Leveraging Randomized Clinical Trials to Generate Real-World Evidence for Regulatory Purposes

The Westin Washington, DC City Center
1400 M St NW • Washington, DC 20005

July 11, 2019

Agenda

8:30 a.m.  Registration

9:00 a.m.  Welcome and Overview
Gregory Daniel, Duke-Robert J. Margolis, MD, Center for Health Policy

9:05 a.m.  FDA Opening Remarks
Jacqueline Corrigan-Curay, U.S. Food and Drug Administration

9:15 a.m.  Leveraging Randomized Designs to Generate RWE
Objective: This workshop will explore key considerations for using randomized designs at the point of care, such as large simple trials or those that incorporate pragmatic elements, to generate RWE for a regulatory purpose. There are practical examples of how such approaches have been implemented in settings of care delivery, and presenters will outline the range of study approaches, their respective potential strengths and limitations, and implementation challenges. Presentations will focus on the mechanics of designing and implementing these trials and highlight key topics that will form the basis of ensuing sessions.

Presenters:
• Robert Temple, U.S. Food and Drug Administration
• Lesley Curtis, Duke University

9:45 a.m.  Selecting Interventions and Study Designs to Generate RWE
Objective: This session will consider the selection of appropriate interventions and study designs for randomized trials implemented to generate RWE. Presenters will draw on lessons learned from previous trials and examine key considerations, including definitions of treatment effects and appropriateness of study designs for regulatory use cases. Additional key issues to be addressed during panel discussion will include assessment of variation of clinical practice when selecting interventions and study designs.

Moderator:
• Gregory Daniel

Presenters:
• Martin Landray, Oxford University
• Elaine Irving, GlaxoSmithKline

Panelists:
• Iris Goetz, Eli Lilly & Company
Discussion Questions:

- Should the intervention be one that is routinely used by clinical providers involved in the trial? Could the intervention be an investigational drug? What are the considerations?
- Is it necessary to assess in advance the degree of variation in clinical practice if the intervention will be compared to standard of care? How can that be accomplished?
- Would a non-inferiority design be appropriate for conducting RWE-based randomized trials given likely heterogeneity in clinical practice and adherence?
- What are appropriate treatment effect definitions in the presence of heterogeneity of treatment exposure, follow-up, and rescue therapy? Can heterogeneity be minimized or managed?
- What are the unique issues for addressing data incompleteness in pragmatic trials versus more traditional trials?

11:00 a.m. Break

11:15 a.m. Outcome Measurement Based on Real-World Data

Objective: Reliably capturing outcomes in practice settings is essential for designing and implementing RCTs. When utilizing RWD for endpoint selection and outcome measurement, challenges arise around the reliability and accuracy of outcomes and the timing of outcome assessments. The session will focus on describing outcome measurement methods for trials that utilize RWD. Panelists will also consider the optimal timing for outcome assessment and the challenges associated with validation and long latency periods.

Moderator:
- Gregory Daniel

Panelists:
- Elizabeth Sugar, Johns Hopkins University
- Cathy Critchlow, Amgen
- David Madigan, Columbia University
- Bill Crown, OptumLabs
- Atul Butte, University of California at San Francisco
- Sean Tunis, Rubix Health

Discussion Questions:

- Assessing the feasibility of reliably capturing outcomes of interest.
  - What characteristics of endpoints can be reliably captured from RWD?
    - What are the key considerations for developing these endpoints (e.g., AUC, mean value, change from baseline, responder)?
    - Real-world outcomes with most potential utility are typically easily determined. For example, hospitalization, death,
emergency room visits, and laboratory findings. What other endpoints could be reliably captured?

- Can composite endpoints be used for outcome ascertainment and what study designs are appropriate for these types of endpoints?
- Would the process for validating real-world endpoints be any different than for non-RWE endpoints?
  - How might endpoints typically captured in clinical trials be used in combination with RWD endpoints to support regulatory decisions?
  - What strategies can be used to supplement data capture for outcome ascertainment (e.g., mHealth and patient-generated data)?
  - When might linkage of data sources (e.g., linking EHR with claims or death registries) be necessary for endpoint selection? What are some examples and how were these data linked endpoints validated?
  - What data sources and other strategies could be used to ensure there is adequate data to document endpoints with longer follow-up periods?

- Timing of outcome assessments.
  - What are the implications of latency of data capture (e.g., lag between an event happening and the availability of claims data that might not appear for nine months)?
  - Given the fluidity of enrollment in healthcare systems, is there an optimum time frame for outcome assessments in these practice settings (e.g., thirty days, six months, one year)?

12:30 p.m. Lunch

1:30 p.m. Key Considerations for Blinding in Randomized Real-World Studies

**Objective:** This session will focus on the role and use of blinding in randomized trials to minimize bias. There are many questions about when blinding is necessary and within which component of the trial blinding should occur. There may also be situations where endpoints are considered objective enough as to not be influenced by unblinded treatment assessments (e.g., mortality or hospitalization). There will be a lead off presentation outlining key blinding considerations based on a randomized control implemented in clinical settings. Discussion topics will focus on when blinding approaches are necessary (e.g., double versus single blind), at what point in the trial blinding should be implemented, and when blinding is potentially unnecessary. Reactants will further consider the appropriateness of different blinding approaches and the potential impact of these approaches on study conduct (e.g., imbalances associated with adverse event reporting, unblinding by social media).

**Moderator:** Gregory Daniel  
**Presenter:** Simon Skibsted, Novo Nordisk  
**Panelists:**
- Rita Redberg, University of California at San Francisco  
- Satrajit Roychoudhury, Pfizer  
- Nancy Dreyer, IQVIA  
- Peter Stein, U.S. Food and Drug Administration
Discussion Questions:

- What are the key considerations for determining when blinding of treatment assignment is needed? Are there any differences for considerations in a real world setting compared to non-RWE settings?
- When is blinding of treatment assignment potentially not necessary?
  - Could endpoints such as death be used as an objective endpoint that would not require blinding of treatment assignment?
  - What other clinical outcomes and lab-based endpoints might be considered objective enough to not require blinding treatment assignment?
- Even if treatment assignment is unblinded, should there be blinding of outcome assessments and safety data for trials intended to support regulatory decisions?
  - When should centralized and blinded adjudication be utilized?
  - How might such blinding overcome any potential bias from investigator/patient knowledge of treatment assignment?

2:45 p.m. Break

3:00 p.m. Real World Designs and Implications for Causal Inference

Objective: The hope is that integrating trials in health care systems and utilizing RWD to identify patients for inclusion will result in a more heterogeneous population with varying stages and different manifestation of the study diseases. Additionally, there are unique challenges about whether study cohorts identified for the treatment actually receive the intended treatment. While a more diverse study population may result in better representation of disease and patient complexities compared to traditional clinical trials, questions remain whether causal inferences can be made in a way that ensures the diagnostic precision needed for regulatory use. This may make traditional intent-to-treat analyses challenging to implement and statistical analysis plans must account for participants who “cross-over” to other arms of the study or do not fully adhere to the treatment. This session will begin with case study examples on the impact of these real-world design issues, and reactants will further consider and discuss key issues raised during the presentation.

Moderator: Gregory Daniel
Presenter: David Price, University of Aberdeen
Panelists:

- Vince Willey, HealthCore
- Mark Levenson, U.S. Food and Drug Administration
- Lisa LaVange, University of North Carolina
- Jesse Berlin, Johnson & Johnson

Discussion Questions:

- What are the implications of leveraging heterogeneous study populations on understanding the effect of the drug?
- What are the considerations for defining an appropriate population for studies utilizing RWD?
- What lessons can be learned from using algorithms or computable phenotypes
to identify eligible patients using RWD, and how does one appropriately balance sensitivity and specificity of these algorithms?

- Given the flexibility and openness of trials implemented in clinical settings, what approaches are available to address potential “cross-over” of study participants from one study arm to another?
- What proven methods are available to identify causal effects of treatments when there might be intermittent exposure or partial adherence to the intended intervention?

4:15 p.m.  Summary of Day One
Gregory Daniel
Leveraging Randomized Clinical Trials to Generate Real-World Evidence for Regulatory Purposes

The Westin Washington, DC City Center
1400 M St NW • Washington, DC 20005
July 12, 2019

Agenda

9:00 a.m.   Key Takeaways from Day One
Mark McClellan, Duke-Robert J. Margolis, MD, Center for Health Policy
TBD, U.S. Food and Drug Administration

9:15 a.m.   Monitoring Randomized Clinical Trials that Generate RWE
Objective: There are many practical questions that must be addressed to ensure appropriate conduct and monitoring of randomized trials in clinical settings, including assignment of responsibility for oversight of data collection and aggregation. This session will delve into key regulatory considerations for both sponsors and regulators in three challenge areas: roles and responsibilities of principal investigators (PI) overseeing trials in clinical settings, safety monitoring, and monitoring data integrity. Each challenge area discussion will consist of one presentation followed by moderated discussion.

Focus Area 1: Sponsor Conduct and Monitoring Challenges
Moderator: Mark McClellan
Presenter: TBD, GlaxoSmithKline
Panelists:
- Adrian Hernandez, Duke University
- Leanne Larson, Parexel (Association of Clinical Research Organizations)

Discussion Questions:
- For large or multi-site studies, how must the usual roles and responsibilities of PIs be adapted to enable efficient data collection and study conduct?
- What considerations should be made for monitoring studies that utilize approved but off-label products? What additional challenges would be present if the randomized study was focused on unapproved investigational products?
  - What are the challenges for stakeholders in complying with regulations regarding tracking of investigational products when delivery is within clinical practices?
  - What are the considerations for establishing a centralized site to be used to distribute and monitor investigational products that are routinely administered on an outpatient basis?
Focus Area 2: Safety Monitoring

Moderator: Mark McClellan
Presenter: Nawar Bakerly, Salford Royal NHS Foundation Trust
Panelists:
- Greg Ball, Merck
- Ellis Unger, U.S. Food and Drug Administration

Discussion Questions
- What factors should be considered when determining the process and responsibility for adverse event reporting using RWD (e.g., what is the role of the practitioner versus sponsor)?
- When might reliance on events recorded during routine practice be sufficient to collect adverse events for regulatory purpose, and when would additional mechanisms need to be considered for capturing safety data (e.g., alerts on hospitalizations and direct reports, mobile technology with targeted outreach)?
- What can or should be done to contact patients for safety issues when relying on RWD for adverse event reporting?
  - Are there mechanisms available to contact patients when appropriate regarding safety concerns during the trial?
  - How would SAE reporting with RWD differ from trials typically used to support regulatory decisions where events may not be captured until a participant has a scheduled visit?

Focus Area 3: Maintaining Data Integrity

Moderator: Mark McClellan
Presenter: Martin Gibson, Salford Royal NHS Foundation Trust
Panelists:
- Paul Harris, Vanderbilt University
- Michael O’Neal, Bioclinica (Association of Clinical Research Organizations)

Discussion Questions:
- What are the major challenges for stakeholders in complying with good clinical practice (GCP) regulations when integrating regulatory trials into clinical practice?
- What challenges exist for appropriately monitoring clinical practices where the intervention occurs?
- FDA’s acceptance of data from clinical investigations for decision-making purposes depends on FDA’s ability to verify the quality and integrity of the data during FDA inspections. What are the considerations for accessing and inspecting the data when EHRs are used as a source of data in clinical investigations?
- For clinical trials utilizing RWD, what are the considerations for protecting patient privacy?

10:45 a.m. Break
11:00 a.m.  Building a Framework for Randomized Clinical Trials: Barriers, Enablers, and Infrastructure

*Objective:* In order to ensure robust clinical studies, a framework must be developed to determine which studies are appropriate for developing RWE to inform regulatory decision making. This session, which will feature speakers from previous panels, will consider possible mechanisms for developing a data infrastructure to leverage EHR data for use in RCTs and barriers to implementation. Discussion will explore key considerations and necessary next steps for providing a regulatory pathway for use of RWD/RWE in RCTs.

*Moderator:* Mark McClellan

12:00 p.m.  Closing Remarks and Adjournment

Mark McClellan

---

*Funding for this conference 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 conference 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.*