ISPOR / ISPE Summit on

Real-World Evidence in Health Care Decision Making

October 20, 2017
Grand Hyatt Hotel, Washington, DC, USA
ispor.org/RWEinHealthcareDecisions

Welcome

Nancy Berg
CEO & Executive Director
ISPOR

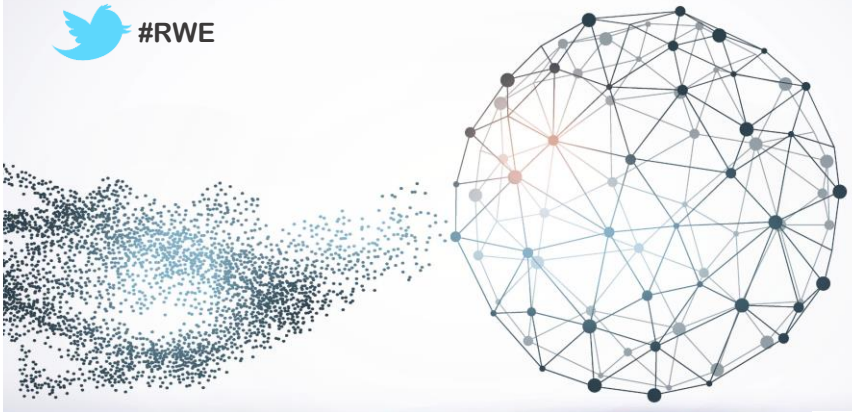
ISPOR's Ambition

To be an innovative catalyst in health care decision making

Welcome to the ISPOR/ISPE Summit on…

Real-World Evidence in Health Care Decision Making

#RWE



Welcome

Harold Sox, MD
PCORI
Washington, DC, USA

Today's Agenda

- 9:15AM – Keynote Address
- 9:30AM – Framing the Problem & Presentation of Recommendations
- 10:40AM – Break
- 11:00AM – Regulatory/HTA Reactions
- 12:00PM – Lunch
- 1:10PM – Afternoon Session Welcome
- 1:15PM – Other Key Stakeholder Perspectives
- 2:15PM – Medical Editor Panel
- 3:15PM – Closing Remarks
- 3:30PM - Adjourn

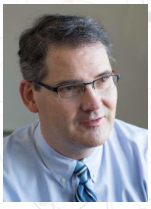
ISPOR/ISPE Joint Task Force Co-Chairs

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

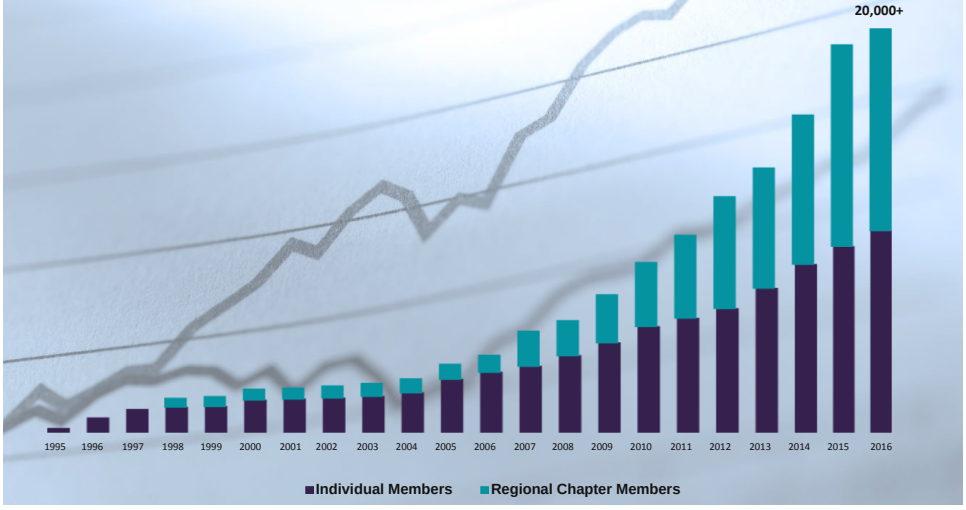
Shirley Wang, PhD, MSc
Harvard Medical School, Boston, MA, USA

ISPOR's Priorities

- Delivering member/customer value
- Continue to improve the science of HEOR through relationships, meetings, and publishing
- Leverage ISPOR's global multistakeholder perspectives
  - Leaders and learners
- Build on ISPOR's role as a convener and catalyst
  - Global networks
  - Shaping future content strategies and consensus building
- Enhance our business models to ensure we have the right platforms to support growth
- Continue to elevate the participation of payers, clinical decision makers, and others throughout ISPOR

Delivering Member Value

20,000+ ISPOR Members



Advancing the Science

Upcoming ISPOR Conferences

20th Annual European Congress
4-8 November 2017
Glasgow, Scotland

23rd Annual International Meeting
May 19-23, 2018
Baltimore, MD, USA

1st Middle East Conference
September 2018
Dubai, United Arab Emirates

8th Asia-Pacific Conference
8-11 September 2018
Tokyo, Japan

Advancing the Science

ISPOR Journals

Collaboration Strategy

Communication and Collaboration

Investing in Our Mission

ISPOR invests in key initiatives that support the future generation of leaders, capacity building, and the science of HEOR.

The Society allocated US $1.6 million in 2016 toward these programs.

Keynote Address

Harold Sox, MD
PCORI
Washington, DC, USA

Spin in reporting study results

Harold C. Sox, M.D. MACP
The Patient-Centered Outcomes Research Institute

The views presented in this address are solely the responsibility of the speaker and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Spin defined: specific reporting that could distort the interpretation of results and mislead readers.

Reporting and interpretation of randomized controlled trials with statistically non-significant primary outcomes

Boutron I, Dutton S, Ravaud P, Altman DG.
JAMA; 2010;303:2058-64

- Study objective: to measure the frequency and nature of spin.
- Sample: PubMed →all 1735 trials in December 2006 →72 included.
- All studies had statistically non-significant results for primary outcome(s).
- Defined spin for study purposes
- Developed classification of spin
- Read in duplicate. Kappa=0.47 (moderate agreement).
- Measured frequency of spin in the 72 articles

Boutron et al. JAMA. 2010;303:2058-64.

Spin: in a trial with statistically non-significant primary outcomes:

Specific reporting strategies to highlight that the experimental treatment is beneficial or to distract the reader from the statistically non-significant results.

- A focus on statistically significant results
  - Within-group comparisons, subgroups, secondary outcomes.
- Interpreting primary outcome as treatment equivalence or comparable effectiveness.
- Claiming beneficial effect for the primary outcome

Characteristics of studies

Characteristic	Result
Specialty journal	95.8%
Primary outcome is efficacy of treatment	87.5%
Sample size (median,)	84 (46-206)
Journal impact factor (median, interquartile range)	2.9 (2.3-4.5)
No. citations in 2008 (median, interquartile range)	4 (1-7)

Results

Outcome	Proportion (%) N=72
Abstract clearly identifies primary outcomes	61%
Abstract reports secondary outcome as primary	4.2%
Abstracts reported the effect size & 95% CI	12.5%
Abstract reported numerical results for primary outcome	61%
Main text reported effect size and 95% CI for primary outcomes	22%

Spin strategies when primary result is statistically non-significant

- Focus on the statistically significant results (within-group, secondary outcomes, subgroup analyses).
- Focus on statistically significant within-study arm improvement from baseline for one arm but not the other (or for both arms combined).
- Focus on *per protocol* results.
- Describe a statistically non-significant outcome as denoting equivalence or non-inferiority.
- Claim efficacy despite the primary outcome result.

Spin strategies when primary result is statistically non-significant

- Acknowledge statistically non-significant primary result but emphasize beneficial effect or other results that are statistically significant.
- Conclude that a statistically non-significant results rules out an adverse event.
- Recommend using the treatment anyway.
- Spin in the abstract but no spin in the main text.

At the 2017 Peer Review Congress, one plenary session was devoted to “bias in reporting and publication of research.”

Two presentations were systematic reviews of the occurrence of spin.

- The starting point for this study was a randomized trial with statistically non-significant results for the primary outcome.
- The starting point for the ISPOR/ISPE declaration is a comparative effectiveness study using observational data.
- The words “primary outcome” does not occur in the ISPOR/ISPE declaration. Nor does it appear in the STROBE reporting standards for observational research (published in 2007).
  - It does appear in the 2010 CONSORT guidelines for reporting randomized trials.

Some questions

- Does the increasing interest in the potential effects of spin call for a statement of good practice about reporting outcomes in STROBE and CONSORT?
- Should reporting guidelines for observational studies follow the CONSORT lead in specifying primary and secondary outcomes?
- Does STROBE need an extension for RWE studies?

FRAMING THE PROBLEM & PRESENTATION OF RECOMMENDATIONS

Marc Berger, MD
Pfizer
New York, NY, USA

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Transparency Issues

Marc Berger, MD
Pfizer, New York, NY, USA

Reproducibility Issues

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

Transparency Recommendations

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

Reproducibility Recommendations

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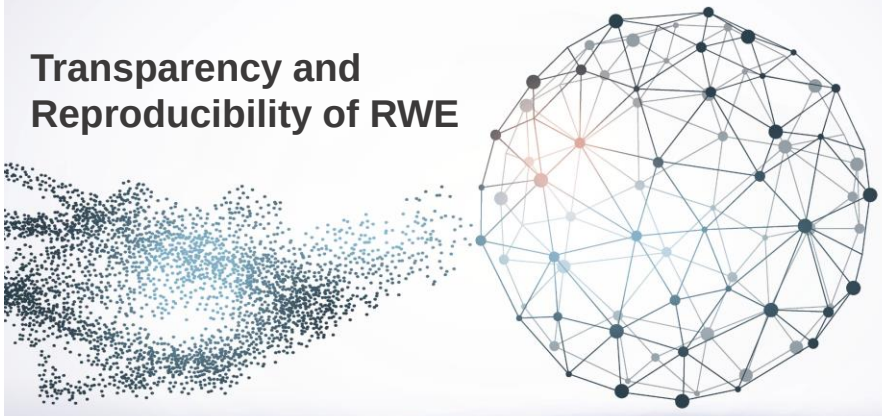
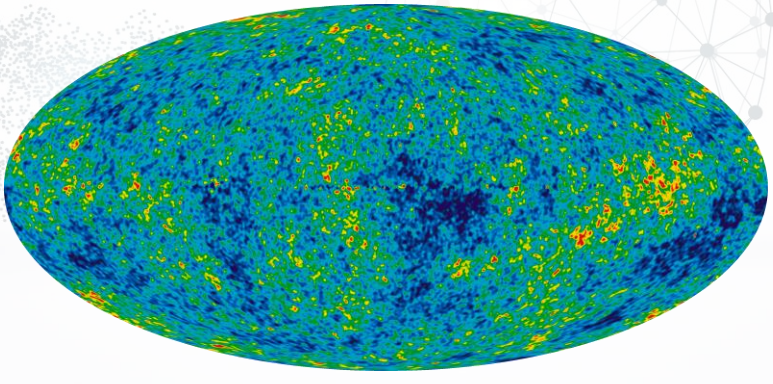
Transparency and Reproducibility of RWE



Marc L. Berger, MD

The Challenge of Real World Evidence

So much data, so much potential information
but is the evidence derived reliable and trustworthy?



Making RWE useful requires:

- **Quality production**
  - Careful data collection and/or curation
  - Good analytic methods
  - Good procedural practices or "study hygiene"
  - Transparent study procedures to enable replication
- **Responsible consumption**
  - Informed interpretation
  - Fit-for-purpose application

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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]

PDS Pharmacoepidemiology & Drug Safety

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

Good Procedural Practices for Clinical Studies ("Study Hygiene")

- **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

Good and Transparent study procedures to enable replication

- 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.

Categories of RWD Studies

- **Safety Studies**
  - **Signal Detection**
  - **Signal Evaluation**
- **Effectiveness 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
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  - **Hypothesis-Evaluating Treatment Effectiveness (HETE) Study**
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Transparency Issues

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Transparency and Reproducibility of RWE

Sebastian Schneeweiss, MD, ScD

Regulatory decision making with RWE

TRANSPARENCY & REPRODUCIBILITY

ROBUSTNESS

DECISION

Can we have clarity on how evidence was generated?

Do we have confidence in the scientific approach?

Is the benefit-harm profile acceptable?

Regulatory decision making with RWE

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Can we have clarity on how evidence was generated?

Do we have confidence in the scientific approach?

Is the benefit-

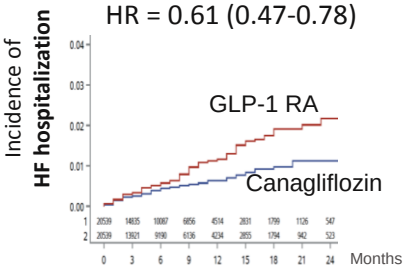
To make a decision we first need to know the validity of findings

Effectiveness Example **blinded** to RCT findings:

Database Study *followed by* **RCT**

Prevention of heart failure hospitalization

HR = 0.61 (0.47-0.78)



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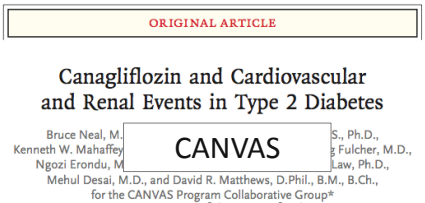

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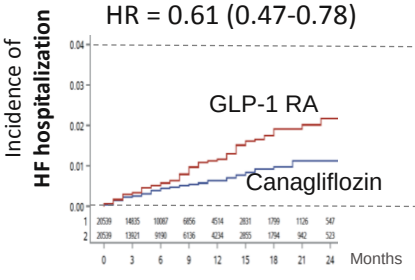
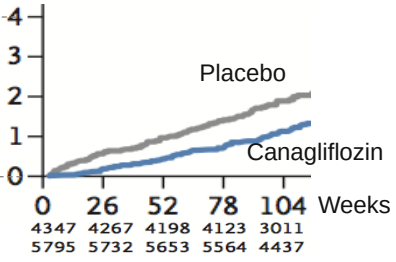


Prevention of heart failure hospitalization

HR = 0.67 (0.52-0.87)



Regulatory decision making with RWE

TRANSPARENCY & REPRODUCIBILITY

ROBUSTNESS

DECISION

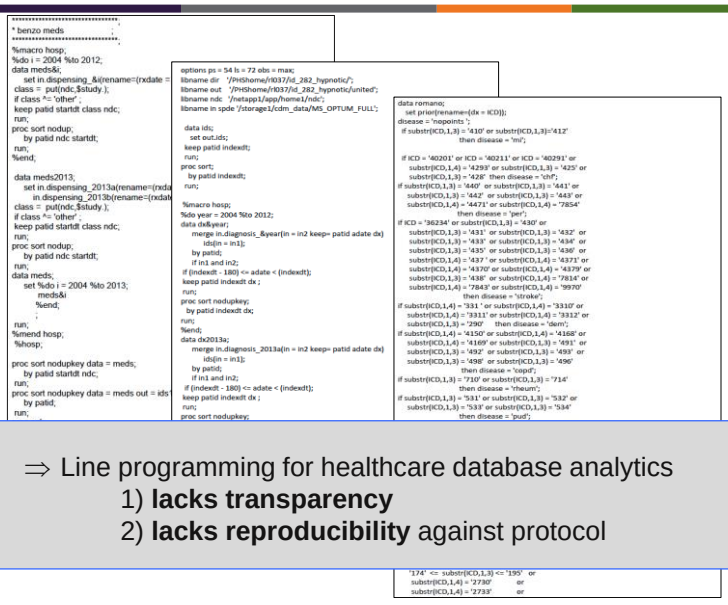
Can we have clarity on how evidence was generated?

Do we have

To assess validity we first need to know how the study was implemented

Is the benefit-harm profile acceptable?

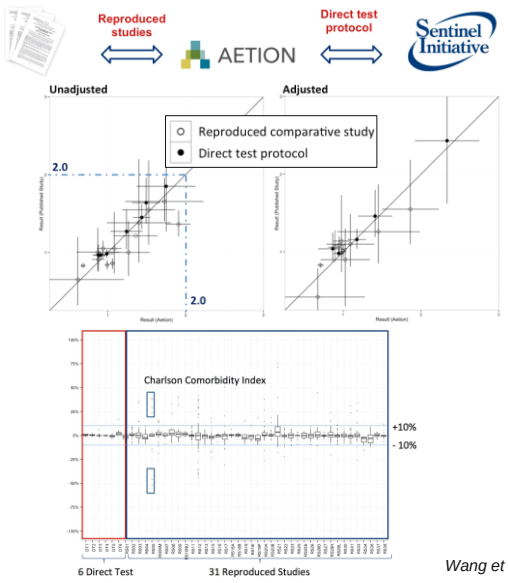
Sharing programming code is not helpful

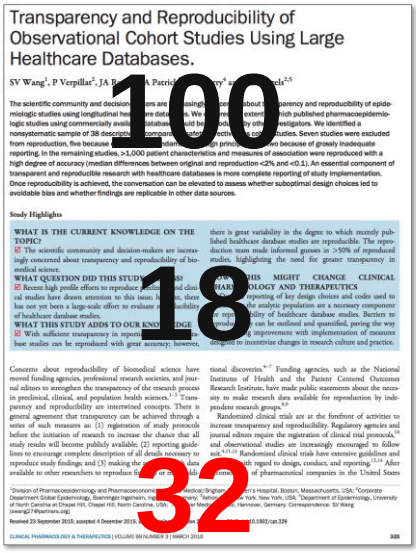


⇒ Line programming for healthcare database analytics

1) **lacks transparency**
2) **lacks reproducibility** against protocol

Pilot study: Lack of reporting details make RWD studies non-reproducible




Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases.

100

18

32

Wang et al. CP&T 2016

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**

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Why are current guidelines insufficient?

Current guidelines are helpful but not on a level of detail that will allow reproducibility of findings

Reproducibility is the foundation of scientific discovery through confirmation and refutation

An inability to reproduce findings will reduce confidence by decision makers in RWD findings

Regulatory decision making with RWE

Can we have clarity on how evidence was generated?

Do we have confidence in the scientific approach?

Is the benefit-harm profile acceptable?

FRAMING THE PROBLEM & PRESENTATION OF RECOMMENDATIONS

Reproducibility Issues

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Task Force Recommendations

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C. Daniel Mullins, PhD

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RECOMMENDATION 1

A priori, determine and declare that study is a “HETE” or “exploratory” study

- Disclose the rationale for the research question and for the study hypothesis
- Study hypotheses may be derived from a variety of sources: an exploratory data analysis on other RWD sources, meta-analyses or reanalyses (possibly on sub-groups)
- If the source was an exploratory analysis of a real-world data set, it should be identified. The rationale for choosing the source of RWD for the HETE study should be described.

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 strongly encouraged.
- Options include EU Post-authorisation Study Register, ClinicalTrials.Gov, and HSRProj
  - None of these options may be ideal

RECOMMENDATION 3

Publish HETE study results with attestation to conformance and/ or deviation from original analysis plan.

- Full and complete reporting of HETE studies is an important step toward earning the confidence of decision makers.
- Publish HETE study results, together with the study protocol
  - Any publication must attest to any deviation from study protocol or the original data analysis plan, detailing the modified elements as they appeared in the original protocol and the final protocol.
  - Reporting Guidelines
    - Companion ISPE – ISPOR Task Force Report (Wang et al)
    - RECORD/STROBE statements reporting guidelines for observational studies
    - SPIRIT recommendations for the content of a clinical trial protocol

RECOMMENDATION 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).

- Full transparency in design and operational parameters, data sharing, and open access in clinical research will not only increase confidence in the results but will also foster the reuse of clinical data (dependent on governance rules regarding data sharing)

RECOMMENDATION 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.

- Good practice generally requires that a HETE study must analyze a different data source and population; otherwise, the HETE analysis risks replicating a finding that is specific to a given data source or population.
- There are situations when replication in another data source is for practical reasons impossible.
- There are other situations where using the same data set may be appropriate. If the study hypothesis is sufficiently sharpened on the basis of the signal from an analysis of a subsample of a data set used for an exploratory study and there are no other available data sets, then the same data source may be considered for hypothesis evaluation.

RECOMMENDATION 6

Authors of the original study should work to publicly address methodological criticisms of their study once it is published.

- Public discussion of disagreements regarding methodology is important to both the credibility of RWD studies and to advancing the field of observational research.
- Authors may want to collaborate on reanalysis with colleagues raising the criticism, while in other cases they may make needed information/data available to facilitate reanalysis.
- Publishing or posting on a public website criticisms and responses or reanalyses based on these comments would be useful.

RECOMMENDATION 7

Include key stakeholders (eg, patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, and manufacturers) in designing, conducting, and disseminating the research.

- Participation of stakeholders in research is evolving, and best practices are still emerging.
- Be clear about the intent of stakeholder engagement, particularly for RWD studies. The specific consultative needs will depend on the intended use of the study, end points involved, novelty of the approach, perceived reliability of the data, and other factors.
- The experience at the Patient-Centered Outcomes Research Institute is a useful benchmark.

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Transparency Recommendations

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

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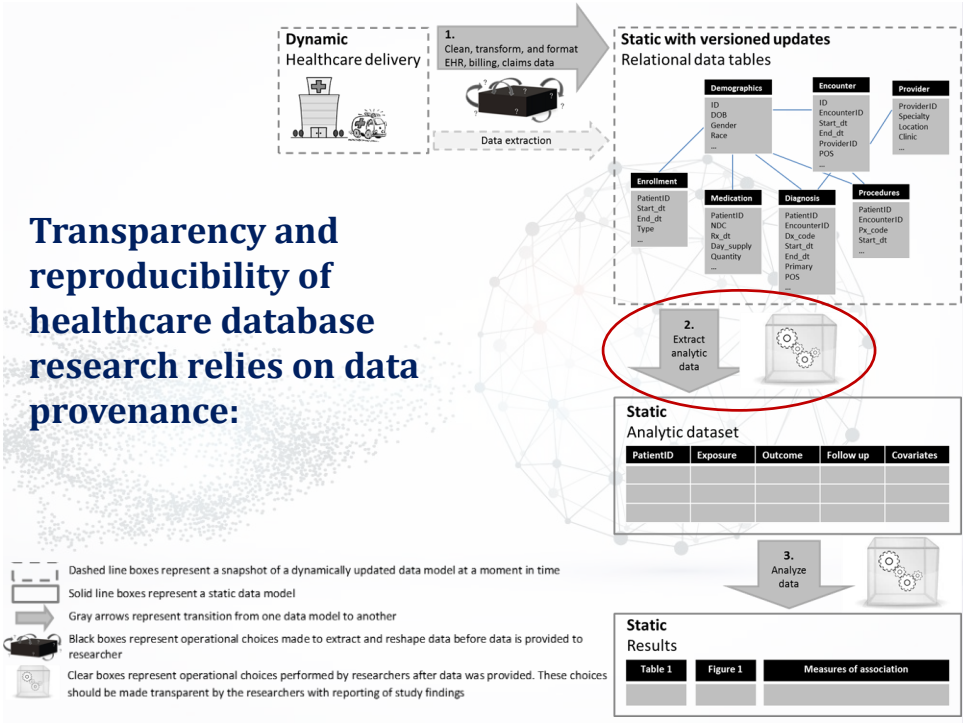
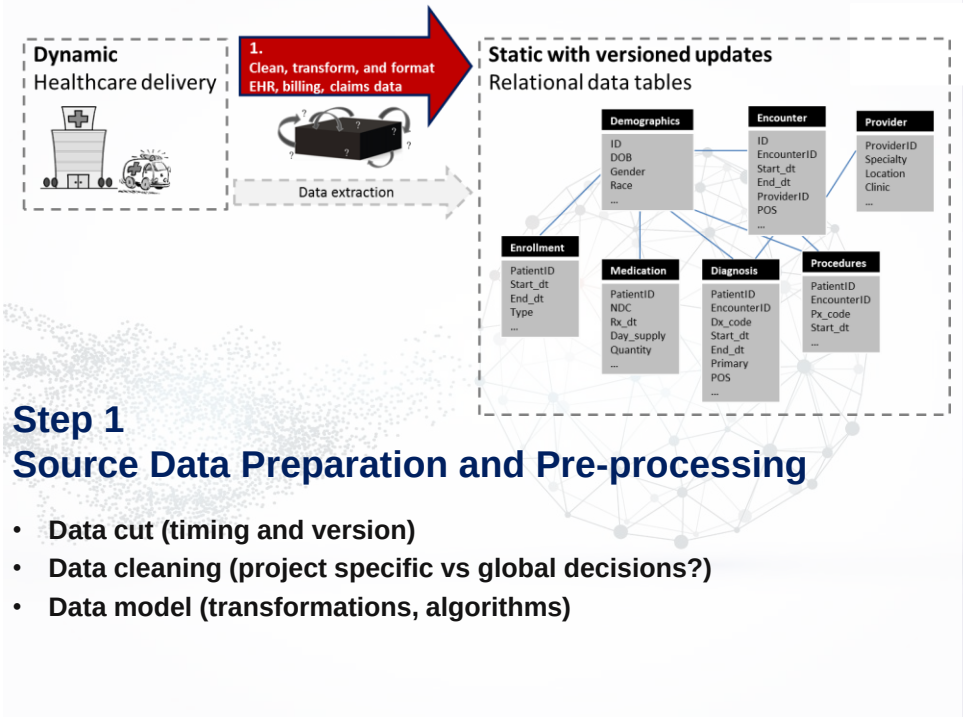
Recommendations – Reproducibility
Shirley V Wang

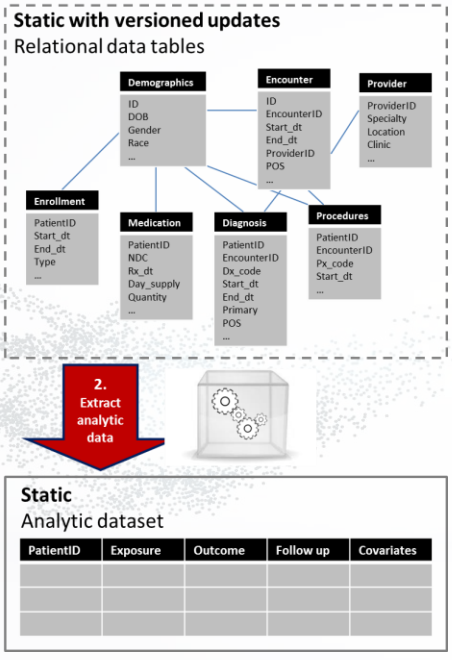


Transparency and reproducibility of healthcare database research relies on data provenance:



Step 1
Source Data Preparation and Pre-processing

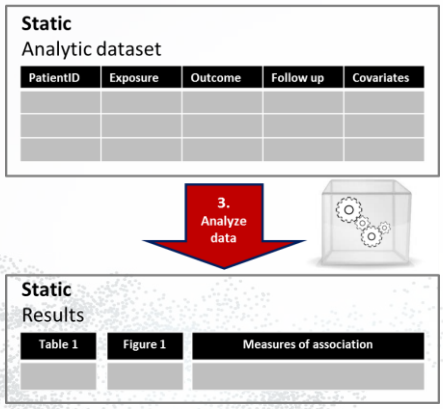
- **Data cut (timing and version)**
- **Data cleaning (project specific vs global decisions?)**
- **Data model (transformations, algorithms)**



Step 2
Parameters for creation of study population

Comprehensive catalogue with 9 sections:

A. Data source
B. Design diagram
C. Inclusion/exclusion criteria (attrition table)
D. Exposure definition
E. Follow up definition
F. Outcome definition
G. Covariates
H. Control sampling
I. Software



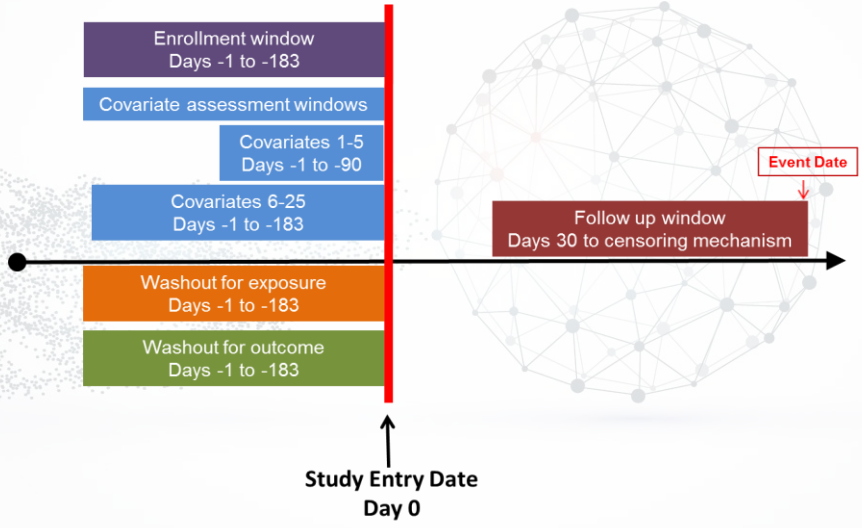
Step 3
Methods for data analysis and reporting results

- Descriptive characteristics (pre and post adjustment)
- Measures of occurrence (risk, rate)
- Measures of association (RD, RR, HR)
- Confidence intervals
- Estimand (ATE, ATT)
- Methods for adjustment, diagnostics (e.g. balance)

A. Data Source

- Data provider
- Data extraction date (DED)
- Data sampling
- Source data range (SDR)
- Type of data (domains of information available)
- Data linkage, supplemental data
- Data cleaning
- Data model conversion

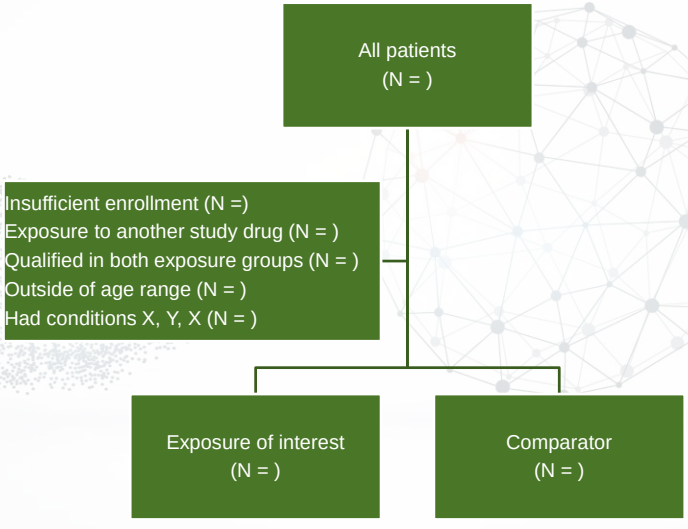
B. Design diagram



C. Inclusion/exclusion (attrition table)

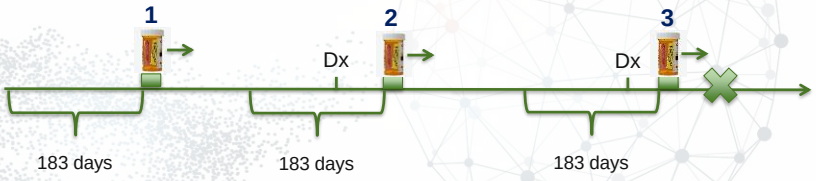
- Study entry date
- Person or episode level entry
- Sequencing of exclusions
- Enrollment window
- Enrollment gap
- Window for assessing inclusion/exclusion criteria
- Code algorithms
  - Frequency and temporality
  - Diagnosis position
  - Care setting
- Washout for exposure
- Washout for outcome

Attrition table showing how the study population was derived



Example specificity in reporting (Step 2)

- Study entry date is first dispensation of metformin after 183 days washout. Patients must have diabetes defined by ICD9 codes 250.* recorded in any care setting and any diagnosis position within 183 days prior to but not including study entry date.

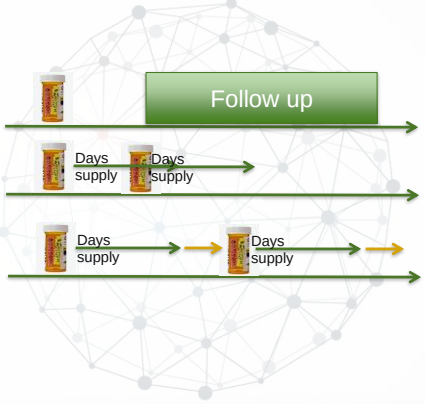


What is the study entry date?

- Consider first new initiation date (1)
  - *Patient does not contribute*
- Consider all new initiation dates (1,2,3), use first that meets inclusion/exclusion
  - *Patient contributes (2)*
- Consider all new initiation dates (1,2,3), use all that meet inclusion/exclusion
  - *Patient contributes (2, 3)*

D. Exposure definition

- Type of exposure
- Exposure risk window
- Induction period
- Stockpiling
- Bridging exposure episodes
- Exposure extension
- Switching/add on
- Codes
  - Frequency and temporality
  - Diagnosis position
  - Care setting



E. Follow up time

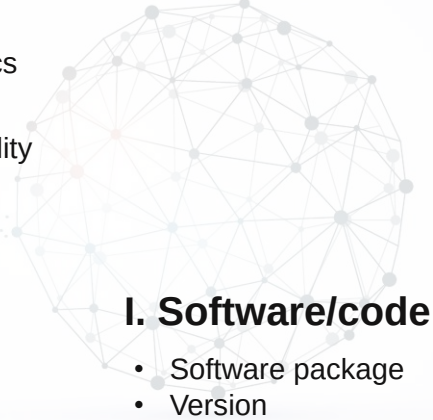
- Follow up window
- Censoring criteria

F. Outcome definition

- Event date
- Codes
  - Frequency and temporality
  - Diagnosis position
  - Care setting
- Validation

G. Covariate definition

- Covariate assessment window
- Comorbidity/risk score
- Healthcare utilization metrics
- Codes
  - Frequency and temporality
  - Diagnosis position
  - Care setting



H. Control sampling

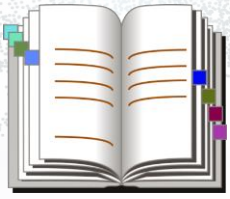
- Sampling strategy
- Matching factors
- Matching ratio (fixed, variable)

I. Software/code

- Software package
- Version
- Analytic procedures
- Code

Summary

- Comprehensive catalogue of **specific operational parameters** representing scientific decisions that define a study population
  - Reporting these will facilitate replicability and validity assessment
  - Expect catalogue will grow and change over time



Consensus - limited number of parameters are absolutely necessary to recreate a study population

Which? *Debatable.*

Next steps

- **Empirical evaluation** of frequency of reporting, impact of transparency on specific study parameters (REPEAT Initiative)
  - *Inform policies/standards/guidelines* on reporting for database studies
  - Parameters infrequently reported with demonstrable↑ influence on replicability or robustness could be prioritized
- **Shared terminology and structured reporting templates**
  - Simplify reporting - terminology used for the same concepts varies
  - Reporting of attrition tables (ordering of exclusion, clarity)
  - Visualization of study design implementation
- **Reporting on research using unstructured data**
  - Clarity in how ground truth/gold standard is defined
  - Scientific decisions/parameter tuning for NLP, machine learning algorithms
- **…**

FRAMING THE PROBLEM & PRESENTATION OF RECOMMENDATIONS

Reproducibility Recommendations

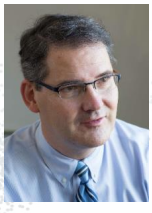
Shirley Wang, PhD, MSc
Harvard Medical School
Boston, MA, USA

FRAMING THE PROBLEM & PRESENTATION OF RECOMMENDATIONS

Transparency Issues

Marc Berger, MD
Pfizer, New York, NY, USA

Reproducibility Issues



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

Transparency Recommendations

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

Reproducibility Recommendations

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

ISPOR / ISPE Summit on

Real-World Evidence in Health Care Decision Making

BREAK

ISPOR / ISPE Summit on

Real-World Evidence in Health Care Decision Making

REGULATORY/HTA REACTIONS

REGULATORY/HTA REACTIONS

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REGULATORY/HTA REACTIONS

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EUnetHTA

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EuNetHTA JA3, Diemen, The Netherlands

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US Food and Drug Administration
Washington, DC, USA

U.S. FOOD & DRUG ADMINISTRATION

Real World Data Studies and Transparency

Jacqueline Corrigan-Curay, JD, MD
Director
Office of Medical Policy
Center for Drug Evaluation and Research
FDA
October 20, 2017

Disclosures

FINANCIAL DISCLOSURE:
No relevant financial relationship exists

The views expressed herein are those of the author and should not be construed as FDA's views or policies

CDER Definitions

- **Real-World Data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- **Real-World Evidence (RWE)** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

RWD include data derived from electronic health records (EHRs), claims and billing

RWE can be generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

FDA Experience with RWD/RWE

425 million person years of observation time
43 million people currently accruing new data
5.9 billion pharmacy dispensings
7.2 billion unique medical encounters
42 million people with at least one laboratory test result

Sentinel Initiative

Network of Collaborators

Sentinel brings together public, academic and private organizations that provide access to healthcare data and expertise.

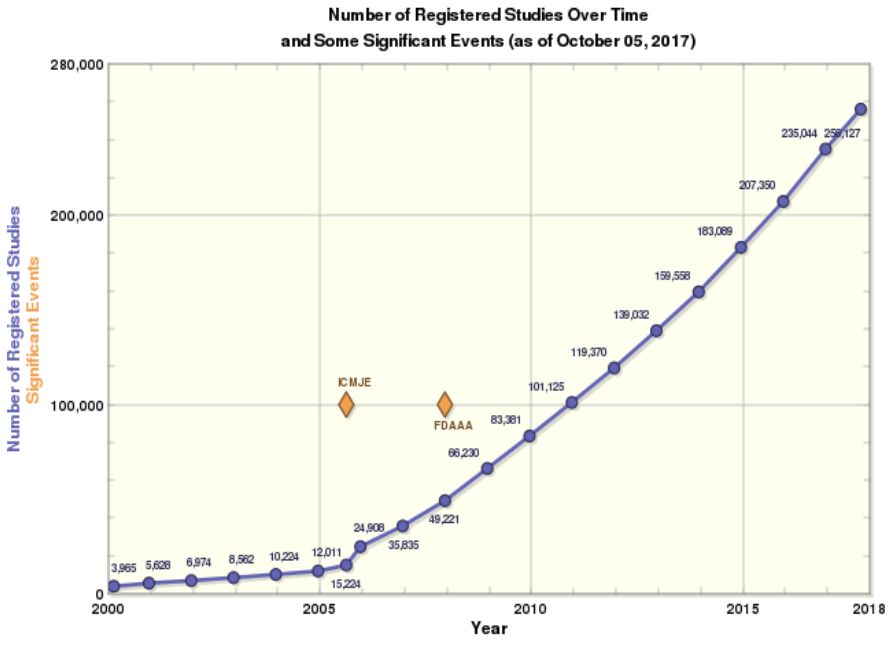
Data at a Glance

The Sentinel Distributed Database is comprised of quality-checked electronic data held by 18 partner organizations.

Statistical Methods

Sentinel explores the application of a wide range of methods to enhance medical product safety assessment.

https://www.sentinelinitiative.org/



Source: https://ClinicalTrials.gov

Bringing it All Together

Leveling the Playing Field

- **RWD vs Non-RWD**
- **Frame the question as totality of evidence**

Questions/ Comments

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

REGULATORY/HTA REACTIONS

US Regulatory

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REGULATORY/HTA REACTIONS

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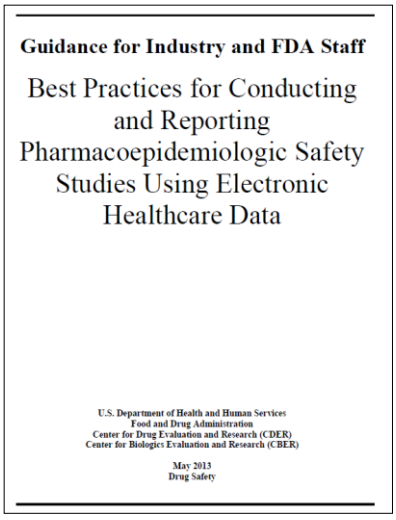
Comments on ISPE/ISPOR Real World Evidence Task Force Reports

Robert Ball, MD, MPH, ScM
Deputy Director
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research
October 20, 2017

The views expressed are those of the speaker and do not necessarily reflect FDA policy

Epidemiology – Final Guidance

- Pertains to pharmacoepidemiology safety studies using electronic healthcare data
- Final guidance was issued May 14, 2013


Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013
Drug Safety

Where might the ISPE/ISPOR reports fit in?

- Similarity in many concepts in the ISPE/ISPOR reports and the FDA guidance on Best Practices for pharmacoepidemiology safety studies using electronic healthcare data
  - Some key areas of similarity for the "Transparency" report
    - focus on hypothesis testing studies
    - need for protocol prior to start of the study
    - need to follow the protocol
  - The "Reproducibility" document is more detailed and uses different terminology in some instances, but is similar conceptually

Lessons from the Sentinel System

- Sentinel is specifically mentioned in the "Reproducibility" document:
  - "Sentinel has committed itself to transparency through online posting of study protocols, final reports, and study specifications, including temporal anchors, how data are processed into a common data model, and study design details."
- FDA remains committed to improving the transparency of and access to the Sentinel System

Lessons from the Sentinel System

- FDA and partners have successfully implemented the Sentinel System to meet the requirements for an **Active Post-market Risk Identification and Analysis (ARIA)** system required by FDA Amendments Act of 2007
  - Reusable tools, high quality data, validation of key data elements, and assessment of "sufficiency"
- What is ARIA Sufficiency?
  - **Adequate data**
  - **Appropriate methods**
  - **To answer the question of interest**
  - **At satisfactory level of precision**

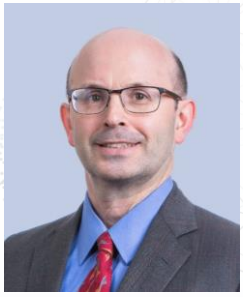
Where might the ISPE/ISPOR reports fit in?

- Question of Interest
  - 21st Century Cures Act - "The Secretary shall establish a program to evaluate the potential use of real world evidence (1) to help to support the approval of a new indication for a drug approved under section 505(c); and (2) to help to support or satisfy postapproval study requirements"
- Can we identify the specific questions, data characteristics, study design attributes, and analysis methods for healthcare database studies of drug effectiveness that we can trust to provide valid and reproducible results?
  - This effort would be assisted if the ISPE/ISPOR report recommendations were followed generally, because there would be an improved empirical basis for understanding "what works"

Thank you

REGULATORY/HTA REACTIONS

US Regulatory



Robert Ball, MD, MPH, ScM
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REGULATORY/HTA REACTIONS

EUnetHTA

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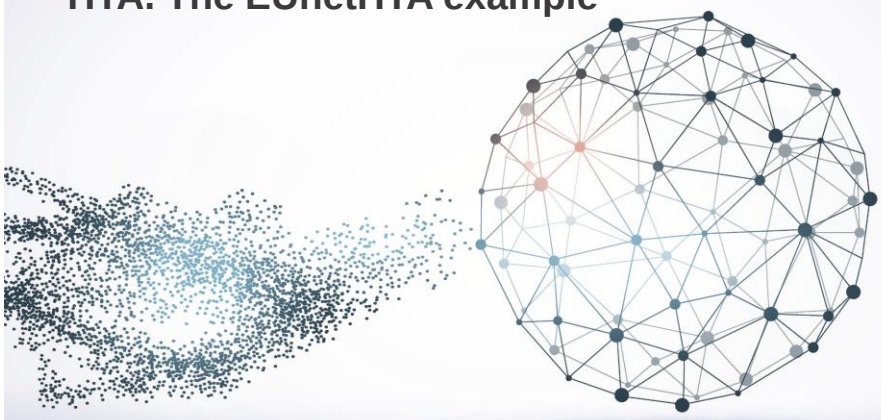
Diemen, The Netherlands

ISPOR / ISPE Summit on

Real-World Data (RWD) in HTA. The EUnetHTA example



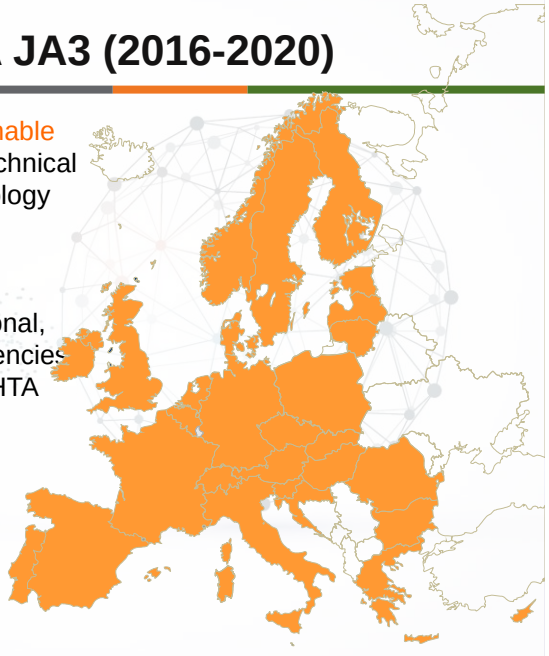
Wim Goettsch
Director EUnetHTA JA3 Directorate
ZIN, The Netherlands

EUnetHTA JA3 (2016-2020)

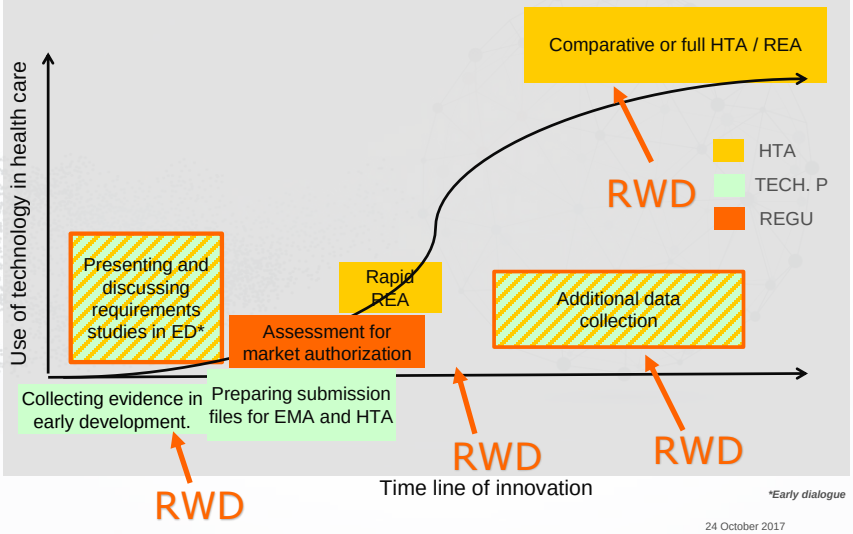
Aims to contribute to a sustainable model for the scientific and technical cooperation on Health Technology Assessment (HTA) in Europe

81 partners consisting of national, regional and non-for-profit agencies that produce or contribute to HTA

Project Coordinator:
Dutch National Health Care Institute (ZIN)

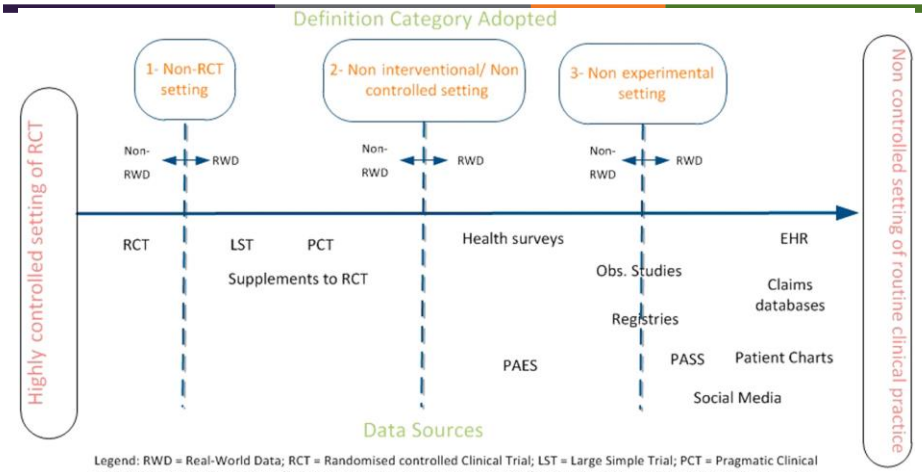


RWD in the life cycle of technologies



24 October 2017

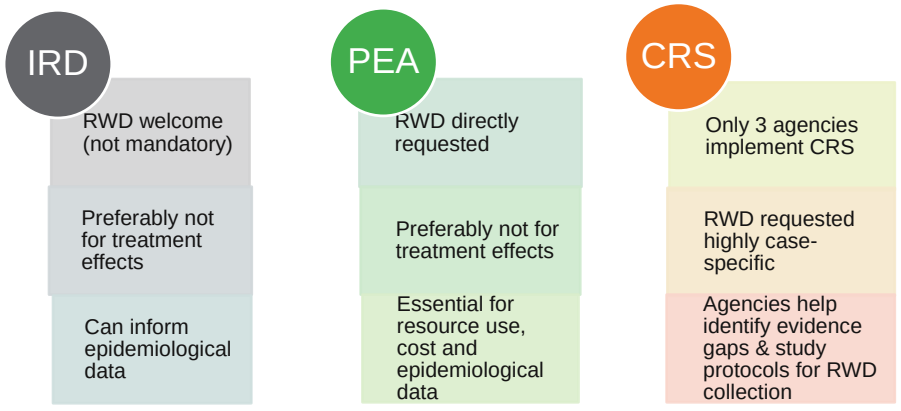
Definition of RWD



Legend: RWD = Real-World Data; RCT = Randomised controlled Clinical Trial; LST = Large Simple Trial; PCT = Pragmatic Clinical Trial; PAES: Post-Authorisation Efficacy Study; PASS = Post-Authorisation Safety Studies; Obs. Studies = Observational studies; EHR = Electronic Health Record.

Makady A, de Boer A, Hillege H, Klungel OH, Goettsch WG,. What Is Real-World Data (RWD)? A Review of Definitions Based on Literature and Stakeholder Interviews. Value in Health 2017; in press

HTA policies on RWD



Makady A, ten Ham R, de Boer A, Hillege H, Klungel OH, Goettsch WG,. Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies. Value in Health 2017; 20: 520-5323

Conclusions

- **Real World Data will become important over the life-cycle**
  - Should we remain to use the term RWD?
  - More clarity and insight on the use of RWD in HTA practice is necessary
  - Access issues remain important
  - What can we do in working together?
- **Quality of RWD remains a crucial issue**
  - Transparent reporting of RWD data studies
  - Guidelines for interpretation of RWD should be implemented
  - Acceptability of RWD for decision-making needs more interaction with the final decision-makers

REGULATORY/HTA REACTIONS

EUnetHTA

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REGULATORY/HTA REACTIONS

US Payer

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EuNetHTA JA3, Diemen, The Netherlands

US Payer

Laura Happe, PharmD, MPH
Humana, Louisville, KY, USA

ISPOR / ISPE Summit on

Real-World Evidence in Health Care Decision Making

LUNCH

Afternoon Session Welcome

Tobias Gerhard, PhD, FISPE, (ISPE)E
Rutgers University
New Brunswick, NJ, USA

ISPOR / ISPE Summit on

Real-World Evidence in Health Care Decision Making

OTHER KEY STAKEHOLDER PERSPECTIVES

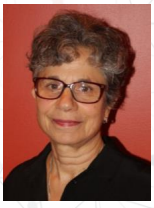
OTHER KEY STAKEHOLDER PERSPECTIVES

Tobias Gerhard, PhD, FISPE, (ISPE)
Rutgers University, New Brunswick, NJ, USA

Patient Representative

Eric Gascho
National Health Council, Washington, DC, USA

Registry Representative



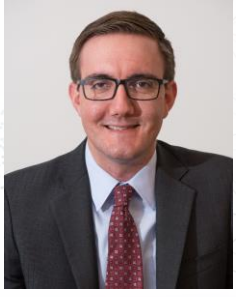
Deborah Zarin, MD
National Institutes of Health, Bethesda, MD, USA

Industry Representative

Cathy Critchlow, PhD
Amgen, Thousand Oaks, CA, USA

OTHER KEY STAKEHOLDER PERSPECTIVES

Patient Representative



Eric Gascho
National Health Council
Washington, DC, USA

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The Patient Perspective on Real-World Evidence

Eric Gascho

ISPOR/ISPE Summit on
Real-World Evidence in Health Care Decision Making
October 20, 2017

The Patient Perspective on Real-World Evidence

- Qualitative research (September 2016 & June 2017)
- Multi-stakeholder Roundtable (July 31, 2017)
- White Paper (September 2017)
  1. Definition and Uses
  2. Understanding and Trust
  3. Skill Sets and Tools Needed

Patient Perspectives on Real-World Evidence:
A Roundtable to Gather Views, Needs, and Recommendations

NATIONAL HEALTH COUNCIL

1730 M Street NW, Suite 500
Washington, DC 20036
202-785-3910
www.nationalhealthcouncil.org

Three Key Findings Related to the ISPOR/ISPE Papers

1. The patient community has little understanding of RWE or that controversies exist
2. Patient groups act as arbiters of evidence quality, and influence trust in the evidence
3. Need for patient-organization education programs/materials on RWE uses, sources, and key issues

Key Findings: Questions that Aid in Patient Understanding and Trust of RWE

1. Who or what group conducted the study? Was it co-developed with patients?
2. What is the purpose/objective of the study? Does it have pre-specified study aims?
3. What are the key findings and how are they meaningful to patients?
4. Who owns (or holds) the data?
5. How many people were included? What were their characteristics?
6. Over what time period did the study take place?
7. Did the methods aligned with question/objective?
8. Who interpreted the study? What are their qualifications?
9. Who is the evidence most likely to interest or benefit?
10. How are the findings actionable for patients and clinicians?
11. How does the study fit into the larger realm of science on this topic??
12. How is this a novel finding, or how does it replicate or refute past work?
13. How does it deal with the reality that, for some treatments, there is no clear consensus?
14. What are the identified limitations, including barriers/challenges, especially for patients?

Recommendations for good procedural practices for HETE Studies

"Include key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, manufacturers) in designing, conducting, and disseminating HETE studies."

VALUE IN HEALTH 20 (2017) 1003–1008

Available online at www.sciencedirect.com

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

ELSEVIER

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]

[1]New York City, NY, USA; [2]Patient-Centered Outcomes Research Institute, Washington, DC, USA; [3]International Society for Pharmacoeconomics and Outcomes Research, Lawrenceville, NJ, USA; [4]University of Utah, Salt Lake City, UT, USA; [5]European Medicines Agency, London, UK; [6]Zorginstituut Nederland and University of Utrecht, Utrecht, The Netherlands; [7]Columbia University, New York City, NY, USA; [8]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [9]Bocconi University, Milan, Italy; [10]Premera Blue Cross, Mountlake Terrace, WA, USA; [11]University of Maryland, Baltimore, MD, USA

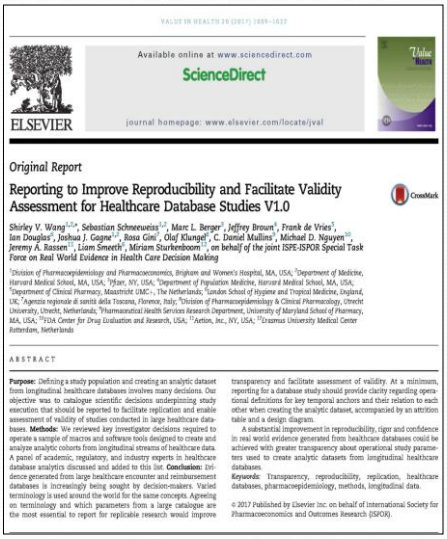
ABSTRACT

Purpose: Real-world evidence (RWE) includes data from retrospective or prospective observational studies and observational registries and provides insights beyond those addressed by randomized controlled trials. RWE studies aim to improve health care decision making. **Methods:** The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) created a task force to make recommendations regarding good procedural practices that would enhance decision makers' confidence in evidence derived from RWD studies. Peer review by ISPOR/ISPE members and task force participants provided a consensus-building iterative process for the topics and framing of recommendations. **Results:** The ISPOR/ISPE Task Force recommendations cover seven topics such as study registration, replicability, and stakeholder involvement in RWE studies. These recommendations, in concert with earlier recommendations about study methodology, provide a trustworthy foundation for the expanded use of RWE in health care decision making. **Conclusion:** The focus of these recommendations is good procedural practices for studies that test a specific hypothesis in a specific population. We recognize that some of the recommendations in this report may not be widely adopted without appropriate incentives from decision makers, journal editors, and other key stakeholders.

Keywords: comparative effectiveness, decision making, guidelines, pharmacoepidemiology, real-world data, treatment effectiveness.

Transparency

"Clear natural language description of key operational and design details should be the basis for sharing the scientific thought process with the majority of informed consumers of evidence."



VALUE IN HEALTH 20 (2017) 1009–1022

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ELSEVIER

Original Report

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

CrossMark

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

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, MA, USA; [2]Department of Medicine, Harvard Medical School, MA, USA; [3]Pfizer, NY, USA; [4]Department of Population Medicine, Harvard Medical School, MA, USA; [5]Department of Clinical Pharmacy, Maastricht UMC+, The Netherlands; [6]London School of Hygiene and Tropical Medicine, England, UK; [7]Agenzia regionale di sanità della Toscana, Florence, Italy; [8]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [9]Pharmaceutical Health Services Research Department, University of Maryland School of Pharmacy, MA, USA; [10]FDA Center for Drug Evaluation and Research, USA; [11]Aetion, Inc., NY, USA; [12]Erasmus University Medical Center Rotterdam, Netherlands

ABSTRACT

Purpose: Defining a study population and creating an analytic dataset from longitudinal healthcare databases involves many decisions. Our objective was to catalogue scientific decisions underpinning study execution that should be reported to facilitate replication and enable assessment of validity of studies conducted in large healthcare databases. **Methods:** We reviewed key investigator decisions required to operate a sample of macros and software tools designed to create and analyze analytic cohorts from longitudinal streams of healthcare data. A panel of academic, regulatory, and industry experts in healthcare database analytics discussed and added to this list. **Conclusion:** Evidence generated from large healthcare encounter and reimbursement databases is increasingly being sought by decision-makers. Varied terminology is used around the world for the same concepts. Agreeing on terminology and which parameters from a large catalogue are the most essential to report for replicable research would improve transparency and facilitate assessment of validity. At a minimum, reporting for a database study should provide clarity regarding operational definitions for key temporal anchors and their relation to each other when creating the analytic dataset, accompanied by an attrition table and a design diagram.

A substantial improvement in reproducibility, rigor and confidence in real world evidence generated from healthcare databases could be achieved with greater transparency about operational study parameters used to create analytic datasets from longitudinal healthcare databases.

Keywords: Transparency, reproducibility, replication, healthcare databases, pharmacoepidemiology, methods, longitudinal data.

Summary

- How can we operationalize these goals?
  - Engage patient advocates in true partnership
  - Begin engagement early and often
  - Provide rationale for decisions made
  - With input from the patient community, communicate with clear, natural language the patient community will understand

Thank you!

NHC Contact:
Eric Gascho
VP of Policy & Government Affairs
email: egascho@nhcouncil.org

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OTHER KEY STAKEHOLDER PERSPECTIVES

Patient Representative

Eric Gascho
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Washington, DC, USA

OTHER KEY STAKEHOLDER PERSPECTIVES

Registry Representative

Deborah Zarin, MD
National Institutes of Health
Bethesda, MD, USA

ISPOR / ISPE Summit on

Real-World Evidence in Health Care Decision Making

Deborah A. Zarin
Director, ClinicalTrials.gov
U.S. National Institute of Health

ClinicalTrials.gov and Real-World Evidence

ISPOR/ISPE Summit on

Real-World Evidence in
Health Care Decision Making

October 20, 2017
Washington, DC, USA

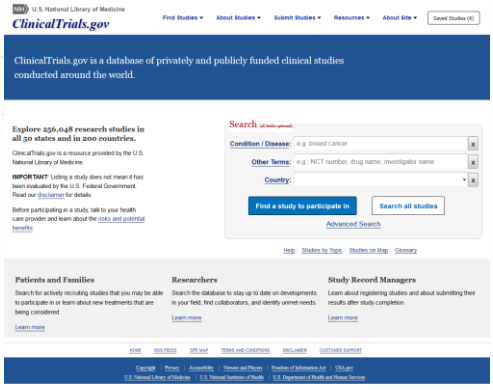
ispor.org/RWEinHealthcareDecisions

ClinicalTrials.gov

- Registry and Results Database
- Tool for providing information about biomedical or “health related” studies in human subjects
- Accommodates various trial reporting policies, e.g.,
  - ICMJE/WHO
  - FDAAA (42 CFR Part 11)
  - NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
  - PCORI
- ClinicalTrials.gov has structured data entry fields
  - Mandatory
  - Optional
- Includes observational and interventional studies
  - Almost all policies focus on interventional studies

ClinicalTrials.gov Overview (as of 5 Oct 2017)

- Study registry includes:
  - 204,400 Interventional studies (clinical trials)
  - 50,500 Observational studies
    - 3,300 Patient registries
  - 400 Expanded access
- Results database includes:
  - 26,800 sets of results for clinical trials
  - 1,800 sets of results for observational studies



Content of a Study Record (Minimum Information Requirements)

- **Registration section**
  - Submitted at study initiation
  - Summarizes information from study protocol: e.g.,
    - Condition
    - Interventions
    - Study design
  - Includes enrollment information (e.g., eligibility, locations)
- **Results section**
  - Submitted after study completion
  - Summarizes study results
    - Participant flow
    - Baseline characteristics
    - Outcome measures (including statistical analyses)
    - Adverse events
    - Protocol document

Registration of Observational Studies

- Accommodated at ClinicalTrials.gov since February 2000
- Standardizes key attributes of study information using established mandatory and optional data elements
- Informed by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
  - October 2007: Modifications made to design-specific data elements for registering observational studies were strongly influenced by STROBE
  - September 2008: Added results-related items identified by STROBE

Definition of Observational Study

- **Observational**: Studies in human beings in which biomedical and/or health outcomes are **assessed in pre-defined groups of individuals**. Participants in the study may receive diagnostic, therapeutic, or other interventions, but the investigator does not assign specific interventions to the study participants. This includes when participants receive interventions as part of routine medical care, and a researcher studies the effect of the intervention.

  Versus:

- **Interventional** (clinical trial): Participants are **assigned prospectively to an intervention or interventions according to a protocol** to evaluate the effect of the intervention(s) on biomedical or other health related outcomes.

Observational Study Design Data Elements

- **Observational Study Model*** - Primary strategy for participant identification and follow-up (e.g., Cohort, Case-Control, Case-Only)
- **Time Perspective*** - Temporal relationship of observation period to time of participant enrollment: e.g.,
  - Prospective: Look forward using periodic observations collected predominantly following subject enrollment
  - Cross-sectional: Observations or measurements made at a single point in time, usually at subject enrollment
  - Retrospective
- **Biospecimen Retention** - Indicate whether samples of material from research participants are retained in a biorepository (e.g., Samples with DNA, None Retained)
  - **Biospecimen Description** - Specify all types of biospecimens to be retained (e.g., whole blood, serum, white cells, urine, tissue).

ANALYSIS CMAJ

Registration of observational studies: Is it time?

Rebecca J. Williams PharmD MPH, Tony Tse PhD, William R. Harlan MD, Deborah A. Zarin MD

Previously published at www.cmaj.ca

Observational studies form an important part of the medical evidence base, particularly for assessing rare adverse events and long-term effectiveness of medications and devices.[1] However, observational studies, like interventional studies (clinical trials), are subject to publication bias and reporting bias.[2–4] Registration of clinical trials is a widely recognized tool for facilitating complete public reporting.[5] Registration of observational studies has received less attention, although interest is growing.[6–8] Because existing registries (e.g., ClinicalTrials.gov) accommodate observational studies, and the rationale and benefits of registration are similar, we ask the scientific community and other stakeholders to consider the systematic, prospective registration of observational studies.

Key points

- Clinical trial registries are established tools for improving access to information on trials and for addressing publication bias and reporting bias.
- Much of the ethical and scientific rationale for registering clinical trials also applies to observational studies.
- The existing infrastructure for trial registration is being used for observational studies, which make up 17% of the studies registered in ClinicalTrials.gov.
- Further discussion is necessary to assess the scope and specific implementation-related issues of systematic registration of observational studies.

Why register observational studies?

Much of the rationale for the prospective registration of clinical trials[9] applies to the registration of observational studies (Table 1).[7] For example, observational studies in which researchers acquire data directly from human participants entail ethical obligations to participants, even though such

ies, a registry containing summary protocol information would allow researchers to track such studies from initiation to completion. Such a tool could be useful to researchers who are evaluating the current evidence, considering initiating similar studies, identifying gaps in research or seeking collaborators.[15] Similarly, a database of summary results could improve access to information about published and unpublished observational

Reporting of Observational Studies

- ClinicalTrials.gov **works best** for reporting studies that use a collection of primary, prospective data in humans: e.g.,
  - Data collected prospectively from well-defined groups of individuals (e.g., exposed and non-exposed) according to a protocol
  - Prospective cohort studies were the most frequently registered in ClinicalTrials.gov (~half of all registered observational studies)

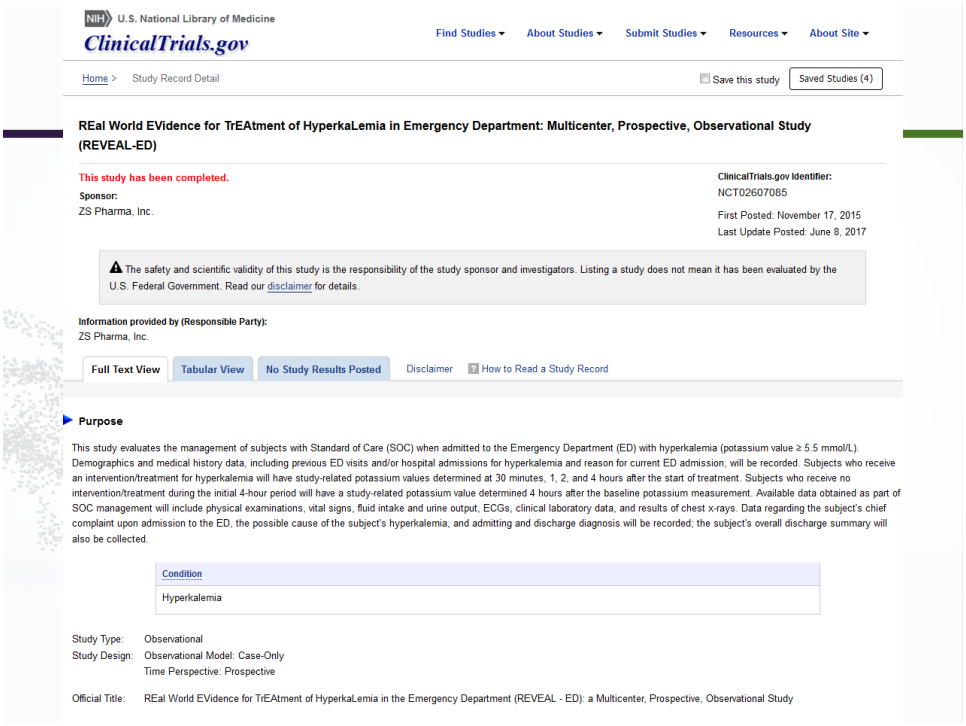
Source: Williams RJ et al. *CMAJ*. 2010;182(15):1638-42.

Sample Registered RWE Study (NCT02607085)

- **Title**: REal World EVidence for TrEAtment of HyperkaLemia in Emergency Department (REVEAL-ED)
- **Sponsor**: ZS Pharma, Inc. (member of the AstraZeneca Group)
- **Purpose**: "This study evaluates the management of subjects with Standard of Care (SOC) when admitted to the Emergency Department (ED) with hyperkalemia (potassium value ≥ 5.5 mmol/L)."
- **Study Design**: Multicenter, Prospective, Observational Study
  - Observational Model: Case-Only
  - Enrollment: 203 participants

Sample RWE Study (NCT02607085) - 2

- **Primary Outcome**: Absolute change in potassium over 4 hours following the initial intervention/treatment for hyperkalemia.
  - If no intervention/treatment for hyperkalemia during ED admission, then change over 4 hours following baseline potassium measurement.
- **Secondary Outcome**: Choice of intervention/treatment [Time Frame: 4 hours]
  - Changes in study-related potassium following intervention/treatment.



U.S. National Library of Medicine
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Save this study | Saved Studies (4)

REal World EVidence for TrEAtment of HyperkaLemia in Emergency Department: Multicenter, Prospective, Observational Study (REVEAL-ED)

This study has been completed.

Sponsor:
ZS Pharma, Inc.

ClinicalTrials.gov Identifier:
NCT02607085

First Posted: November 17, 2015
Last Update Posted: June 8, 2017

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Information provided by (Responsible Party):
ZS Pharma, Inc.

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This study evaluates the management of subjects with Standard of Care (SOC) when admitted to the Emergency Department (ED) with hyperkalemia (potassium value ≥ 5.5 mmol/L). Demographics and medical history data, including previous ED visits and/or hospital admissions for hyperkalemia and reason for current ED admission, will be recorded. Subjects who receive an intervention/treatment for hyperkalemia will have study-related potassium values determined at 30 minutes, 1, 2, and 4 hours after the start of treatment. Subjects who receive no intervention/treatment during the initial 4-hour period will have a study-related potassium value determined 4 hours after the baseline potassium measurement. Available data obtained as part of SOC management will include physical examinations, vital signs, fluid intake and urine output, ECGs, clinical laboratory data, and results of chest x-rays. Data regarding the subject's chief complaint upon admission to the ED, the possible cause of the subject's hyperkalemia, and admitting and discharge diagnosis will be recorded; the subject's overall discharge summary will also be collected.

Condition
Hyperkalemia

Study Type: Observational
Study Design: Observational Model: Case-Only
Time Perspective: Prospective

Official Title: REal World EVidence for TrEAtment of HyperkaLemia in the Emergency Department (REVEAL - ED): a Multicenter, Prospective, Observational Study

Issues in Registering Observational Studies

- Other observational study designs pose variety of challenges (e.g., retrospective data collections)
  - Study start and end dates
  - Definition of study cohort (e.g., secondary data analysis)
- Delineating a single observational study
  - Vs a broad plan for data analysis, and
  - How to handle sub-studies and secondary studies or analyses using the same prospective data set
- Need for other observational study-specific data elements:
  - e.g Baseline characteristics used to characterize a cohort or that will be included in an analysis
- Other concerns:
  - Ambiguity in terms of which hypotheses are prespecified (prespecified when?)
  - Some concern that prespecification of all hypotheses will inhibit exploratory research

Source: Williams RJ et al. *CMAJ*. 2010;182(15):1638-42.

Consider goals of registration and how apply to observational studies

- Help participants find studies
- Mitigate selective publication/reporting
  - Ensure public record of study existence
  - Ensure record of prespecified outcome measures (hypotheses)
- Provide tool for assessing fidelity to protocol
- Other
  - Biospecimen availability
  - Patient registry existence
- Goals depend on clear identification of a single study
  - Defined set of participants
  - Defined protocol for data analysis

OTHER KEY STAKEHOLDER PERSPECTIVES

Registry Representative

Deborah Zarin, MD
National Institutes of Health
Bethesda, MD, USA

OTHER KEY STAKEHOLDER PERSPECTIVES

Industry Representative

Cathy Critchlow, PhD
Amgen
Thousand Oaks, CA, USA

Real-World Evidence in Health Care Decision Making

ISPOR/ISPE Summit on
Real-World Evidence in
Health Care Decision Making

Cathy Critchlow
Center for Observational Research, Amgen Inc.

October 20, 2017
Washington, DC, USA

ispor.org/RWEinHealthcareDecisions

Disclosures

Cathy Critchlow is an employee and shareholder of Amgen Inc.

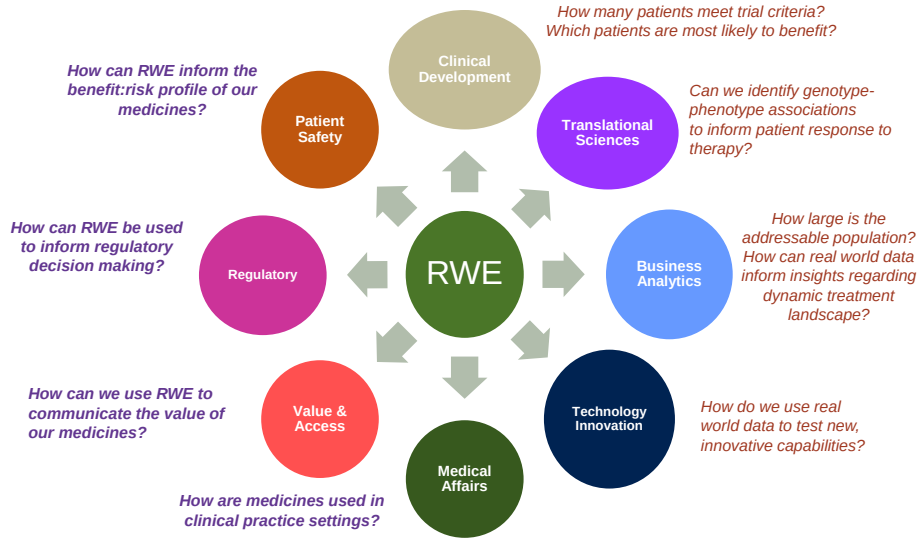
The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of the presenter's employer or any other party.

Landscape

- Limited understanding of non-interventional research designs and methods among clinical researchers
  - General mistrust in Real World Data / Real World Evidence (RWD/RWE)
  - Difficult to distinguish higher vs lower quality RWE
- Increasing focus on RWE by regulators, payers and health policy groups
- Risk aversive culture in biopharma
  - Difficult to mobilize resources to pursue RWE approaches given the absence of clear regulatory pathways and low (perceived) probability of success

ISPOR-ISPE recommendations seek to provide foundation to increase trust in use of RWE in health care decision making

Numerous stakeholders in Biopharma use RWE to address questions not addressable by RCTs



RCT, Randomized Clinical Trial

Good Practices for RWD Studies of Treatment and/or Comparative Effectiveness

	Comment
▪ *A priori*, declare study as Hypothesis Testing (HETE) or Exploratory	★★★
▪ Post protocol and analysis plan prior to data analysis	★1/2
▪ Publish with attestation to conformance/deviation from protocol & analysis plan	★★
▪ Enable opportunities to replicate HETE studies	★1/2
▪ Perform HETE studies on a different data source and population	★1/2
▪ Authors publicly address methodological criticisms	★★★
▪ Include key stakeholders in designing, conducting and disseminating HETE studies	★★

Berger et al. *Pharmacoepidemiol Drug Saf* 2017;26:1033-1039.
HETE, Hypothesis Evaluation Treatment Effectiveness

Credibility of health care database studies

- Database studies are a cornerstone of pharmacoepidemiology. Scrutiny of such studies will be high due to a general lack of understanding and the difficulty in doing them well
- Transparency is critical not only for researchers, but also for other stakeholders, eg database & software vendors
- Analytic methods are increasing in complexity – cognitive AI approaches make it easier to focus on the technical rather than the strengths and weakness of the data and its interpretation
- There is no substitute for asking the right question and using the right data source and methods to answer the question!

Wang et al. *Pharmacoepidemiol Drug Saf* 2017;26:1018-1032.

OTHER KEY STAKEHOLDER PERSPECTIVES

Industry Representative

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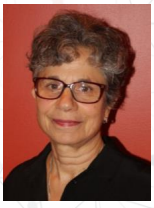
Registry Representative



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CLOSING REMARKS

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ISPOR / ISPE Summit on

Real-World Evidence in Health Care Decision Making

Dick Willke
Chief Science Officer

Closing Remarks

Some reflections

A few points we've heard

Next steps

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ADJOURN