The National Academies of | SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

# Examining the Impact of Real-World Evidence on Medical Product Development: A Three-Part Workshop Series

## Workshop Two: Practical Approaches

**March 6–7, 2018**

National Academy of Sciences Building, Room 120
2101 Constitution Ave. NW, Washington, DC 20418

The National Academies of Sciences, Engineering, and Medicine (National Academies) is convening a three-part workshop series examining how real-world evidence development and uptake can enhance medical product development and evaluation. The workshops will advance discussions and common knowledge about complex issues relating to the generation and utilization of real-world evidence, including fostering development and implementation of the science and technology of real-world evidence generation and utilization.

- Workshop One (*September 19-20, 2017*) focused on how to align incentives to support collection and use of real-world evidence in health product review, payment, and delivery. Incentives need to address barriers impeding the uptake of real-world evidence, including barriers to transparency.
- **Workshop Two (*March 6-7, 2018*) will illuminate what types of data are appropriate for what specific purposes and suggest practical approaches for data collection and evidence use by developing and working through example use cases.**
- Workshop Three (*July 17-18, 2018*) will examine and suggest approaches for operationalizing the collection and use of real-world evidence.

# DAY 1: March 6, 2018

8:30 a.m. Breakfast Available Outside the Room 120

8:40 a.m. **Welcome and Opening Remarks**

GREG SIMON, *Workshop Series Co-Chair*
Investigator
Kaiser Permanente Washington Health Research Institute

## SESSION I: WHEN CAN WE RELY ON REAL-WORLD DATA?

Session discussion questions:

- When can we have confidence in EHR data from real-world practice to accurately assess study eligibility, key prognostic factors, and study outcomes?
- When can we have confidence in data generated outside of clinical settings (e.g., mobile phones, connected glucometers, connected blood pressure monitors)?
- When does adjudication or other post-processing of real-world data add value?

**Moderator**: Greg Daniel, Duke-Margolis Center for Health Policy

*Session Discussants*

JESSE BERLIN
Vice President and Global Head, Epidemiology
Johnson & Johnson

ANDY BINDMAN
Professor of Medicine
University of California San Francisco

9:00 a.m. **Introduction and background to inform the discussion: Novel oral anticoagulants in comparison with warfarin**

ADRIAN HERNANDEZ
Vice Dean for Clinical Research
Duke University School of Medicine

9:20 a.m. **Open discussion with audience**

- What questions can characterize the utility of any real-world data source and signal reliability before a study is performed (examples below)?
    - When is accuracy good enough to reasonably and consistently identify the right population?
    - When is accuracy good enough to reasonably and consistently assess the exposure or intervention?
    - When is accuracy good enough to reasonably and consistently assess the right outcome?
    - Are there any big safety issues that would be missed?
    - Are there concerns about data collection or entry, particularly in relation to creating systemic bias?
    - When is expert adjudication necessary to confirm that the recorded data is reliable and/or reasonably complete?
- What information is needed to answer such questions?

10:40 a.m. **BREAK**
(*Workgroup participants gather to synthesize audience feedback*)

11:00 a.m. **Workgroup presents synthesis of audience feedback**

## SESSION II: WHEN CAN WE RELY ON REAL-WORLD TREATMENT?

Session discussion questions:

- When conducting research in a real-world setting, are there situations that would require special guidance, knowledge, or experience in order for clinicians to adequately monitor participant safety and respond appropriately to adverse events?
- When does variation between comparison groups (socioeconomic, demographic, etc.); in treatment fidelity; in provider behavior and preferences; or in adherence yield a valid signal about real-world effectiveness, and when is it just noise?

**Moderator**: Khaled Sarsour, Genetech|A Member of the Roche Group

*Session Discussants*

MICHAEL HORBERG
Executive Director, Research, Community Benefit, and Medicaid Strategy
Executive Director, Mid-Atlantic Permanente Research Institute
Kaiser Permanente Mid-Atlantic Permanente Medical Group

GREG SIMON
Investigator
Kaiser Permanente Washington Health Research Institute

ROBERT TEMPLE
Deputy Director for Clinical Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

11:15 a.m. **Introduction and presentation to inform discussion on participant monitoring: study on Lithium for Suicidal Behavior in Mood Disorders**

IRA KATZ
Senior Consultant for Program Evaluation
VA Office of Mental Health and Suicide Prevention

11:35 p.m. **Open discussion with audience**

- What conditions make self-monitoring and reporting acceptable?
- Does this vary for treatments at different stages of product development or with different baseline knowledge about use in varied patient types and treatment conditions?
- Can we draw any generalizable lessons about cases in which self-monitoring is acceptable and safe?

12:15 p.m. **Introduction and presentation to inform discussion on signal detection: Novel Oral Anticoagulants in comparison with warfarin**

12:30 p.m. **Open discussion with audience**

- What conditions and training prepare clinical care providers to monitor patient safety outside a tightly controlled environment?
- How does this vary for treatments at different stages of product development or with different baseline knowledge about use in varied patient types and treatment conditions?
- How do you decide which variables require strict adherence to "protocol" and which can be allowed to vary?

1:00 p.m. **BREAK** (Lunch available Outside Room 120)
(*Workgroup participants gather to synthesize audience feedback*)

2:00 p.m. **Workgroup presents synthesis of audience feedback**

## SESSION III: WHEN CAN WE LEARN FROM REAL-WORLD TREATMENT ASSIGNMENT?

Session discussion questions:

- When can we have confidence in inference from cluster-randomized or stepped-wedge study designs?
- Under what conditions can we trust inference from observational or naturalistic comparisons?
- How could we judge the validity of observational comparisons in advance, rather than waiting until we've observed the result?

**Moderator**: Richard Platt, Harvard Medical School

*Session Discussants*
Rob Califf
Vice Chancellor, Health Data Science, Duke University
Verily Life Sciences

DAVID MADIGAN
Professor of Statistics
Dean, Faculty of Arts and Sciences
Columbia University

DAVID MARTIN
Associate Director for Real-World Evidence Analytics
U.S Food and Drug Administration

2:20 p.m. **Introduction and presentation to inform the discussion: Healthcare Database Analyses of Medical Products for Regulatory Decision Making**
SEBASTIAN SCHNEEWEISS
Professor of Medicine and Epidemiology
Harvard Medical School
Brigham & Women's Hospital

2:50 p.m. **Open discussion with audience**

- Random assignment is always preferable, but when is the cost (in time, money, infrastructure, patient exposure) truly necessary?
- How can we know that the effects from unmeasured confounders are not so large that they would change a decision based on information from an observational study?
- What are some of conditions under which there is more confidence in inference from non-randomized comparisons (*examples of some conditions below*)?
    - Expectation of large effects
    - Outcome proximal to treatment
    - High degree of similarity between comparison groups
    - Pathway from treatment to outcome is relatively clear, and without lots of complexity or reciprocal effects
    - Treatment allocation method is relatively transparent

3:40 p.m. **BREAK**

4:00 p.m. **Open discussion with audience and reflections on the discussion from panelists**

5:00 p.m. **ADJOURN WORKSHOP DAY 1**

# DAY 2: MARCH 7, 2018

8:30 a.m. Breakfast Available Outside the Room 120

## SESSION IV: SYNTHESIZING THE USE CASES

Session Objective:

- Discuss key considerations presented in each session on Day 1
- Consider components of a potential "checklist" for using real-world evidence

9:00 a.m. **Welcome and recap of Day 1**

GREG SIMON, *Workshop Series Co-Chair*
Investigator
Kaiser Permanente Washington Health Research Institute

MARK MCCLELLAN, *Workshop Series Co-Chair*
Director
Duke-Margolis Center for Health Policy

9:20 a.m. **Open discussion with audience of outputs from Day 1 and potential components to a "checklist" for using RWE**

10:40 a.m. **BREAK**

11:00 a.m. **Open discussion with audience of outputs from Day 1 and potential components to a "checklist" for using RWE**

12:30 p.m. **ADJOURN WORKSHOP DAY 2**

## Future Workshop Objectives

**WORKSHOP THREE. Examine and suggest approaches for operationalizing the collection and use of real-world evidence.** *(July 17-18, 2018, Washington, DC)*

- Applications for using real-world evidence to supplement traditional clinical trials, pragmatic/effectiveness trials, or routine clinical application.
- Mechanisms for determining which discrete types of real-world evidence could support regulatory decisions.
- Operational challenges and barriers for generating and incorporating real-world evidence in the context of a learning health system and how clinicians can best be involved in the collection and utilization of real-world evidence.