aaps PharmSci 360
OCT 16-19 2022

Hot Topic

Emerging use of real-world data to address data gaps in clinical pharmacology: Opportunities and challenges

17 October 2022

Simon Dagenais, PhD MSc
Real World Evidence Center of Excellence
Pfizer, Inc.

Marc R. Gastonguay, PhD
Metrum Research Group

Abie Ekangaki, PhD
Premier Research

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- The views and opinions expressed in this presentation are those of the individual speaker(s) and do not necessarily represent the views and opinions of their employer(s)

Outline

- RWE in headlines
- RWE in scientific literature
- 21st Century Cures Act
- RWD vs RWE
- Types of RWD
- Data elements commonly available in RWD
- Study designs related to RWE
- Evidence standards with RWE
- FDA approvals based on RWE
- Examples / Case studies

Real world evidence seems to be everywhere recently

US FDA's Stein 'Excited' About Real-World Evidence, Rare Disease Endpoint Pilot Programs

14 Sep 2021 | ANALYSIS

Real-World Evidence Deemed Essential For Breakthrough Designations

30 Sep 2021 | NEWS

Tech

Industry Voices—COVID-19 vaccine rollout shows real-world evidence was ready for the spotlight

by Carolyn Magill, Aetion | Oct 5, 2021 3:30pm

Real-World Evidence Will Take Center Stage At US FDA Advisory Committee On COVID Boosters

15 Sep 2021 | NEWS

How 'Real World Evidence' is Revolutionizing Healthcare

Extracting untold insights with RWE can assist medical professionals evaluate the efficacy of a drug or medical invention. It's time to dig deeper.

Aug 11, 2021, 08:30am EDT | 1,083 views

Will Real-World Evidence Replace Clinical Trials?

Forbes

Morris Panner Forbes Councils Member
Forbes Technology Council COUNCIL POST | Membership (Fee-Based)
Innovation

RWE Alliance aims to boost policies and practices around real-world evidence

Five analytics companies – Aetion, Flatiron Health, IQVIA, Syapse and Tempus – are joining to advance use of data derived from EHRs, claims and other sources outside of clinical trials.

By Mike Miliard | May 20, 2021 | 03:50 PM

Real World Evidence Solutions Market worth $2.3 billion by 2026 - Exclusive Report by MarketsandMarkets™

MARKETSANDMARKETS™

NEWS PROVIDED BY
MarketsandMarkets™
Aug 05, 2021, 11:30 ET

SHARE THIS ARTICLE

Real-World Evidence (RWE) Solutions Market Worth $3.13 Billion by 2027- Market Size, Share, Forecasts, & Trends Analysis Report with COVID-19 Impact by Meticulous Research®

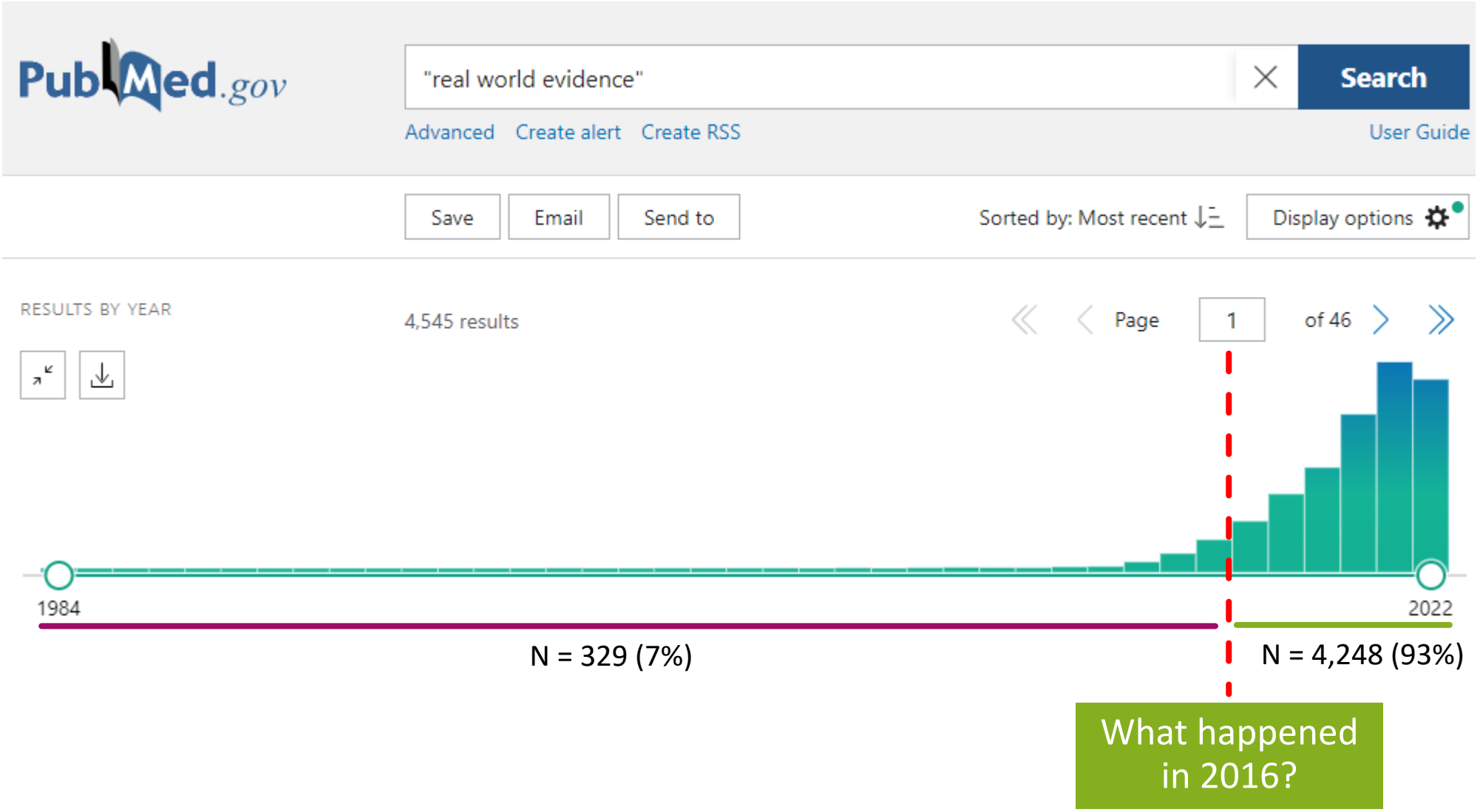
Meticulous Market Research Pvt. Ltd.
September 23, 2021 · 9 min read

The real world evidence (RWE) market is projected to be worth USD 4.5 billion by 2030, growing at a CAGR of 15%, claims Roots Analysis

Real World Evidence Solutions Market to Reach USD 5 Billion Globally by 2031 at 13.7% CAGR, Says Allied Market Research

by PRNewswire
September 12, 2022 7:30 PM | 7 min read

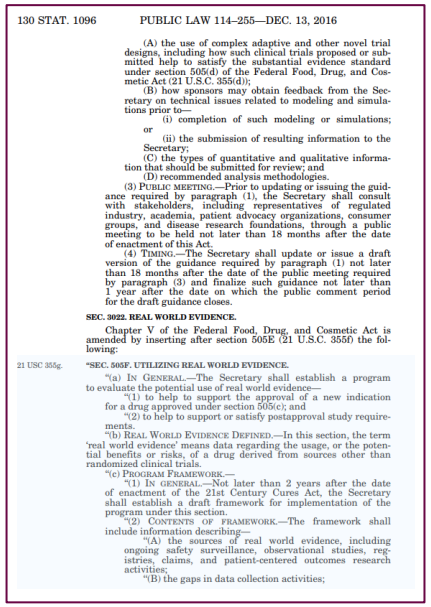
Volume of scientific literature related to RWE is booming



21st Century Cures Act

- Legislation passed on December 13, 2016
- Instructed FDA to evaluate use of RWE in drug approval process and:
  1. Develop framework for using RWE in drug approvals within 2 years
  2. Draft guidance on using RWE in drug approvals within 5 years
  3. Pursue RWE partnerships with industry, academia, professional organizations, etc.
- Act provided marching orders for FDA and prompted stakeholders to start preparing for future in which RWE is used in drug approvals

Full Act is 312 pages long



130 STAT. 1096 PUBLIC LAW 114–255—DEC. 13, 2016

(A) the use of complex adaptive and other novel trial designs, including how such clinical trials proposed or submitted help to satisfy the substantial evidence standard under section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d));
(B) how sponsors may obtain feedback from the Secretary on technical issues related to modeling and simulations prior to—
(i) completion of such modeling or simulations; or
(ii) the submission of resulting information to the Secretary;
(C) the types of quantitative and qualitative information that should be submitted for review; and
(D) recommended analysis methodologies.

(3) PUBLIC MEETING.—Prior to updating or issuing the guidance required by paragraph (1), the Secretary shall consult with stakeholders, including representatives of regulated industry, academia, patient advocacy organizations, consumer groups, and disease research foundations, through a public meeting to be held not later than 18 months after the date of enactment of this Act.

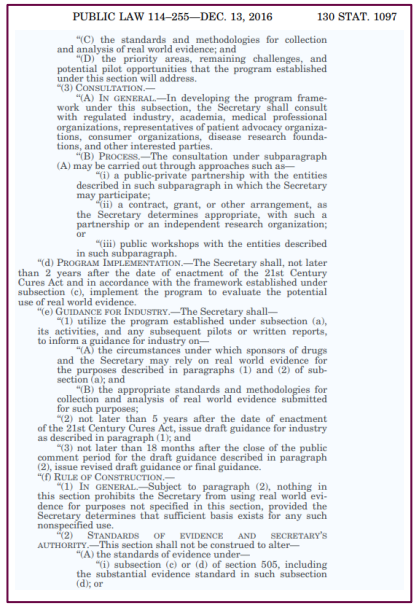
(4) TIMING.—The Secretary shall update or issue a draft version of the guidance required by paragraph (1) not later than 18 months after the date of the public meeting required by paragraph (3) and finalize such guidance not later than 1 year after the date on which the public comment period for the draft guidance closes.

SEC. 3022. REAL WORLD EVIDENCE.

Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by inserting after section 505E (21 U.S.C. 355f) the following:

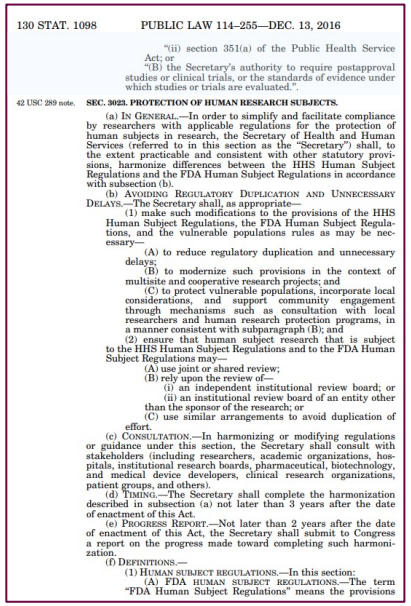
21 USC 355g. "SEC. 505F. UTILIZING REAL WORLD EVIDENCE.

"(a) IN GENERAL.—The Secretary shall establish a program to evaluate the potential use of real world evidence—
"(1) to help to support the approval of a new indication for a drug approved under section 505(c); and
"(2) to help to support or satisfy postapproval study requirements.
"(b) REAL WORLD EVIDENCE DEFINED.—In this section, the term 'real world evidence' means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.
"(c) PROGRAM FRAMEWORK.—
"(1) IN GENERAL.—Not later than 2 years after the date of enactment of the 21st Century Cures Act, the Secretary shall establish a draft framework for implementation of the program under this section.
"(2) CONTENTS OF FRAMEWORK.—The framework shall include information describing—
"(A) the sources of real world evidence, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities;
"(B) the gaps in data collection activities;



PUBLIC LAW 114–255—DEC. 13, 2016 130 STAT. 1097

"(C) the standards and methodologies for collection and analysis of real world evidence; and
"(D) the priority areas, remaining challenges, and potential pilot opportunities that the program established under this section will address.
"(3) CONSULTATION.—
"(A) IN GENERAL.—In developing the program framework under this subsection, the Secretary shall consult with regulated industry, academia, medical professional organizations, representatives of patient advocacy organizations, consumer organizations, disease research foundations, and other interested parties.
"(B) PROCESS.—The consultation under subparagraph (A) may be carried out through approaches such as—
"(i) a public-private partnership with the entities described in such subparagraph in which the Secretary may participate;
"(ii) a contract, grant, or other arrangement, as the Secretary determines appropriate, with such a partnership or an independent research organization; or
"(iii) public workshops with the entities described in such subparagraph.
"(d) PROGRAM IMPLEMENTATION.—The Secretary shall, not later than 2 years after the date of enactment of the 21st Century Cures Act and in accordance with the framework established under subsection (c), implement the program to evaluate the potential use of real world evidence.
"(e) GUIDANCE FOR INDUSTRY.—The Secretary shall—
"(1) utilize the program established under subsection (a), its activities, and any subsequent pilots or written reports, to inform a guidance for industry on—
"(A) the circumstances under which sponsors of drugs and the Secretary may rely on real world evidence for the purposes described in paragraphs (1) and (2) of subsection (a); and
"(B) the appropriate standards and methodologies for collection and analysis of real world evidence submitted for such purposes;
"(2) not later than 5 years after the date of enactment of the 21st Century Cures Act, issue draft guidance for industry as described in paragraph (1); and
"(3) not later than 18 months after the close of the public comment period for the draft guidance described in paragraph (2), issue revised draft guidance or final guidance.
"(f) RULE OF CONSTRUCTION.—
"(1) IN GENERAL.—Subject to paragraph (2), nothing in this section prohibits the Secretary from using real world evidence for purposes not specified in this section, provided the Secretary determines that sufficient basis exists for any such nonspecified use.
"(2) STANDARDS OF EVIDENCE AND SECRETARY'S AUTHORITY.—This section shall not be construed to alter—
"(A) the standards of evidence under—
"(i) subsection (c) or (d) of section 505, including the substantial evidence standard in such subsection (d); or



130 STAT. 1098 PUBLIC LAW 114–255—DEC. 13, 2016

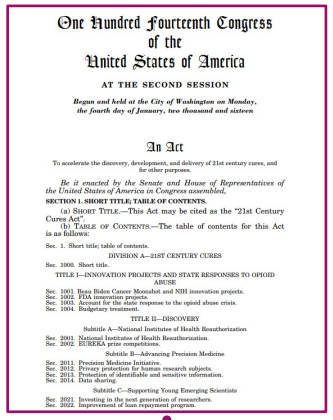
"(ii) section 351(a) of the Public Health Service Act; or
"(B) the Secretary's authority to require postapproval studies or clinical trials, or the standards of evidence under which studies or trials are evaluated.".

42 USC 289 note. SEC. 3023. PROTECTION OF HUMAN RESEARCH SUBJECTS.

(a) IN GENERAL.—In order to simplify and facilitate compliance by researchers with applicable regulations for the protection of human subjects in research, the Secretary of Health and Human Services (referred to in this section as the "Secretary") shall, to the extent practicable and consistent with other statutory provisions, harmonize differences between the HHS Human Subject Regulations and the FDA Human Subject Regulations in accordance with subsection (b).
(b) AVOIDING REGULATORY DUPLICATION AND UNNECESSARY DELAYS.—The Secretary shall, as appropriate—
(1) make such modifications to the provisions of the HHS Human Subject Regulations, the FDA Human Subject Regulations, and the vulnerable populations rules as may be necessary—
(A) to reduce regulatory duplication and unnecessary delays;
(B) to modernize such provisions in the context of multisite and cooperative research projects; and
(C) to protect vulnerable populations, incorporate local considerations, and support community engagement through mechanisms such as consultation with local researchers and human research protection programs, in a manner consistent with subparagraph (B); and
(2) ensure that human subject research that is subject to the HHS Human Subject Regulations and to the FDA Human Subject Regulations may—
(A) use joint or shared review;
(B) rely upon the review of—
(i) an independent institutional review board; or
(ii) an institutional review board of an entity other than the sponsor of the research; or
(C) use similar arrangements to avoid duplication of effort.
(c) CONSULTATION.—In harmonizing or modifying regulations or guidance under this section, the Secretary shall consult with stakeholders (including researchers, academic organizations, hospitals, institutional research boards, pharmaceutical, biotechnology, and medical device developers, clinical research organizations, patient groups, and others).
(d) TIMING.—The Secretary shall complete the harmonization described in subsection (a) not later than 3 years after the date of enactment of this Act.
(e) PROGRESS REPORT.—Not later than 2 years after the date of enactment of this Act, the Secretary shall submit to Congress a report on the progress made toward completing such harmonization.
(f) DEFINITIONS.—
(1) HUMAN SUBJECT REGULATIONS.—In this section:
(A) FDA HUMAN SUBJECT REGULATIONS.—The term "FDA Human Subject Regulations" means the provisions

Section on RWE is only 2 pages and worth reading

Regulatory guidance on real world evidence in the US


One Hundred Fourteenth Congress
of the
United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Monday, the fourth day of January, two thousand and sixteen

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

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. 1. Short title; table of contents.

DIVISION A—21ST CENTURY CURES

Sec. 1000. Short title.

TITLE I—INNOVATION PROJECTS AND STATE RESPONSES TO OPIOID ABUSE

Sec. 1001. Beau Biden Cancer Moonshot and NIH innovation projects.
Sec. 1002. FDA innovation projects.
Sec. 1003. Account for the state response to the opioid abuse crisis.
Sec. 1004. Budgetary treatment.

TITLE II—DISCOVERY

Subtitle A—National Institutes of Health Reauthorization

Sec. 2001. National Institutes of Health Reauthorization.
Sec. 2002. EUREKA prize competitions.

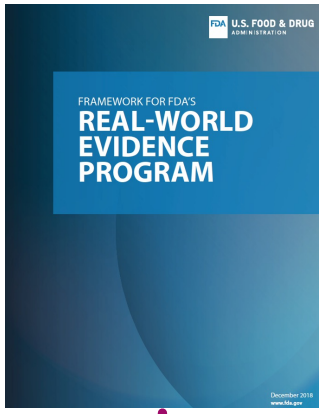
Subtitle B—Advancing Precision Medicine

Sec. 2011. Precision Medicine Initiative.
Sec. 2012. Privacy protection for human research subjects.
Sec. 2013. Protection of identifiable and sensitive information.
Sec. 2014. Data sharing.

Subtitle C—Supporting Young Emerging Scientists

Sec. 2021. Investing in the next generation of researchers.
Sec. 2022. Improvement of loan repayment program.

12/2016

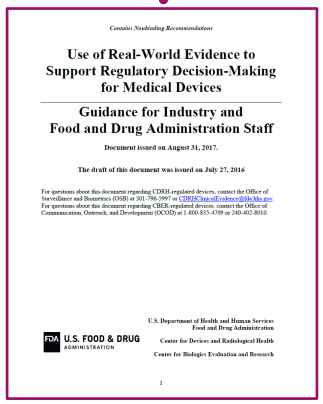

U.S. FOOD & DRUG ADMINISTRATION

FRAMEWORK FOR FDA'S

REAL-WORLD EVIDENCE PROGRAM

December 2018
www.fda.gov

12/2018


Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

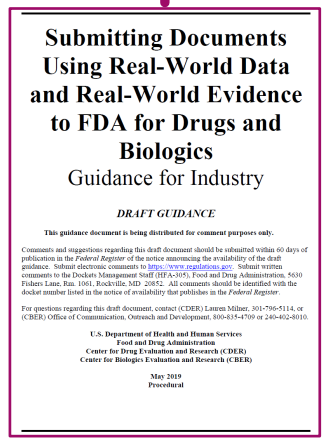
For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRH-RealEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

1

8/2017


Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

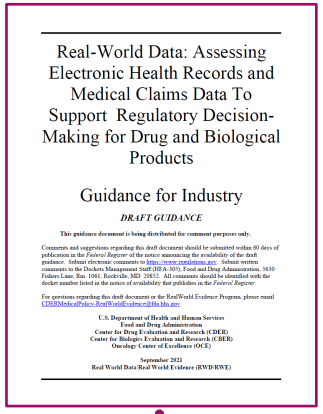
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Procedural

5/2019


Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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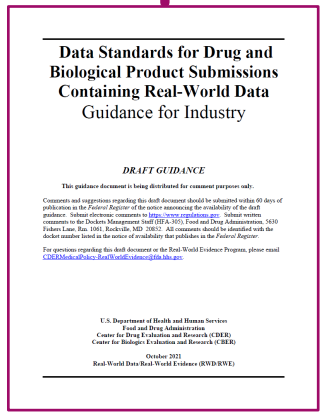
For questions regarding this draft document or the Real-World Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real-World Data/Real-World Evidence (RWD/RWE)

9/2021


Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Guidance for Industry

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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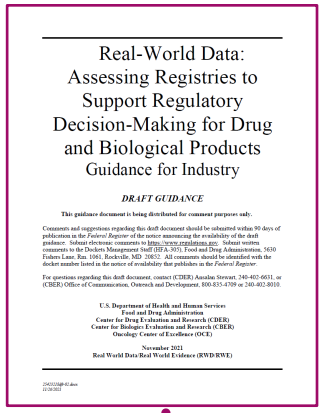
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2021
Real-World Data/Real-World Evidence (RWD/RWE)

10/2021


Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

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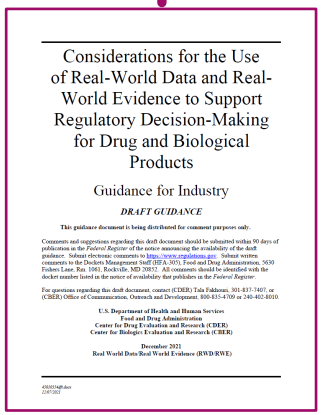
For questions regarding this draft document, contact (CDER) Anzalan Stewart, 240-402-6631, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

November 2021
Real-World Data/Real-World Evidence (RWD/RWE)

11/2021


Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2021
Real World Data/Real World Evidence (RWD/RWE)

12/2021

Note: Similar efforts for RWE also in development at EMA, MHRA, PMDA, Health Canada, etc.

RWD vs RWE

Real world data

Data relating to patient health status and/or delivery of health care routinely collected from a variety of sources

- Medical claims and billing
- Electronic health records
- Patient/product registries
- Patient surveys

Reference

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

Types of RWD

Source	Type	Subtype	Examples
Administrative	Third-party payer claims	Closed networks	IBM MarketScan, IQVIA PharMetrics, Optum Clinformatics
		Open networks	IQVIA LAAD, DRG RWD, Symphony IDV
		Government	CMS FFS Medicare, Medicaid, VA/DOD
	Hospital chargemaster		Premier, Vizient, IQVIA CDM
	Pharmacy		Surescripts, IQVIA NDTI

1

IBM

2

IQVIA

OPTUM

3

Clarivate Analytics

TriNetX

OM1

4

labcorp

Quest Diagnostics

5

PREMIER

Cerner

PointClickCare

flatiron

ontada

COREVITAS Excellence in Evidence

healthverity

DATAVANT

komodohealth

Data elements commonly available in RWD

	Variable
Patient	Age
	Sex
	Race / ethnicity
	Insurance coverage / type
HCP	Identifier
	Specialty
	Location
Visit	Date
	Procedure codes
	Diagnosis codes
Rx	Generic / brand name
	Description (eg, strength, formulation)
	Quantity (eg, number, days supply)
	Indication (reason for prescribing)
Notes	Measurements (eg, vitals)
	Observations (eg, notes)
	Rationale (eg, reason for prescribing)
Test	Description
	Code (eg, LOINC)
	Results

Study designs related to RWE

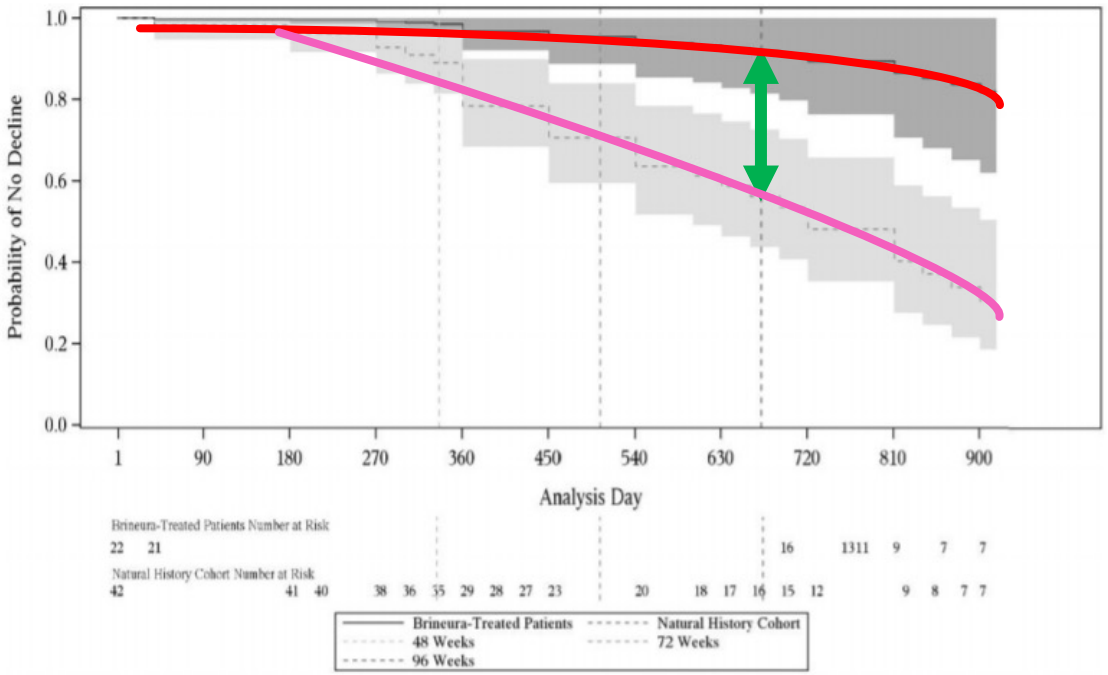
Concept	Description
Single-arm study	• Prospective study with 1 arm in which all participants receive therapy • Often paired with external control group

FDA approvals based on RWE

New product

BRINEURA (cerliponase alfa) was approved for Batten disease (rare genetic condition) based on single-arm, non-randomized, dose-escalation study on LOA compared to natural history using RWD (ie, registry)

Figure 7. Estimated Time to Unreversed (Sustained) 2-Category Decline or Unreversed Score of Zero in Motor Domain for Symptomatic Pediatric Patients in the Brineura Single-Arm Clinical Study with Extension and for Patients in a Natural History Cohort (Based on the Cox Proportional Hazards Model Adjusting for Covariates)



New indication

IBRANCE (palbociclib) was approved for male breast cancer based on analyses of EHR data from Flatiron, health insurance claims from IQVIA, FAERS, literature, and a safety database

CLINICAL CANCER RESEARCH | CCR DRUG UPDATES

FDA Approval Summary: Palbociclib for Male Patients with Metastatic Breast Cancer

Suparna Wedam[1], Lola Fashoyin-Aje[1], Erik Bloomquist[1], Shenghui Tang[1], Rajeshwari Sridhara[1], Kirsten B. Goldberg[2], Marc R. Theoret[1,2], Laleh Amiri-Kordestani[1], Richard Pazdur[1,2], and Julia A. Beaver[1]

- Approved by FDA in 2016 for women with breast cancer
- Pivotal trials excluded male participants
- Product was used off-label in males with breast cancer
- RWD was submitted to FDA in sNDA
- Label was expanded in 2019 to include males

Evidence standards with RWE

RWE for regulatory decisions

- Governed by 21st Century Cures Act
- FDA still requires substantial evidence from adequate and well-controlled investigations
- If evidence standards cannot be lowered, RWE must be elevated to reach them

Common features of regulatory approvals based on RWE:

- ☑ Indication is rare
- ☑ Primary endpoint is objective
- ☑ Natural history is well understood
- ☑ No change in standard of care
- ☑ Observed effect size is large

RWE for internal decisions

- Not impacted by 21st Century Cures Act
- "Use of RWD to improve efficiencies of drug development programs that rely primarily on traditional clinical trials is already **well established and generally encouraged by FDA**"
- Potential uses of RWD to plan traditional RCT
  1. To assess enrollment criteria and trial feasibility
  2. To support selection of trial sites

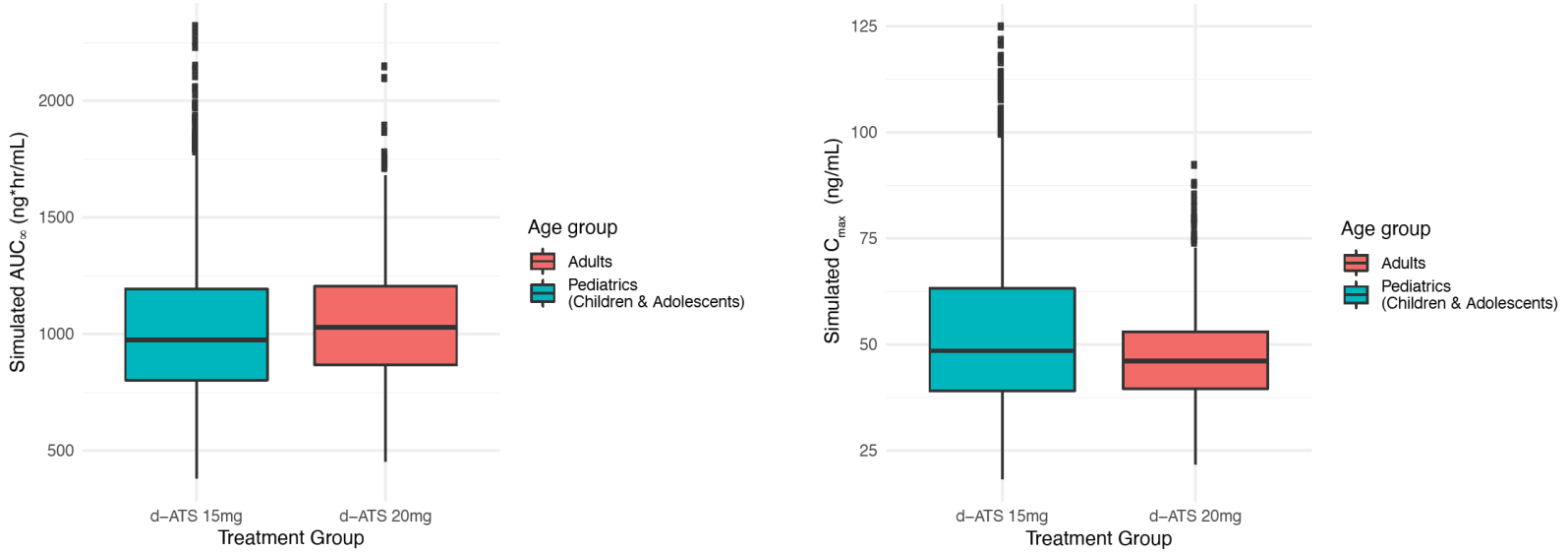
Reference
Concato J, Corrigan-Curay J. Real-World Evidence - Where Are We Now? N Engl J Med. 2022;386(18):1680-2.

Case Studies

Case Study 1:	Model based pediatric exposure extrapolation for a dextroamphetamine transdermal system: a common use of real world data in clinical pharmacology (*Castelli et al. American Society of Clinical Psychopharmacology, 2022*)
Problem	• Define doses of the dextroamphetamine transdermal system in children and adolescents which achieve exposures similar to adults.
Data Sources	• National Health and Nutrition Examination Survey (NHANES) database (https://www.cdc.gov/nchs/nhanes/index.htm) • Controlled clinical trial data in adults
Use of RWD	• Demographic covariates were sampled from the NHANES database and incorporated into a population pharmacokinetic model in order to create realistic Monte Carlo simulations of pediatric populations. • Candidate transdermal doses were evaluated and compared with prior data from adults.
Results	• Exposure was dependent on body size (body weight) • A pediatric transdermal dose of 15 mg produced comparable exposures to 20 mg in adults.

Case Study 1:	Model based pediatric exposure extrapolation for a dextroamphetamine transdermal system: a common use of real world data in clinical pharmacology (*Castelli et al. American Society of Clinical Psychopharmacology, 2022*)

Figure 3. Simulated amphetamine exposures for pediatric patients at d-ATS 15 mg and adult patients at ATS 20 mg



Median values are designated by a line in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR, and outliers are indicated outside the whiskers by black circles.
AUC, area under the concentration-time curve; C_{max}, maximum concentration; IQR, inter-quartile range.

Opportunities & Challenges	• This example illustrates a common use of real world data to inform clinical pharmacology decision making. • NHANES is based on healthy volunteer data and may not be reflective of pediatric covariate distributions in all disease states. Assess sensitivity to this assumption.

Case Study 2:	The use of real world data to inform a real world insulin glargine trial design: a clinical trial simulation. *(Barret et al. American Conference on Pharmacometrics, 2017)*
Problem	• Explore the probability of success and dependence on design characteristics for a future real world (post-approval) study of insulin glargine (Toujeo®) in type 2 diabetes mellitus (T2DM) patients.
Data Sources	• Electronic medical records data from 65,000 T2DM patients • Data from 4 controlled clinical trials in T2DM
Use of RWD	• Explore causal relationships between treatment and clinical outcomes for competing therapies • Patient demographic/covariate distributions
Results	• Ultimately, clinical trial simulations were implemented given models based on the controlled clinical trial data with demographics and covariates informed by the RWD. • Expected power and probability of success were determined for various study sample sizes and other design elements.
Opportunities & Challenges	• The unstructured nature of RWD often leads to confounded relationships and difficulties in establishing quantitative causal relationships. Proceed with caution. • Nevertheless, RWD were useful to inform other aspects of the problem… such as the expected multivariate covariate distribution for a real world patient population

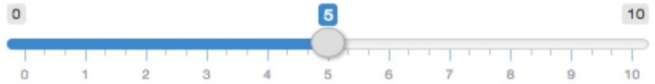
Case Study 2: The use of real world data to inform a real world insulin glargine trial design: a clinical trial simulation. *(Barret et al. American Conference on Pharmacometrics, 2017)*

RWE Simulator | Data Sources | Demographics | Lantus / SOC | Toujeo | Simulation Summary | Advanced

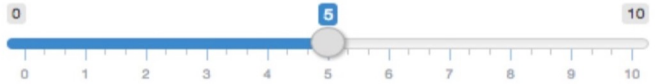
Population Specification

Weight for each data source

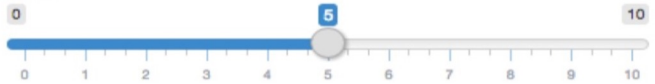
Edition3



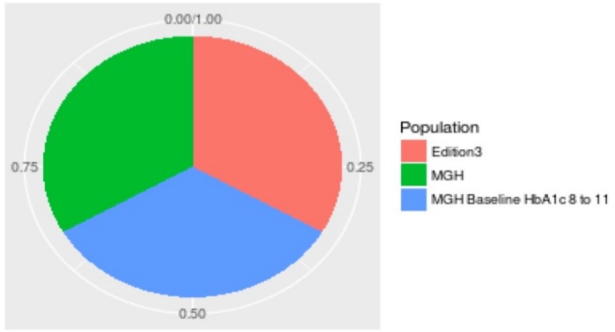
MGH Baseline HbA1c 8 to 11



MGH



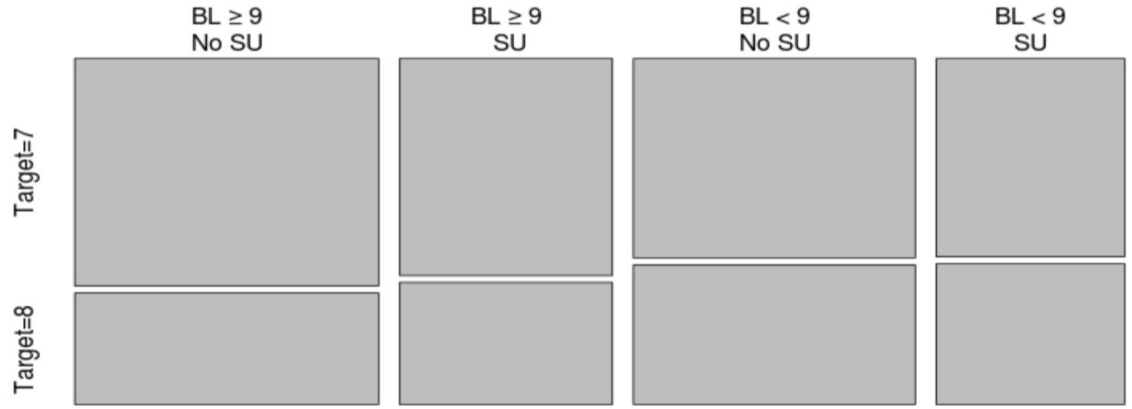
Summary of relative weights



Relative weighting of populations

Summary of Specified Population

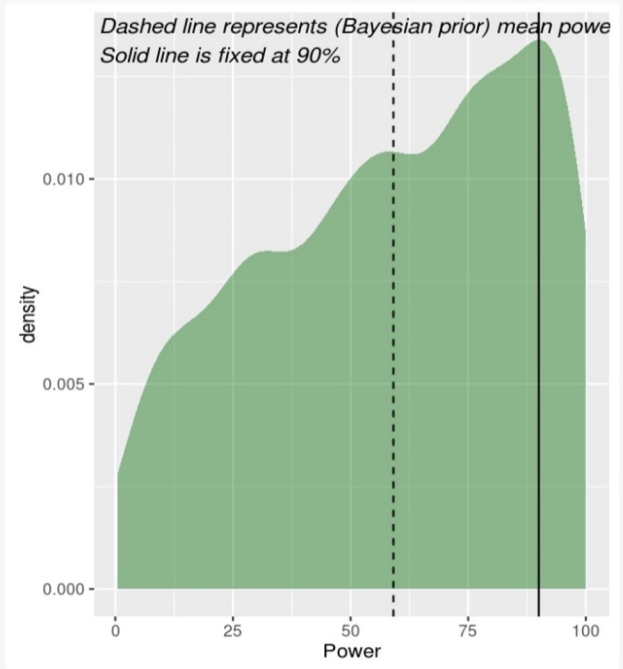
%	BL ≥ 9 No SU	BL ≥ 9 SU	BL < 9 No SU	BL < 9 SU	Marginal Total
Target=7	20.7	13.8	16.8	11.2	62.5
Target=8	10.1	7.8	11.8	7.9	37.5
Marg. Tot.	30.8	21.6	28.6	19.1	100.0

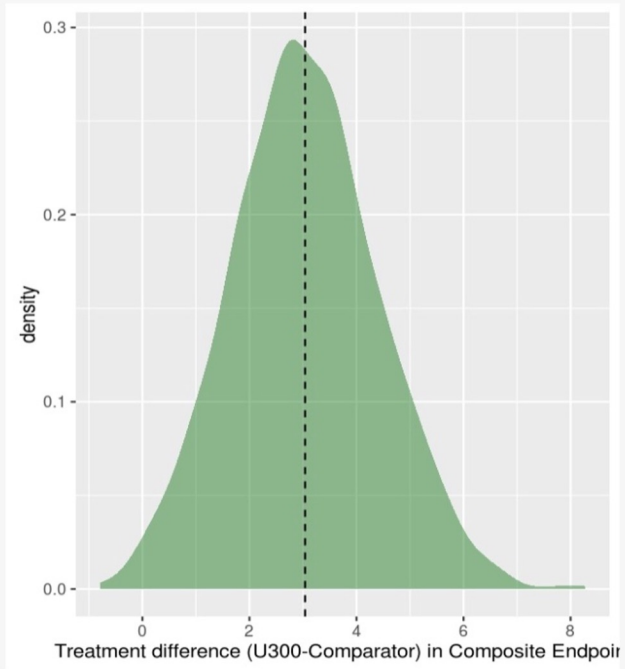


Slide courtesy of Jeffrey Barrett, ACoP 2017

Case Study 2: The use of real world data to inform a real world insulin glargine trial design: a clinical trial simulation. *(Barret et al. American Conference on Pharmacometrics, 2017)*

RWE Simulator | Data Sources | Demographics | Lantus / SOC | Toujeo | Simulation Summary | Advanced





Current Scenario Statistics

	Estimate (%)
Toujeo Composite Endpoint Rate	18.68
Lantus / SOC Composite Endpoint Rate	15.64
Expected Treatment Difference (U300-Comparator)	3.04
Average (Bayesian Predictive) Power	59.10

MGH 8-11 with E3 Effect

Save Scenario

Saved scenarios can be reviewed by toggling to "Multi-scenario Summary" on the Navigation Bar

Slide courtesy of Jeffrey Barrett, ACoP 2017

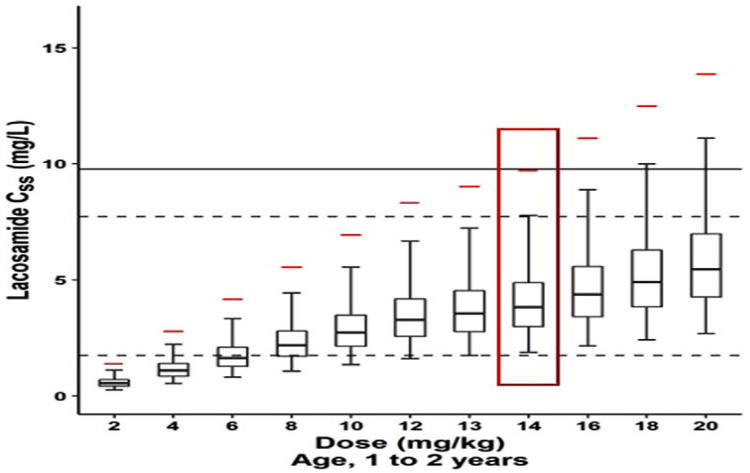
Case Study 3:	Use of Real-World Data and Pharmacometric Modeling in Support of Lacosamide Dosing in Pediatric Patients Under 4 Years of Age (*Lukka et al, 2021, Journal of Clinical Pharmacology*)
Background	• Lacosomide (Vimpat) approved for Refractory Focal Seizures (RFS) for children and adults ≥4 years of age BUT not approved for pediatrics <4 years. • The Prediatric Epilepsy Academic Consortium for Extrapolation (PEACE) recommends that antiepileptic drugs approved in adults for RFS are considered effective for children ages ≥2 years . This position is supported by FDA CDER. • Lacosomide is used *off-label* for treatment of RFS in pediatric patients <4 years.
Problem	• No confirmed guideline on appropriate dosing of adjuctive lacosomide for patients <4 years. • Few trials in ages <4yrs
Analysis Goals	**STAGE 1:** Use RWD to characterize PK of Lacosomide in ages 1 month to <18 years using pharmacometrics analysis. **STAGE 2:** Use resulting PK models to derive age-appropriate dosing recommendations using simulation-based exposure-matching

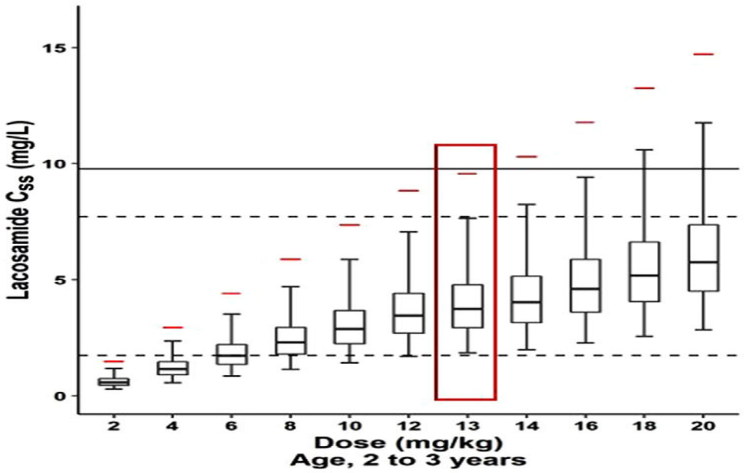
Case Study 3 cont'd:	Use of Real-World Data and Pharmacometric Modeling in Support of Lacosamide Dosing in Pediatric Patients Under 4 Years of Age (*Lukka et al, 2021, Journal of Clinical Pharmacology*)

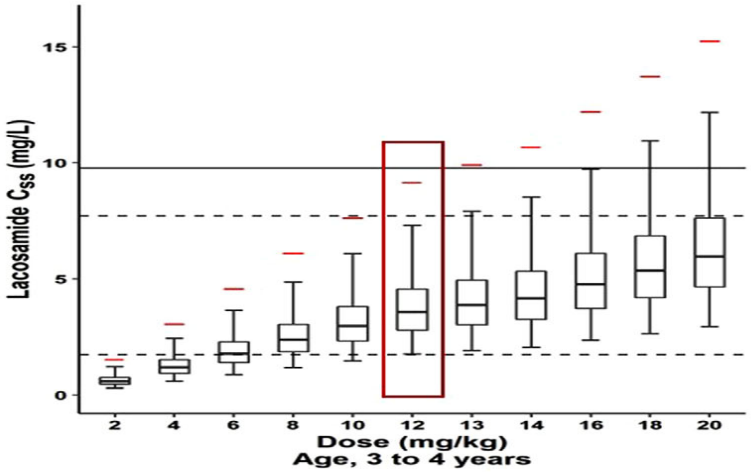
Analysis Stage 1	• RWD data source: EMR - routinely captured therapeutic drug monitoring assessments.
	• Identified 315 pediatric patients >1 month to <18 years who received Lacosomide.
	• Conduct pop-PK modeling using mixed-effects structural models
	  • Outcome = PK Clearance
	  • Linear predictor: Trt dose; Age; Sex; Race; Other concomitant epileptic drugs (Phenobarbital/Felbamate)

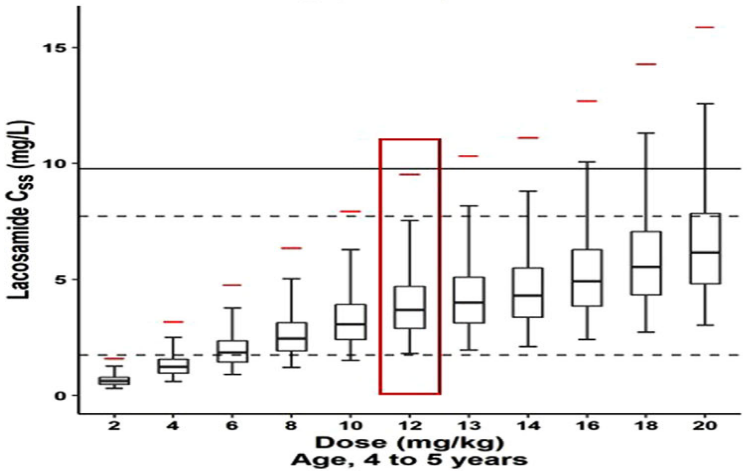
Analysis Stage 2	• Use resulting PK model • Simulate virtual pediatric patients to explore age-associated dose requirements • Age groups: A: 1 month - <1 year; B: 1 year - <3 years; C: 3 years - <5 years ⟷ Compared to established FDA-approved pediatric dosing groups ⟷ D: 4 years – 12 years; E: 4 years – 18 years

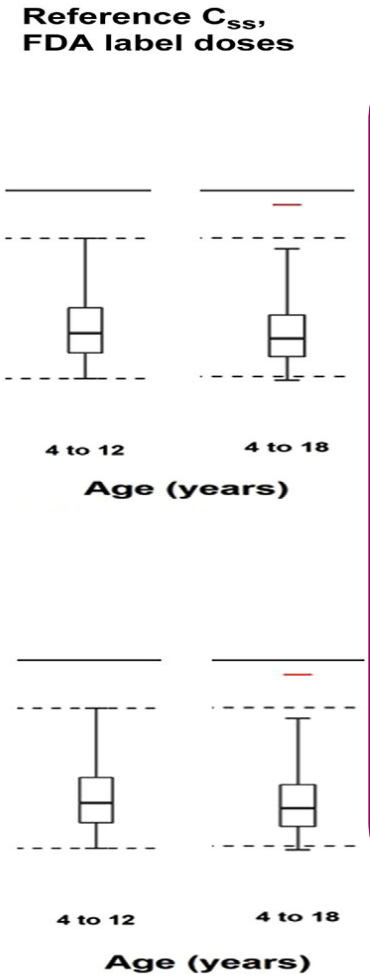
Case Study 3 cont'd:	Use of Real-World Data and Pharmacometric Modeling in Support of Lacosamide Dosing in Pediatric Patients Under 4 Years of Age (*Lukka et al, 2021, Journal of Clinical Pharmacology*)







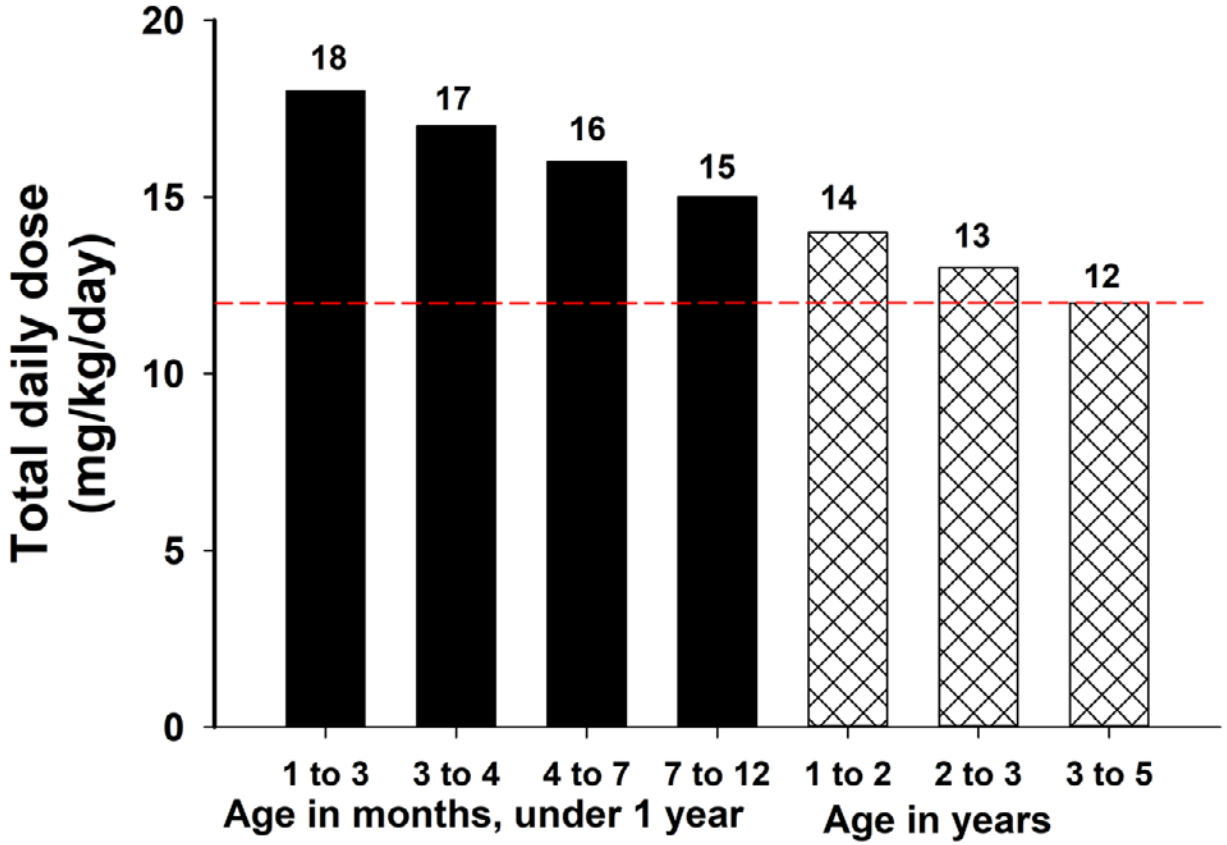




RESULTS

- Children ≥3 years need same dosing as FDA requirement for ages ≥4 years (i.e. 12 mg/kg/d)
- Children 1 -3 years need slightly more (i.e. 13-14 mg/kg/d)

Case Study 3 cont'd:	Use of Real-World Data and Pharmacometric Modeling in Support of Lacosamide Dosing in Pediatric Patients Under 4 Years of Age (*Lukka et al, 2021, Journal of Clinical Pharmacology*)

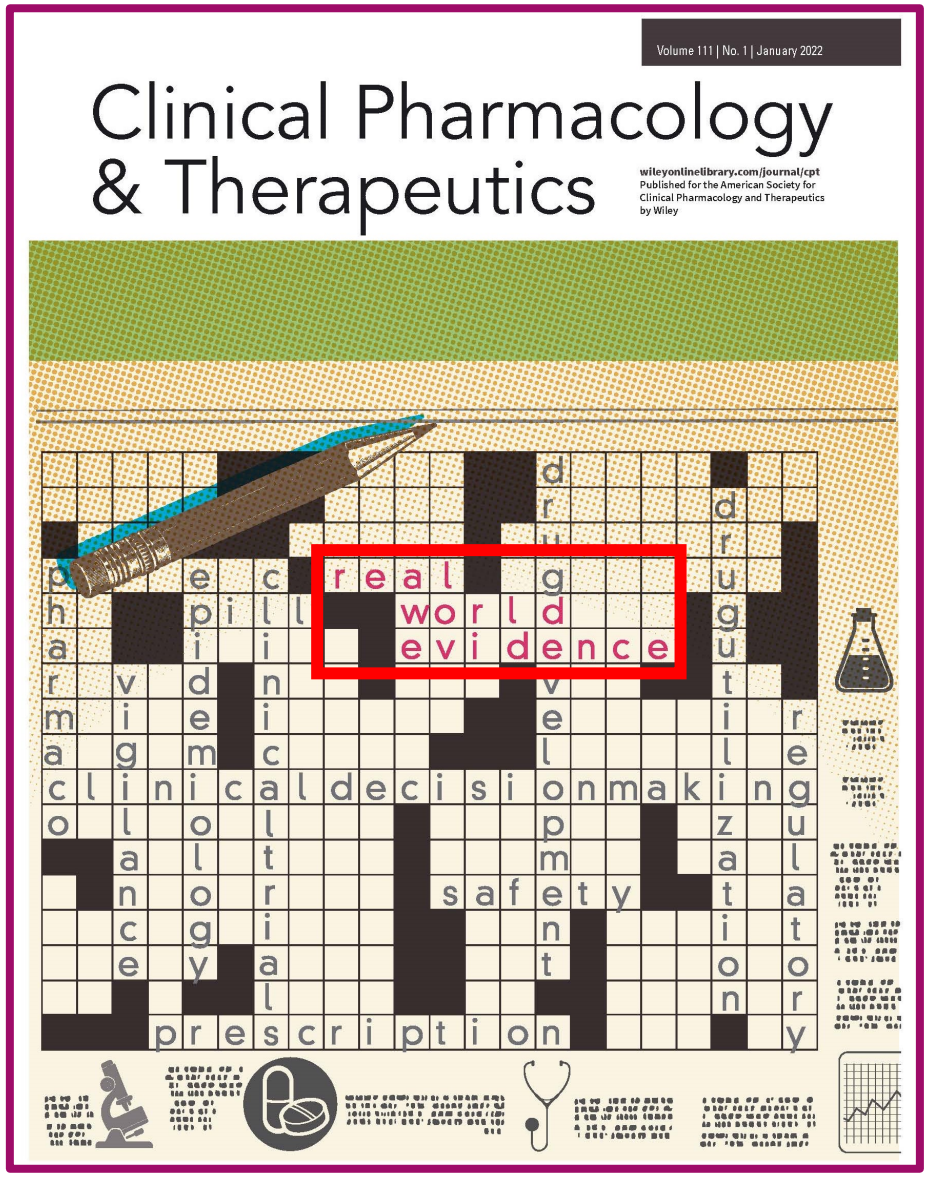


RESULTS

- Children 1 month – 1 year need slightly more (i.e. 15-18 mg/kg/d)

Back up Slides

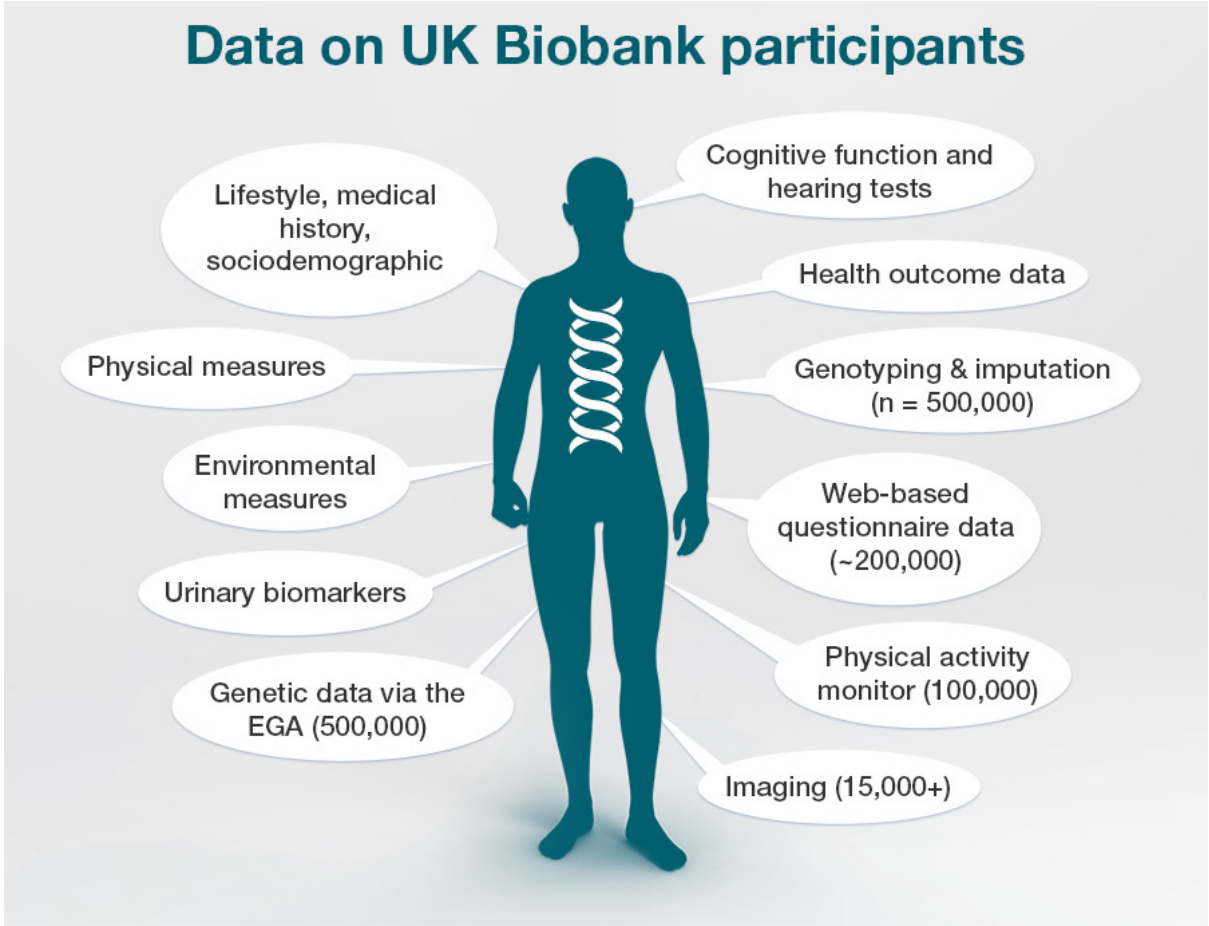
January 2022 issue of CPT



Potential uses of RWD/RWE in clinical pharmacology

1. Identifying new genetic targets and biomarkers
2. Understanding natural history to enrich clinical trial population
3. Informing sample size calculations for clinical trials
4. Assessing real-world prescribing patterns and dosing
5. Identifying new DDIs that increase risk of AEs
6. Identifying new DDIs related to QT prolongation
7. Assessing clinical impact of DDIs from pharmacology studies

Identifying new genetic targets and biomarkers

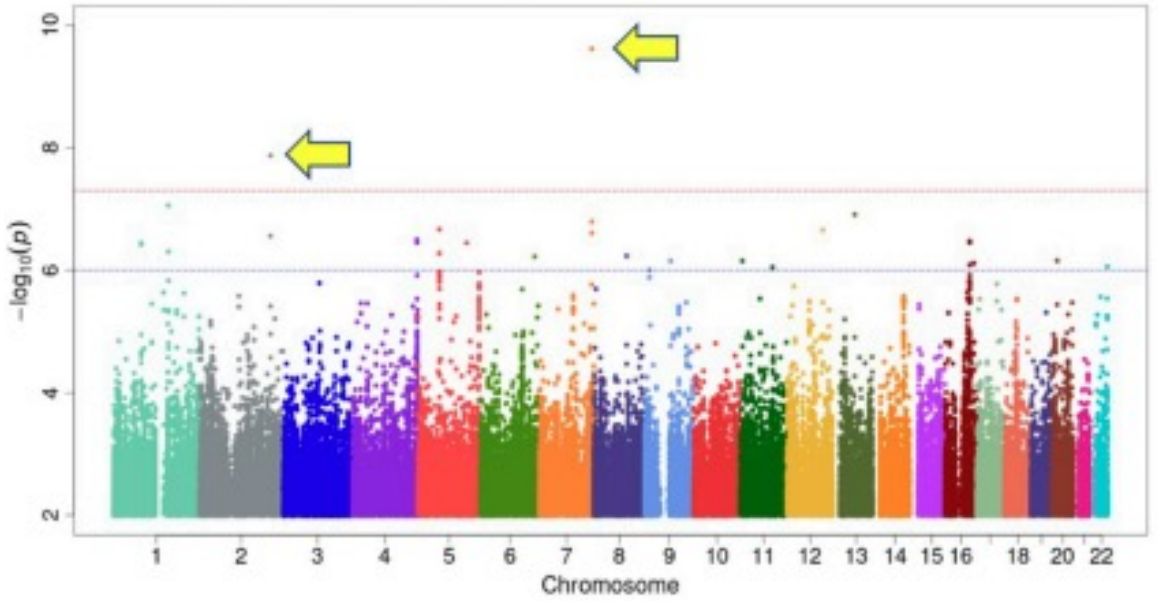


RWI

- Identified 2 novel genetic variants associated with HCM
- Found new biometrics and biomarkers associated with HCM

Hypertrophic cardiomyopathy (HCM)

- Disorder of heart muscles associated with variants in 8 genes
- Compared genomes of 363 individuals with HCM to 7,260 controls matched for age, sex, and ancestry
- Examined comorbidities based on ICD diagnosis codes



Gene	rs Number	Chromosome	Position	Variant Type	OR	P-value	Minor Allele Frequency
KMT2C	rs78630626	7	152,056,039	Intronic	3.8	2.4×10^{-10}	1.6%
PARD3B	rs188937806	2	205,754,718	Intronic	3.8	1.3×10^{-8}	1.0%

References
Gyftopoulos A, et al. Identification of Novel Genetic Variants and Comorbidities Associated With ICD-10-Based Diagnosis of Hypertrophic Cardiomyopathy Using the UK Biobank Cohort. Front Genet. 2022;13:866042.

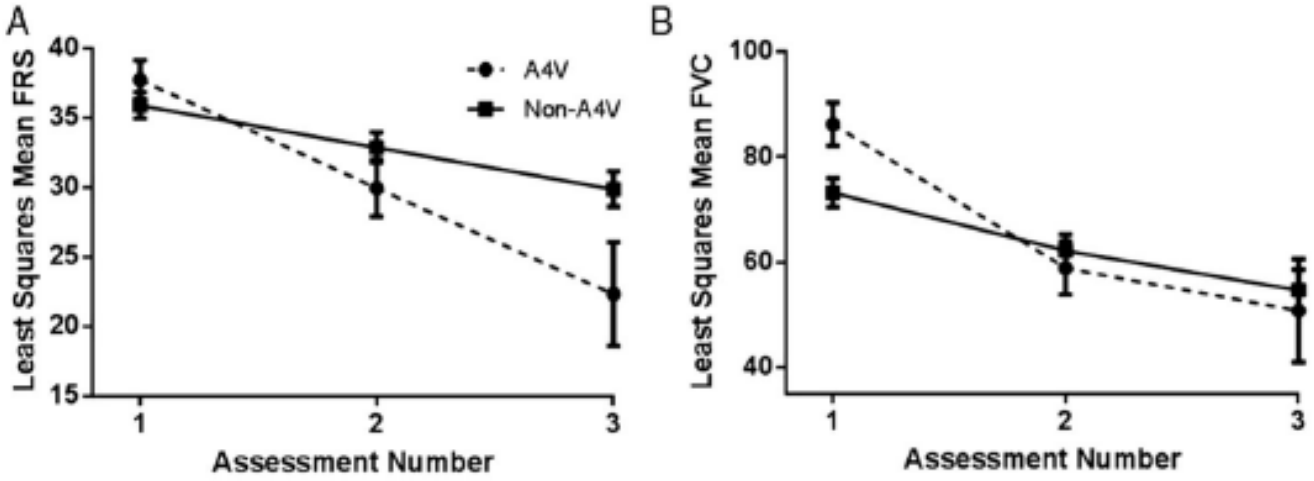
Understanding natural history to enrich clinical trial population

Background

- Amyotrophic lateral sclerosis (ALS) is a fatal and progressive neurological disease with few therapies
- A subgroup of patients with familial ALS have mutations in the SOD1 gene
- Therapies aimed at SOD1 need to understand natural history of disease progression

Methods

- Consortium conducted retrospective chart review to identify 175 patients with ALS and SOD1 mutations
- Results were pooled to analyze changes in ALS-Functional Rating Scale (FRS) and forced vital capacity (FVC) over time
- Compared 2 subgroups of SOD1 mutations (A4V vs non-A4V)



- Outcomes within A4V subgroup were homogeneous
- Focusing on A4V subgroup could reduce sample size required by ~40%

Group	Sample size
SOD1 overall	N = 88
SOD1 A4V	N = 52

RWI

- Significant differences were found in disease progression between A4V and non-A4V SOD1 mutations

References

Bali T, Self W, Liu J, Siddique T, Wang LH, Bird TD, et al. Defining SOD1 ALS natural history to guide therapeutic clinical trial design. J Neurol Neurosurg Psychiatry. 2017;88(2):99-105.

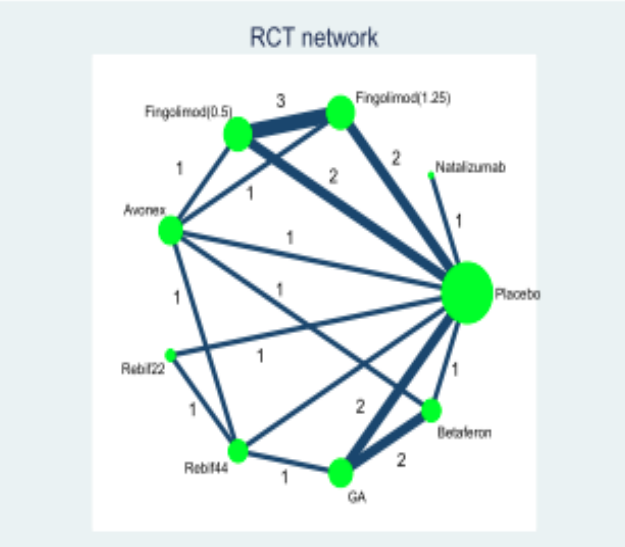
Informing sample size calculations for clinical trials

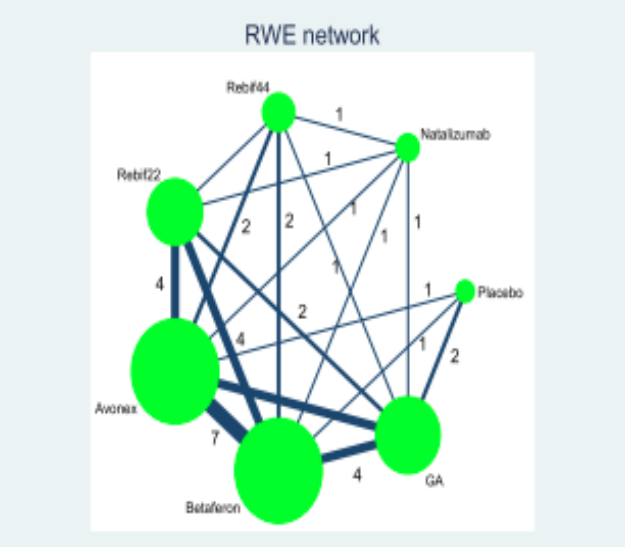
Background

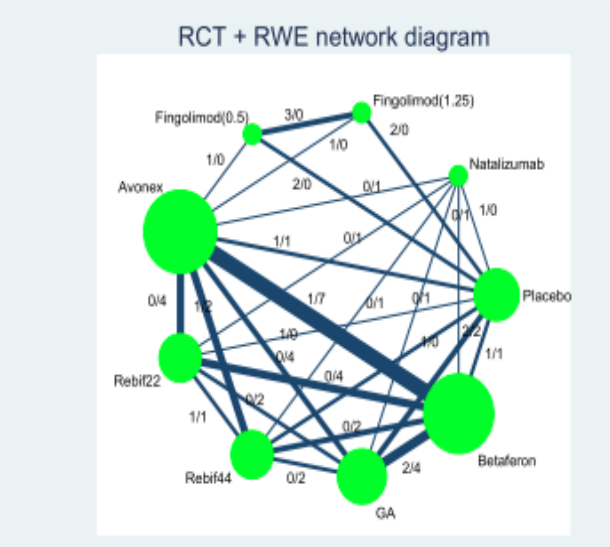
- Biopharma companies generally use best available information to inform sample size calculations for phase 3 RCTs
- Network meta-analysis (NMA) synthesizes published literature on effect sizes for available therapies
- Incorporating RWE into NMA could increase available comparisons and improve information for sample size calculations

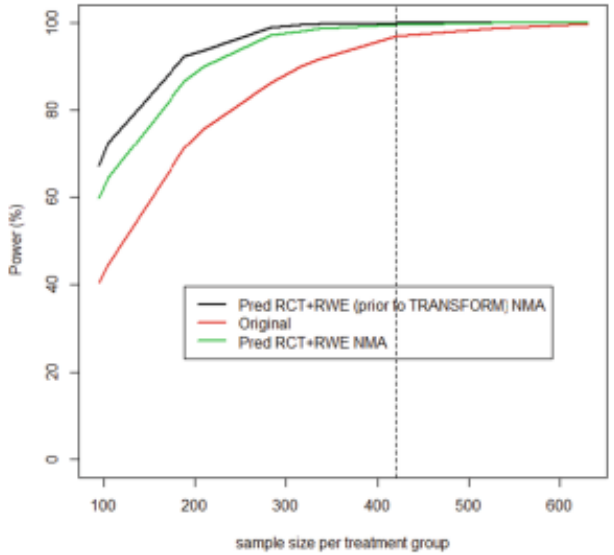
Methods

- Used NMA to estimate effect size for annualized relapse rate (ARR) with therapies studied for multiple sclerosis
- Simulated phase 3 RCT using effect sizes from NMA with vs without RWE
- Compared sample size required to achieve 90% power in future phase 3 RCT with vs without RWE









Findings

- Sample size calculation based on NMA with RWE predicted that required sample size could be reduced by ~32%

References

Martina R, Jenkins D, Bujkiewicz S, Dequen P, Abrams K, GetReal W. The inclusion of real world evidence in clinical development planning. Trials. 2018;19(1):468.

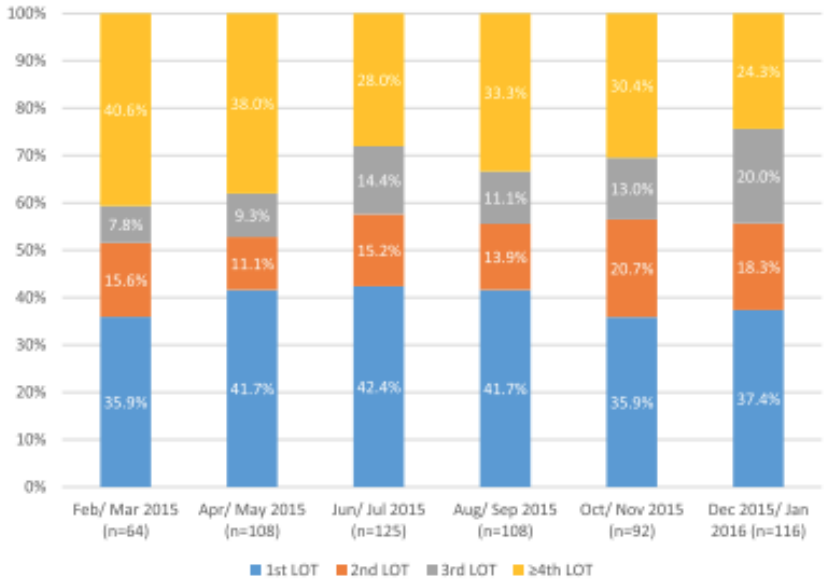
Assessing real-world prescribing patterns and dosing

Background

- Palbociclib is CDK 4/6 inhibitor approved by FDA in 2015 for HR+/HER2- breast cancer in women
- RCTs evaluated Palbociclib 125mg + letrozole or fulvestant daily for 21 days

Methods

- Analyzed EHR data from US community oncology practices in the 12 months after approval
- Identified women with breast cancer and claim for Palbociclib + letrozole
- Assessed lines of therapy prior to Palbociclib use, starting dose, and dose changes based on treatment cycles



	Overall		Number of palbociclib cycles received[a]					
			6 cycles[b]		4 cycles[c]		2 cycles[d]	
Total patients (*n* (%)	612	(100)	336	(54.9)	445	(72.7)	524	(85.6)
Starting dose (*n* (% of patients with known starting dose))								
125 mg	367	(88.0)	237	(88.1)	283	(87.6)	321	(87.5)
100 mg	46	(11.0)	30	(11.2)	38	(11.8)	42	(11.4)
75 mg	4	(1.0)	2	(0.7)	2	(0.6)	4	(1.1)
Type of first dose reduction (*n* (% of patients with known dose))								
Reduction from 125 mg to 100 mg	65	(15.6)	65	(24.2)	64	(19.8)	45	(12.3)
Reduction from 100 mg to 75 mg	6	(1.4)	6	(2.2)	6	(1.9)	5	(1.4)
Reduction from 125 mg to 75 mg	13	(3.1)	13	(4.8)	13	(4.0)	8	(2.2)
Days to first dose reduction (mean, SD)	48	(31)	48	(31)	48	(31)	46	(31)

Findings

- Identified 417 patients who met eligibility criteria and had known starting dose; 64.6% received 6 cycles
- 88.0% started on 125mg dose; 20.1% had dose reduction, most commonly from 125mg to 100mg

References

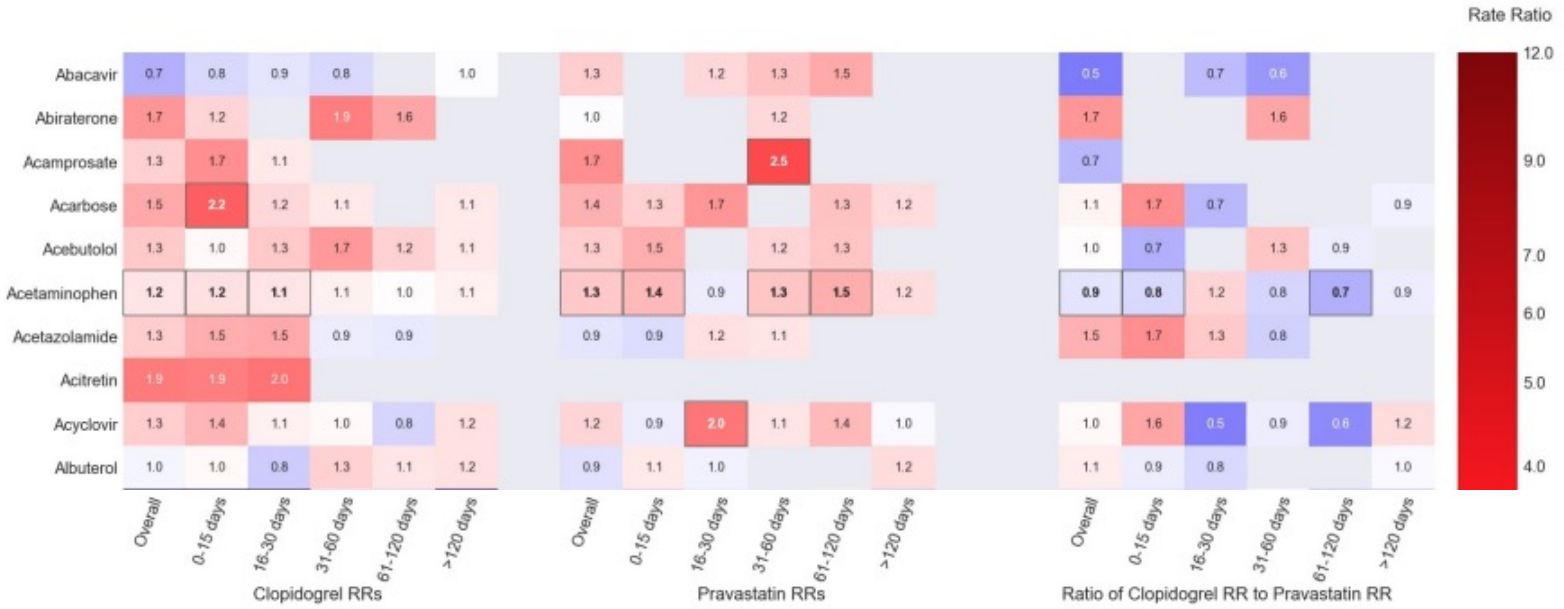
Kish JK, et al. Real-world evidence analysis of palbociclib prescribing patterns for patients with advanced/metastatic breast cancer treated in community oncology practice in the USA one year post approval. Breast Cancer Res. 2018;20(1):37.

Identifying new DDIs that increase risk of AEs

Background
- Clopidogrel is associated with increased risk of serious bleeding (eg, gastrointestinal bleeding, intracranial hemorrhage)
- Limited research on whether DDIs may potentiate risk of serious bleeding with clopidogrel

Methods
- Analyzed Optum claims database to identify concomitant medications for patients taking clopidogrel
- Used self-control design to compare risk of serious bleeding for clopidogrel + other vs. pravastatin + other

RWI
- Compared risk of serious bleeding for 431 pairs of medications common to clopidogrel and pravastatin



- Identified 28 pairs with SS increased risk
- 13 pairs were expected
- 15 pairs were new signals of DDIs

References

Leonard CE, et al. Clopidogrel Drug Interactions and Serious Bleeding: Generating Real-World Evidence via Automated High-Throughput Pharmacoepidemiologic Screening. Clin Pharmacol Ther. 2019;106(5):1067-75.

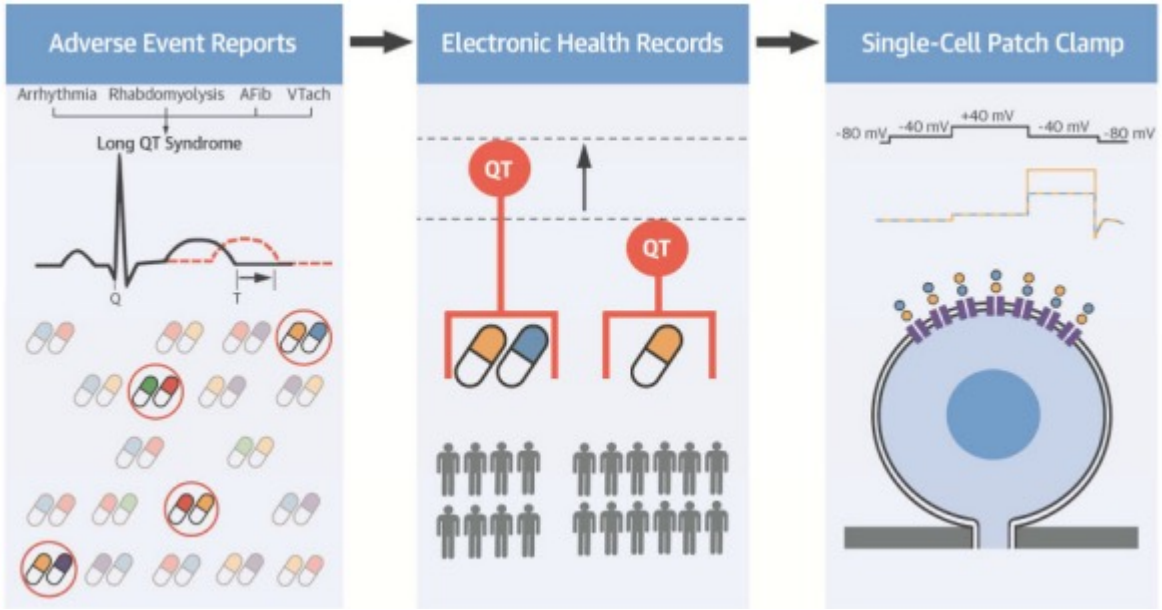
Identifying new DDIs related to QT prolongation

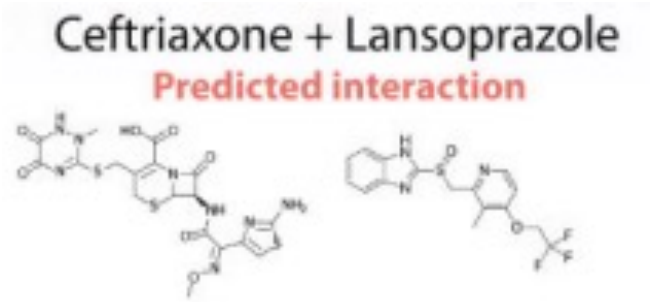
Background

- QT prolongation can result in ventricular tachycardia and sudden death
- Over 40 medications are associated with prolonged QT interval; DDIs may also result in prolonged QT interval

Methods

- Analyzed FDA adverse event reporting system (FAERS) and EHR data from Columbia University Medical Center
- Examined ECGs for patients taking suspected drug pairs where DDIs could prolong QT interval
- Conducted single-cell patch clamp tests to evaluate top drug pairs where DDIs could prolong QT interval





RWI

- Identified 889 signals in FAERS, 34 corroborated by EHR, and 8 new drug pairs associated with prolonged QT interval
- Confirmed that ceftriaxone + lansoprazole block hERG channel in single cell study

References

Lorberbaum T, Sampson KJ, Chang JB, Iyer V, Woosley RL, Kass RS, et al. Coupling Data Mining and Laboratory Experiments to Discover Drug Interactions Causing QT Prolongation. J Am Coll Cardiol. 2016;68(16):1756-64.

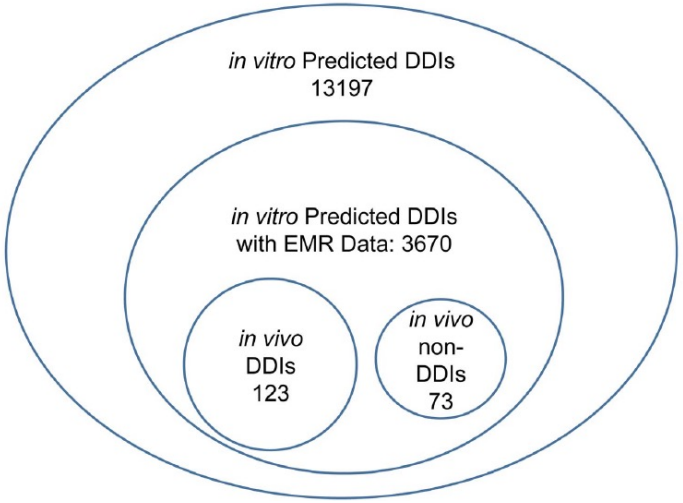
Assessing clinical impact of DDIs from pharmacology studies

Background

- Findings from *in vitro* studies on potential DDIs can be evaluated further with *in vivo* and *in populo* studies
- Study focused on potential DDIs that increase the risk of myopathy

Methods

- Identified potential drug-drug pairs that could result in DDIs based on CYP substrates or inhibitors
- Searched literature for *in vivo* studies related to potential drug-drug pairs of interest
- Analyzed EHR data to examine medications used by individuals with myopathy
- Compared risk of myopathy for drug-drug pairs vs. individual drugs



Drug 1	Drug 2	Enzymes	Metabolism Routes	Inhibition potency	DDI Prediction
Loratadine	**Simvastatin**	CYP3A	major	strong	Strong
Loratadine	**Alprazolam**	CYP3A	minor	moderate	Moderate
Loratadine	**Duloxetine**	CYP2D6	major	moderate	Moderate
Loratadine	**Ropinirole**	CYP2D6	major	moderate	Moderate
promethazine	**tegaserod**	CYP2D6	minor	strong	Strong

Findings

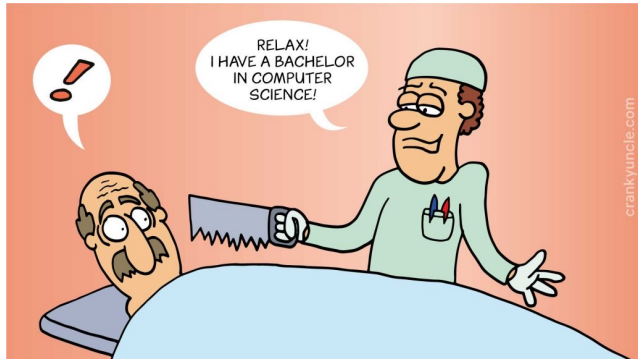
- 13,197 drug pairs had potential DDIs; 3,670 (27.8%) were co-prescribed; 196 (1.5%) had *in vivo* studies related to DDIs
- Identified 59,572 patients with myopathy, including 53 with rhabdomyolysis
- Identified 5 new drug-drug pairs potentially associated with an increased risk of myopathy when co-prescribed

References

Duke JD, et al. Literature based drug interaction prediction with clinical assessment using electronic medical records: novel myopathy associated drug interactions. PLoS Comput Biol. 2012;8(8):e1002614.

Limitations of RWD/RWE

1. High costs of data and resources to analyze data
2. Single datasets have limited available information
3. Limited follow-up available in single datasets
4. Challenging to link multiple datasets
5. Data are messier than expected
6. Large sample sizes can be deceiving
7. Best practices are still being developed
8. Limited expertise in RWD and RWE methods
9. External stakeholders concerned about “P hacking”
10. Unknown disposition of regulators for novel studies



Discussion