Clinical Research Forum IT Roundtable: FDA REAL-WORLD EVIDENCE PROGRAM

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OBJECTIVES

Objectives

- review FDA initiatives involving “real-world evidence” (RWE)
- highlight challenges of determining whether “real-world data” (RWD) are fit for use
- discuss ongoing and emerging activities involving RWD/RWE

Disclaimers

- no conflict of interest; no endorsement of products, institutions, companies
- views and perspectives are those of the presenter and should not be attributed to the FDA
‘REAL-WORLD EVIDENCE’

Public Law 114–255
114th Congress

An Act
To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes. Dec. 13, 2016

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the “21st Century Cures Act”.
(b) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

[...]

Sec. 3022. Real world evidence.

DEFINITIONS

Public Law 114-255: Real-world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized controlled trials

FDA:

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.

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.
**WHY THE INTEREST IN RWD/RWE?**

- *Everything old is new again*: fit-for-purpose data are always crucial, and observational study designs existed before emergence of RWE, *but*...
  - era of “big data” offers potential for detection of infrequent events, including long-term yet infrequent outcomes
  - additional settings provide access to more diverse populations
  - broader populations address effectiveness as well as efficacy
  - lower resource intensity = more questions answered for same investment
  - opportunity to narrow the divide between research and clinical care via digitization of health care

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**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)
  - satisfying post-approval study requirements

- Requirement to “establish a draft **framework**” within two years (by Dec 2018)

- Requirement to “issue draft **guidance for industry**” within five years (by Dec 2021)
FDA REAL-WORLD EVIDENCE: FRAMEWORK

- Published Dec 2018; applies to Center for Drug Evaluation & Research (CDER) and Center for Biologics Eval & Rsch (CBER)
- Comment period closed in April 2019; feedback informing ongoing efforts
- Multifaceted program to implement RWE:
  - Internal processes
  - Stakeholder engagement
  - Demonstration projects
  - Guidance development

https://www.fda.gov/media/120060/download

RWD/RWE: DEC 2018 FRAMEWORK

Considerations:

- Whether the real-world data 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
REAL-WORLD DATA: FITNESS FOR USE

- FDA does not endorse any one type of RWD
- A single source of RWD may not capture all data elements, and multiple data sources may be needed to address a given research question
- Consider data reliability (data accrual/data quality control) and relevance
  - Reliability: data must be collected and maintained in a way that provides an appropriate level of accuracy, consistency, and completeness
  - Relevance: data must be suitable to address specific regulatory question of interest
- Other considerations (e.g., data standards, digital health tools, interoperability)

SPECTRUM OF RWD/RWE DESIGNS

<table>
<thead>
<tr>
<th>Traditional Randomized Trial, Using RWD Elements</th>
<th>Trials in Clinical Practice Settings</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RWD to assess enrollment criteria &amp; trial feasibility</td>
<td>eCRF + selected outcomes identified using EHR/claims data</td>
<td>RCT using eCRF (+/- EHR data)</td>
</tr>
<tr>
<td>RWD to support site selection</td>
<td>Mobile technology used to capture supportive endpoints (e.g., to assess ambulation)</td>
<td>RCT using claims and EHR–pragmatic design</td>
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<td></td>
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<td>Single arm study using external control</td>
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</tbody>
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Increasing reliance on RWD
REGULATORY BENCHMARK

- Code of Federal Regulations – Sec. 314.126 “adequate and well-controlled studies”
  - Goal is to distinguish the effect of the drug from other influences, such as spontaneous change in disease course, placebo effect, or biased observation

- Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is “substantial evidence” to support the claims of effectiveness for new drugs

- Established practices, using traditional randomized controlled trials, include probabilistic control of confounding through randomization, blinding, standardized outcome assessment, adjudication criteria, and audits of study data

- “Observational” methods are currently being evaluated

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INTERNAL PROCESSES; STAKEHOLDER ENGAGEMENT

• Real-World Evidence Subcommittee internal activities (membership includes FDA staff from multiple CDER and CBER Offices): provides oversight of policy development on RWE (e.g., guidances); offers resources and leadership (e.g., to review divisions); other activities

• RWE Subcommittee external activities: provides feedback on early-stage proposals from sponsors, vendors, other stakeholders

• Public meetings on RWE-related topics on RWE

• Small business & industry webinars; speaking engagements

CHALLENGES IN RWD/RWE

Selected demonstration projects:

• HARMONY-OUTCOMES ancillary study (see 2018 Framework, p. 35)
  - whether EHRs are suitable for trial recruitment, baseline assessment, and endpoint ascertainment [https://rethinkingclinicaltrials.org/news/grand-rounds-7-14-17/]

• IMPACT-Afib study [https://clinicaltrials.gov/ct2/show/NCT03259373]
  - proof of concept for conducting randomized trials using FDA Sentinel infrastructure involving distributed database and common data model (17 data partners; >300M unique patient IDs; >70M pts accruing data)

• RCT DUPLICATE [https://www.rctduplicate.org/]
  - longitudinal insurance claims data used in observational cohort analyses to emulate randomized controlled trials on the same topic; n= 30 trials
**DEMONSTRATION PROJECTS: RCT DUPLICATE**

- Structured assessment of non-randomized analyses compared to randomized trial of same drug-outcome association
  - study design = observational (retrospective cohort); use similar inclusion/exclusion criteria
  - source of data = claims
  - comparable results with similar clinical questions?
  - reasons for differences?
- Goal: approximately 30 retrospective trial analyses to be completed by Spring 2020

**RWD/RWE: NEED FOR TRANSPARENCY**

- Transparency about study design and analysis, before execution, is critical for ensuring confidence in results

*Figure 1 – Recommendations for good procedural practices*

1. A priori, determine and declare that a study is a hypothesis
   Evaluation Treatment Effectiveness (HETE) study or an Exploratory study based on conditions outlined below
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/or deviation from the study protocol and original analysis plan. Possible publication sites include a medical journal, or a publicly available web-site.
4. Enable opportunities to replicate HETE studies (i.e., for other researchers to be able to reproduce the same findings using the same data set and analytic approach). The ISPE companion paper lists information that should be reported in order to make the operational and design decisions behind a RWD study transparent enough for other researchers to reproduce the conduct of the study.
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested unless it is not feasible (e.g., another data set is not available)
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, manufacturers) in designing, conducting, and disseminating HETE studies.
EXISTING GUIDANCE DOCUMENTS

- Assess gaps in current guidance documents on use of electronic source data
- Develop new guidance documents, as needed, for ‘RWD’

RWE: GUIDANCE DEVELOPMENT

- Real-world evidence topics (from 2018 RWE Framework)
  - Using Trials or Studies with RWD/RWE for Effectiveness Decisions
  - Assessing Fitness of RWD for Use in Regulatory Decisions
  - Potential for Study Designs Using RWD to Support Effectiveness
  - Regulatory Considerations for Study Designs Using RWD
  - Data Standards — Appropriate Data Standards for Integration and Submission to FDA

- Work ongoing to develop specific draft guidance documents by end-2021
EMERGENCE OF RWE: DATA FROM EHR

• **Advantages:**
  – Capture more complete (“granular”) clinical picture vs. claims data
  – Include labs/imaging/pathology reports

• **Challenges:**
  – Data in pathology/radiology/clinical notes often unstructured (≈80%)
  – Typed note ≠ consistency or complete documentation
  – Clinical outcome measures suitable for drug approvals may not be used or recorded consistently in practice
  – Interoperability issues

ONGOING & EMERGING RWD/RWE

Representative (non-mutually exclusive) topics and examples:

• Specific initiatives using existing data sources
• New digital health technologies
• Applications of artificial intelligence
• Changes to data sources themselves
‘INFORMATICS CONSULT SERVICE’ (STANFORD)

PERSPECTIVE  OPEN
It is time to learn from patients like mine
Saurabh Gombar1,2, Alison Callahan2, Robert Califf3, Robert Harrington2 and Nigam H. Shah2

- Examine medical records of similar patients to help select among treatment options
- Create cohorts of similar patients, & provide analytic tools, at bedside
- Supported by informatics-trained physicians, EHR data specialists, data scientists

npj Digital Medicine (2019)2:16; https://doi.org/10.1038/s41746-019-0091-3

‘CHART ANNOTATION TOOL’ (VETERANS AFFAIRS)

“Big data” for research: natural language processing algorithm

‘CD2H’ (CTSA)

- "CD2H aims to advance translational research and accelerate informatics innovation through the development and sharing of platforms, best practices and standards to maximize data quality, usability and interoperability"

https://ctsa.ncats.nih.gov/cd2h/

‘PRECISION MED ANALYTICS PLATFORM’ (HOPKINS)

- "The Precision Medicine Analytics Platform (PMAP) is a way to get data sets from multiple sources" (https://pm.jh.edu/)
EVLING DIGITAL HEALTH TECHNOLOGY

FDA MYSTUDIES MOBILE APP

**Preventing Extension of Oligoarticular Juvenile Idiopathic Arthritis (Limit-JIA) – NCT03841357:**

- Use MyStudies app to support:
  - Collection of primary outcome (uveitis) from ophthalmology appointments, with appointment reminders
  - Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry
**ARTIFICIAL INTELLIGENCE – OVERVIEW**

# Papers w/ “Artificial Intelligence”

# Clinical Trials Incorporating AI

Data from March 2019

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**ARTIFICIAL INTELLIGENCE – ‘BENCH’**

**Advancing Drug Discovery via Artificial Intelligence**

H.C. Stephen Chan,1,2 Hanbin Shan,3 Thamani Dahoun,2,4 Horst Vogel,2,4 and Shuguang Yuan1,2,4,*

Drug discovery and development are among the most important translational science activities that contribute to human health and wellbeing. However, the development of a new drug is a very complex, expensive, and long process which typically costs 2.6 billion USD and takes 12 years on average. How to decrease the costs and speed up new drug discovery has become a challenging and urgent question in industry. Artificial intelligence (AI) combined with new experimental technologies is expected to make the hunt for new pharmaceuticals quicker, cheaper, and more effective. We discuss here emerging applications of AI to improve the drug discovery process.

_Highlights_

AI-based algorithms are also being developed to efficiently probe the pathways of synthesis of novel drug candidates.

In combination with robotic platforms, the chemical space for novel reactions can be explored by learning from automated analysis of reaction feasibility.

Trends in Pharmacological Sciences, August 2019, Vol. 40, No. 8  [https://doi.org/10.1016/j.tips.2019.06.004](https://doi.org/10.1016/j.tips.2019.06.004)
Clinical trials consume the latter half of the 10 to 15 year, 1.5–2.0 billion USD, development cycle for bringing a single new drug to market. Hence, a failed trial sinks not only the investment into the trial itself but also the preclinical development costs, rendering the loss per failed clinical trial at 800 million to 1.4 billion USD. Suboptimal patient cohort selection and recruiting techniques, paired with the inability to monitor patients effectively during trials, are two of the main causes for high trial failure rates: only one of 10 compounds entering a clinical trial reaches the market. We explain how recent advances in artificial intelligence (AI) can be used to reshape key steps of clinical trial design towards increasing trial success rates.

EHR DATA STRUCTURE

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
‘ICAREDATA’ FOR OUTCOME STATUS

ICAREdata: Develop and validate mCODE-based outcome measures

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

Sample Resulting Structured Phrase*

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

* Blue font denotes controlled vocabularies

Treatment change

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

ICAREdata Question Format

Sample Resulting Structured Phrase*

#Treatment change #yes-disease not responding

* Blue font denotes controlled vocabularies

‘ONESOURCE’ FOR MULTIUSE RECORDS

• 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

Courtesy of Dr. Laura Esserman and Susan Dubman
EVALUATION OF REAL-WORLD DATA

Considerations when evaluating submissions that include “real-world data”

• Multiple potential levels of inconsistency: data sources, internal standards, formats, vocabularies, etc.
  – Original sources: claims, EHRs, devices, lab output, etc.
    ▪ variability in how content is recorded and in application of data standards
  – Curated sources: public common data models (e.g., OMOP, PCORnet, etc), proprietary/private data curators
    ▪ variability in curation processes, data transformations, availability of data elements

• How detailed do record-level data need to be (including for audits)?
• What metadata are required to ensure trust in RWD?

EVALUATION OF RWD (cont’d)

• Current healthcare data landscape
  – What types of data are used commonly in research & submission?
  – What is the range of variability in data representation?
  – Can commonalities be identified?
  – Can emerging healthcare data standards serve as RWE submission standards?

• Current regulatory standards landscape
  – How do common data types (e.g., SDTM, ADaM) map to existing standards?
  – What level of effort is needed to fill identified gaps?

• Anticipation of future healthcare data landscape
  – Consideration of emerging technologies and industry trends
Challenges regarding interoperability:

- Are the remaining problems too difficult for standards to solve?
- How can remaining technical hurdles be addressed?
- What incentives can advance progress?

‘Classification, ontology, and precision medicine’

- [Intro:] “In this review, we describe ontologies and their use in computational reasoning to support precise classification of patients, patients for diagnosis, care management, and translational research.”
- Described as logical extension of the “learning health system”
OVERVIEW OF RWE LANDSCAPE

Data
- Relevance
- Quality
- Linkage

Tools
- Common data models
- Analytics
- Mobile technologies

Study Design
- Clinical trials
- Observational methods

DATA STANDARDS & IMPLEMENTATION

Identify and assess data standards and implementation strategies needed to use RWD/ RWE

Identify gaps between RWD/ RWE data standards and existing systems

Collaborate with stakeholders to adopt or develop data standards and implementations strategies

RWD Submission Standard
SUMMARY

Take-home points

- FDA has ongoing initiatives evaluating “real-world evidence” (RWE)
- numerous challenges exist in determining whether “real-world data” (RWD) are fit for use
- complexities of the current and evolving healthcare data landscape can be mapped to existing and to-be-developed regulatory standards

Questions?