FDA Real-World Evidence Program

Liver Forum

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Disclaimer

• The views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration

• No conflicts of interest exist related to this presentation
21st Century Cures Act (2016)

- FDA shall establish a program to evaluate the potential use of real-world evidence (RWE) to:
  - Support new indication for a drug approved under section 505(c)
  - Satisfy post-approval study requirements
- Draft framework to be issued by December 2018:
  - Describe sources of RWE, challenges, pilot opportunities, etc.
- Draft guidance for industry to be issued by December 2021
- Standard for substantial evidence remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA)
• Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)

• Multifaceted program to implement RWE:
  - internal processes
  - external stakeholder engagement
  - guidance development
  - demonstration projects
‘Real-World’ Definitions (from FDA’s 2018 Framework)

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

- electronic health records (EHRs)
- medical claims data
- product and disease registries
- patient-generated data, including from in-home settings
- other sources that can inform on health status, such as “wearable” devices

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

Generated using different study designs, including but not limited to randomized trials (e.g., large simple trials, pragmatic trials), externally controlled trials, or observational studies.
FDA Approach to Evaluating RWE

Key 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
In the current era of RWE, the FDA is evaluating whether and how observational studies intended to evaluate efficacy can contribute persuasive results from scientific and regulatory perspectives. In this context, a “randomized trial versus observational study” dichotomy is overly simplistic as short hand for strength of study design to support causal inference. Clarity is needed regarding interventional or noninterventional design, primary collection or secondary use of data, and characteristics of comparison group(s), as well as an assessment of prognostic determinism for the corresponding cause-effect association.

*Pharmacoepidemiol Drug Saf.* 2020;29:1514–1517
Overview of Real-World Data and Study Design

Randomized/interventional

Traditional randomized trial, using elements of RWD
- RWD to assess enrollment criteria & trial feasibility
- RWD to support site selection

Trials in clinical practice settings (with pragmatic elements)
- Selected outcomes identified using EHR/claims data, etc.
- Mobile technology used to capture supportive endpoints
- RCT using electronic case report forms or EHR or claims data (or combination)

Non-randomized/non-interventional

Non-randomized/interventional

Observational studies
- Single-arm study with external control arm
- Observational cohort study
- Case-control study

Increasing reliance on RWD

Selected outcomes identified using EHR/claims data, etc.
Individual Drug Queries

*FDA queries and studies conducted in the Sentinel System from the start of Mini-Sentinel in 2009 to present

<table>
<thead>
<tr>
<th>Title</th>
<th>Medical Product</th>
<th>Outcomes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence Rate of Severe Uterine Bleeding Among New Users of Oral Anticoagulants: A Descriptive Analysis Exploratory Analyses</td>
<td>apixaban, dabigatran, oral anticoagulant, rivaroxaban, warfarin</td>
<td>severe uterine bleed</td>
<td>05/18/2021</td>
</tr>
<tr>
<td>Angioedema following Sacubitril/Valsartan Use in Patients with Heart Failure: A Propensity Score Analysis Safety Analyses</td>
<td>sacubitril/valsartan</td>
<td>angioedema</td>
<td>04/21/2021</td>
</tr>
</tbody>
</table>

Example of Demonstration Project to Improve RWD

‘ICAREdata’: Develop and validate EHR-based measures in oncology

**Cancer disease status**

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

**ICAREdata Question Format**

<table>
<thead>
<tr>
<th>Cancer disease status</th>
<th>&lt;lesion evaluated&gt;</th>
<th>&lt;status value&gt;</th>
<th>&lt;reason value&gt;</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</td>
</tr>
<tr>
<td>stable disease</td>
<td>stable disease</td>
<td>symptoms</td>
<td>disease not responding</td>
</tr>
<tr>
<td>progressive disease</td>
<td>not evaluated</td>
<td>physical exam</td>
<td>due to AE/toxicity</td>
</tr>
<tr>
<td>not evaluated</td>
<td></td>
<td>markers</td>
<td>yes-pre-planned therapy transition</td>
</tr>
</tbody>
</table>

**Example of Resulting Structured Phrase**

#Cancer disease status observed for #primary tumor was #progressive disease based on #imaging and #symptoms*

**Treatment change**

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

**ICAREdata Question Format**

<table>
<thead>
<tr>
<th>Treatment change</th>
<th>&lt;treatment change?&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>disease not responding</td>
</tr>
<tr>
<td>Yes</td>
<td>due to AE/toxicity</td>
</tr>
<tr>
<td>Yes</td>
<td>pre-planned therapy transition</td>
</tr>
<tr>
<td>Yes</td>
<td>patient request</td>
</tr>
<tr>
<td>Yes</td>
<td>due to other</td>
</tr>
</tbody>
</table>

**Example of Resulting Structured Phrase**

#Treatment change and #yes-disease not responding*

* Blue font denotes controlled vocabularies
New RWE Development Projects

Funding Opportunity Title: Exploring the use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making (U01) Clinical Trials Optional

**RFA-FD-20-030** (N=31 applications received; n=4 applications funded)

<table>
<thead>
<tr>
<th>Number</th>
<th>Applicant</th>
<th>Project Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 U01FD007213-01</td>
<td>Brigham and Women’s Hospital</td>
<td>Enhancing evidence generation by linking RCTs to RWD</td>
</tr>
<tr>
<td>1 U01FD007206-01</td>
<td>Genentech-UNC</td>
<td>Applying novel statistical approaches to develop a decision framework for hybrid RCT designs, combining internal control arms with data from RWD sources</td>
</tr>
<tr>
<td>1 U01FD007172-01</td>
<td>Verantos, Inc.</td>
<td>Transforming RWE with Unstructured and Structured data to advance Tailored therapy (TRUST)</td>
</tr>
<tr>
<td>1 U01FD007220-01</td>
<td>Critical Path Institute</td>
<td>Advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project</td>
</tr>
<tr>
<td>DRUG</td>
<td>INDICATION</td>
<td>APPROVED</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Carbaglu</strong>&lt;br&gt;(carglumic acid)</td>
<td>Treatment of NAGS deficiency</td>
<td>2010</td>
</tr>
<tr>
<td><strong>Voraxaze</strong>&lt;br&gt;(glucarpidase)</td>
<td>Treatment of MTX toxicity</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Blincyto</strong>&lt;br&gt;(Blinatumomab)</td>
<td>Treatment of Acute Lymphoblastic Leukemia</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Vistogard</strong>&lt;br&gt;(uridine triacetate)</td>
<td>Overdose of chemotherapy drugs 5-fluorouracil (5-FU)</td>
<td>2015</td>
</tr>
</tbody>
</table>

List not exhaustive  

**Bold = RWE**
<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATION</th>
<th>APPROVED</th>
<th>DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defitelio (defibrotide sodium)</td>
<td>Severe hepatic veno-occlusive disorder</td>
<td>2016</td>
<td>Two prospective clinical trials enrolling 179 patients and an expanded access study with 351 patients</td>
</tr>
<tr>
<td>Lutathera (lutetium 177 dotate)</td>
<td>Gastroenteropancreatic neuroendocrine tumours (GEP-NETs)</td>
<td>2017</td>
<td>Open-label clinical trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Analysis of a subset of 360 patients who participated in an investigator sponsored, open-label, single-arm, single institution study of 1214 patients that started as an expanded access program</td>
</tr>
<tr>
<td>Zostavax (Zoster Vaccine Live)</td>
<td>Prevention of herpes zoster (shingles) in persons 50 years of age and older</td>
<td>2018</td>
<td>Prospective, observational cohort study using electronic health records in Kaiser Permanente Northern California (KPNC) to characterize the duration of protection in persons 50 years of age and older</td>
</tr>
<tr>
<td>Ibrance (palbociclib)</td>
<td>Men with certain types of advanced or metastatic breast cancer</td>
<td>2019</td>
<td>Data from electronic health records and postmarketing reports of the real-world use of IBRANCE in male patients</td>
</tr>
</tbody>
</table>

List not exhaustive

**Bold** = RWE
Prograf (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart), based on RCT evidence

RCTs not done for lung transplant, but drug is used widely in clinical care; sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA

Study data and design were evaluated according to FDA standards

Approval for preventing rejection/death in lung transplant granted 16 Jul 2021
Data: US Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US during 1999–2017

Design: non-interventional (observational) treatment arm, compared to historical controls

Review: FDA determined this non-interventional study w/ historical controls to be adequate and well-controlled. Of note, outcomes of organ rejection and death are virtually certain without therapy, and the dramatic effect of treatment helps to preclude bias as explanation of results.