Framework for FDA’s Real-World Evidence Program

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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Objectives

At the end of this presentation, participants will:

1. Describe the main elements of FDA’s real-world evidence (RWE) Program.

2. List FDA considerations for evaluating the use of real-world data to generate RWE for regulatory decisions.

3. Explain program items the Agency plans to address in the RWE Program.

4. Describe at least one demonstration project that will help inform the use of RWD and RWE.
21st Century Cures Deliverables

• FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to:
  - Help support approval of a new indication for a drug approved under section 505(c)
  - Help satisfy post-approval study requirements

• Program will be based on a framework that was to be issued by 2018

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials
• Intended for drug and biological products

• Outlines FDA’s plan to implement the RWE program

• Multifaceted program
  – Internal processes
  – Guidance development
  – Stakeholder engagement
  – Demonstration projects

• Comment period closes April 16, 2019
Scope of the RWE Program

Evaluates the potential use of RWE to support changes to labeling about drug product effectiveness, including:

– Adding or modifying an indication, such as a change in dose, dose regimen, or route of administration

– Adding a new population

– Adding comparative effectiveness or safety information
Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies

Different challenges and opportunities for each approach

<table>
<thead>
<tr>
<th>Randomized Intervenional</th>
<th>Intervenional non-randomized</th>
<th>Non-randomized / non-interventional</th>
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</thead>
<tbody>
<tr>
<td><strong>Traditional Randomized Trial Using RWD Elements</strong></td>
<td><strong>Trials in Clinical Practice Settings</strong></td>
<td><strong>Observational Studies</strong></td>
</tr>
<tr>
<td>RWD to assess enrollment criteria / trial feasibility</td>
<td>RCTs with Pragmatic designs</td>
<td>Prospective data collection</td>
</tr>
<tr>
<td>eCRF + selected outcomes identified using EHR/ claims data</td>
<td>RCT using eCRF (+/- eHR data)</td>
<td>Registry trials/study</td>
</tr>
<tr>
<td>Mobile technology used to capture supportive endpoints (e.g., to assess ambulation)</td>
<td>RCT using claims and eHR data</td>
<td>Prospective Cohort Study</td>
</tr>
</tbody>
</table>

Increasing reliance on RWD

Traditional RCT

RCTs using RWD

Observational studies

Courtesy of Peter Stein, OND
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
RWD Fitness for Use

• Data reliability (data accrual and data quality control) and relevance
  – Data must be collected and maintained in a way that provides an appropriate level of reliability
  – Data must be suitable to address specific regulatory question of interest
    • Challenges of capturing clinical effectiveness outcomes

• FDA does not endorse any one type of RWD

• **Challenge:** A single source of RWD may not capture all data elements, and multiple data sources may be needed
  – How to integrate data sources and address duplication
Gained Experience

- 18 data partners
- **Sentinel 5-year Strategic Plan 2019-2023**
  - One strategic aim is to leverage the Sentinel System to accelerate access to and broader use of RWD for RWE generation
- FDA-Catalyst
Sources of Patient-Centric RWD
Beyond Health Care Records

JAMA Cardiology | Original Investigation
Passive Detection of Atrial Fibrillation Using a Commercially Available Smartwatch

Geoffrey H. Tison, MD, MPH; José M. Sanchez, MD; Brandon Ballinger, BS; Avesh Singh, MS; Jeffrey E. Olgin, MD; Mark J. Fletcher, MD, MPH; Eric Vittinghoff, PhD; Emily S. Lee, BA; Shannon M. Fan, BA; Rachel A. Gladstone, BA; Carlos Mikell, BS; Nimit Sohoni, BS; Johnson Hsieh, MS; Gregory M. Marcus, MD, MAS
RWD Fitness for Use

- Guidance on how to assess whether RWD from medical claims, EHRs and/or registries are fit for use to generate RWE in support of drug product effectiveness

- Explore the use of digital technology tools, electronic PROs, and wearables to potentially fill gaps
Potential for Study Designs Using RWD to Support Effectiveness

Factors when considering embedding a randomized trial in clinical settings in order to access RWD

– What types of interventions and therapeutic areas might be well-suited to routine clinical care settings?
– What is the quality of data that can be captured in these settings?
– Bridging between regulatory endpoints and clinical practice

Guidance on considerations for using RWD in randomized clinical trials for regulatory purposes, including use of pragmatic design elements
Non-randomized, single arm trials with external RWD control

– RWD as a basis for external controls is not without challenges given potential differences between trial participants and non-trial participants

– However, robust RWD on patients currently receiving other treatments together with statistical methods could improve quality of external control data

PROGRAM ITEM:
Guidance on the use of RWD to generate external control arms is also being considered
Potential for Study Designs Using RWD to Support Effectiveness

Observational studies

- Transparency about study design and analysis before execution is critical for ensuring confidence in the result.
- What should transparency for observational studies look like?
Observational Studies: Initial Questions

• What are the characteristics of the data?
  ✓ Diagnostic precision, consistency in data on exposure, relevant endpoint outcome captured across populations, lack of missing data, robust data on covariates

• What are the characteristics of the study design and analysis that improve the chance of a valid result?
  ✓ Can use of an active comparator improve the chance of a valid result?
  ✓ Are there prespecified sensitivity analyses and statistical diagnostics that can provide confidence that the effect of unmeasured confounders would not change the causal inference?

1- not all-inclusive
Guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision making
Regulatory Considerations

• Identify potential questions regarding the applicability of regulatory requirements to use of RWD for regulatory decisions in RCTs and observational studies, including informed consent and oversight

• Assess whether current guidance documents on the use of electronic source data are sufficient
Foundation for Use of Electronic Source Data

Use of Electronic Informed Consent Questions and Answers
Guidance for Institutional Review Boards, Investigators and Sponsors

Use of Electronic Health Record Data in Clinical Investigations


Guidance for Industry

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes. Comments and suggestions regarding this draft document should be submitted in writing to the person listed in the notice announcing the availability of this draft guidance. A comment submission form is available via the Division of Dockets Management (HFA-305). Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments of the docket number listed in the notice of availability that publishes in the Federal Register. For questions regarding this draft document, contact CBER’s Cheryl C. Nault at 301-796-2986, CBER’s Office of Communications, Outreach, and宁静Phone: 202-408-9216, 202-408-3572, 202-408-3580, 202-408-3590, or CBER’s Program Operations Staff at 202-408-3580.

U.S. Department of Health and Human Services
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June 2018

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Regulatory Considerations

• Guidance as needed on regulatory considerations raised by different study designs to generate RWE that is submitted to support drug product effectiveness

• Consider whether additional guidance on use of electronic source data is needed
Data Standards and Implementation

Activities include:

• Identifying and assessing data standards and implementation strategies required to use RWD/ RWE

• Identifying gaps between RWD/ RWE data standards and existing FDA systems

• Collaborating with stakeholders to adapt or develop standards and implementation strategies
Continued Active Stakeholder Engagement

A Framework for Regulatory Use of Real-World Evidence

September 13, 2017

The National Academies of Sciences Engineering Medicine

National Academies RWE Workshop Series

Real world evidence scoping roundtable

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

Primer
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

The Academy of Medical Sciences
Stakeholder Engagement

Internal Engagement

• Launched internal website and outreach to engage FDA staff

• Established the RWE Subcommittee of the Medical Policy Program and Review Committee, which...
  – Includes leadership from CDER Offices, CBER, and CDRH.
  – Serves as a cross-cutting forum for RWD/RWE issues; focuses on CDER's evaluation of RWE and guides policy development.
  – Provides advisory recommendations on whether the underlying data, methods, and study design elements are appropriate for regulatory decisions.
  – Provides a platform to engage with stakeholders as the community at large continues to explore the utility of RWD.
Demonstration Projects

Data
- Relevancy
- Quality
- Linkage

RWE Tools
- Common data models
- Digital technology tools

RWE Study Design
- Randomized trials
- Assessment of observational studies
EHRs: Greatest Potential and Challenge

EHR data have advantages of:

• Presenting a more complete and granular clinical picture
• Including labs/imaging/pathology reports

Challenges include:

• Data in pathology/radiology and clinical notes are often unstructured (80%)
• Typing ≠ consistency/complete documentation
• Clinical outcome measures for drug approvals may not be used or consistently recorded in practice
Creating Quality Clinical/Research Records – Design for Multiuse

- **OneSource**: “enter the right clinical data once, use many times”
- FDA collaboration with Dr. Laura Esserman (UCSF)
- Integration of standards based tools into the EHR to bring together health care and research
- Demonstration in breast cancer clinical trials

**Good quality clinical care, clinical trials, registries, quality improvement, researchers, scientists, payors, regulators and others all require the same data elements...**

Courtesy of Dr. Laura Esserman and Susan Dubman
HARMONY-Outcomes Ancillary Study

- Collaboration with Duke Clinical Research Institute and Glaxo SmithKline
- Supported by FDA
- Assess EHR ability to:
  - Facilitate recruitment
  - Populate baseline characteristics
  - Identify clinical endpoints

July 14, 2017: Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings from the HARMONY-OUTCOMES EHR Ancillary Study

http://www.rethinkingclinicaltrials.org/grand-rounds-7-14-17/

Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus – NCT02465515
Demonstration Project

LimitJIA

Table 1: Primary Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria:</th>
<th>Exclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical diagnosis JIA by a pediatric rheumatologist within the past 6 months</td>
<td>• Systemic JIA as defined by 2004 ILAR criteria¹</td>
</tr>
<tr>
<td>• Arthritis affecting ≤4 joints between disease onset and enrollment</td>
<td>• Sacroiliitis (clinical or radiographic)</td>
</tr>
<tr>
<td>• Clinically active arthritis of at least 1 joint at the time of enrollment</td>
<td>• Inflammatory bowel disease</td>
</tr>
<tr>
<td>• Age ≥ 2 years old and &lt; 17 years old</td>
<td>• Psoriasis</td>
</tr>
<tr>
<td>• Prior or concurrent enrollment in the CARRA Registry</td>
<td>• History of uveitis or currently active uveitis</td>
</tr>
<tr>
<td></td>
<td>• Prior treatment with systemic DMARD(s) or biologics</td>
</tr>
<tr>
<td></td>
<td>• Current treatment with systemic glucocorticoids (past 30 days)</td>
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</tbody>
</table>

- FDA-Catalyst is planning to align with the trial by providing support from the My Studies App
  - Collection of primary outcome (uveitis) from ophthalmology appointments (also reminders for appointments)
  - Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry

Table of Scheduled Visits for Uveitis Screening[^85]

<table>
<thead>
<tr>
<th>ILAR Category</th>
<th>ANA</th>
<th>Age at JIA Onset</th>
<th>Screen</th>
<th>M 3</th>
<th>M 6</th>
<th>M 9</th>
<th>M 12</th>
<th>M 15</th>
<th>M 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarthritis, Psoriatic arthritis, Undifferentiated</td>
<td>+</td>
<td>≤ 6</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Enthesitis-related arthritis</td>
<td>Any</td>
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</table>
Demonstration Project

• SPARC Inflammatory Bowel Disease cohort within the IBD Plexus research exchange platform
  – Provider based recruitment of individuals >18 years of age with a confirmed IBD diagnosis from academic and community sites

• FDA-Catalyst will align with the registry by providing support from the My Studies App
Demonstration Project –
Impact AFib – Large Randomized Trial

- Implementation of an individually randomized controlled trial within the FDA-Catalyst distributed database environment
- Test the ability of an education intervention to increase the appropriate use of oral anticoagulants in a patient population with atrial fibrillation (AFib) at high risk of stroke
- Intervention materials include letter from health plan to describe project, patient brochure (additional information on AF and OACs), and patients pocket card (tool to facilitate conversation between patients and providers)
- Enrollment of approximately 80,000 individuals in the early and late intervention arm
- Protocol available at:
Demonstration Project

• RofLumilast or Azithromycin to prevent COPD Exacerbations
  – Randomized “real world” trial, 1,600 adults in each arm
  – Azithromycin - macrolide with anti-inflammatory properties
  – Roflumilast - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor
  – Both guideline recommended but Roflumilast is FDA approved for this indication

• Primary outcomes
  – All cause hospitalization
  – All cause mortality

• Follow-up
  – 6-36 months
  – No visits
  – Call Center
  – Patient Portal
  – Site EMR
Demonstration Project: Assessment of Non-Interventional Designs

• Attempted duplication of results of phase 3 & 4 RCTs over three years to provide empirical evidence base that could inform our level of confidence in high quality non-interventional designs

• FDA reviewers and researchers from the Brigham and Women’s Hospital/Harvard Medical School Division of Pharmacoepidemiology
  – Selected trials in which claims data are sufficiently fit for purpose in a research environment
    • Oral hypoglycemic, novel oral anticoagulant, antiplatelet, antihypertensive, anti-osteoporosis, asthma, COPD, heart failure, anti-arrhythmic, and lipid lowering medications
  – Concurred with pre-specified measures of agreement
  – Established an implementation process

• Goal: 30 trials completed by March 2020

https://www.rctduplicate.org/
Conclusion

• Framework serves as a roadmap for more fully incorporating RWD and RWE into the regulatory paradigm

• RWE remains a top FDA priority

• FDA is committed to understand its full potential

• Multi-stakeholder effort
Acknowledgements

- Khair ElZarrad
- Peter Stein
- David Martin
- Dianne Paraoan
- FDA RWE Committee
Q&A and Resources

Click for:

- FDA Real World Evidence webpage
- Framework for FDA’s RWE Program
- FDA MyStudies Application
- PDF of today’s slides

- Additional questions on the webinar?
  Email: CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

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