# Randomized Trials to Generate Real-World Evidence

**Jacqueline Corrigan-Curay, J.D., M.D.**
Director, Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration

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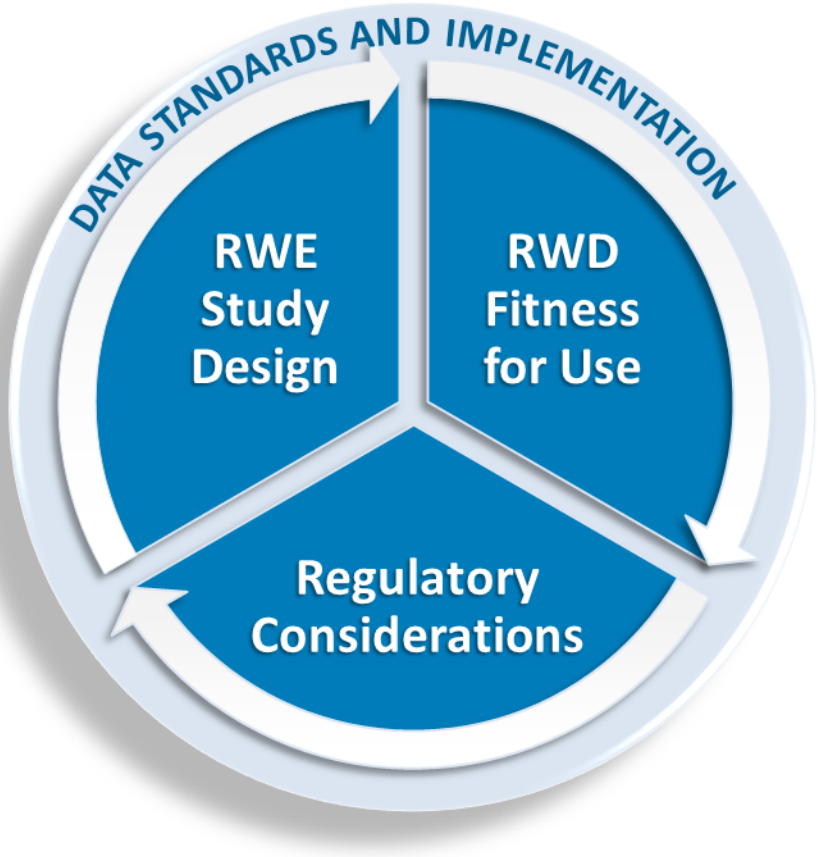
# FDA Real-World Evidence Program


- **2018 Framework for FDA'S RWE Program outlines FDA's plan to implement the RWE Program**
- **RWE Program:**
  - **Will focus on adding or modifying an indication, comparative effectiveness, and comparative safety**
  - **Is a multifaceted program that includes:**
    - **Internal processes**
    - **Guidance development**
    - **Stakeholder engagement**
    - **Demonstration projects**




https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

# Framework for Evaluating RWD/RWE for Use in Regulatory Decisions




**Considerations**

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

# The Current System has Value and Limitations

- **Traditional RCTs can provide a precise assessment of efficacy and safety**
  - Potential for **valid causal inferences** to be drawn

    = *does the drug work – strong internal validity*
  - Well-characterized response (**standardized endpoints**) in patients with the disease (**standardized diagnosis**) responsive to treatment (**enhanced adherence, exclusion criteria**)

    = effect size in patients in trial – *potential issue of external validity*
  - Reliable data set upon which to base regulatory decisions
- **But have limitations:**
  - Resource-intensive and take a long time to complete
  - Selected population vs post-approval use; internal validity vs external validity/ generalizability
    - Limitations: fewer who are older, with multiple co-morbidities, on many concomitant medications

# Why Expand Use of RCTs to Generate RWE?

- **Potential for a broader and more diverse patient experience vs traditional Phase 3 clinical studies**
  - Includes “real-world” settings and patients who will use the drug post-approval (vs more restricted population in Phase 3 program)
  - Has broader representation of patients characteristics, such as age, racial/ethnic background, co-morbid disease, disease severity, concomitant medications
- **Potential lower resource intensity – utilizing practice data vs extensive trial infrastructure**

# Research Question: What are We Trying to Learn?

- **Does the drug work in a broader range of patients**?
  - i.e., patients who often do not participate in Phase 3 studies: older, co-morbidities, wider range of stages of disease
- **Which therapy works better in a practice setting**?
  - Comparative effectiveness of similarly administered treatments (i.e., both tablets) or non-similarly administered treatments (SQ vs oral treatment)
  - Adherence versus effectiveness

# Integrating RCTs into Clinical Practice Settings

- **What types of interventions might be well-suited to be administered in routine clinical care settings?**
  - **What are the implications of heterogeneity between clinical practices for regulatory research?**

- **What is the quality of the data that can be captured?**
  - **Can the physician/investigator reliably capture the endpoint of interest?**
  - **Will there be challenges with measuring disease progression/changes versus more objective measures, labs, imaging?**
  - **Is there a network to capture all relevant outcomes – drug dispensing, ER visits, specialist referrals, hospitalization, death?**

# Reliance on Real World Data


**Traditional Study Elements**

- Protocol defined procedures (at entry, study visits, study endpoint), defined study visits (detailed time and event schedule)
- Defined study periods; data collected through specific forms (eCRFs) with extensive data cleaning

**Pragmatic Study Elements**

- Follow up care based upon clinical practice: physician determination of clinically appropriate intervals for visits; procedures/laboratory studies as decided necessary by physician
- Study data extracted from EHR, claims, laboratory, pharmacy databases, publically available health records (e.g. death records)

**It is not dichotomous – can include elements of both**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- **Nature of endpoint**
- **Context of disease**
- **“Therapeutic equipoise”**
- **Others?**

# Monitoring RCTs in Clinical Practice Settings

- **Safety monitoring**
  - Implementation of a fit for purpose safety plan
  - *FDA Guidance – Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations*
- **Oversight of clinicians/investigators**
  - What is an optimum PI/sub investigator structure?
- **Meeting GCP requirements in a clinical care setting**

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- Incorrect to contrast the term “real-world evidence” with the use of randomization in a manner that implies that they are disparate or even incompatible concepts.
- Must consider the components of such trials that are critical to obtaining valid results and minimizing bias.

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# Thank you

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov