The Use of Real-World Evidence in Regulatory Decision-Making for Medical Products

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Disclaimer

This talk reflects the views of the author and should not be construed to represent FDA's views or policies.

FDA Definitions

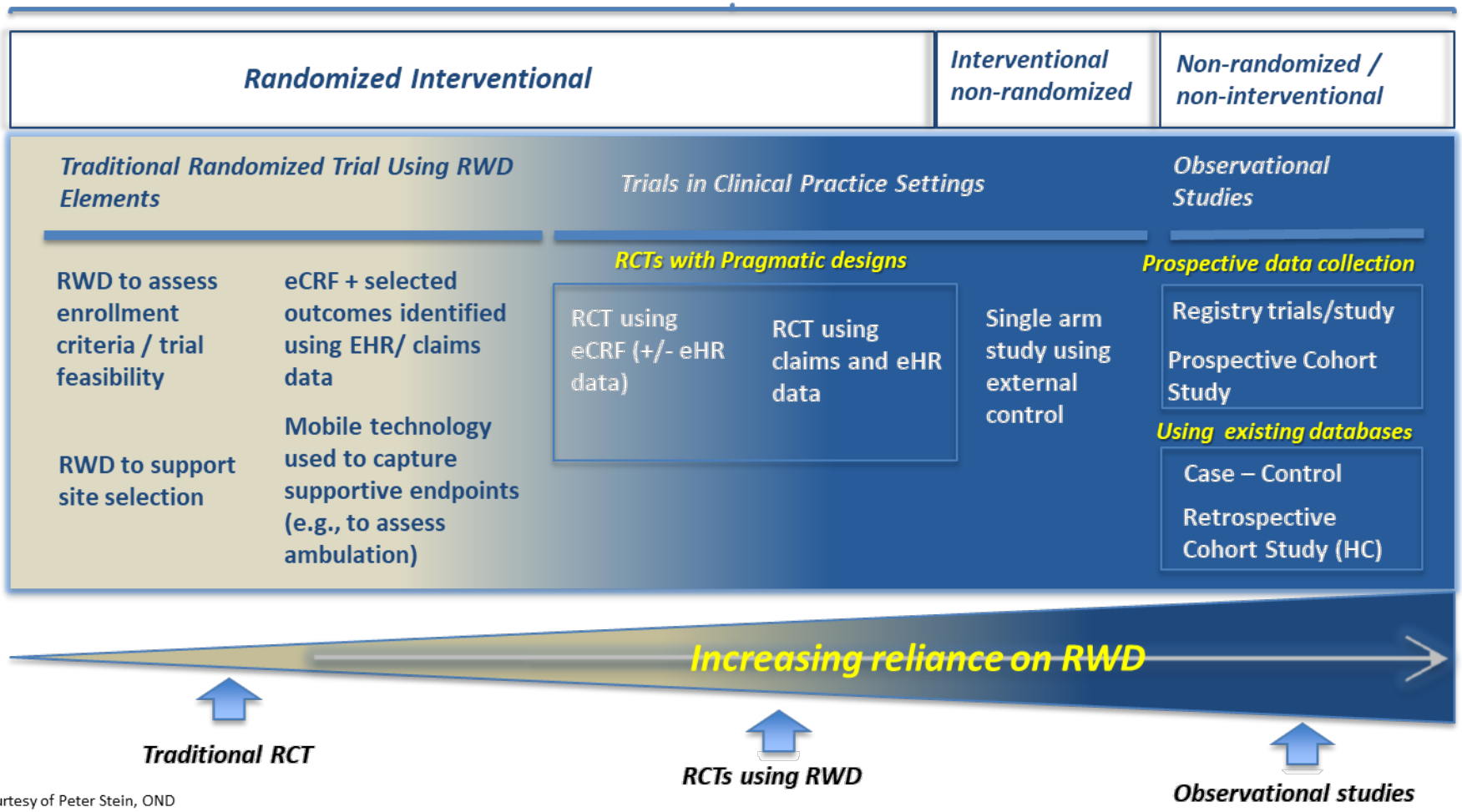
Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- **electronic health records (EHRs)**
- **claims and billing data**
- **data from product and disease registries**
- **patient-generated data including in home-use settings**
- **data gathered from other sources that can inform on health status, such as mobile devices**

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.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.

Spectrum of Potential Uses of Real-World Data



Courtesy of Peter Stein, OND

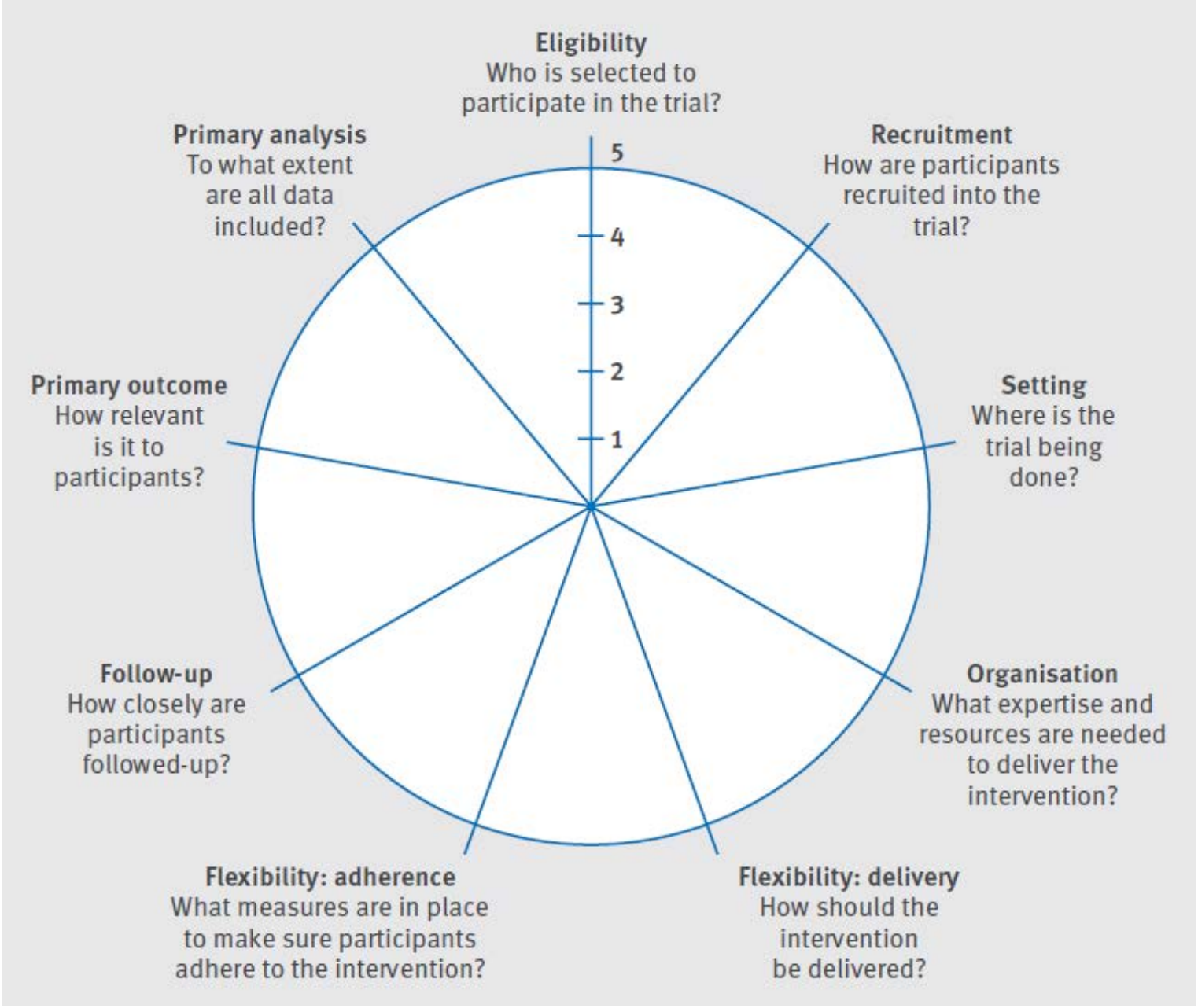
RWD/RWE: What Are the Goals?

Traditional RCTs typically

- Use select groups of patients
- Involve special infrastructure and data collection
- Maximized sensitivity

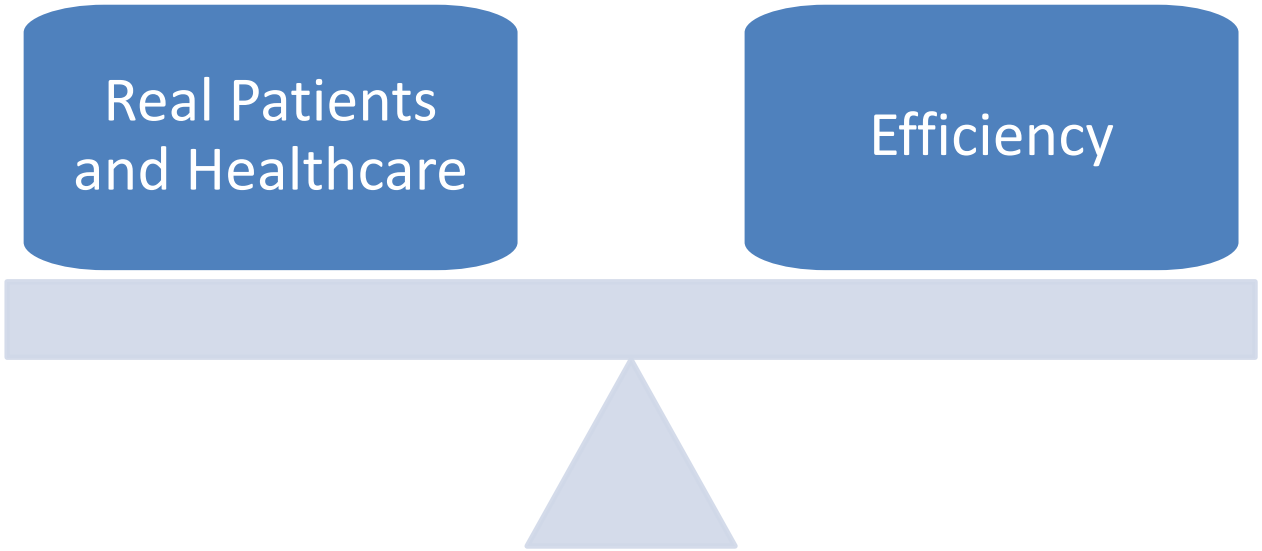
RWD/RWE Goals

- Reflect the diversity of patients and actual health-care practices
- Improve efficiency by making use of existing data and infrastructure
- Maintain evidentiary standards



PRECIS-2 Tool: Loudon et al., BMJ 2015

RWE Give and Take



Substantial Evidence Efficacy

"**evidence consisting of adequate and well-controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involve on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Federal Food, Drug, and Cosmetic Act 1962

Drug Regulation History:
https://www.fda.gov/AboutFDA/History/ProductRegulation/ucm593465.htm

Adequate and Well-Controlled Study

- Clear objectives, summary of metho
- Design permits a valid comparison with a control (concurrent and historical controls)
- Adequate selection of patients
- Assigning patients to treatment and control g minimizes bias
- Adequate measures to minimize biases on subjects, observers, and analysts
- Well-defined and reliable assessment of subjects' responses
- Adequate analysis to assess drug results

Reserved for special circumstances

Ordinarily rand

Blinding

Regulations 21CFR314.126

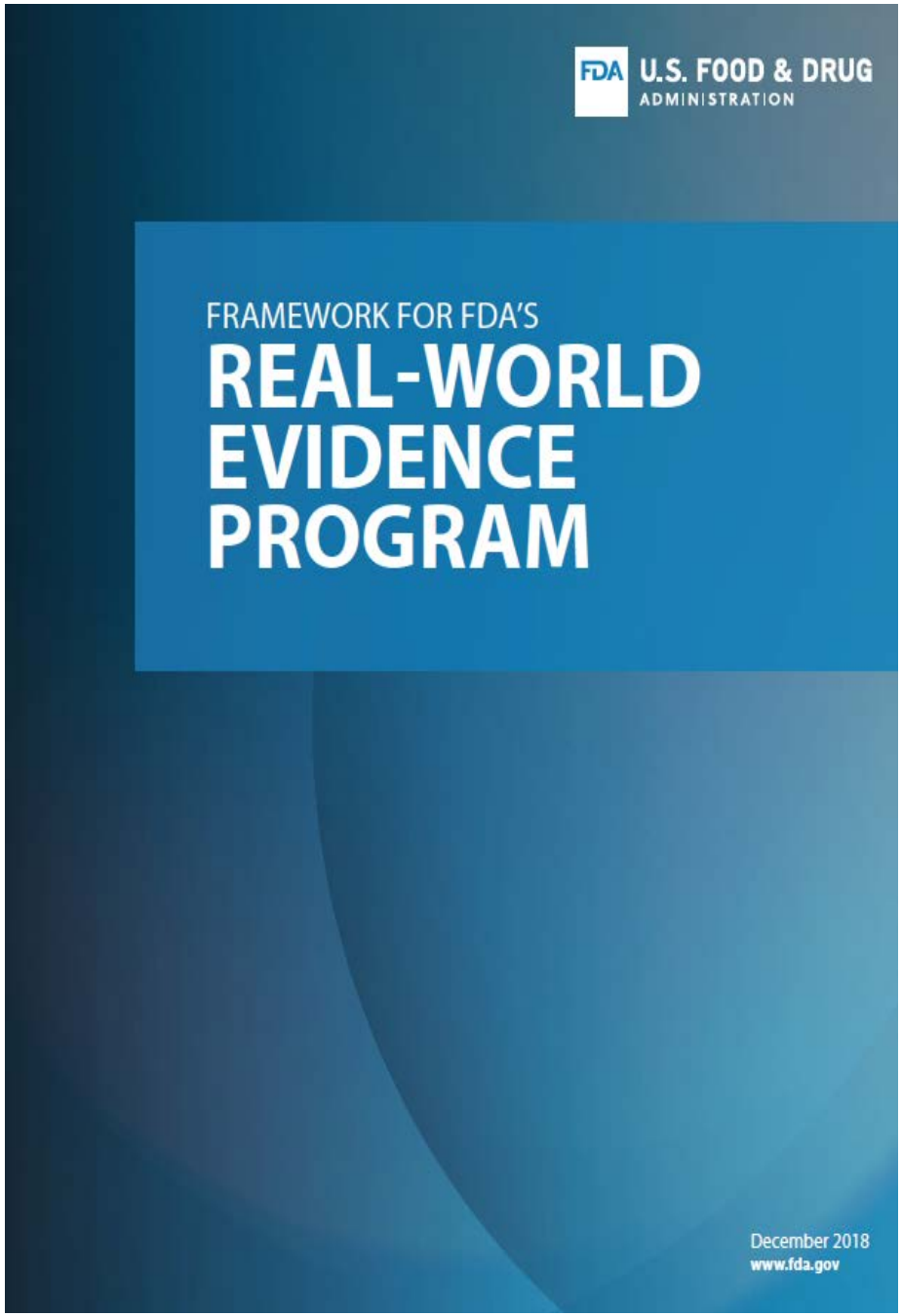
21st Century Cures Act (2016)

establish a program to evaluate the potential use of real world evidence-

- to help to ...cation for a drug ...his title; and
- to help to support or satisfy postapproval study requirements.

No change in evidentiary standard

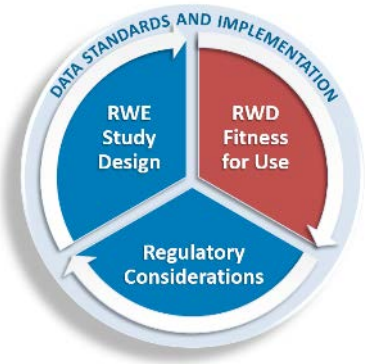
SEC. 505F. UTILIZING REAL WORLD EVIDENCE. Amended by Food and Drug Administration Reauthorization Act 2017



- **Intended for drug and biological products**
- **Outlines FDA's plan to implement the RWE program**
- **Multifaceted program**
  - **Internal processes**
  - **Guidance development**
  - **Stakeholder engagement**
  - **Demonstration projects**

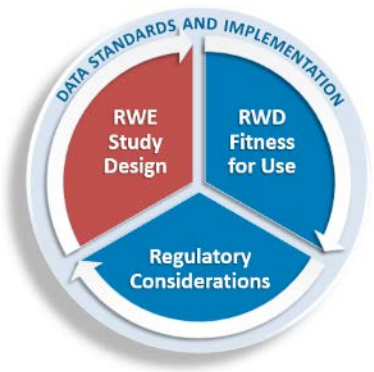
https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



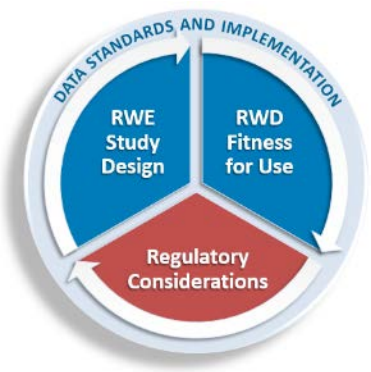
RWD Fitness for Use

- Data uses
  - Population selection
  - Outcome ascertainment
  - Covariates
  - Safety and study monitoring
- Data reliability, validity, relevance
- Multiple data sources may be needed



RWE Study Design

- Population selection
- Comparator group
- Outcome ascertainment, blinding
- Treatment definition (estimand)



Regulatory Considerations

- Human subject protection
- Data traceability, auditing, and record keeping
- Safety reporting
- Study integrity and responsibility

ASA BIOP RWE Scientific Working Group

- Research Focused: Focus on specific research questions, concerning data sources and methodologies
- Statistics Focused: Address the statistical aspects of RWD and RWE research and utilization
- Regulatory Focused: Engage regulators on providing guidance and principles to facilitate utilization of RWD and RWE in clinical research and medical product life cycle.

ASA BIOP RWE Scientific Working Group

Precompetitive Space

Industry member		Academic/FDA member †	
Weili He, Co-Chair	AbbVie	Martin Ho, Co-Chair	CBER
Jie Chen	Merck	Telba Irony	CBER
Yixin Fang	AbbVie	Mark van der Laan	UC Berkeley
Qi Jiang	Seattle Genetics	Hana Lee	CDER
Kwan Lee, Co-Lead	Janssen	Mark Levenson, Co-Lead	CDER
Xiwu Lin	Janssen	Zhaoling Meng	BMGMRI‡
Yang Sung	Vertex Pharma. Inc.	Pallavi Mishra-Kalyani	CDER
Hongwei Wang	AbbVie	Frank Rockhold	Duke
Roseann White	The Third Opinion	Tingting Zhou	CBER
Richard Zink	Target Pharma. Solution	Ben Goldstein	Duke

ASA BIOP RWE Scientific Working Group

- Two workstreams:
  - **WS 1: Label expansion** (Weili He & Mark Levenson co-lead)
  - **WS 2: Inform study design** (Martin Ho & Kwan Lee co-lead)
- Apply same approach for both workstreams

- Deliverables (in progress)
  - Publish 2 complementary papers on findings & recommended research agenda in the same issue of a peer-reviewed journal

ASA BIOP RWE Scientific Working Group

WS1: Label Expansion	WS2: Inform Study Design
Reg., scientific, & ethical issues	Study of retrospective data only
Data sources & study types	Prospective study with external data
Estimands (treat. effect) in RW setting	Causal inference issues in reg. setting
Confounding control	

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Thank you

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