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Improving the Acceptability of RWE: What's New in 2022?

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- **Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**
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21st Century Cures Act (2016) – RWE



- **FDA *established* a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support a new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework *issued* in December 2018:**
  - **Describe sources of RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry *issued* in Sep, Oct, Nov, Dec 2021**
- **Standard for substantial evidence remains unchanged; *commitments met* for Prescription Drug User Fee Act (PDUFA) VI**

Background: 'Real-World' Definitions (FDA 2018)

Real World Data (RWD) are data relating to patient health status and/or delivery of health care routinely collected from a variety of sources

- electronic health records (EHRs)
- medical claims data
- product and disease registries
- patient-generated data, including from in-home settings
- other sources that can inform on health status, such as "wearable" devices

Real World Evidence (RWE) is clinical evidence regarding the usage and potential benefits/risks of a medical product derived from analysis of RWD

Generated using different study designs, including but not limited to randomized trials (e.g., pragmatic clinical trials), externally controlled trials, or observational studies

Current Status of Real-World Evidence

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

Issue being addressed: More than five years after passage of the 21st Century Cures Act, the terms RWD and RWE are being used inconsistently and interchangeably

Content of article:

- **addressed two common misconceptions**
- **provided conceptual overview of study design**
- **described FDA demonstration projects and guidance**
- **highlighted regulatory approvals**
- **offered path forward**

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Misconceptions regarding RWD & RWE

Frequent instances of:

- ***Misconception #1 – RWD & RWE are new concepts*: "In reality, sources of data and types of study design haven't fundamentally changed, but electronic access to more detailed clinical data is evolving & the data are becoming more relevant and reliable"**

- ***Misconception #2 – A simple dichotomy of randomized trials vs. observational studies exists*: "In reality, clinical trials are defined by assignment of treatment according to an investigational protocol, and single-arm trials face challenges similar to those in observational studies in determining whether difference in clinical outcomes (compared to an external control group) represent actual treatment effects"**

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Misconceptions (cont'd)

Additional comment on terminology:

- **"Including 'RWD' or 'RWE' in the description of a study […] doesn't tell us exactly where the data came from or what kind of study architecture involved"**

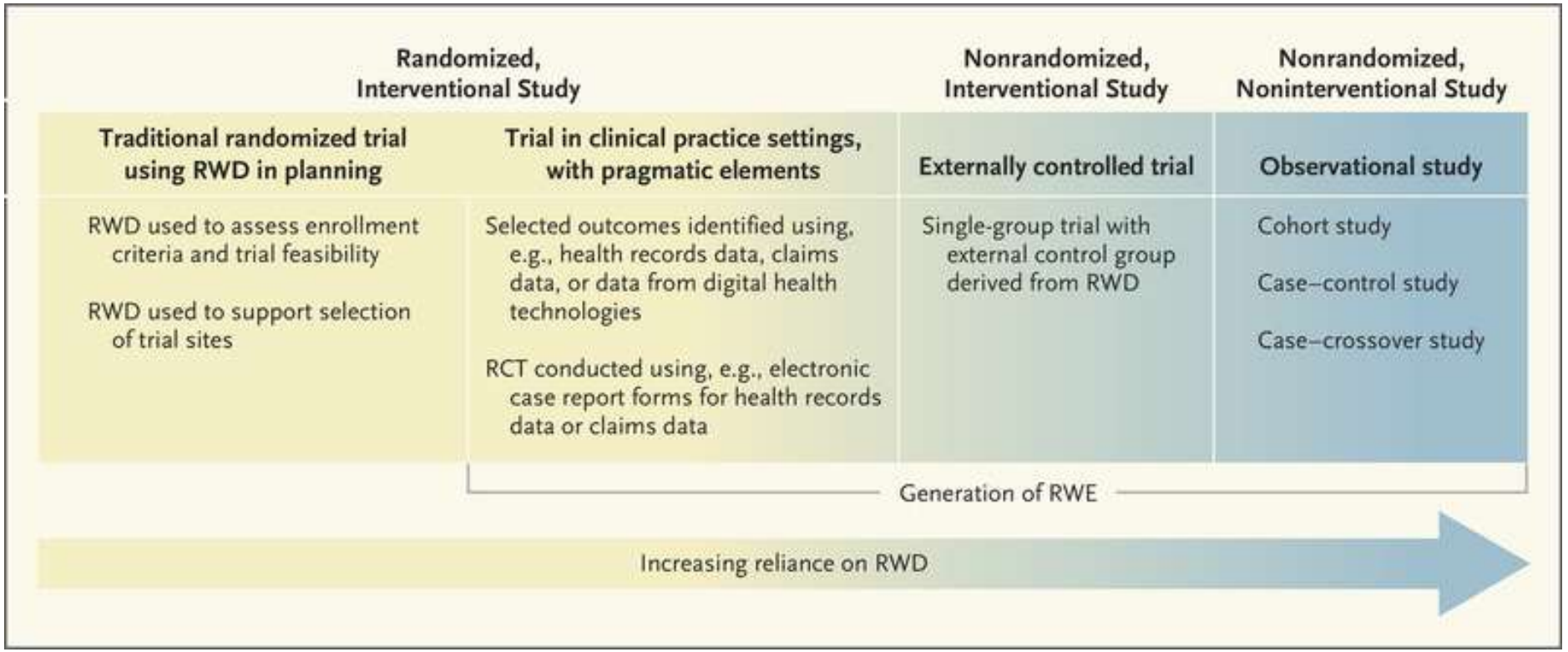
Additional comment on a spectrum—not a dichotomy:

- **"[We should recognize that] the degree of reliance on RWD varies with the type of study design and that, by definition, RCTs that incorporate RWD generate RWE"**

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Reliance on RWD in Representative Types of Study Design.

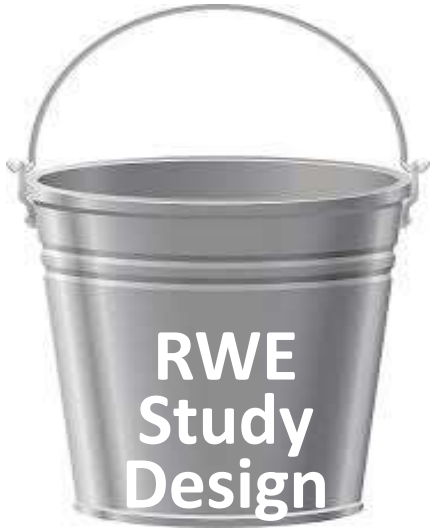
RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

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Ongoing RWE Demonstration Projects - Examples



- ‘OneSource’ project
- Linking RCTs w/ RWD
- Transforming RWE w/ unstructured and structured data



- RCT-DUPLICATE trial emulations
- Statistics for RCT designs w/ hybrid controls



- Evaluating confounded treatment effects
- Targeted learning framework for causal effect estimation

FDA 'RWE' Guidance: Sep-Dec 2021

Guidance for Industry

DRAFT GUIDANCE

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Data Standards for Drug and Biological Product Submissions Containing Real-World Data
Guidance for Industry

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

New Indication for Prograf Based on RWE



- **Prograf® (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart) based on RCT evidence, and the drug is used widely in clinical care**
- **RCTs not done for lung transplant, but sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA with non-interventional 'RWE' study**
- **Study data and design were evaluated according to FDA standards**
- **Approval for preventing rejection/death in lung transplant granted 16 Jul 2021**

New Indication for Prograf Based on RWE (cont'd)

Data: US Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US during 1999–2017

Design: non-interventional (observational) treatment arm, compared to historical controls

Review: FDA determined this non-interventional study w/ historical controls to be adequate and well-controlled. Of note, outcomes of organ rejection and death are virtually certain without therapy, and the dramatic effect of treatment helps to preclude bias as explanation of results.

RWE – Looking Forward

Closing paragraph from recent NEJM article:

- **"The FDA remains committed to robust policy development aligned with the 21st Century Cures Act while maintaining evidentiary standards in honoring our obligation to protect and promote public health. Focusing on the distinction between interventional studies and noninterventional studies can help researchers, sponsors, and regulators better understand and describe relevant methodologic issues. Gaining more experience, including conduct of rigorous noninterventional studies, will help to advance drug development."**

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