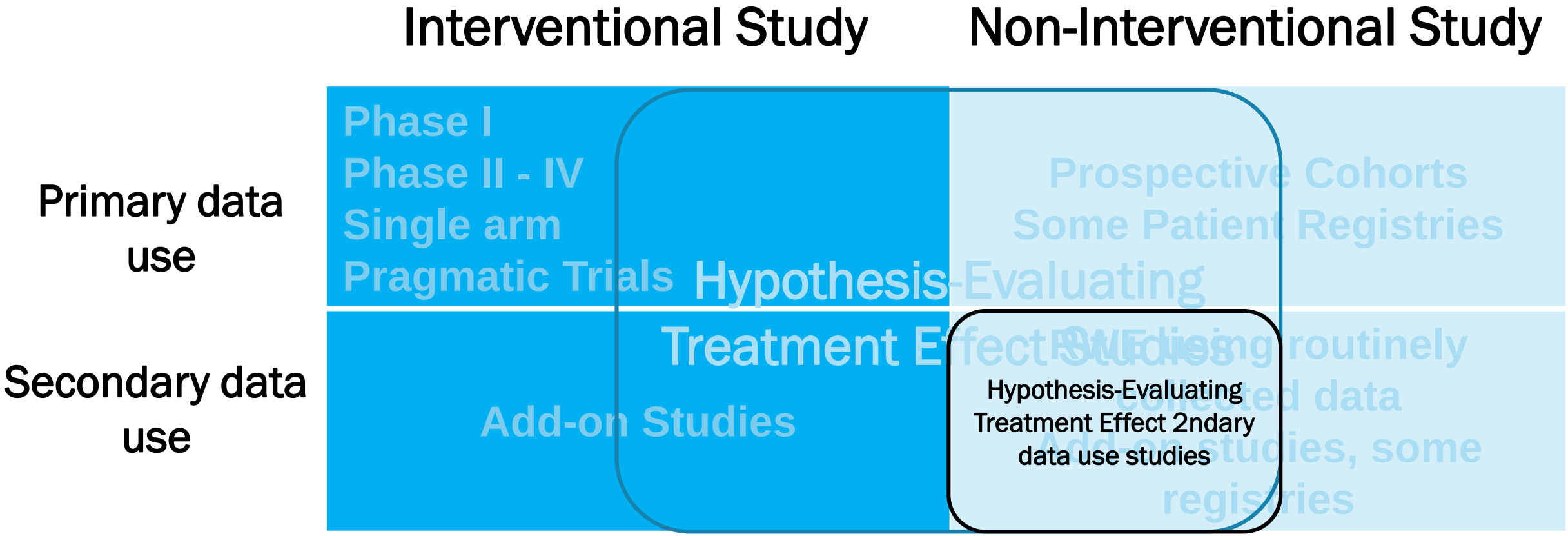
Which studies?

	Interventional Study	Non-Interventional Study
Primary data use	**Phase I** **Phase II - IV** **Single arm** **Pragmatic Trials**	**Prospective Cohorts** **Some Patient Registries**
Secondary data use	**Add-on Studies**	**RWE using routinely collected data** **Add-on studies, some registries**

Which studies?



Which studies?



Transparency of Process - Primary Recommendations

1. A priori, determine and declare that study is a “HETE” or “exploratory” study
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/ or deviation from original analysis plan.
4. Enable opportunities for replication of HETE studies whenever feasible (ie, for other researchers to be able to reproduce the same findings using the same data set and analytic approach).
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested, unless it is not feasible.
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (eg, patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, and manufacturers) in designing, conducting, and disseminating the research.

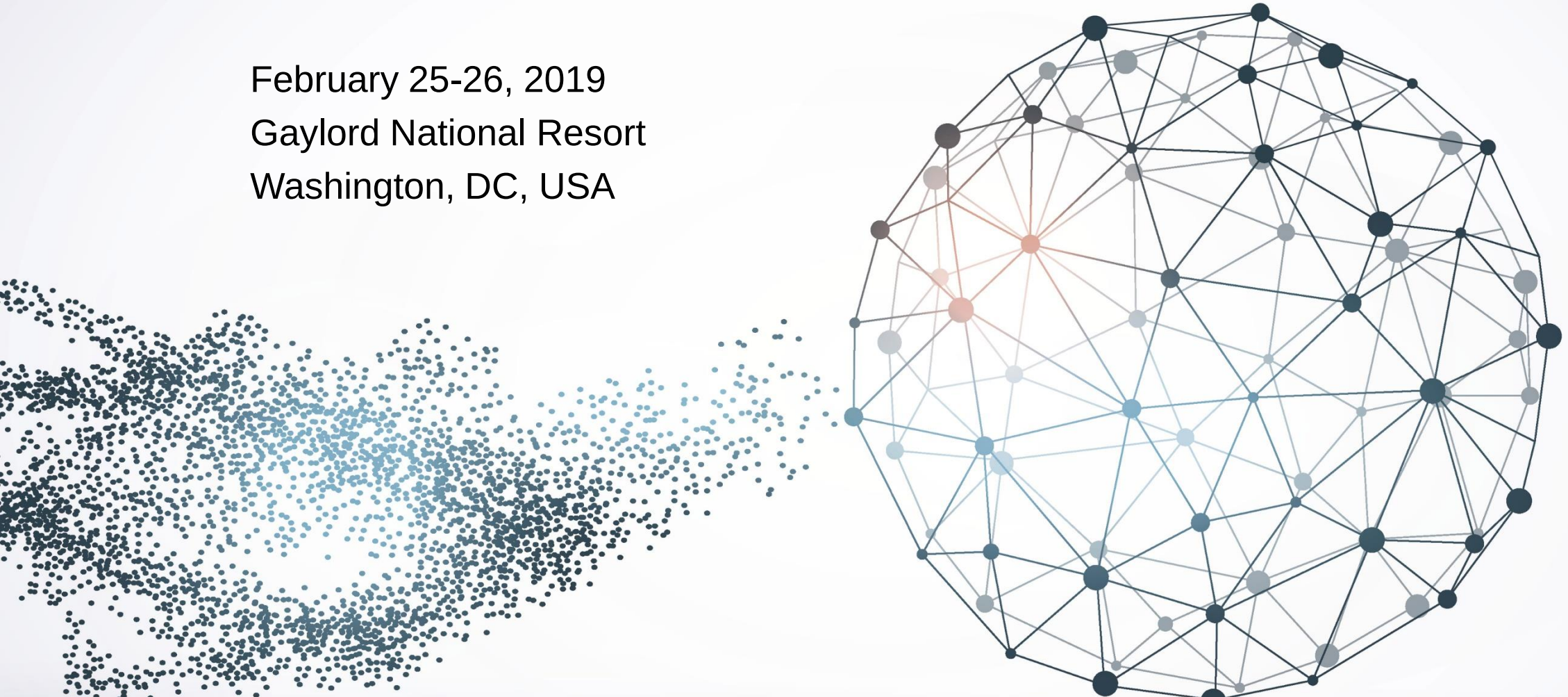
ISPOR

Real-World Evidence Transparency Study Registration Working Group

February 25-26, 2019

Gaylord National Resort

Washington, DC, USA



Real-World Evidence Transparency Partnership

ispe International Society for Pharmacoepidemiology
ISPOR
Duke MARGOLIS CENTER for Health Policy
National Pharmaceutical Council NPC
NIH U.S. National Library of Medicine ClinicalTrials.gov
INAHTA
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH
FDA
CADTH
AHRQ Agency for Healthcare Research and Quality Advancing Excellence in Health Care
PUTTING PATIENTS FIRST NATIONAL HEALTH COUNCIL
Zorginstituut Nederland
AMCP Academy of Managed Care Pharmacy
Anthem
Syneos Health
flatiron
OPTUM Labs
NICE National Institute for Health and Care Excellence
patientslikeme

Representatives from 7 pharma companies

Objective: Building trust and transparency in secondary observational research

Focus on:

- Studies using secondary (retrospective) use of data
- Objective of studying comparative treatment effects (including safety)

What is needed to ensure transparency of study process?

- What ‘mechanism’ is needed? Is pre-registering the best way to build credibility?
- Which data and documents are required? And When?
- How do we hold investigators accountable, and Who does so?

Starting point: ISPOR/ISPE RECOMMENDATION 2

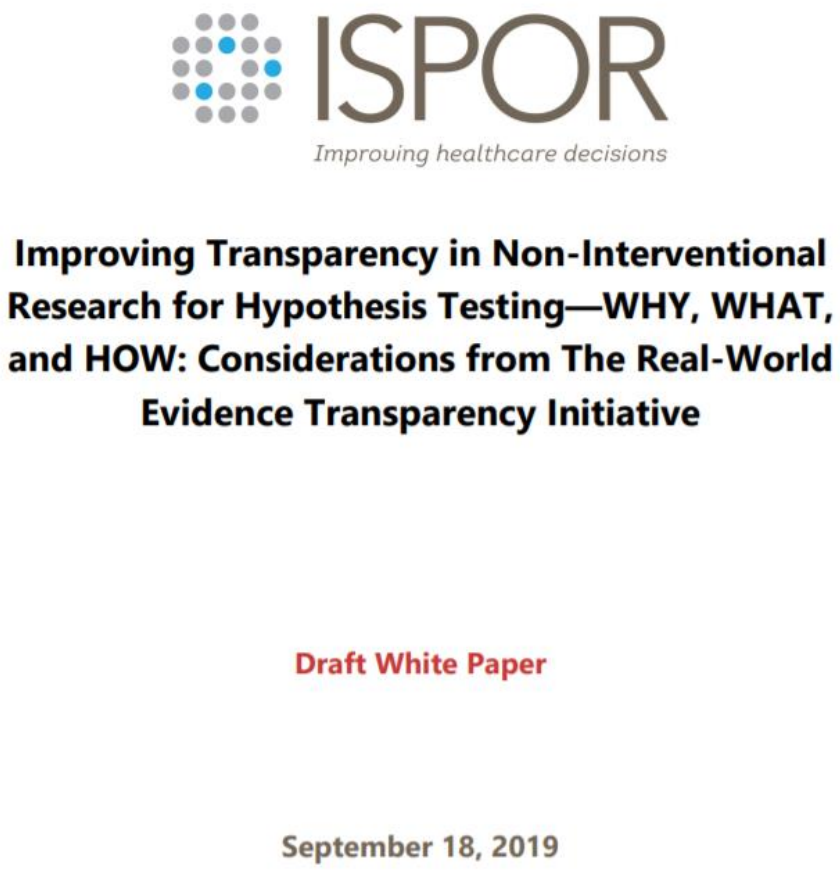
Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.

- Publicly declare the “intent” of the study—exploratory or hypothesis evaluation—as well as basic information about the study.
- Registration in advance of beginning a study is a key step in reducing publication bias
- For transparency, posting of exploratory study protocols is also encouraged.
- Options include EU Post-Authorisation Study Register (ENCePP), clinicaltrials.gov, and perhaps others
  - None of these options may be ideal as they currently stand

Key Areas of Discussion

- Rationale for pre-registration
- Review of potential registries and general need for modifications
- Definition of a study
- Need to provide a basis/rationale for study hypothesis as part of the protocol
- Reporting of “pre-looks” and study verification
- Need for confidential “lockbox”
- Philosophy about enforcement
- Need for evolution of technical solutions and business processes
- Potential use cases
- Key issues for technical groups to address

Draft White Paper Released on Sept. 18th – Open for Public Comment



This White Paper was authored by the Steering Committee of the Real-World Evidence Transparency Initiative Partnership. The Initiative is led by ISPOR, the International Society for Pharmacoepidemiology, Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council, with involvement of a number of other organizations and stakeholders. A list of all authors can be found in the appendix.

The white paper comment period remains open through Nov. 15: https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative

White paper recommendations (1 of 3)

1. Near term: Identify location for pre-registration of secondary observational research studies

   Considerations
   - with a view to modify or enhance existing registration sites
   - clearly define the study type – hypothesis evaluating treatment effect studies (HETE) for decision making

   Actions
   - Actively encourage registration on current sites NOW
   - Initiate discussion with leaders of current registries, clinicaltrials.gov and ENCePP/EMA
   - Look at the Center for Open Science format for possible new site, if needed

Potential Registries for Non-interventional RWE Studies

- NIH clinicaltrials.gov
- ENCePP EU-PAS Register
- Center for Open Science OSFRegister

White paper recommendations (2 of 3)

2. Medium term: Determine what a “good” registration process entails to fit the purpose

Considerations

- Feasibility - research and reviewer workload
- Core elements of study registration including website fields and associated documents (e.g. protocol content)
- Transparency vs confidentiality ("lock box" with different access levels)
- Time-stamped registration including data looks
- Don’t let perfect be the enemy of good - this should be a progressive effort

Actions

Consider creating ‘task forces’ to:

- Survey potential users about needs and considerations regarding feasibility, transparency and confidentiality
- Design core elements of registration and protocol
- Design timing of release of information
- Pilot test registration site updates and update partner site or new site if required

White paper recommendations (3 of 3)

3. Long term: Incentives for routine pre-registration for HETE studies

   Considerations
   - End users start requiring registration: funding bodies, journals, regulators, payers/health technology assessors
   - Provide register ‘use reports’ (quarterly report of registered studies, with key information): e.g. on the website; from time to time published

   Actions
   - Build off collaboration with key stakeholders from task force activities to encourage adoption of pre-registration requirements.
   - Involve key stakeholders from survey of potential users.

ISPOR

ISPOR Summit 2019

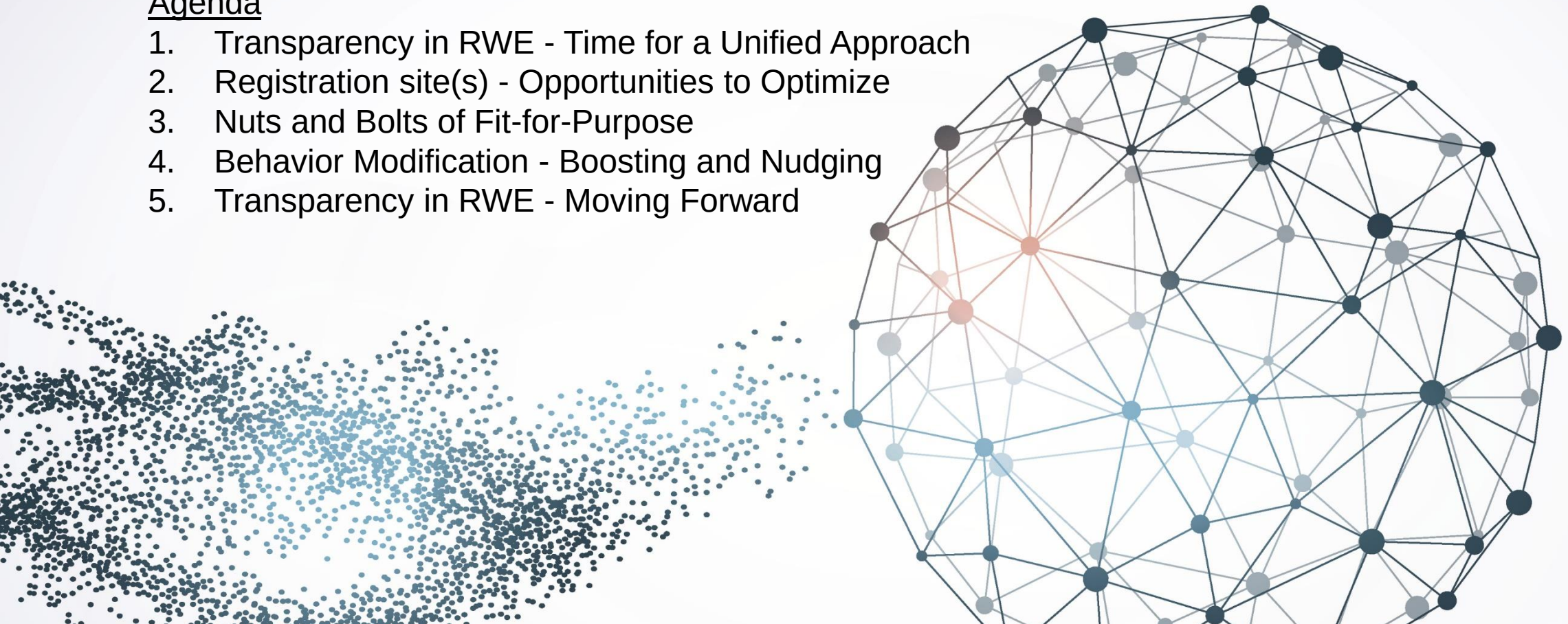
Real-World Evidence Transparency Initiative

October 11, 2019 | Baltimore, MD, USA

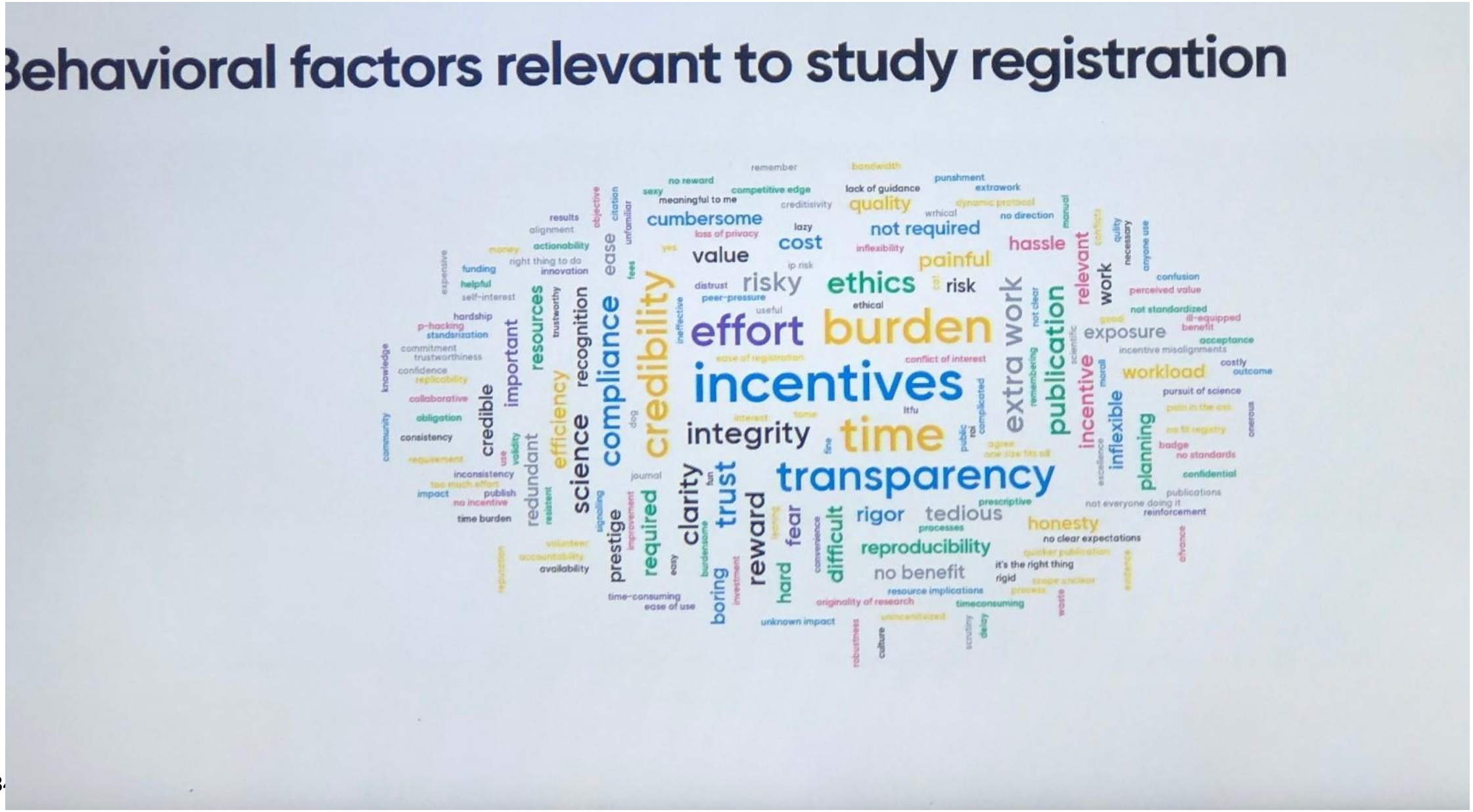
www.ispor.org/Summit2019

Agenda

1. Transparency in RWE - Time for a Unified Approach
2. Registration site(s) - Opportunities to Optimize
3. Nuts and Bolts of Fit-for-Purpose
4. Behavior Modification - Boosting and Nudging
5. Transparency in RWE - Moving Forward



Behavioral factors relevant to study registration



RWE Credibility

Data Quality

Analytic Methods

Process Transparency

Reproducibility

Richard Willke, PhD, Chief Science Officer | CSO@ispor.org