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:
  o support approval of new indication for a drug approved under section 505(c)
  o satisfy post-approval study requirements

• Ongoing CDER/Center for Biologics Evaluation and Research (CBER) RWE program based on December 2018 “RWE Framework”:
  o 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
  o 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.
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

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

List not exhaustive

*Bold = RWE*
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

<table>
<thead>
<tr>
<th>Type of endpoint</th>
<th>Studies %</th>
<th>Examples of endpoints measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>21%</td>
<td>HbA1c, pregnancy test, GFR</td>
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<tr>
<td>Hematology</td>
<td>4%</td>
<td>Severe neutropenia</td>
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<tr>
<td>Apheresis yield &gt; 5 million CD34+ cells/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td>1%</td>
<td>Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells</td>
</tr>
<tr>
<td>Microbiology</td>
<td>9%</td>
<td>Sustained virological response, plasma viral load, conversion to negative sputum</td>
</tr>
<tr>
<td>Imaging +/- (survival, clinical signs)</td>
<td>10%</td>
<td>Bone mineral density; vertebral fractures, spleen volume, progression free survival</td>
</tr>
<tr>
<td>Physiological/functional measurement</td>
<td>10%</td>
<td>6 minute walk, normal sinus rhythm, FEV1, sleep studies</td>
</tr>
<tr>
<td>Clinical event /clinical sign</td>
<td>13%</td>
<td>Death, hospitalization, MACE, MS relapse, Lice free head</td>
</tr>
<tr>
<td>CRO/PRO</td>
<td>31%</td>
<td>Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score</td>
</tr>
</tbody>
</table>

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
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

eCRF - electronic case report form

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

FDA MyStudies to support the Crohn’s and Colitis Registry

* 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**
  - Traditional randomized trial, using elements of RWD
    - RWD to assess enrollment criteria & trial feasibility
    - RWD to support site selection
  - Trials in clinical practice settings
    - RCTs with Pragmatic Design Elements
      - RCT using eCRF (+/- EHR data)
      - RCT using claims and EHR (pragmatic design)
  - Observational studies
    - Prospective data collection
      - Registry study
      - Prospective cohort study
      - Existing databases
        - Case – control study
        - Retrospective cohort study

- **Non-randomized/interventional**
  - eCRF + selected outcomes identified using EHR/claims data
  - Mobile technology used to capture supportive endpoints

- **Non-randomized/non-interventional**
  - Mobile technology used to capture supportive endpoints

Increasing reliance on RWD

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RCT- randomized clinical trial
eCRF - electronic case report form
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

Clinical Trials.gov NCT03259373
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
Evaluating RWE from Observational Studies in Regulatory Decision-Making: Lessons Learned from Trial Replication Analyses

February 16 & 17, 2021
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):
  - Assessing Fitness of RWD for Use in Regulatory Decisions .......................................................... 14
  - Potential for Study Designs Using RWD to Support Effectiveness ....................................................... 19
  - Regulatory Considerations for Study Designs Using RWD ................................................................. 22
  - Data Standards — Appropriate Data Standards for Integration and Submission to FDA............. 24

• “Submitting Documents Using RWD and RWE to FDA [..]” Guidance, May 2019
Summary

- FDA was accepting RWD/RWE before 21st 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
Designing External Controls using Real World Data for Pediatric Cancer Drug Development

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Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee
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 investigative agent; i.e., there is no concurrently randomized control group.”

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
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)
# Use of External Controls

**Rationale for lack of randomization**

- When randomized trials are infeasible or impractical
- 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 Conceptualization

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
Design is a pivotal step:
Careful planning in the design phase prior to study initiation can reduce issues in the analysis phase.
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 evaluable
- 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!

Acknowledgements
• Paul Kluetz
• Pallavi Mishra-Kalyani
• Amy Barone
• Sonia Singh
• Diana Bradford
• Gautam Mehta
• Martha Donoghue
• Harpreet Singh
Statistical Considerations for External Controls in Pediatric Trials

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Division of Biometrics V, Office of Biostatistics
Center for Drug Evaluation and Research (CDER), FDA

Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee
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 (measurable 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

<table>
<thead>
<tr>
<th>Type of Bias</th>
<th>Statistical methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection Bias</td>
<td>• Balancing scores, e.g. propensity scores (matching, weighting, stratification)</td>
</tr>
<tr>
<td></td>
<td>• Inverse probability weighting</td>
</tr>
<tr>
<td>Confounding</td>
<td>• Balancing scores, e.g. propensity scores (matching, weighting, stratification)</td>
</tr>
<tr>
<td></td>
<td>• Inverse probability weighting</td>
</tr>
<tr>
<td></td>
<td>• Marginal structural models</td>
</tr>
<tr>
<td>Misclassification</td>
<td>• Measure misclassification or “validate” measurements of external data by measuring sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)</td>
</tr>
</tbody>
</table>

www.fda.gov
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

• 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

• 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
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

<table>
<thead>
<tr>
<th>Surveillance Type</th>
<th>AAEDC</th>
<th>AAEDP</th>
<th>CER-Squared</th>
<th>CIQN</th>
<th>Kidnet</th>
<th>Pediatrix</th>
<th>PEDSNet</th>
<th>PHIS</th>
<th>VON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Ac</td>
<td>Re</td>
<td>Ob</td>
<td>Re</td>
<td>Ob</td>
<td>Re/Ob</td>
<td>Ob</td>
<td>Ob</td>
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<td>EMR Use</td>
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<td>Automated Trigger Tools</td>
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<td>Inpatient Data</td>
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<td>x</td>
<td>x</td>
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</tr>
</tbody>
</table>


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

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

<table>
<thead>
<tr>
<th>Age Range</th>
<th>AAEDC</th>
<th>AAEDP</th>
<th>CER-Squared</th>
<th>CIQN</th>
<th>Kidnet</th>
<th>Pediatrix</th>
<th>PEDSNet</th>
<th>PHIS</th>
<th>VON</th>
</tr>
</thead>
<tbody>
<tr>
<td>[0,&gt;18]</td>
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<td>O</td>
<td>[0,18]</td>
<td>[0,&gt;18]</td>
<td>[0,7]</td>
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<td>[0,&gt;17]</td>
<td>[0,&gt;18]</td>
<td>[0,1]</td>
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</tbody>
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*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

<table>
<thead>
<tr>
<th>Usage Data*</th>
<th>AAEDC</th>
<th>AAEDP</th>
<th>CER-Squared</th>
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<th>Kidnet</th>
<th>Pediatrix</th>
<th>PEDSNet</th>
<th>PHIS</th>
<th>VON</th>
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<tbody>
<tr>
<td>O</td>
<td>O</td>
<td>O</td>
<td>X</td>
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<table>
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<th>CER-Squared</th>
<th>CIQN</th>
<th>Kidnet</th>
<th>Pediatrix</th>
<th>PEDSNet</th>
<th>PHIS</th>
<th>VON</th>
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<tr>
<td>Variable</td>
<td>Variable</td>
<td>1.2M</td>
<td>1.7M</td>
<td>380</td>
<td>1M</td>
<td>3.8M</td>
<td>6M</td>
<td>2M</td>
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<table>
<thead>
<tr>
<th>Vaccine Data</th>
<th>AAEDC</th>
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<th>Kidnet</th>
<th>Pediatrix</th>
<th>PEDSNet</th>
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<th>AAEDC</th>
<th>AAEDP</th>
<th>CER-Squared</th>
<th>CIQN</th>
<th>Kidnet</th>
<th>Pediatrix</th>
<th>PEDSNet</th>
<th>PHIS</th>
<th>VON</th>
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<th>CIQN</th>
<th>Kidnet</th>
<th>Pediatrix</th>
<th>PEDSNet</th>
<th>PHIS</th>
<th>VON</th>
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<th>Pediatrix</th>
<th>PEDSNet</th>
<th>PHIS</th>
<th>VON</th>
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SELECT EXAMPLES OF STUDIES HIGHLIGHTING PEDIATRIC RWD/RWE SAFETY RESEARCH
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Range</th>
<th># Patients</th>
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<tbody>
<tr>
<td>Gestational age</td>
<td>38 weeks</td>
<td>28-40 weeks</td>
<td>84</td>
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<tr>
<td>Birth weight</td>
<td>3.7 kg</td>
<td>1.0-5.6 kg</td>
<td>50</td>
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<tr>
<td>Age at study entry</td>
<td>15.2 weeks</td>
<td>0.9- 313.2 weeks</td>
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<tr>
<td>Weight at study entry</td>
<td>6.4 kg</td>
<td>2.3-31.4 kg</td>
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<tr>
<td>Hospital length of age</td>
<td>24.5 days</td>
<td>1-90 days</td>
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<tr>
<td>Octreotide daily dose</td>
<td>8.96 mcg/kg</td>
<td>1.33-96 mcg/kg</td>
<td>100</td>
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<tr>
<td>Octreotide duration</td>
<td>8 days</td>
<td>1-84 days</td>
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Acute Kidney Injury During Treatment with IV Acyclovir for Suspected or Confirmed Neonatal Herpes Simplex Virus Infection

- 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

1) Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry; May 2019


