Use of Real-World Evidence (RWE) to Drive Drug Development Strategy and Inform Clinical Trial Design

Speakers:
Jennifer Webster, RWE COE
Simon Dagenais, RWE COE

Moderator:
Jing Liu, Clinical Pharmacology

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Brief history of RWE in the US

- Congress passed 21st Century Cures Act in December 2016
- Included a provision on Real World Evidence (Section 3022)
- Modified Federal Food, Drug, and Cosmetic Act to add section 505F
- 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 Draft guidance on using RWE in drug approvals within 5 years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.

References

https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.xml
https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

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## Important terminology related to RWE

| Real world data                          | Real world insights                                         | Real world evidence                                           |
|------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------|
| **Definition**                           | Answers to internal research questions derived from analyzing real world data | Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD |
| Data relating to patient health status and/or delivery of health care routinely collected from a variety of sources | | |
| **Examples**                             | Hypothesis generation                                       | Evidence supporting:                                         |
| • Medical claims and billing             | • Feasibility                                               | • Effectiveness                                              |
| • Electronic health records              | • Patient journey                                           | • Safety                                                     |
| • Patient/product registries             | • Unmet needs                                               | • Outcomes                                                   |
| • Patient surveys                        | | |
| **Analogy**                              | | |

References
https://www.fda.gov/media/120060/download
| Source                          | Type                     | Examples                                      |
|-------------------------------|--------------------------|-----------------------------------------------|
| Administrative                | Closed networks          | IBM MarketScan, IQVIA PharMetrics, Optum Clininformatics |
| Hospital chargemaster         | Open networks            | IQVIA LAAD, DRG RWD, Symphony IDV           |
| Government                    | CMS FFS Medicare, Medicaid, VA/DOD |
| Pharmacy                      | Premier, Vizient, IQVIA CDM |
| Electronic health records     | Core setting             | Cerner, Epic, Athena                         |
| Clinics                       | IQVIA AEMR, Optum Panther, IBM Explorx |
| Disease                       | Oncology                 | Flatiron, Ontada, ConcertAI                  |
| Behavioral health             | Kaleo, SimplePractice, Valiant |
| Patient                        | Health surveys           | Kantor Health NHWS, Gallup National Health   |
| Outcome measures              | Public                   | NHANES, MEPS                                |
| Multidimensional              | PatientsLikeMe, Citizen  |
| Consumer genetic testing      | 23andMe, Ancestry.com    |
| Social determinants of health | IQVIA/Experian, MarketScan HPM, Optum SES |
| Medical devices               | Glocke, Livongo          |
| Mobile device biometrics      | Smartphones              | iPhone (HealthKit), Android (Google Fit)     |
| Diagnostics                   | Smart watches            | Apple Watch (HealthKit), Fitbit (Google Fit) |
| Laboratory testing            | Genetic testing          | Invitae, Neogenomics, Ambry Genomics         |
| Clinicogenomics               | Oncology                 | AACR GENIE, Optum Clinicogenomics            |
| Population genomics           | NHGRI 1000 Genomes Project, NIH All of Us |
| Diagnostic imaging            | Life Image, Ambra Health |
| Other                         | Disease registries       | CorEvitas, Target RWE                        |
| Other                         | Other                    | OM1, COTA Healthcare                         |
| Adverse event reports         | Regulatory               | FDA FAERS, FDA YAES                          |
| Mortality                      | Social media             | Twitter, Facebook                            |
| Tokenization                   | Public/Private           | CDC WONDER, ObituaryData.com                |
|                              |                          | HealthVerity, Datavant, Komodo               |
RWE can be a powerful tool at every step of the product development process.
Today’s Encore Webinar will review R&D applications of RWE based on our article in the January 2022 issue of *Clinical Pharmacology & Therapeutics*

**Learning objectives**

At the end of this webinar, participants will understand how biopharmaceutical companies can leverage RWD, RWI, and RWE (collectively termed “RWE”) to inform internal decisions throughout the product development process, including:

1. Use of RWE to guide pipeline and portfolio strategy
2. Use of novel sources of RWE to inform product development
3. Use of RWE to inform clinical development
1. Use of RWE to guide pipeline and portfolio strategy
While there are many examples of using RWE to guide R&D portfolio strategy, today we will focus on 3 examples:

| Citation          | Study Objective                                           | Data Source(s)                                      | Insight                                                                 |
|-------------------|-----------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------|
| Broder et al. (2018)\(^{17}\) | Estimate prevalence and incidence of neuroendocrine tumors | IBM MarketScan and IQVIA PharMetrics claims databases | Prevalence and incidence increasing over time.                         |
| Dellon et al. (2014)\(^{66}\) | Estimate prevalence of EE                                 | IQVIA PharMetrics claims databases                 | Updated estimates for number of patients with EE in the United States following the introduction of a new ICD-9 diagnosis code specific to EE. |
| Wallin et al. (2019)\(^{16}\) | Estimate national prevalence for MS by analyzing multiple US databases, covering different population segments. | Optum, IBM, Kaiser Permanente, Department of Veterans Affairs, and the Centers for Medicare and Medicaid claims databases | The 3-year prevalence of MS was 309.2 per 100,000, with an estimated 727,344 cases in the United States, higher than previous studies. |
| Halpern et al. (2019)\(^{67}\) | Estimate prevalence of agitation among patients with AD     | Optum EHR database                                  | Prevalence of agitation over a 2-year period was 44.6%. NLP was used to analyze unstructured data for keywords related to agitation. |
| Chehade et al. (2021)\(^{68}\) | Describe patient journey for individuals with EG/EoD       | Symphony Health Patient Source claims database       | Many EG/EoD patients initially diagnosed with irritable bowel syndrome or dyspepsia, highlighting the need for improved diagnosis. |
| Morgan et al. (2021)\(^{69}\) | Describe diagnostic journey of patients with PSP          | Patient interviews and physician chart reviews in France, Germany, Italy, Spain, the United Kingdom, and the United States | Diagnostic delays may be related to patients first presenting to primary care providers before being evaluated by movement disorder specialists. |
Background

- Estimates on prevalence and incidence of neuroendocrine tumors (NETs) in the US based on SEER registry suggest they are ultrarare
- Objective was to update estimates of NETs using insurance claims in the US

Methods

- Analyzed claims data from MarketScan and PharMetrics that together include ~100 million individuals in the US
- Estimated annual prevalence and incidence rates based on ICD-9 diagnosis codes among insured

Findings

RWD insights

- Although NETs are rare, claims in the US suggest annual prevalence and incidence may be increasing

References

Broder MS, Cai B, Chang E, Neary MP. Incidence and prevalence of neuroendocrine tumors of the lung: analysis of a US commercial insurance claims database. BMC Pulm Med. 2018;18(1):135.
Combining multiple sources of RWE can help size entire target population

Background
- Older estimates based on literature suggest there are 300,000-400,000 patients with multiple sclerosis (MS) in the US
- Objective was to generate an updated and robust estimate of national prevalence of MS in US using RWD

Methods
- Analyzed claims data from Optum, MarketScan, Kaiser, VA, and CMS
- Combined estimates from different population subgroups into comprehensive national estimate

Findings

RWD insights
- Estimates from 5 recent sources of claims data suggest that 727,344 individuals in the US have MS

References
Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 2019;92(10):e1029-e40.
Background
- Literature suggests that eosinophilic gastrointestinal diseases (EG/EoD) are commonly misdiagnosed
- Objective was to understand the diagnostic journey of patients with EG/EoD in the US

Methods
- Analyzed data from Symphony Health, a large database of insurance claims for multiple payers in the US
- Estimated interval between symptom presentation, gastroenterologist visit, diagnostic test (EGD), and diagnosis

Findings

RWD insights
- Mean delay from symptom presentation to diagnosis of EG/EoD was 4.1 years in the US

References
Chehade M, Kamboj AP, Atkins D, Gehman LT. Diagnostic Delay in Patients with Eosinophilic Gastritis and/or Duodenitis: A Population-Based Study. J Allergy Clin Immunol Pract. 2021;9(5):2050-9 e20.
**Background**

- Early in COVID-19 pandemic, researchers were interested in repurposing existing drugs to minimize development time
- 25 drugs (anti-microbials and anti-inflammatories) were evaluated in clinical trials for COVID-19
- Based on cell line studies, these drugs were predicted to impact 11 transporter pathways that could result in DDIs

**Methods**

- Analyzed EHR data from Cerner and USCF to determine if predicted DDIs were occurring based on lab test values

**Findings**

**RWD insights**

- 20/25 (80%) existing drugs evaluated for COVID-19 were predicted to cause transporter-mediated clinical DDIs

**References**

Yee SW, Vora B, Oskotsky T, Zou L, Jakobsen S, Enogieru OJ, et al. Drugs in COVID-19 Clinical Trials: Predicting Transporter-Mediated Drug-Drug Interactions Using In Vitro Assays and Real-World Data. Clin Pharmacol Ther. 2021;110(1):108-22.
2. Use of novel sources of RWE to inform product development

Jennifer Webster
Publicly available resources like SEER & WHO offer high level epi & trends

Scenario: Your team is concerned that incidence rates from the literature give an inaccurate picture within the TPP for MSI-H mCRC, with an opportunity to use large scale RWD for pharmacometric modeling.

The SEER registry aggregates data from cancer registries in a selection of states. Incidence and death rates per 100,000 for colorectal cancer are shown.
Claims and EHR data give insights on more refined subpopulations

Identifying subpopulations in real world data. Example: MSI-H mCRC patients

Option 1: Expert knowledge

Ontologies beyond ICD-9/10

Evidence of Molecular Testing

Line of Therapy Business Rules

Targeted Therapies as Proxies

Option 2: Machine Learning

Deep learning for the detection of microsatellite instability from histology images in colorectal cancer: A systematic literature review

Echle, A., Laleh, N. G., Schrammen, P. L., West, N. P., Trautwein, C., Brinker, T. J., ... & Kather, J. N. (2021). Deep Learning for the detection of microsatellite instability from histology images in colorectal cancer: A systematic literature review. Immunoinformatics, 100008.
Adding endpoints allows us to understand heterogeneity among subpopulations

Using real world data to challenge epi assumptions in TPP

- MSI-H widely reported to be 15% of CRC
- Only 6% of Stage 4
3. Use of RWE to inform clinical development
Data mining for endpoint discovery: hypothesis generation
Scenario: clinical trial planning for Duchenne Muscular Dystrophy

Mining real world clinical data for safety and efficacy biomarkers

GLDH detects the onset of liver injury in a subject with rhabdomyolysis in a real world prospective trial

FDA guidance on DMD efficacy endpoints

“FDA encourages sponsors to propose and, if necessary, develop endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages. Sponsors should engage FDA early during the selection and/or development of efficacy endpoints. The sponsor should include an assessment of multiple efficacy endpoints, when feasible.”
Simulations to explore optimal clinical trial designs
Use to inform trial enrichment strategies throughout all stages of the asset lifecycle

Example: Simulation of 100 trials, 50 patients/arm, baseline age 6-12 yrs, duration 3 years, drug predicted to have 30% effect on maximum FVC achieved
Including geographic information allow us to open trials where the patients are treated.
Real world genomics for target discovery and validation
• Genomic data from real world care and from biobanks

Prospective observational studies can be started as soon as FIH

Use of organoids and xenografts to inform disease model and understand drug response and resistance

Causal Inference Modeling for hypothesis generation

Tokenization for long term follow up

RW Single-cell RNAseq to understand tumor microenvironment throughout patient journey
Thank you!