Evaluating RWE from Observational Studies in Regulatory Decision-Making: Lessons Learned from Trial Replication Analyses

Duke-Margolis Center for Health Policy | 2-Day Virtual Meeting
February 16 & 17, 2021

Observational (non-interventional) studies—typically involving analyses of real-world data (RWD) from administrative claims and electronic health records—can broaden our understanding about the effectiveness of medical products, but questions remain about the credibility of observational studies using data generated for non-research purposes (secondary use of health data). As part of its Real-World Evidence (RWE) Program, FDA is evaluating the potential role of observational studies in contributing to evidence of drug product effectiveness. This virtual conference will consider attributes of observational study design and conduct to better understand considerations for using evidence from observational studies to inform regulatory decisions.

The meeting will focus on sharing preliminary results from ongoing trial replication efforts to better understand strengths and limitations of observational studies when considering their potential use to answer questions about drug product effectiveness and inform regulatory decision-making. The conference will explore challenges with data adequacy, bias in observational studies that may impact causal inference, including provider- and patient-based perceptions of the assigned treatment and differential adherence to treatment. Panel discussions will explore how benefits can be realized, identify gaps in knowledge, and consider strategies for addressing those gaps.

Day 1 Agenda

Objective: Well-conducted observational studies have the potential to contribute to evidence regarding medical product effectiveness, but appropriate use of these studies is dependent on confidence in their validity. Various projects are underway seeking to replicate the results of randomized clinical trials using rigorously designed observational studies, with the goal of understanding when evidence from these studies may be credible. In this meeting, experts will consider strategies to understand and evaluate RWD and RWE, including trial emulation approaches that apply design principles from randomized trials to analyses of observational data. Researchers will present interim results from efforts to replicate clinical trials using trial emulation approaches. Presentations will discuss the principles and criteria utilized and trade-offs made when designing these replication studies as well as consideration of their potential impact on results. In addition, panel discussions will explore insights gained from these preliminary efforts regarding the potential use of RWE from observational studies in regulatory decision-making.

1:00 pm **Welcome and Overview**

- **Mark McClellan**, Duke-Robert J. Margolis, MD, Center for Health Policy

1:10 pm **Opening Remarks from FDA**

- **Jacqueline Corrigan-Curay,** U.S. Food and Drug Administration

1:25 pm **Session 1: Principles for Using Rigorous Observational Study Designs to Replicate the Results of Clinical Trials**

Objective: This session will feature a presentation on the target trial[*] approach to trial emulation, which can serve as an evaluation tool for considering observational studies and their ability to replicate the results of clinical trials. The presentation will be followed by a series of panelists discussing the strengths and weaknesses of RWE from observational studies, including considerations for suitable clinical contexts and appropriate use.

Presentation:

- **Miguel Hernán,** Harvard T.H. Chan School of Public Health

Panel Discussion:

- **Adrian Hernandez**, Duke University
- **Nandita Mitra,** University of Pennsylvania
- **Jennifer Graff**, National Pharmaceutical Council
- **Gerald Dal Pan**, U.S. Food and Drug Administration

2:25 pm **Break**

2:45 pm **Session 2: Presentations from Trial Replication Projects**

Objective: This session will present preliminary results from ongoing trial replication efforts to better understand strengths and limitations of observational studies focused on questions about drug product effectiveness and regulatory decision-making.

2:45 pm **Session 2a: RCT Duplicate Presentation**

Presentation:

- **Sebastian Schneeweiss,** Harvard Medical School

3:30 pm **Session 2b: OPERAND Presentation**

Presentation:

- **William Crown**, Brandeis University

3:45 pm **Session 2c: Yale-Mayo Clinic CERSI Presentation**

Presentation:

- **Nilay Shah**, Mayo Clinic

4:00 pm **Break**

[*] Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-764. doi:10.1093/aje/kwv254

4:15 pm **Session 3: Reactions to Replication Results**

Objective: Panelists will identify common themes and react to emerging insights from the replication efforts. Experts will consider the potential lessons learned.

Panel Discussion:

- **Sebastian Schneeweiss,** Harvard Medical School
- **William Crown**, Brandeis University
- **Nilay Shah**, Mayo Clinic
- **Joseph Ross**, Yale University
- **Miguel Hernán**, Harvard T.H. Chan School of Public Health
- **Robert Temple,** U.S. Food and Drug Administration

5:00 pm **Day 1 Closing Remarks and Adjournment**

Day 2 Agenda

Objective: Building on presentations from Day 1, discussion on Day 2 will consider common themes and applications of trial replications and reflect on potential strategies to facilitate credible observational research. The discussion will explore insights from the replication projects regarding the potential use of RWE generated from observational studies for regulatory decision-making. Experts will consider circumstances for possibly using observational studies, the importance of utilizing fit-for-use data, and the transparency and processes needed to ensure the reproducibility of this evidence.

1:00 pm **Welcome and Overview**

- **Mark McClellan**, Duke-Robert J. Margolis, MD, Center for Health Policy

1:10 pm **Session 4: Key Themes Emerging from Replication Efforts**
Objective: This session will build on the discussion of replication project results and emerging themes by focusing on the types of study questions that may be appropriate for consideration through observational studies, including which endpoints can be identified using real-world data, and where additional methodologic improvements are still needed. Experts will also discuss lessons learned during the COVID-19 pandemic.

Panel Discussion:

- **Lucinda Orsini**, COMPASS Pathways
- **Josie Briggs**, Patient-Centered Outcomes Research Institute
- **Michele Jonsson-Funk**, UNC Gillings School of Public Health
- **Robert Ball**, U.S. Food and Drug Administration

2:25 pm **Break**

2:40 pm **Session 5: Observational Studies: Opportunities, Limitations, and Next Steps**
Objective: Panelists in this session will synthesize relevant aspects of previous sessions regarding the design of observational studies that may be useful in regulatory decision-making. The discussion will focus on next steps for understanding the potential role of observational studies in contributing to evidence of drug product safety and effectiveness. The panelists will seek to identify remaining gaps in knowledge and strategies for addressing those gaps.

Panel Discussion:

- **Nancy Dreyer**, IQVIA
- **Frank Harrell**, Vanderbilt University
- **Rob Reynolds**, GlaxoSmithKline
- **John Concato**, U.S. Food and Drug Administration

3:30 pm **Day 2 Closing Remarks and Adjournment**

- **Mark McClellan**, Duke-Robert J. Margolis, MD, Center for Health Policy

Funding for this workshop was made possible in part by a cooperative agreement from the U.S. Food and Drug Administration Center for Drug Evaluation and Research. The views expressed in written workshop materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.