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Improving healthcare decisions

Transparency in RWE - Moving Forward

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Copenhagen

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Presenters

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Three Sessions on RWE Transparency

1. Transparency in RWE - Time for a Unified Approach
   - Spotlight session, Monday 2:15 pm
2. Transparency in RWE - Can We Navigate the Key Challenges?
   - Issue Panel, Tuesday 11 am
3. Transparency in RWE - Moving Forward
   - Forum, Tuesday 12:30 pm

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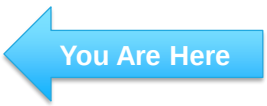

https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative

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ISPOR/ISPE Joint Special Task Force on Real-World Evidence in Healthcare Decision Making

Transparency of Study Processes

Reproducibility of Study Implementation

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Primary Recommendations

1. A priori, determine and declare that study is a “Hypothesis-Evaluating Treatment Effectiveness” (ie, 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.

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Real-World Evidence Transparency Partnership

ispe International Society for Pharmacoepidemiology
ISPOR
Duke Margolis Center for Health Policy
National Pharmaceutical Council
U.S. National Library of Medicine ClinicalTrials.gov
INAHTA
European Medicines Agency
FDA
CADTH
AHRQ Agency for Healthcare Research and Quality
National Health Council
Zorginstituut Nederland
AMCP Academy of Managed Care Pharmacy
Representatives from 7 pharma companies
Anthem
Syneos Health
flatiron
OPTUM Labs
NICE National Institute for Health and Care Excellence
patientslikeme

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Meeting Objective: Building Trust and Transparency in Secondary Observational Research

- Focus on:
  - Studies using secondary (retrospective) use of data
  - Focus HETE (not exploratory) studies
- 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?

Which studies?

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

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Hypothesis-Evaluating Treatment Effect Studies

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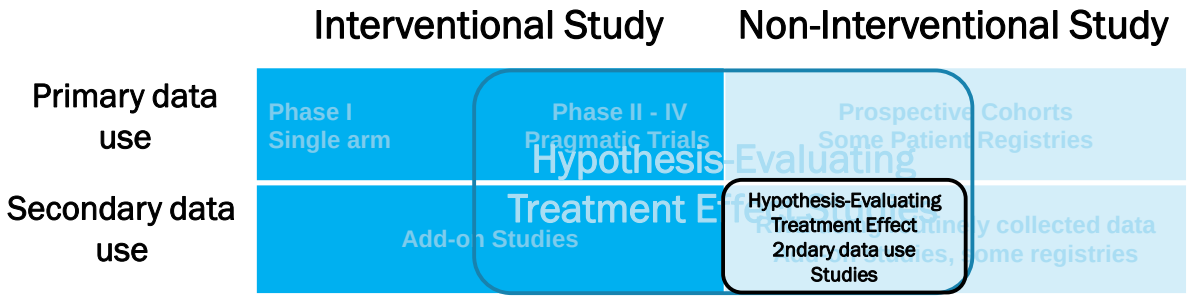
Which studies?



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Why……

	Rationale –	Goals –	Potential solutions –
	Decision makers see **lack of transparency** regarding **how evidence is generated** in hypothesis evaluating treatment studies using secondary data **as a major barrier to using RWE for high-stakes decisions.**	Researcher: First **encourage transparency of study processes**, including reporting on study design and implementation prior to study start, including posting of results when available Recipient: Over time - **increase confidence of decisions makers in these studies, elevating the credibility** All: **Provide insight into the totality of evidence** so reviewers can gauge reproducibility and replicability as part of the credible use of RWE	Post a study protocol reporting key study parameters so that a decision-maker can be confident that they understand how the study arrived at its findings. Use structured reporting templates to improve readability, encourage completeness of reporting, and increase efficiency for researchers and reviewers by making it clear what to look for and where to look for it.

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Specific concerns include:

Concern	Goal	Potential Solution
Results-driven selection of study parameters Ease of rerunning analyses with altered study parameters.	Provide **clarity** about the degree to **which study parameter selection** could have been **driven by results**. **Revisions** to the initial plan **are often necessary** when working with secondary data and **need to be clearly reported.**	Date-stamp the deposited study protocol with attestation regarding the nature of data pre-looking (e.g. feasibility numbers to support power calculation vs outcome rates by exposure) Date-stamp all revisions to the protocol with rationale for changes
Selective reporting of favorable findings A non-randomly selected denominator of studies makes it difficult to conduct comprehensive evidence reviews	**Avoid selective reporting of studies** so that evidence aggregators and decision-makers **can conduct balanced evidence summaries**.	Establish a comprehensive repository containing date-stamped protocols and results tables for all studies that are initiated to facilitate evaluation of publication bias Create incentives to register hypothesis-evaluating RWE studies like the requirements that journal editors have placed on RCTs, and EMA for PAS studies.

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Real-World Evidence Transparency Initiative: Recommendations

Nirosha Mahendraratnam Lederer, PhD MSPH
RWE Collaborative, Duke-Margolis Center for Health Policy
November 5, 2019

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Register HETE studies using secondary data (e.g., insurance claims and electronic health records) particularly those testing hypotheses regarding effectiveness and/or safety of two or more interventions

HETE: Hypothesis Evaluating Treatment Effectiveness

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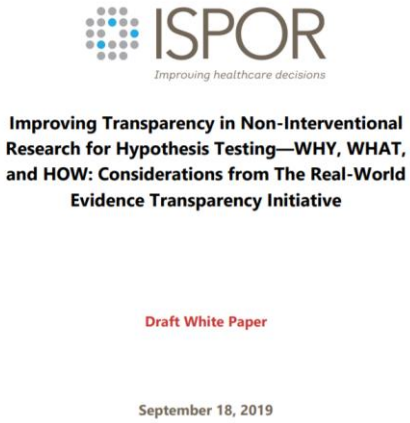
Draft White Paper Released on Sep 18th – Open for Public Comment



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

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Recommendations Focus on Study Protocol and Analysis Plan Registration Prior to Study Execution

Goals

- Improve replicability / reproducibility of the study
- Limit the concern for data dredging and 'cherry-picking' positive results
- Limit (peer review) publication bias

Near | Medium | Long

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Near

Identify Location for Registration of HETE Studies Using Secondary Data

Considerations

- Clearly define the study type that should be registered - HETE for decision making
- Existing expertise/resources to reduce redundancies and create efficiencies
- Feasibility of registering RWE studies in existing sites

HETE: Hypothesis Evaluating Treatment Effectiveness

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Near

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Actions

- Actively encourage registration of HETE studies on current sites NOW
- Understand landscape of existing registration sites (required and optional):
  - Initiate discussion with leaders of currently required registries, CT.gov and ENCePP/EMA
  - Look at the Center for Open Science format for possible new site, if needed

Medium

Determine What a “Good” Registration Process Entails to Fit the Purpose

Considerations

- Don’t let perfect be the enemy of good - this should be a progressive effort
  - Core elements of study registration including website fields and associated documents (e.g., protocol content)
  - Required website features including ability 1) for time-stamped registration (for data looks and change auditing) and 2) to balance transparency vs confidentiality ("lock box" with different access levels)
  - Feasibility - research and reviewer workload

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Actions

- Identify and standardize core elements of registration and protocol
- Evaluate website features such as time stamps and ability to stagger information release
- Survey potential users about needs and considerations regarding feasibility, transparency, and confidentiality
- Pilot test registration site updates and update partner site or new site if required

Long

Incentives for Routine Pre-registration for HETE Studies

Considerations

- End users start requiring registration: funding bodies, journals, regulators, payers/health technology assessors
- Provide registry 'use reports' (e.g., quarterly report of registered studies, with key information) from time to time

Long

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Actions

- Build off collaborations with key stakeholders from task force activities to encourage adoption of pre-registration requirements
- Involve key stakeholders from survey of potential users
- Foster publications on registry findings, similar to research on registers for clinical trials

HETE: Hypothesis Evaluating Treatment Effectiveness

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Reflections

- Transparency does not equate to study quality
- Defining:
  - 1) Spectrum of studies (exploratory vs. hypothesis evaluating)
  - 2) "Pre-looks"
  - 3) Protocol revisions
- Encouragement vs. enforcement of study registration

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Conclusion

- Appropriate transparency in data, methods, analyses as well as results posting increases confidence in HETE RWE study credibility
- RWE Transparency Initiative aimed to:
  - Understand how to feasibly build on the foundation of existing study registration sites
  - Identify practical elements associated with what the registration process will entail
  - Consider how to facilitate routine registration for HETE RWE studies
- Culture of transparency for non-interventional RWE studies will take time and multi-stakeholder commitment

HETE: Hypothesis Evaluating Treatment Effectiveness

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Putting this Work Into Context

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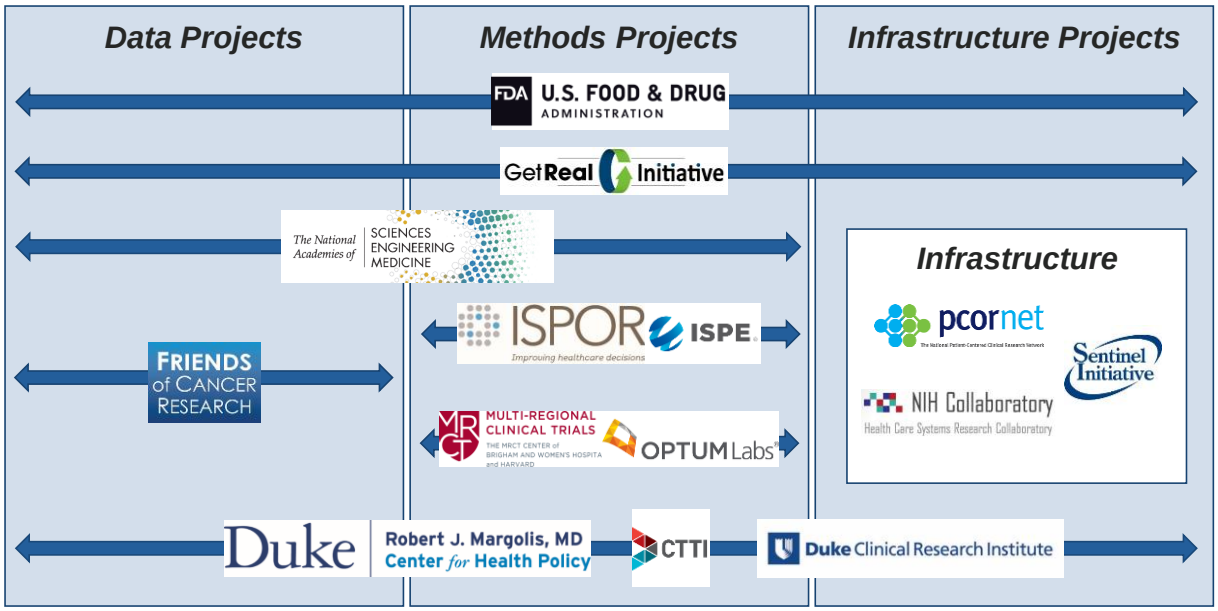

Duke-Margolis RWE Collaborative Aims to Advance Regulatory Use of RWD/RWE

Data Curators

evidation
Evidera | PPD
flatiron HealthCore
IQVIA
OPTUM Labs
patientslikeme
Syneos Health
veradigm

Sponsors

abbvie
Genentech
A Member of the Roche Group
gsk
Johnson & Johnson
Lilly
MERCK INVENTING FOR LIFE
NOVARTIS
teva
ucb

Other

HARVARD MEDICAL SCHOOL
ISPOR
Improving healthcare decisions
MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD
NATIONAL HEALTH COUNCIL

Observers

U.S. FDA & NASEM

Duke-Margolis RWE Collaborative 2019 Workstreams

Fit-for-Use	• Develop minimum set of reliability checks for assessing whether RWD is reliable
Observational Study Credibility	• Using observational studies designs to generate regulatory-grade RWE
Totality of Evidence (ToE)	• Determine how RWE studies can support regulatory decisions based on ToE
RWEndpoints	• Establish principles/guideposts for development of real-world endpoints

Duke-Margolis RWE Collaborative engages stakeholders to guide high-priority efforts aimed at improving the development and use of RWE for regulatory decision-making (focusing on effectiveness)

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Many Drivers for RWD and RWE Development Throughout Healthcare Ecosystem

Real-World Data and Evidence

1. Medical Product Development

- Inform biological understanding of disease through registries
- Identify unmet need
- Improved RCT recruitment efficiency

2. Regulatory Review

- Inform new approvals in rare diseases
- Inform indication and labeling decisions
- Inform PM safety

3. Care Delivery

- AI-enabled CDS to personalize dx and tx decisions
- Support patients' engagement in their own care decisions
- Help drive higher-value care

4. Value-Based Payment and Coverage

- Increase stakeholder understanding of "value"
- "De-risk" payment for high cost treatments to allow access
- Value-based insurance design

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