Duke | Robert J. Margolis, MD Center for Health Policy

Understanding the Use of Negative Controls to Assess the Validity of Non-Interventional Studies of Treatment Using Real-World Evidence

Zoom (Virtual)

March 8, 2023

Real-world evidence (RWE) generated from real-world data (RWD) is increasingly being utilized to address scientific and regulatory questions at the Food and Drug Administration (FDA), including both product safety and effectiveness. Evaluating RWE for regulatory use, however, depends on a robust causal inference framework, and there is growing stakeholder interest to understand how methodological advances with negative controls can improve causal inference.

On March 8, 2023, the Duke-Margolis Center for Health Policy, under cooperative agreement with the FDA, will convene a workshop on how negative controls could support new methodological approaches for causal inference in the Sentinel System. Discussion will inform the methods development projects aimed at: 1) establishing empirical methods to automate the negative controls identification in Sentinel and integrate it into the Sentinel Initiative tools, and 2) developing approaches to use a double-negative control adjustment to reduce unmeasured confounding in studying effectiveness of vaccines. This workshop will fulfill a Prescription Drug User Fee Act (PDUFA) VII Commitment.

10:00 a.m. **Welcome and Overview**
TBD, Duke-Robert J. Margolis, MD, Center for Health Policy

10:10 a.m. **Introduction to Negative Controls**
A key challenge when working with RWE is identifying and reducing bias and confounding in observational studies due to limitations of the underlying data and available study designs. Negative controls are potentially useful methodological tools to address these issues and support the validity of results. This session will provide a level-setting discussion on how negative controls can support more robust analyses to support causal inferences in medical product safety and effectiveness studies.

10:55 a.m. **Overview of Analytic Techniques: A review of Negative Controls**
This session will provide an overview of techniques related to the use of negative controls. A series of focused presentations will consider existing methods with regard to strengths, limitations, key assumptions, and readiness of these techniques for regulatory assessments.

12:15 p.m. **Break**

12:45 p.m. **Utilizing Negative Controls in Safety and Effectiveness: Methods development and key considerations**

This session includes two presentations that will outline key FDA methodological and operational considerations for both safety and effectiveness studies when utilizing negative controls as part of regulatory assessment. Following the presentations, panelists will provide feedback on FDA proposed projects and further explore to further inform the development and use of negative controls in support of regulatory decision-making.

2:00 p.m. **Key Stakeholder Perspectives**

Stakeholders will provide their feedback and comments on the approaches and proposed demonstration projects presented throughout the workshop with a focus on key opportunities and challenges for incorporating negative controls as a tool in FDA's regulatory toolbox.

2:45 p.m. **Closing Remarks and Adjournment**

TBD, Duke-Robert J. Margolis, MD, Center for Health Policy