Real-World Evidence: US Regulatory Landscape

PhUSE SDE
April 9th, 2020

Rebecca Lipsitz, PhD
Director, Global Regulatory Policy & Intelligence
Global Regulatory Affairs

janssen
PHARMACEUTICAL COMPANIES
OF Johnson & Johnson

Global Regulatory Affairs

Legislative and Regulatory Mandates in RWE

Definitions:

From the FDA RWE Framework:

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

Real-World Evidence (RWE): *Clinical* evidence about the usage and potential benefits or risks of a medical product derived form analysis of RWD.

RWE Started with HITECH:

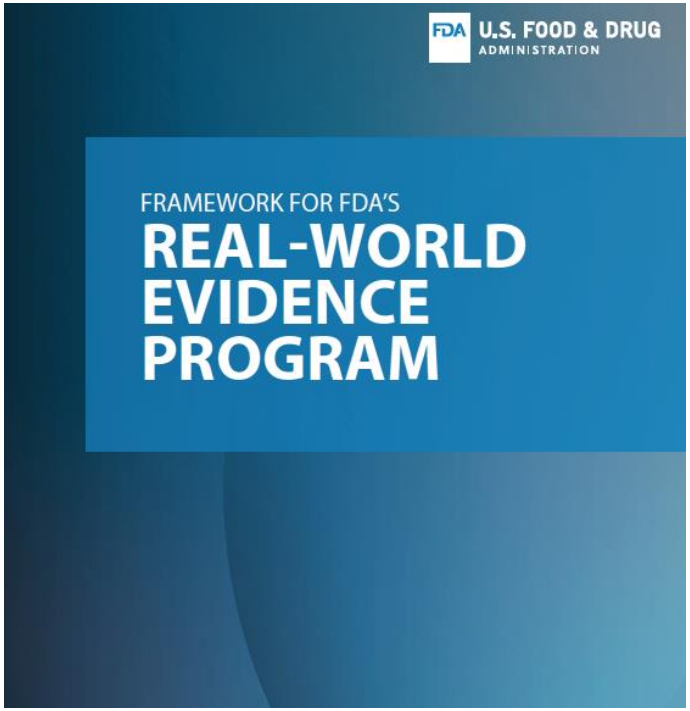
- 2009: President Obama signed legislation that included the Health Information Technology for Economic and Clinical Health (HITECH) Act.
  - This was part of the economic stimulus package to address the 2008 financial crisis
- HITECH: $35 billion in incentives to promote and expand the use of Electronic Health Records (EHRs) by hospitals and health care professionals.
- HITECH spurred a significant growth in the availability of electronic health data or "Real-World Data"

RWE PDUFA VI and 21st Century Cures Deliverables

PUDFA VI		21st Century Cures	
Activity	**Due Date**	**Activity**	**Due Date**
• One or more **public workshop(s)** with key stakeholders to gather input into issues related to RWE use in regulatory decision-making	By the end of FY 2018 (Sept 2018)	• Establish a draft **implementation framework** • Identify potential **pilot opportunities**	By Dec 2018
• **Pilot study** or methodology development to address key outstanding concerns and considerations in the use of RWE for regulatory decision-making	By the end of FY 2019 (Sept 2019)	• **Implement a program** to evaluate the potential use of real world evidence	By Dec 2018
• Issue **draft guidance**	By the end of FY 2021 (Sept 2021)	• Issue **draft guidance**	By Dec 2021

FDA RWE Framework

December, 2018 (link)



Focus Areas:

- Sources of Real-World Evidence
- Gaps in data collection activities
- Standards and methodologies for collection and analyses of Real-World Evidence
- Priority areas, remaining challenges, and potential pilot opportunities

FDA's RWE Program

- Multifaceted
  - Demonstration projects
  - Stakeholder engagement
  - Internal processes to bring senior leadership input into the evaluation of RWE and promote shared learning and consistency in applying the framework

RWD/RWE for Effectiveness Decisions

- FDA's RWE's Program will look at potential uses of RWE to support label changes about effectiveness, e.g., change in dose, dose regimen, route of administration, adding a new population, adding comparative effectiveness or safety information.

- The following criteria will be used to evaluate supplemental indications:

  1. Whether the RWE are **fit for use**
  2. Whether the trial or study design used to generate RWE can provide **adequate scientific evidence** to answer or help answer the regulator question
  3. Whether the study conduct meets FDA **regulatory requirements**, e.g., study monitoring and data collection

FDA RWE Framework Action Items

1. Issue guidance on how to assess the reliability and relevance of RWD from medical claims and EHRs used to generate RWE regarding drug product effectiveness; examine how to assess the reliability and relevance of registry data and international electronic health care data
2. Review and, where applicable, publish guidance on potential gaps in RWD sources and strategies to address them
3. Develop guidance on considerations for designing clinical trials that include pragmatic design elements and that generate evidence of effectiveness for regulatory decisions; explore pragmatic approaches to each stage of a clinical trial, including recruitment and enrollment of patients, strategies for facilitating interventions, and approaches to assessing outcomes
4. Consider issuing guidance on the use of RWD to generate external control arms
5. Issue guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision-making; consider reporting requirements for such studies used to support effectiveness determinations

FDA RWE Framework Action Items

6. Consider whether existing guidance documents on use of electronic data in clinical investigations adequately address concerns relevant to different study designs using RWD to generate RWE for drug product effectiveness determinations and whether additional guidance on use of electronic source data is needed

7. Finalize the guidance, "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR part 11 – Questions and Answers," and consider its applicability to different study designs; issue additional guidance as needed on regulatory considerations raised by different study designs using RWD to generate RWE submitted to support drug product effectiveness

RWE Tools and Pilot Projects

FDA MyStudies App Overview

- A patient-centered app-based electronic method suitable for capturing the patient perspective and linking it to existing electronic health data that is scalable, secure, configurable, reusable, *compliant with clinical research and regulatory needs*, and capable of supporting defined research cohorts
  - Necessary to expand the capacity of comparative effectiveness and drug safety research

- The app is specifically designed to collect patient reported data in a clinical study and store them in a central location. It does not interact directly with an EHR system, but it can be linked.

- The data storage environment is secure and supports auditing necessary for compliance with 21 CFR Part 11 and the Federal Information Security Management Act, so it can be used for trials under IND oversight.

Purpose of MyStudies App

- Direct patient input
- Can capture outcomes that may not be in EHR and claims
  - Medication adherence, non-medically attended outcomes, illicit drug use, tobacco use, supplement use, socio-economic indicators, OTC use, other information
  - Functional status scales
- Expand capacity of comparative effectiveness and drug safety research
- Supports
  - Traditional clinical trials
  - Pragmatic trials
  - Observational studies
  - Registries

Project DUPLICATE: RCT Replication with RWE

Collaboration with FDA, Aetion, & Harvard Brigham and Women's Hospital)

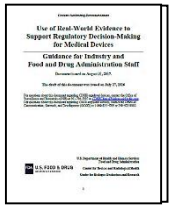
- Two 'flavors'
  - Post-replication: replicating the finding of a completed RCT using RWD sources
    - Replicate 30 completed studies (cardiovascular, endocrinology, musculoskeletal, and pulmonary)
    - 23 FDA approvals, 7 not-approved by FDA
  - Pre-replication: replicating a RCT that started, before the RCT findings are known.
    - Pre-Replicate the results of seven ongoing Phase IV trials
- Learning objectives:
  - Which methods perform better in real data and real clinical questions
  - Which questions can be answered with nonrandomized RWE

Project DUPLICATE: RCT Replication with RWE, cont'd

- Potential issues:
  - Efficacy vs. effectiveness. What constitutes agreement?
  - How does the role of real-world adherence impact effectiveness findings?
- Disease focus areas:
  - Diabetes, antiplatelets, novel oral anticoagulants, antihypertensives, anti -osteoporosis medications, asthma, COPD, heart failure, statins,

External RWE Regulatory Activities

Key Issues, Topics of Workshops, :



- Data quality: when is RWD 'fit for purpose'?
- Sources of bias and confounding, analytic methods to reduce them
- Use of RWE synthetic control arms
- RWE Endpoints – validation, defining key parameters
- Transparency, data drudging, reporting studies, enhancing reproducibility
- Data Standards
- Demonstration that RWE can help fulfill the substantial evidence requirements for causal inference
- Demonstration projects, e.g., replicating RCTs with RWE (Project DUPLICATE)

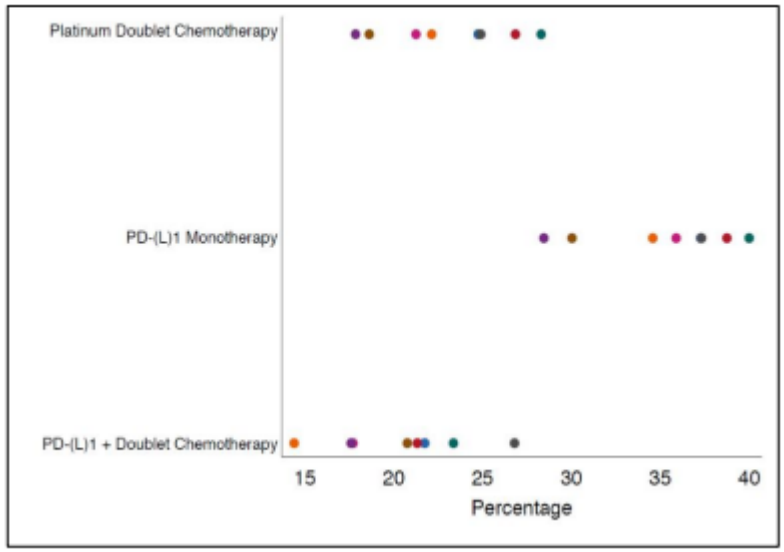
Friends of Cancer Research: Validating Real-World Endpoints for an Evolving Regulatory Landscape, Endpoints in NSCLC (link)

- First effort in 2018 (4 data partners): 'tell what your results looks like for rwOS'. But, each partner used their own definition of rwOS and the other endpoints, and definitions therein.
- 2019: 6 new data partners, 10 in total. Focus on aligning key definitions, e.g., treatment regimen duration that impact endpoint determinations.
- The data collection was retrospective, 2011 – 2018. (Challenge = Rapidly changing nature of first line care and the lack of long-term follow up for the latter enrolled patients)
- Results stratified according to 3 types of treatment
  - Platinum Doublet Chemotherapy
  - PD-(L)1 Monotherapy
  - PL-(L)1 + Doublet Chemotherapy
- Results shown in 2019 were "in progress".

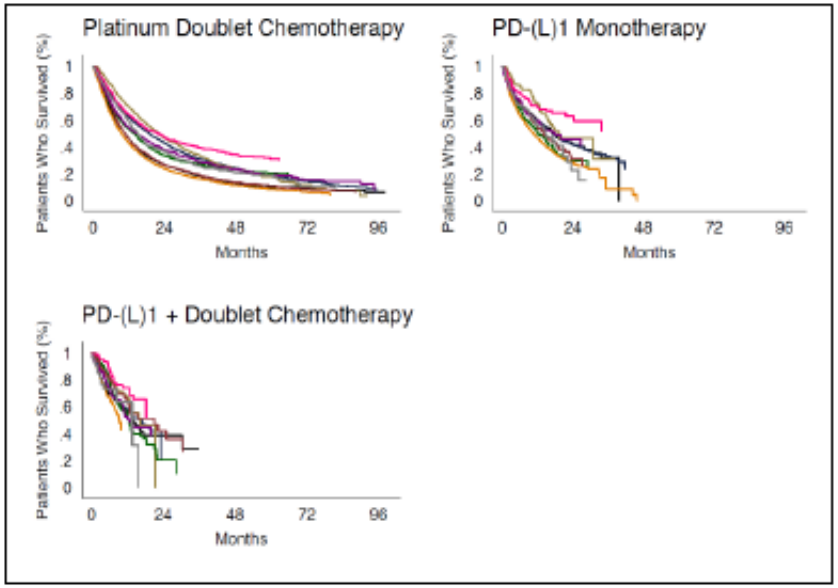
Friends of Cancer Research: Validating Real-World Endpoints for an Evolving Regulatory Landscape, Endpoints in NSCLC:

Examples of Demographic Results and RWE Endpoint Results

Graph 2. Percentage of aNSCLC Patients Age 75 or Older at Index



Graph 14. Kaplan-Meier Curve of rwOS by Treatment Category



Reference (link)

FDA Takeaways from Recent Meetings:

- Duke-Margolis, Generating RWE in Clinical Trials, July 11-12th, 2019
- AACR-FDA RWE Policy Meeting, July 19th, 2019
- **RANDOMIZATION:** 'Our chief concern is the believability of the result. Blinding and randomization aid believability' (Peter Stein, CDER, Director, Office of New Drugs)
  - Randomization is really key. it balances for things that are unknown.
  - FDA still requires adequate and well-controlled studies. Blinding and randomization are important aspects.
- **HISTORICAL CONTROLS**: "reserved for special circumstances". May not be possible to control for bias in external controls. Should be used in very limited circumstances.
- **RW ENDPOINTS**: Subjective endpoints are a concern. Endpoints like walk tests can be influenced by motivation. These effects are transient.
- **GENERALIZABILITY**: The idea that traditional trials aren't generalizable, don't give you the right answer is wrong. Biggest issue in the real-world is adherence.

BACKGROUND

Intent of the FDA RWE Framework (specified in 21CC language):

- the sources of real world evidence, including ongoing safety surveillance, observational studies, registries, claims, and patient6 centered outcomes research activities;
- the gaps in data collection activities
- the standards and methodologies for collection and analysis of real world evidence
- the priority areas, remaining challenges, and potential pilot opportunities that the program established under this section will address