

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

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Discussion Guide

Evidence from randomized controlled trials (RCTs) is traditionally used by the U.S. Food and Drug Administration (FDA) to evaluate a product's safety and effectiveness. Although long considered the gold standard for evidence development, RCTs are often resource-intensive and require both significant time and financial investment. Although the evidence from these trials clearly has high internal validity and documents the effectiveness of treatments, concerns have been expressed that these trials may not reflect outcomes in the broader populations that will use these treatments or the effects of the treatments in real world use. Because of these challenges with the traditional RCT paradigm, the stakeholder community is actively exploring new ways to increase the efficiency of trials by embedding them into clinical care settings and making better use of real-world data (RWD) routinely collected in these settings - with the aim of optimizing drug development and accelerating the availability of effective products in areas of unmet medical need.

For example, the use of computer systems, mobile devices, wearables, and other technologies are enabling the large-scale capture of RWD that can improve the efficiency of key trial processes including rapid cohort identification, communication with enrolled participants, randomization of patients in routine care settings, and clinical data capture to power real-world study endpoints. The type and variety of data found in electronic health records and payer claims data also present potentially useful sources of RWD for augmenting trial data and the development of real-world evidence (RWE). By embedding trials in clinical settings and leveraging appropriate methods, it may be possible to generate a broader range of evidence, including novel endpoints providing additional insights into patient's functioning compared to traditional trials.

Despite demonstrated successes designing and implementing randomized trials in clinical settings, there are unique challenges that require careful consideration when resultant RWE is intended to be used in regulatory contexts. Not all research questions may be suitable for these types of trials, and traditional inferential statistics may be unable to identify clear treatment effects given variations in treatment effect definitions, clinical practice, and partial compliance with the treatment. Additionally, it is unclear how current regulatory standards and compliance requirements designed for traditional RCTs apply to these trials. For example, there may be new roles and responsibilities of Principal Investigators (PI) needed to properly oversee the trial. Collectively, these unique considerations can introduce challenges when evaluating RWE for regulatory use.

The FDA is working to address these challenges through research, convening, and demonstration projects under their RWE Program. The Program, formally outlined in December 2018 following congressional mandates in the 21st Century Cures Act and the sixth Prescription Drug User Fee Act (PDUFA VI), will help the Agency and partner stakeholders better elucidate the potential utility of RWD to generate RWE capable of supporting the approval of new indications for drugs and biologics or meeting post approval

study requirements.¹ The FDA's framework for this Program outlines key considerations for exploring better use of RWD and RWE, including through randomized approaches in clinical settings. It establishes the important factors that the Agency will use to guide their decision-making, including:

- Is the RWD fit for purpose?
- Does the trial or study design used to generate RWE provide adequate scientific evidence to answer or help answer the regulatory question of interest?
- Did the conduct of the study meet FDA regulatory requirements?

On July 11 and 12, 2019, under a cooperative agreement with the FDA, the Robert J. Margolis, MD, Center for Health Policy at Duke University will convene a public workshop for the stakeholder community to explore key considerations for utilizing RWD and randomized designs to generate RWE. Discussion will focus on key components of trial design including intervention selection, outcome measurement, blinding, and study population characteristics as well as important compliance requirements for monitoring the conduct of trials. The public workshop will inform continued refinement of the Agency's RWE Program and eventual guidance for industry.

Overview of Workshop Sessions

Leveraging Randomized Designs to Generate RWE

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.

Selecting Interventions and Study Designs to Generate RWE

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.

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?

¹ <https://www.fda.gov/media/120060/download>

Outcome Measurement Based on Real-World Data

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 consider the optimal timing for outcome assessment and the challenges associated with validation and long latency periods.

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 and how would you validate these endpoints?
 - 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)?

Key Considerations for Blinding in Randomized Real-World Studies

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 presentation outlining key blinding considerations for randomized control trials embedded 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).

Discussion Questions:

- What are the key considerations for determining when blinding of treatment assignment is needed? Are there any differences for real-world settings compared to non-RWE settings?

- When is blinding of treatment assignment potentially not necessary?
 - What endpoints can 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 in open label studies?

Real World Designs and Implications for Causal Inference

The expectation 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 disease stages and different manifestation of the studies diseases. Additionally, there are unique challenges about whether study cohorts identified for the treatment actually receive the intended treatment and their adherence to assigned treatment. Real-world patterns of treatment adherence are likely to be more heterogeneous than in traditional trials, including more cross-over, early stopping, and intermittent use. There may be additional concerns about obtaining the necessary follow-up data. This may make traditional intent-to-treat analyses challenging to implement or not appropriate. This session will begin with case study examples on the impact of these real-world design issues, and discussants will further consider and discuss key issues raised during the presentation.

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 methods are available to identify causal effects of treatments when there might be intermittent exposure or partial adherence to the intended intervention?

Monitoring Randomized Clinical Trials that Generate RWE

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 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

Discussion Questions:

- For large or multi-site studies, is there a need to adjust the roles and responsibilities of PIs 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 sites of clinical practice?
- 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

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 purposes, 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?
 - What are the best mechanisms to contact patients when appropriate regarding safety concerns during the trial?
 - How would AE monitoring and 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

Discussion Questions:

- Are there challenges for stakeholders in appropriately monitoring clinical practices and complying with good clinical practice regulations when integrating regulatory trials into clinical practice?
- 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?

Building a Framework for Randomized Clinical Trials: Barriers, Enablers, and Infrastructure

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 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 and RWE in RCTs.

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