Real World Evidence Program
Looking Forward

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Center for Drug Evaluation and Research
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Expectations in Law for Real-World Evidence: The 21st Century Cures Act

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

- Program is based on a framework that:
  - Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address

- Draft Guidance to be issued by 2021
- PDUFA commitments aligned with 21st Century Cures Act

Substantial Evidence standard remains unchanged
FDA Definitions

Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- electronic health records (EHRs)
- claims and billing data
- data from product and disease registries
- patient-generated data including in home-use settings
- data gathered from other sources that can inform on health status, such as mobile devices

Real World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.
Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

Consider:

• 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
Demonstration Projects

- Data
  - Relevancy
  - Quality
  - Linkage

- RWE Tools
  - Common data models
  - Analytics
  - Mobile technologies

- RWE Study Design
  - Randomized trial design
  - Assessment of observational methods
RWD FIT FOR USE
In the real world, nothing happens at the right place at the right time . . .

~ Mark Twain
EHRs – Quality and Relevance

• Certain endpoints – labs, pathology, imaging are used in clinical practice and research
  – Challenge is curation of unstructured and inconsistent data format

• Timing of assessment in clinical practice may be variable
  – Censoring for those without data may create a bias as those who show up for follow up are often different than those who do

• Clinical outcome measures for disease progression may not be used or consistently recorded in practice
  – Are there ways to bridge that gap

• Interoperability will be necessary for studies outside of small populations
  – Including linkage to claims for longitudinal data
Demonstration Projects - Data

Comparing data collected from EHR to a Pragmatic Trial to assess fit-for-use

Developing a Reusable Framework for transforming raw data in fit-for-purpose data

Creating a “One Source” EHR for Research and Clinical Care

Feasibility of transforming structured-based EHR data to FDA submission standards
Patient-Generated Health Data (Digital Health Tools)
FDA MyStudies

• **Mobile App**
  • Standard frameworks - ResearchKit (iOS), ResearchStack (Android)

• **Web-based Configuration Portal (WCP)**
  • Enables support of multiple types of medical product effectiveness and safety studies with minimal software development

• **Secure Storage Environment**
  • Generates secure tokens
  • Separates registration information and responses
  • Partitioned for multisite, decentralized, or distributed models

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System
Demonstration Projects – RWE Tools

Developing tool to improve data collection from mobile technology-wearables and accelerometers

Evaluating the performance of wearables and health platforms for real-world surveillance surrogate endpoints

FDA MyStudies in a Juvenile Idiopathic arthritis trial to capture an endpoint

FDA MyStudies to support the Crohns and Colitis Registry
Google Cloud and FDA MyStudies: Harnessing real-world data for medical research

Google Cloud is committed to helping customers conduct life-saving research that results in new medications, devices and therapeutics by unlocking the knowledge hidden in real-world data. That’s why we’re supporting the goals of the U.S. Food & Drug Administration, by making the FDA’s open-source MyStudies platform available on Google Cloud Platform. By building on the platform developed by the FDA, we hope to stimulate an open ecosystem that will improve the ability of organizations to perform research that leads to better patient outcomes. This collaboration continues our long history of open-source work, and our commitment to producing easy-to-use tools that serve the healthcare and life sciences community.

Google Cloud is also working with the FDA to help advance the agency’s effort to modernize and digitize its operations, and to support the agency’s mission to help patients from all over the world. By collaborating on projects like these, we can help to make sure that the latest technology is available to those who need it the most. Whether it’s helping to improve patient outcomes or supporting research and development, our goal is to make sure that everyone has access to the tools they need to succeed.
RWD Fitness for Use

Leveraging the principles from the 2013 guidance on electronic health care data and our demonstration projects:

• How to assess RWD from medical claims and EHRs and registry data to generate RWE regarding drug product effectiveness

• The use of mobile technologies, electronic PROs, and wearables to potentially fill gaps
# Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies

<table>
<thead>
<tr>
<th>Randomized interventional</th>
<th>Interventional non-randomized</th>
<th>Non-randomized / non-interventional</th>
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<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>
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<tr>
<td>RWD to assess enrollment criteria / trial feasibility</td>
<td>RCTs Leveraging RWD</td>
<td>Prospective data collection</td>
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<tr>
<td>eCRF + selected outcomes identified using EHR/claims data</td>
<td>RCTs with pragmatic design elements using claims/EHR data</td>
<td>Registry trials/study</td>
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<tr>
<td>Mobile technology used to capture supportive endpoints (e.g., to assess ambulation)</td>
<td>Single arm study using external control</td>
<td>Prospective Cohort Study</td>
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<td>RWD to support site selection</td>
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<td>Using existing databases</td>
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**Increasing reliance on RWD**

- Traditional RCT
- RWE / pragmatic RCTs
- Observational cohort
Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer.

The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe, the incidence of oesophageal cancer at age 60–79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years’ use of oral bisphosphonates.

Studies utilising the same datasource, over a very similar time period with the same drug of interest and the same outcome delivered opposing results.
Demonstration Projects

DUPLICATE Projects: Retrospective and Prospective replication to gain confidence in non-interventional designs

Applying targeted learning statistical methods and comparing other methods in RCTs and observational studies

RELIANCE

CMS linkage to the PCORI RELIANCE Trial to provide additional information on exposure and outcomes that can be assessed through Medicare

Pre-replication of RELIANCE Trial

IMPACT AFib: Educational intervention - SENTINEL

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<th>Regulatory Agreement</th>
<th>Estimate Agreement</th>
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![Diagram of heart conditions: Normal, Atrial Fibrillation, Electrical activity comparison]
Internal Stakeholder Engagement

- Assess Discipline needs and Provide training
- Participate in Guidance and Policy Development
- Capture RWD and RWE Use-Cases
- Make Internal Resources Available
- Committee of Senior FDA Leaders to facilitate consistency
Acknowledgements

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