FDA Real-World Evidence Embedded RCTs

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Disclaimer

• This talk reflects the views of the author and should not be construed to represent FDA’s views or policies.

• The speaker has no relevant financial conflicts.
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 will be based on a framework that will be issued by December 2018:
  - 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- Draft Guidance to be issued by 2021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
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

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
Substantial Evidence of Effectiveness

Substantial evidence means “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

*Federal Food, Drug, and Cosmetic Act 1962 (21 USC Sec. 355)*
What is an “adequate and well-controlled investigation”?

<table>
<thead>
<tr>
<th>Selected Key Characteristics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a <strong>clear statement of objectives</strong> of the investigation and <strong>methods of analysis</strong></td>
</tr>
<tr>
<td>The study uses a <strong>design</strong> that permits a <strong>valid comparison</strong> with a <strong>control</strong> to provide a <strong>quantitative assessment of drug effect</strong>: placebo-control, dose-comparison control, no treatment control, active-treatment control, historical control</td>
</tr>
<tr>
<td>Adequate measures are taken to <strong>minimize bias</strong> on the part of the subjects, observers, and analysts of the data</td>
</tr>
<tr>
<td>The <strong>methods of assessment</strong> of subjects’ response are <strong>well defined and reliable</strong></td>
</tr>
<tr>
<td>The <strong>method of selection</strong> of subjects provides adequate assurance that they have the disease/condition being studied</td>
</tr>
<tr>
<td>The <strong>method of assigning patients</strong> to treatment and control groups <strong>minimizes bias</strong> and is intended to <strong>assure comparability of the groups</strong> with respect to pertinent variables. Ordinarily...assignment is by randomization...</td>
</tr>
<tr>
<td>There is an <strong>analysis of the results of the study</strong> adequate to assess the effects of the drug</td>
</tr>
</tbody>
</table>

*From 21 CFR 314.126*
Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies

- **Randomized interventional**
  - **Traditional Randomized Trial Using RWD Elements**
    - RWD to assess enrollment criteria / trial feasibility
    - RWD to support site selection
  - **Trials in Clinical Practice Settings**
    - eCRF + selected outcomes identified using EHR/claims data
    - Mobile technology used to capture supportive endpoints (e.g., to assess ambulation)
  - **RCTs Leveraging RWD**
    - RCTs with pragmatic design elements using claims/EHR data

- **Interventional non-randomized**

- **Non-randomized / non-interventional**
  - **Observational Studies**
    - Single arm study using external control
    - Prospective data collection
      - Registry trials/study
      - Prospective Cohort Study
    - Using existing databases
      - Case – Control
      - Retrospective Cohort Study (HC)

**Increasing reliance on RWD**

- Traditional RCT
- RWE / Embedded RCTs
- Observational cohort
Use of RWD in RCTs

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

– How will RWD be captured in these settings?
  • Impact on lags in data capture

– Blinding/Masking?

– Bridging between regulatory endpoints and clinical practice

– Site inspections and monitoring
Adopting “Pragmatism” into Regulatory RCTs

• The issue is reliability – persuasiveness – of the results, not trial methodology

• Randomization supports strong causal inference

• Blinding supports strong causal inference vs unblinded

• Appropriate enrollment criteria assures patients have the target condition (that the study objective is aimed to address)

• A well-constructed endpoint means that the study can determine if the purported effect of the drug is observed, and that effect is meaningful to patients

• Reliable data, that accurately collects the patient experience, and is accurately transferred into the analysis datasets supports reliable conclusions

• Adequate monitoring means complete collection of important, relevant efficacy and safety endpoints
<table>
<thead>
<tr>
<th>Type of endpoint</th>
<th>Studies %</th>
<th>Examples of endpoints measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>21%</td>
<td>HBA1c, pregnancy test, GFR</td>
</tr>
<tr>
<td>Hematology</td>
<td>4%</td>
<td>Severe neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apheresis yield &gt; 5 million CD34+ cells/kg</td>
</tr>
<tr>
<td>Pathology</td>
<td>1%</td>
<td>Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells</td>
</tr>
<tr>
<td>Microbiology</td>
<td>9%</td>
<td>Sustained virological response, plasma viral load, conversion to negative sputum</td>
</tr>
<tr>
<td>Imaging +/- (survival, clinical signs)</td>
<td>10%</td>
<td>Bone mineral density; vertebral fractures, spleen volume, progression free survival</td>
</tr>
<tr>
<td>Physiological/ functional measurement</td>
<td>10%</td>
<td>6 minute walk, normal sinus rhythm, FEV1, sleep studies</td>
</tr>
<tr>
<td>Clinical event /clinical sign</td>
<td>13%</td>
<td>Death, hospitalization, MACE, MS relapse, Lice free head</td>
</tr>
<tr>
<td>CRO/PRO</td>
<td>31%</td>
<td>Toronto western spasmodyc torticollis rating scale, Hamilton depression rating scale, Rheumatology scale, ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score</td>
</tr>
</tbody>
</table>
Real World Data

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

• 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

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

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

Feasibility of transforming structured-based EHR data to FDA submission standards
Minimal Clinical Oncology Data Elements

Data standards to improve the quality and usability of EHR data

Courtesy of ASCO/MITRE
Common EHR Data Structure

mCODE™

Minimal Clinical Oncology Data Elements
Data standards to improve the quality and usability of EHR data

Collection of clinical trials data using the EHR

Courtesy of ASCO/MITRE
ICARE: Develop and validate mCODE-based outcome measures embedded in the EHR

**Disease Status**

**Clinical Assessment**
Based on the data available today (at the time of evaluation), categorize the patient's disease extent.

**Question Format**

<table>
<thead>
<tr>
<th>Cancer disease status</th>
<th>Status evaluated</th>
<th>Status value</th>
<th>Reason value</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary tumor</td>
<td>complete response</td>
<td>imaging</td>
<td>no</td>
</tr>
<tr>
<td>metastatic lesion</td>
<td>partial response</td>
<td>pathology</td>
<td>Yes-disease not responding</td>
</tr>
<tr>
<td></td>
<td>stable disease</td>
<td>symptoms</td>
<td>Yes-due to AE/toxicity</td>
</tr>
<tr>
<td></td>
<td>progressive</td>
<td>physical exam</td>
<td>Yes-pre-planned therapy transition</td>
</tr>
<tr>
<td></td>
<td>disease</td>
<td>markers</td>
<td>Yes-patient request</td>
</tr>
<tr>
<td></td>
<td>not evaluated</td>
<td></td>
<td>Yes-due to other</td>
</tr>
</tbody>
</table>

**Treatment change**

**Clinical Assessment**
Based on your evaluation today, are you making a change in treatment?

**Question Format**

- No
- Yes-disease not responding
- Yes-due to AE/toxicity
- Yes-pre-planned therapy transition
- Yes-patient request
- Yes-due to other
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
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 therapies 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.

Because of the FDA’s focus on real-world evidence, drug and device organizations are increasingly looking to incorporate patient-generated data into regulatory submissions for new products and treatment indications. But until recently, there haven’t been mobile technologies or methodologies to help collect, store and submit this kind of data in a regulatory-compliant manner. In order to address this gap, the FDA developed MyStudies.
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
Adopting “Pragmatism” into Regulatory RCTs

• The issue is **reliability – persuasiveness** – of the results, not trial methodology

• **Randomization** supports strong causal inference

• **Blinding** supports strong causal inference vs unblinded

• **Appropriate enrollment criteria** assures patients have the target condition (that the study objective is aimed to address)

• A **well-constructed endpoint** means that the study can determine if the purported effect of the drug is observed, and that effect is meaningful to patients

• **Reliable data**, that accurately collects the patient experience, and is accurately transferred into the analysis datasets supports **reliable conclusions**

• Adequate monitoring means complete collection of important, relevant efficacy and safety endpoints
IMplementation of a randomized controlled trial to imProve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation

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

Enrollment of approximately 80,000 individuals in the early and late intervention arms
- Atrial fibrillation /CHADS –VASc ≥2
- No oral anticoagulant
- No contraindications

Endpoint – initiation of oral anticoagulation
- Stroke, hospitalization, bleeding

ClinicalTrials.gov Identifier: NCT03258373

• 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

• Population
  – Clinician considering treatment intent to intensify therapy with roflumilast or azithromycin
  – > 40 years with severe COPD or associated chronic bronchitis
  – Current or past smoker – 10 pack/ years
  – Hospitalized with COPD exacerbation in past 12 months
  – Current medications include long acting – muscarinic antagonist, beta agonist or inhaled corticosteroid
  – No contraindications to the medications

• Primary outcomes
  – All cause hospitalization
  – All cause mortality

• Follow-up
  – 6-36 months, no visits, call center, Patient Portal, Site EMR
  – CMS linkage through FDA-Catalyst for outcomes and exposures
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It may be appropriate to use a selective approach to safety data collection for common, non-serious adverse events that have already been well-characterized through data collection in earlier stages.

Excessive safety data collection may:
1. Discourage the conduct of these types of trials by increasing the resources needed to perform them and
2. Be a disincentive to investigator and patient participation in clinical trials.

Selective safety data collection may:
1. Facilitate the conduct of larger trials without compromising the integrity and the validity of trial results or losing important information
2. Facilitate investigators’ and patients’ participation in clinical trials, and
3. Help contain costs by making more-efficient use of clinical trial resources.
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- Pragmatic clinical trial of 9300 patients over 4 influenza season to compare the effectiveness of an annual vaccination strategy of high-dose trivalent versus standard-dose quadrivalent influenza vaccine in patients with a history of recent heart failure or myocardial infarction hospitalization

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• Masking: to minimize cross-over related to perceived benefit of one vaccine formulation over another, participants, site investigators, study personnel, persons performing follow-up surveillance, and study statisticians will remain masked to the identity of the treatment from the time of randomization until database lock
Prospective, Randomized, Active-controlled, Open-label, Flexible Dose Study of Paliperidone Palmitate Compared With Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults With Schizophrenia Who Have Been Incarcerated (PRIDE) NCT01157351

- The PRIDE study design had both explanatory and pragmatic features
  - Explanatory analysis to demonstrate that treatment with Paliperidone palmitate (PP) significantly delayed treatment failure versus daily oral antipsychotics
  - Pragmatic features:
    - Population with history of incarceration, flexible treatment management
    - Pragmatic analysis included all data related to treatment failures from randomization until the end of the 15-month period regard-less of whether subjects were maintained on their initial randomized treatment
  - Treatment failures: composite measure any of the following events:
    - arrest or incarceration
    - psychiatric hospitalization
    - suicide; discontinuation of treatment due to inadequate efficacy, safety, or tolerability;
    - treatment supplementation with another antipsychotic due to inadequate efficacy;
    - increase in psychiatric services to prevent imminent psychiatric hospitalization.
The primary study end point was time to first treatment failure, as determined by an independent event-monitoring board that was blinded to individual subject treatment assignment.

All treatment failures used for the pragmatic analysis were identified and reported by investigators who were not blinded to their study medication.

There was little difference in timing or number of events when determined by these blinded raters.
COVID-19

• 15,000 Health Care workers
• Randomized, blinded
• Primary Endpoint
  • To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in healthcare workers (HCWs)
• Secondary Endpoint
  • Efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs
• Safety and tolerability of HCQ
• Under an FDA IND

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Courtesy of Adrian Hernandez
Clinical Practice vs Clinical Trials

Retrospective claims data comparing new users of glucagon-like peptide 1 receptor agonist (GLP-1 RA) or a dipeptidyl peptidase 4 (DPP-4) inhibitor, to quantify the gap between real-world (i.e., usual c...
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- How do we create a **research infrastructure** that can provide reliable, persuasive results?
- **Randomization methods** adapted to investigational sites
- **If blinding needed** – adapted to practices, such as central dispensing to patients
- **Simpler monitoring** – focused on endpoints that matter, but collected reliably
- **Endpoints utilizing digital tools**, in-home collection
- **Decentralized** sites
- **Enrollment criteria that are broad** but define properly the patient population
  - The issue isn’t the enrollment criteria – it’s doing studies in sites that bring in patients across a broader spectrum
Acknowledgements

- Peter Stein
- David Martin
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- Khair ElZarrad
- Juanita Marner