# The FDA Real-World Evidence (RWE)  Framework and Considerations for

# Use in Regulatory Decision-Making

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**Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee**

**May 12, 2021**

# Overview

- **21st Century Cures Act of 2016 – FDA shall establish a program to evaluate the potential use of RWE to:**
  - support approval of new indication for a drug approved under section 505(c)
  - satisfy post-approval study requirements

- **Ongoing CDER/Center for Biologics Evaluation and Research (CBER) RWE program based on December 2018 "RWE Framework":**
  - describes priority areas, remaining challenges, and potential pilot opportunities that the FDA RWE program will address

- **Draft RWE guidance anticipated to be issued by December 2021**
  - informed by demonstration projects and experience with submissions

# FDA Definitions

**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

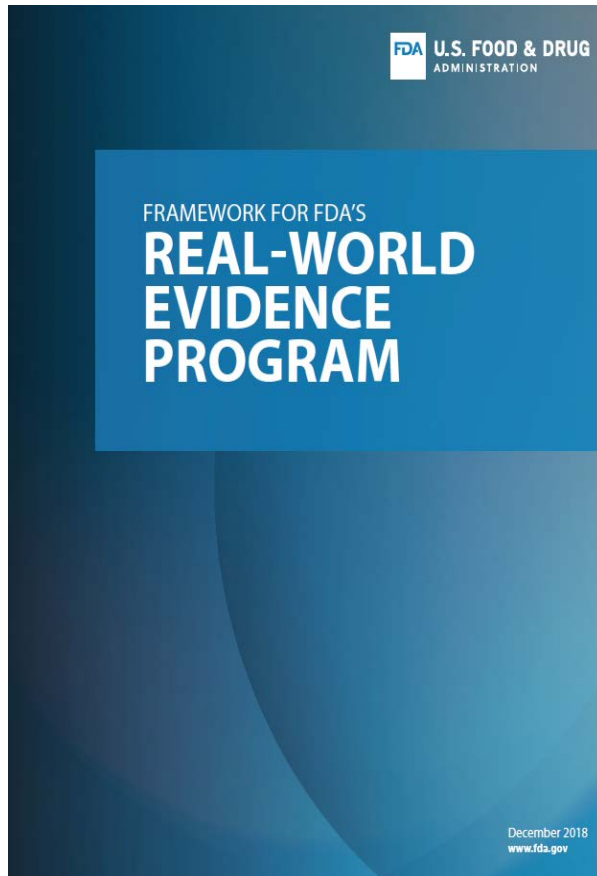> **electronic health records (EHRs)**

> **medical claims data**

> **product and disease registries**

> **patient-generated data, including in-home settings**

> **data gathered from other sources, such as mobile devices, that can inform on health status**

**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 different study designs, including but not limited to randomized trials (e.g., large simple trials, pragmatic trials), externally controlled trials, and observational studies**

# FDA RWE Framework: Dec 2018

**FRAMEWORK FOR FDA'S**
**REAL-WORLD EVIDENCE PROGRAM**

FDA U.S. FOOD & DRUG ADMINISTRATION

December 2018
www.fda.gov

## Key considerations:

The framework will include consideration of the following:

1. Whether the RWD 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 regulatory question

3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

# Considerable Experience with RWE For Safety

# RWE Can Inform Effectiveness

**FDA**

| DRUG | INDICATION | APPROVED | DATA |
|------|------------|----------|------|
| **Defitelio** *(defibrotide sodium)* | Severe hepatic veno-occlusive disorder | 2016 | ▪ Two prospective clinical trials enrolling 179 patients and **an expanded access study with 351 patients** |
| **Lutathera** *(lutetium 177 dotate)* | Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) | 2017 | ▪ Open-label clinical trial<br>▪ **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** |
| **Zostavax** *(Zoster Vaccine Live)* | Prevention of herpes zoster (shingles) in persons 50 years of age and older | 2018 | ▪ **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 |
| **Ibrance** *(palbociclib)* | Men with certain types of advanced or metastatic breast cancer | 2019 | ▪ Data from electronic health records and postmarketing reports of the **real-world use of Ibrance in male patients** |

List not exhaustive

**Bold** = RWE

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# FDA Real-World Evidence Program

# FDA Real-World Evidence Program

# Quality RWE can't be Built without Quality RWD

# RWD and Clinical Endpoints

Unpublished data on >600 registrational trials submitted to FDA

FDA

Biomarker ↑

Clinical endpoint ↓

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



The Power of Healthcare Data
The Body as a Source of Big Data

HbA1c – hemoglobin A1c,  GFR – glomerular filtration rate,  FEV1- forced expiratory volume, MACE – Major cardiovascular event,    MS- multiple sclerosis
CRO – clinician reported outcome,  PRO – patient  reported outcome

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# Demonstration Projects - Data



Transforming RWE with Unstructured and Structured data to advance Tailored therapy (TRUST)
VERANTOS

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

# 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

CARRA
Childhood Arthritis and Rheumatology Research Alliance

LimitJIA *

pcori **

FDA MyStudies to support the Crohns and Colitis Registry

CROHN'S & COLITIS FOUNDATION

IBD®*** PLEXUS

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

** Patient Centered Outcomes Research Institute

*** https://www.crohnscolitisfoundation.org/research/current-research-initiatives/ibd-plexus

# Study Design and Real-World Evidence

| Randomized/interventional | | Non-randomized/ interventional | Non-randomized/ non-interventional |
|---|---|---|---|

**Traditional randomized trial, using elements of RWD**

**Trials in clinical practice settings**

**Observational studies**

RWD to assess enrollment criteria & trial feasibility

eCRF + selected outcomes identified using EHR/claims data

*RCTs with Pragmatic Design Elements*

RCT using eCRF (+/- EHR data)

RCT using claims and EHR (pragmatic design)

Single arm study, using external control

*Prospective data collection*

**Registry study**

**Prospective cohort study**

RWD to support site selection

Mobile technology used to capture supportive endpoints

*Existing databases*

**Case – control study**

**Retrospective cohort study**

**Increasing reliance on RWD** →

RCT- randomized clinical trial
eCRF - electronic case report form

# Evidentiary Benchmark

- **FDA standard for "substantial evidence" unchanged**

  – **Goal is to distinguish the effect of the drug from other influences such as spontaneous change in disease course, placebo effect, or bias**

  – **Common practices:**

    - **Probabilistic control of confounding through randomization**

    - **Blinding**

    - **Controlled/standardized outcome assessment**

    - **Adjudication criteria**

    - **Audits**

# Demonstration Project Results: IMPACT-AFib *RCT*

- Implementation of a randomized controlled trial (RCT) within the FDA-Catalyst distributed database environment that links FDA Sentinel System data with patient/provider generated data

- Patients with atrial fibrillation at high risk of stroke were enrolled and randomized into early- and late-intervention arms to evaluate whether an educational intervention could increase appropriate use of oral anticoagulants (OACs)

- Early educational intervention failed to improve the rate of new OAC use among 47,000 enrolled participants

- Project demonstrates the feasibility of identifying, enrolling, and obtaining outcomes in RCTs using the FDA-Catalyst Network; future trials can assess strategies for patient consent and repeat patient interactions



Normal     Atrial Fibrillation

Left atrium

right atrium

noatrial node (acemaker)

trioventricular ode

Electrical activity of a normal heart (left) and a heart with atrial fibrillation (right).

Clinical Trials.gov NCT03259373

# Demonstration Project Results: RCT-DUPLICATE

FDA

## Emulating Randomized Clinical Trials with Nonrandomized Real-World Evidence Studies: First Results from the RCT DUPLICATE Initiative

**Conclusions:** Agreement between RCT and RWE findings varies depending on which agreement metric is used. Interim findings indicate that selection of active comparator therapies with similar indications and use patterns enhances the validity of RWE. Even in the context of active comparators, concordance between RCT and RWE findings is not guaranteed, partially because trials are not emulated exactly. More trial emulations are needed to understand how often and in what contexts RWE findings match RCTs.

**Originally published** 17 Dec 2020 | https://doi.org/10.1161/CIRCULATIONAHA.120.051718

# RWD During COVID

- Urgent need to rapidly understand the natural history of COVID-19
- Many critical clinical evidence needs but limited clinical trial resources (patients, time, competing tasks)
  - RWD evaluation of treatment patterns and impact provides understanding
  - RWD can help prioritize research questions to be answered with clinical trials
  - RWD can improve study design and support participant enrollment
  - Pragmatic and platform/adaptive study designs can improve efficiency and generalizability

# RWE and COVID-19 – Representative Comments

The pandemic is prompting widespread use–and misuse–of real-world data

"**The dangers of COVID-19 present an unprecedented opportunity to leverage diverse, real-world data sources to inform medical and regulatory responses. But researchers and clinicians must be careful not to sacrifice methodological rigor.**"

PNAS | **November 10, 2020** | vol. 117 | no. 45

# FDA Guidance Development

- **Real-world evidence topics (from 2018 RWE Framework):**

- **"Submitting Documents Using RWD and RWE to FDA [...]" Guidance, May 2019**

# Summary

- **FDA was accepting RWD/RWE before 21$^{st}$ Century Cures Act**

- **FDA continues to accumulate experience with RWE submissions**

- **Demonstration projects advance understanding of RWD/RWE**

- **RWE guidance development will reflect learnings from applications and demonstration projects**

- **FDA will maintain evidentiary standards with RWD/RWE**

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# Designing External Controls using Real World Data for Pediatric Cancer Drug Development

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May 12, 2021

# What is an Externally Controlled Trial?

"An externally controlled trial is one in which the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent; i.e., there is no concurrently randomized control group."

Reference: ICH Harmonized Guideline: Choice of Control Group and Related Issues in Clinical Trials E10. 2000.
FDA Guidance. E10 Choice of Control Group and Related Issues in Clinical Trials. 2001.

# External Controls

**Challenge**

Interpreting Time to Event Endpoints in Single Arm Trials

**Potential Solution**

Use of Well Constructed External Control Designs

**Primary Methodological Concern**

Ensuring Balance of Factors for Evaluation in the Absence of Randomization

# STUDY DESIGN

# External Controls

**Types**

> **External Control Arm**

> **Synthetic Control Arm**

**Temporality**

> **Concurrent Control**

- Patient population treated during the same or similar time period, reflecting a similar standard of care

> **Historical Control**

- Non contemporaneous patient population where retrospective or retrospectively analyzed data is used as comparator

FDA

# External Control Arms

## External Control Designs

- Previously Conducted Clinical Trial(s) (including pooled trial data)
- Historical Real World Data (single source)
- Historical Real World Data (pooled data)
- Prospective Real World Data
- Hybrid Prospective Designs (e.g. concurrently randomized control as well as external control)
- Other Designs

## Uses of External Controls

- As benchmark or natural history study (epidemiology)
- As individual patient level matched data for comparative study (effectiveness)

### Real World Data (RWD)

**Data Source**

- Electronic Health Records (EHR)
- Administrative Claims
- Registries
- Patient Generated Health Data (PGHD)
- Environmental Data

**Clinical Data Type**

- Medical
- Labs
- Pharmacy
- Radiology/Imaging
- Genomic
- Radiation Oncology
- Demographics, Census
- Diagnostics
- Digital Health, SDOT, Environment
- Patient Reported Outcomes

# Use of External Controls

**FDA**

## Rationale for lack of randomization

When randomized trials are

Infeasible or Impractical

Unethical

Lack of equipoise

## Applications

Pediatrics

Rare Diseases

Significant unmet medical need
Limited treatment options or Standard of care

Molecular subgroups

Under-represented populations

# Study Conceptulization

**Study Type (Design)**

Natural History/
Epidemiology
or Benchmark

External Comparator
(e.g. Historical, Synthetic,
Combination)

Hybrid Design

Pragmatic Trial

**Fit-for-Purpose**

Data Source

Patient Population

Appropriate
Comparator

Available Data

Measurement

Endpoints

# METHODOLOGICAL APPROACHES

# Methodological Concerns

Design is a pivotal step:

Careful planning in the design phase prior to study initiation can reduce issues in the analysis phase.

DATA QUALITY AND METRICS
(INTERNAL VALIDITY)

COHORT DEFINITIONS

RWD HETEROGENEITY
(EXTERNAL VALIDITY)

ENDPOINT ASCERTAINMENT
AND VALIDATION
(RESPONSE AND TIME TO
EVENT)

BIAS
(SELECTION, CONFOUNDING
MISCLASSIFICATION)

FIT FOR PURPOSE:
IS DATA COMPLETE,
CONSISTENT, ACCURATE,
LONGITUDINAL?

# Specific Considerations

## Availability of Key Covariates

- Specific patient-level data on key clinical covariates
- Selection bias & confounding can render the results uninterpretable

## Population of Interest and Data Source Selection

- External control arm patients should meet the same or similar eligibility criteria as patients in the trial or prospective study for evaluability
- Prior to analysis of a pooled external control data evaluate appropriateness and feasibility

## Data Quality and Missingness

- Complete data characterization and transparency in reporting (e.g. missingness, provenance, reliability)
- Include specific methods for handling missing data in the external control group and sensitivity analyses

# Specific Considerations

## Temporality

- Retrospective vs Concurrent
- Standard of Care

## Measurement

- Comparability of data sources and elements
- Exposure: Treatment and treatment related factors
- Outcomes: Differential capture of endpoints (ascertainment) and validation
- Follow-up: Survival should be as complete as possible, with limited censoring or missing data
- Temporal Issues and Intercurrent Events

## Protocol and Statistical Analysis Plan (apriori)

# Examples of Regulatory Use

**Clinical Scenario**: Limited or no randomized studies available (to evaluate a time to event endpoint)

**Use of External Controls**
- Use has been limited to providing important clinical context
- Often exploratory and only considered supportive data

**Limitations**
- Limited information on patient demographic and clinical characteristics (differences in treatment rates, geography)
- No pre-specified protocol to ensure the selection of a comparable patient population; Selection bias concerns
- No formal statistical comparisons; Analysis plan to outline the statistical methodology not established a priori
- Variance in follow up
- Measured and unmeasured confounding

**Approvals** based on clinical trials (e.g. single arm) where durable ORR was considered evidence of clinical benefit.

# Key Design Questions

1. What is the Real World Data (RWD) study question?

2. Is the Data Fit for Purpose?

# Thank you!

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U.S. FOOD & DRUG ADMINISTRATION

# Statistical Considerations for External Controls in Pediatric Trials

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May 12, 2021

# Introduction

- In general, randomized trials are preferred for providing evidence of drug efficacy
  - Randomized control trials (RCTs) are the gold standard for comparing treatments as the process of randomization removes confounding by known and unknown factors

- In the case that a randomized control arm is not possible, an external control (EC) arm may be an option for estimating comparative treatment effect

# Potential Use of External Controls

- External controls could be considered to demonstrate:
  - Natural history of disease
  - Contribution of components to treatment effect
  - Established efficacy from prior trials (e.g. establishing the null hypothesis for a single arm trial)
  - Comparing efficacy across treatment arms by supplementing or replacing concurrent controls in a prospective trial

- Source of data for controls would determine potential use (e.g. published literature, registry data, electronic health records, prior CT data)
  - If we want to compare efficacy endpoints, then high-quality and complete patient-level data is required

# **Importance of Study Design**

- What are the principles of good study design for a study utilizing external control data?
  - Avoid differences in the populations that result in groups that cannot be compared (measureable endpoints, temporality, availability of variables, etc.)
  - Minimize the need for analytic tools to deal with bias or confounding

- Using the estimand framework[1] for designing a study and corresponding analysis plan allows for a detailed approach to determining important aspects including:
  - Population of interest
  - Treatment/intervention to be studied
  - Endpoint or outcome
  - Intercurrent events (occur post-randomization and interfere with the interpretation of results)
  - Summary measure

[1]ICH E9 Statistical Principles for Clinical Trials (https://www.fda.gov/media/71336/download)

# Considerations for SAPs when using External Controls

- All statistical analysis plans (SAPs) should be pre-specified, preferably prior to any looks at outcome data

- Formal sample size and power calculations are still relevant (and you can prespecify a stringent alpha)

- Methods to control for various types of bias (selection bias, confounding, etc) should be specified
  - Some types of bias cannot be addressed with analytic methods; instead, sensitivity analyses can be used to understand the effect of these potential biases

- Consider hybrid designs (usually with Bayesian methods) to supplement concurrently randomized controls with external control data

# Statistical Methods to Control for Bias

| Type of Bias | Statistical  methods |
|---|---|
| Selection Bias | • Balancing scores, e.g. propensity scores (matching, weighting, stratification)<br>• Inverse probability weighting |
| Confounding | • Balancing scores, e.g. propensity scores (matching, weighting, stratification)<br>• Inverse probability weighting<br>• Marginal structural models |
| Misclassification | • Measure misclassification or "validate" measurements of external data by measuring sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) |

# General Considerations for Balancing Scores

- Idea is to "balance" the two populations (experimental treatment vs. external control), so that any remaining differences can be attributed to treatment effect

- The score may come for a model of the treatment group that includes any covariates that may be related to both treatment assignment and outcome

- Score can be used for matching/stratification/ weighting of analysis for treatment effect, but requires certain strong assumptions (no unmeasured confounding, sufficient overlap, correct model specification)

# Summary

- Trials that compare an experimental arm to an external control require a high volume of good quality, complete data
  - Want to avoid bias in ascertainment/definitions of data across treatment groups – even small discrepancies may make a big difference

- Good study design can help to avoid many of the pitfalls of using non-concurrent or non-randomized data as external controls

- Analytic methods may help to address any bias or confounding that may remain after good study design – but cannot eliminate the threat of bias completely
  - Methods require strong assumptions, including that no unknown confounders exist
  - Sensitivity analyses can assess how robust results are to assumptions

# Some Final Thoughts on External Controls

- The burden of proof to demonstrate that external controls meet the bar for comparative analyses should not be underestimated

- When considering a trial design that includes external controls, other options that preserve principal of randomization should be considered:
  - N:1 randomization ratios
  - Pragmatic trials
  - Decentralized trials

- Hybrid trial design (with Bayesian or frequentist methods) offer a unique benefit of allowing for both external and concurrent controls, which minimizes risk

- If ultimately an externally controlled trial design is chosen, all operating characteristics and statistical methods should be prespecified

# REAL-WORLD EVIDENCE (RWE) TO ASSESS PEDIATRIC MEDICAL PRODUCT SAFETY

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Office of Pediatric Therapeutics (OPT)

Office of Clinical Policy and Programs

Office of the Commissioner

# Disclaimer

FDA

- This presentation reflects my opinion and not necessarily the opinion of the Food and Drug Administration

# Outline

1) Pediatric Advisory Committee
2) Special considerations of RWD/RWE* in pediatrics
3) Select examples of databases that support pediatric RWD/RWE safety
4) Select examples of studies highlighting pediatric RWD/RWE safety research
5) Systematic review of pediatric RWD/RWE
6) Takeaways regarding pediatric RWD/RWE
7) Conclusions

*Real-World Data/Real-World Evidence

# Pediatric Advisory Committee (PAC)

- Congressionally mandated in 2002

- Ethics and neonatology subcommittees

- All logistics for PAC activities managed in OPT (unlike other advisory committees)

- Mandate that 18 months after pediatric labeling changes, FDA will conduct post-marketing safety reviews of those drugs and present the information to the PAC

- In 2017, worked with the Division of Pediatrics and Maternal Health and Office of Surveillance and Epidemiology to develop a process to review the safety data and post the reviews to the web if no safety issues identified (low safety risk)

  - The first web posting of safety reviews was done on September 12, 2016

  - To date, there have been 166 product reviews posted to the web

- May be a higher percentage of products going to PAC with the RACE for Children Act*

  * Research to Accelerate Cures and Equity for Children Act

# Special Considerations in Pediatric Real-World Data (RWD)/Real-World Evidence (RWE)*[1]

FDA

- Data that may be especially important in children

  - Birth date

  - Gestational age

  - Data related to families

    - Demographics

    - Health status

  - School performance and school records

*Definition of Real-World Data (RWD)/Real-World Evidence (RWE) can be found in "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics" Guidance for Industry; May 2019

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# Special Considerations in Pediatric RWD/RWE (cont.)



- Large enough sample size to detect rare adverse events

- Denominator within the database

- Growth and development

# Select Examples of Databases that Support Pediatric RWD/RWE Safety*[2]

| | AAEDC | AAEDP | CER-Squared | CIQN | Kidnet | Pediatrix | PEDSNet | PHIS | VON |
|---|---|---|---|---|---|---|---|---|---|
| Surveillance Type | Ac | Ac | Re | Ob | Re | Ob | Re/Ob | Ob | Ob |
| EMR Use | X | X | X | X | X | X | X | X | X |
| Incidence Rates | X | X | X | X | X | X | X | X | X |
| Longitudinal Data | O | X | X | X | | X | X | X | O |
| Automated Trigger Tools | X | X | | | | | | | |
| Inpatient Data | X | X | X | X | X | X | X | X | X |
| Outpatient Data | | X | X | X | | | X | X | |

*EMR= Electronic Medical Record, AAEDC= Automated adverse event detection collaborative, AAEDP= Automated
*Adverse Event Detection Program, CER-squared=Comparative Effectiveness Research through Collaborative Electronic Reporting, CIQN=
Children's IQ Network, Kidnet= network of pediatric hospitals working with FDA, Pediatrix= Collaborative of multiple Neonatal Intensive Care
Units, PEDSNet= Pediatric Electronic Data Sharing Network, PHIS= Pediatric Health, Information System, VON= Vermont Oxford Network
X- system captures this type of data. O- system captures a limited amount of this kind of data, <blank>- system does not capture this type of data.
Ac= Active surveillance, Re= Retrospective chart review, Ob= Observational data

# Select Examples of Databases that Support Pediatric RWD/RWE Safety*[2]

FDA

| | AAEDC | AAEDP | CER-Squared | CIQN | Kidnet | Pediatrix | PEDSNet | PHIS | VON |
|---|---|---|---|---|---|---|---|---|---|
| **Age Range** | [0,>18] | [0,>18] | [0,18] | [0,>18] | [0,7] | [0,<2] | [0,>17] | [0,≥18] | [0,1] |
| **Usage Data‡** | O | O | X | X | X | X | X | X | X |
| **Approx. Sample Size** | Variable | Variable | 1.2M | 1.7M | 380 | 1M | 3.8M | 6M | 2M |
| **Vaccine Data** | | O | | X | | X | X | X | |
| **Medical Device Data** | X | O | | | | | X | O | X |
| **Geographic Population** | DC, OH | Global | USA | DC, MD, VA | USA | USA | USA | USA | Global |
| **Earliest Data Collected** | 2006 | 2006 | 2012 | 2008 | 2010 | 1996 | 2009 | 1999 | 1989 |

*System captures this type of data, O- system captures a limited amount of this kind of data,
  <blank>- system does not capture this type of data from one database

# SELECT EXAMPLES OF STUDIES HIGHLIGHTING PEDIATRIC RWD/RWE SAFETY RESEARCH

# Octreotide in Infants and Children – A Use Case of Pediatric RWD Safety[4]

- Octreotide is a synthetic peptide analog of naturally occurring somatostatin
  - Used off-label in children <6 years of age for hyperinsulinism
  - Lack of controlled data on efficacy or potential adverse events from off-label use
- Three pediatric hospitals in this study. Patients hospitalized in three pediatric hospitals 2007–2010 and administered octreotide for congenital hyperinsulinism
  - Variables assessed included octreotide dosage, patient demographics, medical interventions, concomitant medicines, serious adverse events (SAEs) including necrotizing enterocolitis (NEC), and mortality
  - 103 patient sample had a median gestational age of 38 weeks
  - During the study period, two patients died: one from NEC 3 days after octreotide
  - Comorbidities included patent ductus arteriosus (PDA), respiratory distress, and heart block type 1. 11 other SAEs in the 101 surviving patients
- Study highlights potential risks in administering octreotide off-label. Fatal NEC in a full-term infant treated with temporal association with octreotide

# Clinical Information for Infants Treated with Octreotide for Hyperinsulinism

FDA

| Variable | Median | Range | # Patients |
|---|---|---|---|
| Gestational age | 38 weeks | 28-40 weeks | 84 |
| Birth weight | 3.7 kg | 1.0-5.6 kg | 50 |
| Age at study entry | 15.2 weeks | 0.9- 313.2 weeks | 103 |
| Weight at study entry | 6.4 kg | 2.3-31.4 kg | 103 |
| Hospital length of age | 24.5 days | 1-90 days | 102 |
| Octreotide daily dose | 8.96  mcg/kg | 1.33-96 mcg/kg | 100 |
| Octreotide duration | 8 days | 1-84 days | 103 |

# Acute Kidney Injury During Treatment with IV Acyclovir for Suspected or Confirmed Neonatal Herpes Simplex Virus Infection

**FDA**

- Described epidemiology of and risk factors associated with acute kidney injury (AKI) during acyclovir treatment in neonates and infants

- Multicenter (n = 4), retrospective cohort study hospitalized infants age <60 days treated with intravenous acyclovir (at least 1 dose) for suspected or confirmed neonatal herpes simplex virus disease from January 2011 to December 2015
  - Classified AKI based on changes in creatinine according to published neonatal AKI criteria and performed Cox regression analysis

- 1017 infants: majority received short courses of acyclovir (median, 5 doses)
  - Fifty-seven infants (5.6%) developed AKI during acyclovir treatment
  - Cox regression: confirmed herpes simplex virus disease (OR, 4.35; P = .002), receipt of at least 2 concomitant nephrotoxic medications (OR, 3.07; P = .004), receipt of mechanical ventilation (OR, 5.97; P = .001), and admission to an intensive care unit (OR, 6.02; P = .006) risk factors for AKI during acyclovir treatment

- Rate of AKI low with sicker infants and those exposed to additional nephrotoxic medications seem to be at greater risk for acyclovir-induced toxicity and warrant closer monitoring

# Systematic Review of Pediatric RWE Safety and Efficacy[5]

- Objectives/Methods: To describe the state of RWE in pediatrics by identifying observational studies published during 2016 that used RWE to assess medication safety or effectiveness in children: a systematic review

# Conclusion from Pediatric RWE Safety and Efficacy[5] (Systematic Review)

- A small body of observational studies published in 2016 (N=29) were categorized as using RWD to assess medication safety or effectiveness in children

- Studies varied in age groups, diseases or conditions, and methods

- Most studies relied on data collected at single institutions

- One quarter of studies did not use well established statistical methods to control for confounders

# Takeaways Regarding Pediatric RWD/RWE

- In working with pediatric RWD/RWE:
  - Can be difficult to adjust for growth and development
  - Can be difficult to obtain records outside of medical records, such as school records

- Confounding not always able to be fully controlled: example of Acyclovir users, "sicker" patients more likely to have AKI

- Sample sizes can be small in pediatric patients with rare diseases, especially if using medication off-label such as Octreotide for hyperinsulinism

# Conclusions

- RWD/RWE in pediatrics may be useful to fill in gaps in pediatric knowledge

    – Identification of a more diverse population from a demographic perspective

    – Reflection of product use in the general population

    – Understanding the variable nature of the underlying illness outside Randomized Clinical Trials

# References

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