Hot Topic

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

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Disclaimer

• 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

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.

Will Real-World Evidence Replace Clinical Trials?

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.

Real World Evidence Solutions Market to Reach USD 5 Billion Globally by 2031 at 13.7% CAGR, Says Allied Market Research
Volume of scientific literature related to RWE is booming

What happened in 2016?
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 Draft guidance on using RWE in drug approvals within 5 years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

Section on RWE is only 2 pages and worth reading
Regulatory guidance on real world evidence in the US

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](https://www.fda.gov/media/120060/download)
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<th>Source</th>
<th>Type</th>
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## Data elements commonly available in RWD

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<td>Results</td>
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## Study designs related to RWE

<table>
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<tr>
<th>Concept</th>
<th>Description</th>
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| 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).

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.

- 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
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)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Define doses of the dextroamphetamine transdermal system in children and adolescents which achieve exposures similar to adults.</th>
</tr>
</thead>
</table>
| 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)

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)
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)*

| Background | • Lacosamide (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.  
• Lacosamide is used *off-label* for treatment of RFS in pediatric patients <4 years. |
| --- | --- |
| Problem | • No confirmed guideline on appropriate dosing of adjunctive lacosamide for patients <4 years.  
• Few trials in ages <4yrs |
| Analysis Goals | **STAGE 1**: Use RWD to characterize PK of Lacosamide 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:

<table>
<thead>
<tr>
<th>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)</th>
</tr>
</thead>
</table>

#### Analysis Stage 1

- **RWD data source:** EMR - routinely captured therapeutic drug monitoring assessments.
- Identified 315 pediatric patients >1 month to <18 years who received Lacosamide.
- 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
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

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

Data on UK Biobank participants
- Cognitive function and hearing tests
- Health outcome data
- Genotyping & imputation (n = 500,000)
- Environmental measures
- Web-based questionnaire data (~200,000)
- Urinary biomarkers
- Genetic data via the EGA (500,000)
- Physical activity monitor (100,000)
- Imaging (15,000+)

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

References
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%

RWI

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

References

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
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

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
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
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
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

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

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References
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