

# Interpreting and Conducting Practice-Based Research: An Overview of Real-World Evidence

*June 29, 2021*





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# Webinar Agenda and Faculty

- Overview of Real-World Evidence (RWE)
- Conducting Real-World Studies
- Payer Use of RWE
- RWE and the Managed Care Pharmacy Research Agenda
- Q&A



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# Overview of Real-World Evidence (RWE)





## Real-World Data (RWD)

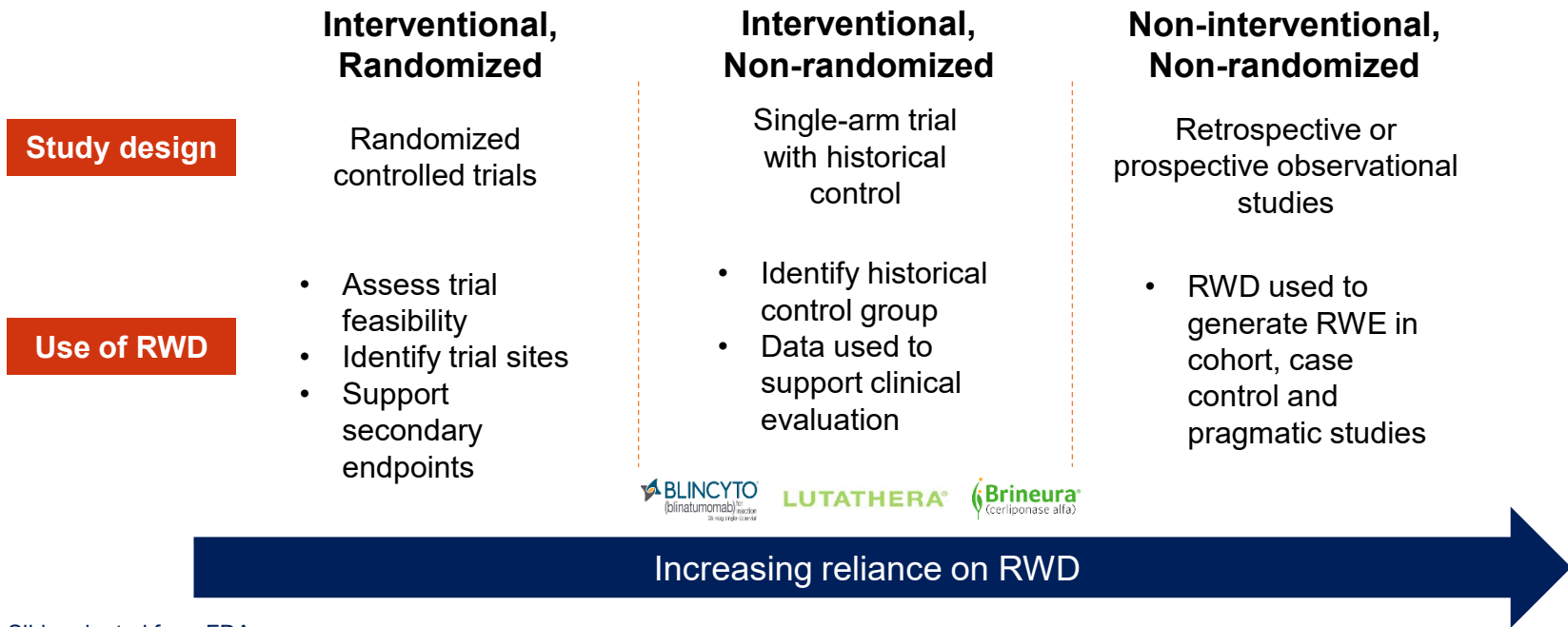
- Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources
- Example sources:
  - claims and billing data
  - electronic health record (EHR)
  - clinical registries
  - digital health data

## Real-World Evidence (RWE)

- The clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD
- Example study designs:
  - case control
  - retrospective cohort
  - prospective cohort
  - pragmatic trials



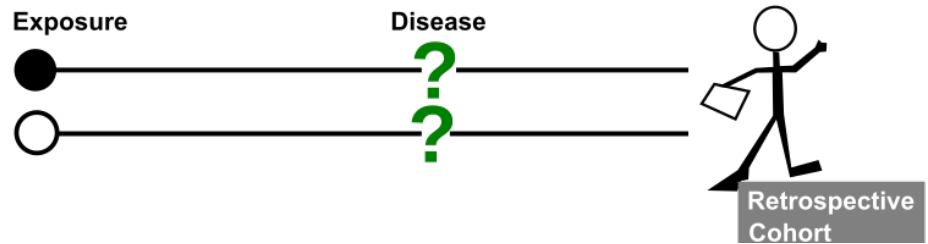
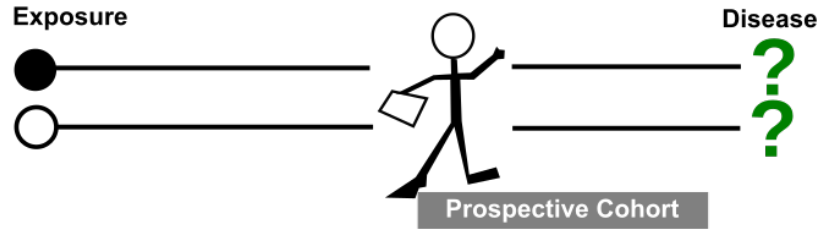
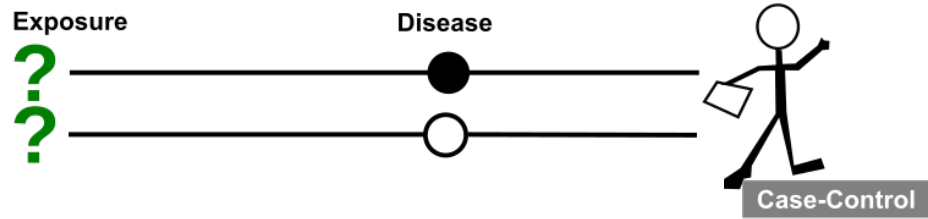
# Spectrum of RWD in Clinical Studies



Slide adopted from FDA












# Observational Study Designs





# Pragmatic Trial Designs

		Randomized controlled trial	Pragmatic clinical trial
Selection criteria		Predefined inclusion and exclusion criteria	Minimal; real-world patient population(s)
Data collection		Rigorous process	Real world + additional sources
Monitoring		Strict monitoring	Routine clinical care
Follow-up		Usually shorter follow-up and frequent visits	Longer follow-up, with few mandatory visits
Medication adherence		High	Low
Outcomes		Usually include hard or objective outcomes; few may be patient reported	May be entirely subjective or patient reported; occasionally objective
Data quality and internal validity		Excellent	Intermediate
Cost per patient		High	Intermediate
Stakeholder audience		Traditionally of value to regulatory authorities and clinicians	Of value to regulatory authorities, payers, and clinicians

<https://www.sciencedirect.com/science/article/pii/S2590143520300038>



# Conducting Real-World Studies



# RWE Gaining Prominence Among Regulatory, Policy, Provider and Payer Decision Makers

FDA U.S. FOOD & DRUG  
ADMINISTRATION

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

December 2018  
www.fda.gov

## 21st Century Cures Act



## 21ST CENTURY CURES ACT:

An Act to accelerate the discovery, development, and delivery of 21st century cures, ....

Signed into law on December 13, 2016



Provisions for sNDA allowing companies to provide ... "real world evidence" such as observational studies, insurance claims data, patient input, and anecdotal data ... ,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/oc/2016/12-35/america-new-21st-century-cures-act-will-speed-drug-approvals-good-things](https://www.accessdata.fda.gov/drugsatfda_docs/oc/2016/12-35/america-new-21st-century-cures-act-will-speed-drug-approvals-good-things)

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doi:10.1017/S02644331000000

## PAYER PERSPECTIVES ON FUTURE ACCEPTABILITY OF COMPARATIVE EFFECTIVENESS AND RELATIVE EFFECTIVENESS RESEARCH

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## SOUNDING BOARD

### Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P.,  
Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H.,



# RWE and Efficacy/Effectiveness Measures

## *Example: Multiple Sclerosis (MS)*

### Efficacy Measures

- ✓ Expanded Disability Status Scale (EDSS)
- ✓ MRI activity
- ✓ Number of relapses

### Effectiveness Measures

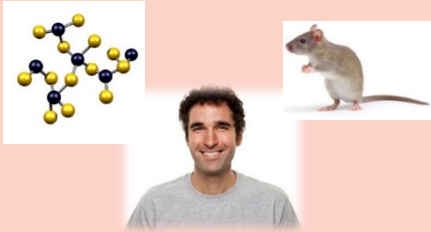
- ✓ Reduction in mortality
- ✓ Number of symptom-free days
- ✓ Patient quality of life (QoL)
- ✓ Absenteeism and productivity





# Experimental vs. Observational

## Experimental



- Efficacy: “Can it work?”
- Causation
- Randomization
- Low generalizability

## Observational



- Effectiveness: “Does it work?”
- Correlation
- Non-randomized (self-selected)
- High generalizability



# RWE Applications

RWE can be useful for many activities:





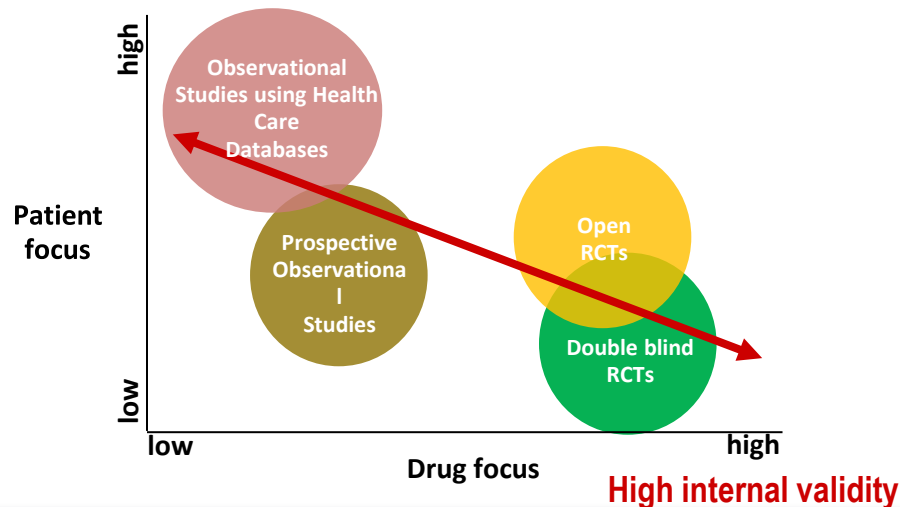
# Limitations of RWE

- RWE is subject to numerous biases:
  - Bias is prejudice in favor of or against one thing, person, or group compared with another, usually in a way considered to be unfair.
    - Selection bias (where patient groups are not comparable)
    - Performance bias (where patients are exposed to different interventions)
    - Exclusion bias (when patients are lost to follow-up because of sickness)
    - Detection bias (where patients are assessed at different points in time)
- Confounding
  - Confounding is when the measured association between an exposure and disease occurrence is distorted by an imbalance between exposed and non-exposed persons with regard to one or more risk factors for the disease
- Observational studies potentially have high external validity and low internal validity
  - Reduction of bias can enhance internal validity



# Trade-Off Between Internal and External Validity

High external validity





# Sources of Real-World Evidence

## Healthcare Databases



Systems into which healthcare providers enter routine clinical and laboratory data during usual clinical practice

- Typically electronic health records (EHRs)
- Document the care that was provided to a patient

## Administrative Claims Databases

Medical and pharmacy claims systems

- Document the care that was paid for by a payer

***The ideal source would be an EHR that is linked to a claims database, with PRO data, biomarker test results and data on mortality and health care disparities!***



# Sample Study



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## Retrospective Analysis of Clinical Outcomes

### Real-world disease response to second-line pomalidomide for relapsed/refractory multiple myeloma: A US, multisite, retrospective chart review study

Tomer Mark, Zoe Clancy, Ryan Thomas, Angelica Falkenstein, Jonathan Kish

### Real-world disease response to second-line pomalidomide for relapsed/refractory multiple myeloma: a US, multisite, retrospective chart review study

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#### Introduction

The standard of care for patients with newly diagnosed multiple myeloma (MM) includes the immunomodulatory agent lenalidomide (LEN), either in combination with daratumumab (DAR) or in combination with DEX plus bortezomib (BORT), a proteasome inhibitor (PI).<sup>1</sup>

Although first-line (1L) LEN-based therapy has dramatically increased time to relapse and overall survival (OS) in patients with MM, all patients eventually relapse and require further therapy.

Pomalidomide (POM), in combination with DEX, is indicated for the treatment of adult patients with MM who have received a prior therapy including LEN and a PI, and have demonstrated disease progression on within 60 days of completion of the last therapy.<sup>2</sup>

Moreover, POM has been shown to induce apoptotic activity in LPL-enriched cell lines.<sup>3</sup>

There is a lack of consensus on the most appropriate therapy for patients following 1L LEN induction therapy, particularly for patients refractory to LEN.

Few real-world studies have evaluated clinical outcomes for patients prescribed 1L LEN who subsequently receive second-line (2L) POM.

**Objective**

To compare real-world disease response (very good partial response or better [VGPR]), median progression-free survival (PFS), and 12-month OS rates for patients with MM who have received 1L LEN and who receive 2L POM-based or 2L non-POM-based clinical regimens, in a 2-site, 1L LEN-based treatment.

#### Methods

An observational, retrospective cohort study of patients with MM treated by physicians in the Central Health Oncology Practice Extended Network (OPEN).

OPEN is a multicenter, multi-practice practice and hospital-based oncology/hematology network across the US.

Data were abstracted into an electronic case report form (eCRF) by the physicians responsible for the care and management of the patients.

Hematology providers (physician selected patients, based on the inclusion/exclusion criteria (Figure 1)) until 300 patients were enrolled across 2 cohorts.

Figure 1. Study selection criteria and cohorts

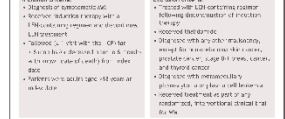


Figure 1. Study selection criteria and cohorts

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Patients were treated with either a 2L POM-containing or a 2L non-POM-containing clinical regimen.

Patients were required to have 1L LEN at 7, 10, or 12 months prior to data collection, which began on November 15, 2019 and concluded on March 13, 2020 (Figure 2).

**Figure 2. Study period**



Patients treated prior to 6 months were eligible for follow-up period.

Data points collected in the eCRF included:

HCP characteristics and patient demographics.

Clinical characteristics at diagnosis and initiation of therapy, including International Staging System (ISS) stage, cytogenetics, Eastern Cooperative Oncology Group (ECOG) performance status, and prior therapy.

Treatment outcomes, including dates of initiation, discontinuation, dose modification, and adverse events for chemotherapy.

Clinical outcomes, including time to relapse, and response to therapy, minimal residual disease, and date of progression/death.

Response to therapy was assessed for analysis.

Demographics and clinical characteristics were compared between 2L POM and 2L non-POM cohorts using  $\chi^2$ -test for categorical variables and t-test for continuous variables with  $P < 0.05$  as the threshold for statistical significance.

Logistic regression was used to estimate the likelihood of disease response to 2L (i.e., VGPR) adjusted for demographic and clinical variables.

The Kaplan-Meier method was used to estimate time to event outcomes.

**Results**

**Overview of cohorts**

128 2L POM-treated and 174 2L non-POM-treated patients were included by 49 HCPs.

Of the 49 HCPs, 41% practiced in the South, 23% in the Midwest, 20% in the West, and 16% in the East region of the US.

Most HCPs practiced in small-to-medium practices (mean 6.1 HCPs, 120% and range 1-10 HCP [27%]).

The most common prior 1L POM regimen was POM-dexamethasone (POM-DEX) (44%) and 2L non-POM regimen was DEX-dexamethasone (DEX-DEX) (73%) (Figure 3).

**Clinical outcomes**

VGPR was achieved by 78.6% of 2L POM-treated and 51.7% of 2L non-POM-treated patients ( $P < 0.0001$ ) (Figure 4).

Adjusted for all other clinical factors (Table 2), patients treated with 2L POM-based regimens were 4.3 times more likely to achieve VGPR compared with those who received 2L non-POM-based regimens.

Table 1. Cohort demographics and clinical characteristics

Characteristic	2L POM (n = 128)	2L non-POM (n = 174)	P value
Age at initiation of 2L, mean (SD), years	66.0 (12.1)	65.3 (10.9)	0.57
Male, n (%)	85 (66.4)	96 (55.2)	0.03
Race, n (%)			0.04
White	88 (68.7)	116 (66.7)	
Black/African American	27 (21.1)	52 (29.9)	
Other	13 (10.2)	6 (3.4)	
Duration of 1L therapy, mean (SD), months	8.1 (5.8)	8.4 (6.0)	0.43
1L treatment-free interval <sup>a</sup> , mean (SD), months	12.1 (11.6)	12.3 (11.8)	0.92
Outcome of 1L therapy, n (%)			
Relapsed	29 (22.6)	28 (16.1)	
Stem cell transplant prior to 2L initiation, n (%)	38 (30.2)	55 (31.5)	0.09
OS stage at initiation of 2L, n (%)			0.02
I	2 (1.6)	10 (5.8)	
II	41 (32.1)	40 (23.0)	
III	20 (15.6)	10 (5.8)	
Unknown	12 (9.4)	21 (12.1)	
High-risk cytogenetics, n (%)	85 (66.4)	111 (63.8)	0.51
ECOG PS, n (%)			0.03
0-1	95 (74.2)	111 (63.8)	
≥2	33 (25.8)	63 (36.2)	

1L, first-line therapy; 2L, second-line therapy; OS, overall survival; SD, standard deviation.

<sup>a</sup>Time from discontinuation of 1L therapy to initiation of 2L therapy.

ECOG PS, Eastern Cooperative Oncology Group performance status; I, stage I; II, stage II; III, stage III; IV, stage IV; V, stage V; VI, stage VI; VII, stage VII; VIII, stage VIII; IX, stage IX; X, stage X; XI, stage XI; XII, stage XII; XIII, stage XIII; XIV, stage XIV; XV, stage XV; XVI, stage XVI; XVII, stage XVII; XVIII, stage XVIII; XIX, stage XIX; XX, stage XX; XXI, stage XXI; XXII, stage XXII; XXIII, stage XXIII; XXIV, stage XXIV; XXV, stage XXV; XXVI, stage XXVI; XXVII, stage XXVII; XXVIII, stage XXVIII; XXIX, stage XXIX; XXX, stage XXX; XXXI, stage XXXI; XXXII, stage XXXII; XXXIII, stage XXXIII; XXXIV, stage XXXIV; XXXV, stage XXXV; XXXVI, stage XXXVI; XXXVII, stage XXXVII; XXXVIII, stage XXXVIII; XXXIX, stage XXXIX; XL, stage XL; XLI, stage XLI; XLII, stage XLII; XLIII, stage XLIII; XLIV, stage XLIV; XLV, stage XLV; XLVI, stage XLVI; XLVII, stage XLVII; XLVIII, stage XLVIII; XLIX, stage XLIX; L, stage L; LI, stage LI; LII, stage LII; LIII, stage LIII; LIV, stage LIV; LV, stage LV; 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# Sources of Real-World Evidence (cont.)

## Patient Registries



Organized systems to prospectively collect, analyze and disseminate observational data on a group of patients with specific characteristics

- Cystic Fibrosis Foundation Patient Registry (<https://www.cff.org/Research/Researcher-Resources/Patient-Registry/>)
- Upper Limb International Spasticity (ULIS-III) prospective longitudinal cohort study (<https://bmjopen.bmj.com/content/3/3/e002230>)

## Patient-Powered Research Networks (PPRNs)

Online platforms by patients, advocacy groups or others (caregivers, clinicians or researchers)

Goal is to conduct outcomes research that matters to patient to impact development of new therapeutic interventions

- PCORnet (<https://pcornet.org>)

## Social Media

Internet platform for patients to share information

- Find info about their condition, discuss their experience (with disease or treatments) and find social support
- Adverse effects, treatment adherence and discontinuation and QoL



# Real-World Study Designs and Data Sources Summary

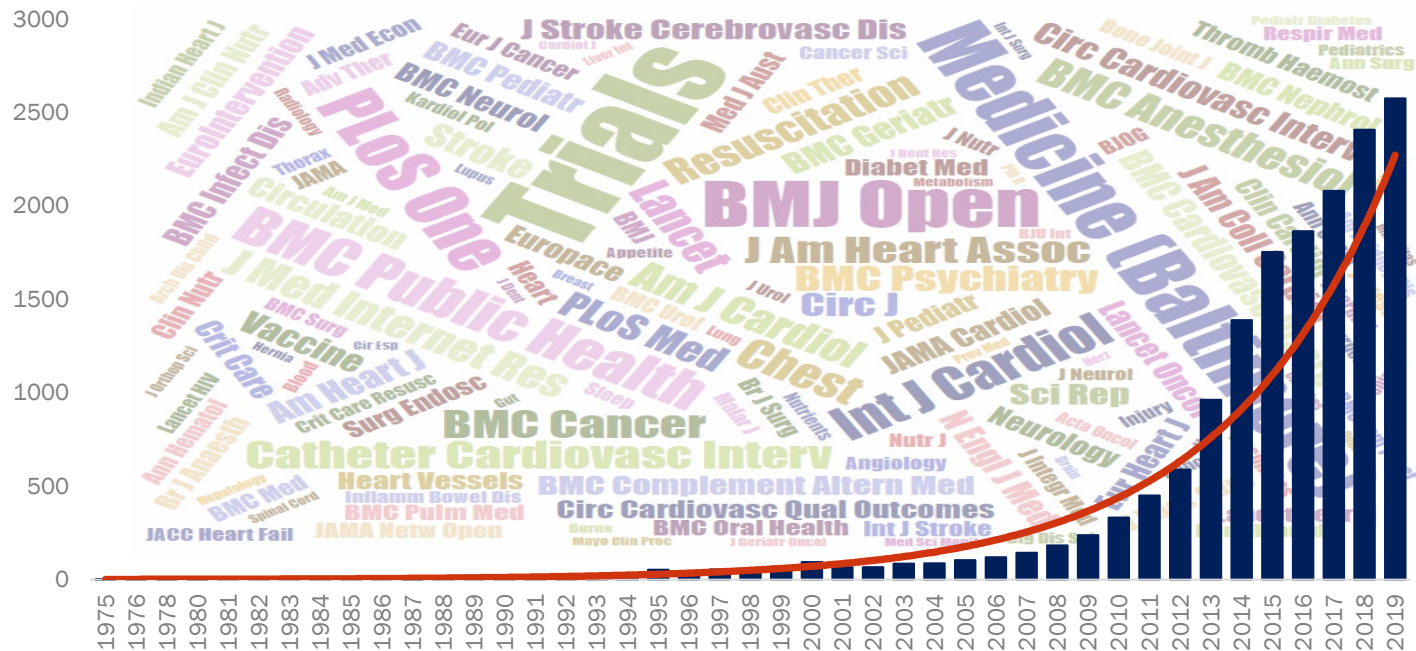
- There are many sources of data for observational research – the key is to match the right data to the right question.
- The limitations of real-world data require adjustments to methodology.
  - Choosing the appropriate study design
  - Considering confounding and the appropriate methods to address it
  - Considering the influences of various types of biases and how to control for them.



# Payer Use of RWE



# Growth in RWE Publications

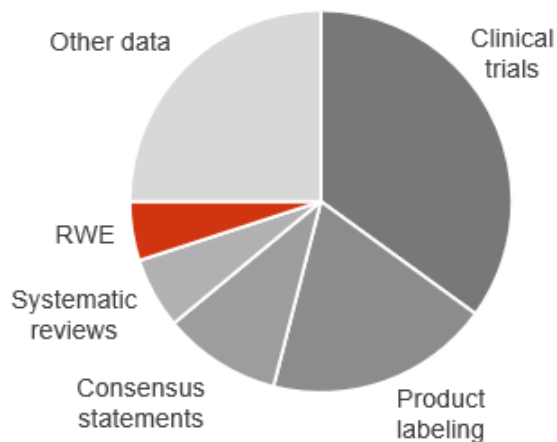


Search query: (((("Health claims"[Title/Abstract]) or ("real-world evidence"[Title/Abstract])) OR ("registry"[Title/Abstract])) OR ("electronic medical records"[Title/Abstract])) OR ("cost-effectiveness analysis"[Title/Abstract])) AND ("clinical study"[Publication Type] OR "observational study"[Publication Type])



# RWE Use by Payers

## FORMULARY MONOGRAPHS

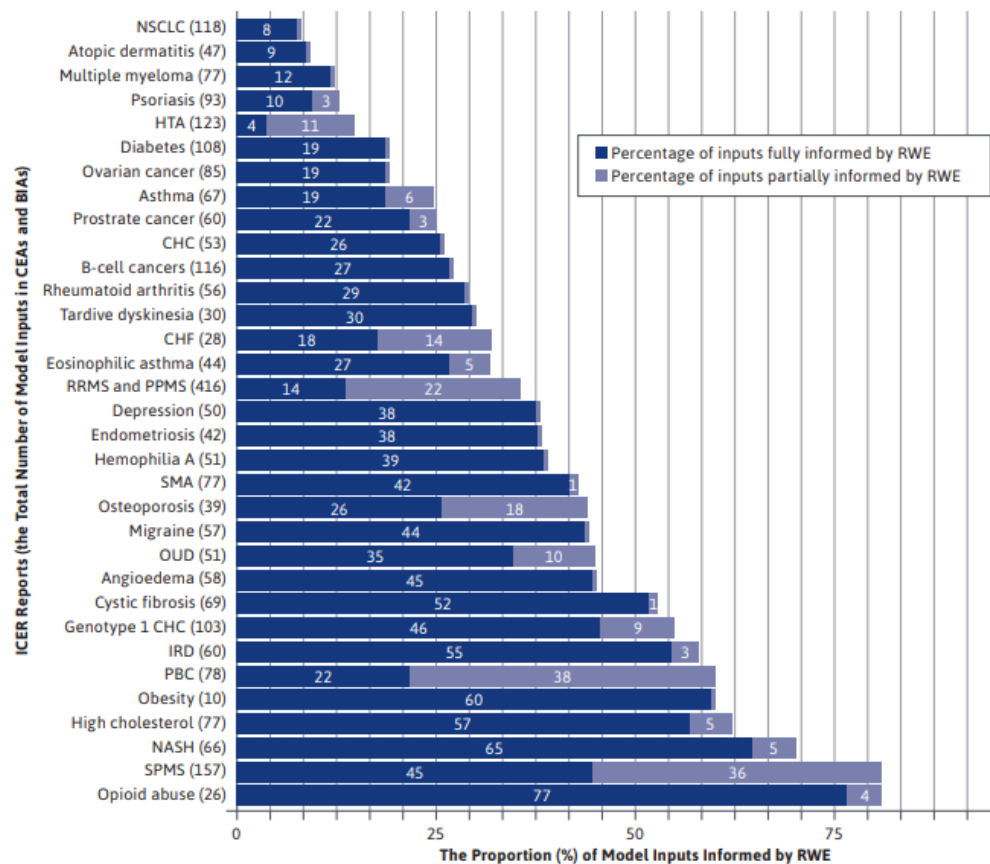


**Beyond formulary decisions...**

Safety programs  
Value Assessment

Quality measurement  
Clinical programs  
Utilization management  
Outcomes-based contracts

**FIGURE 2** The Number of Model Inputs and Proportion Informed by RWE





# Evaluation of persistence, switch patterns, and costs among migraine patients utilizing calcitonin gene-related peptide (CGRP) inhibitors in a U.S. Medicaid population

Kayla Thompson,  
PharmD; Majid Mirza,  
PharmD; Timothy  
Crabtree, PharmD;  
Jessica Zhang, PhD;  
Jeramie Thomas,  
PharmD; Leigh Anne  
Kustra, MBA, MHA



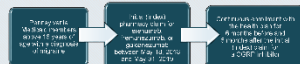
## EVALUATION OF PERSISTENCE, SWITCH PATTERNS, AND COSTS AMONG MIGRAINE PATIENTS UTILIZING CALCITONIN GENE-RELATED PEPTIDE (CGRP) INHIBITORS IN A U.S. MEDICAID POPULATION

Kayla Thompson, PharmD; Majid Mirzai, PharmD; Timothy Crabtree, PharmD; Jessica Zhang, PhD;  
Jeramie Thomas, PharmD; Leah Anne Kustra, MBA, MHA | Gateway Health Plan®, Pittsburgh, PA

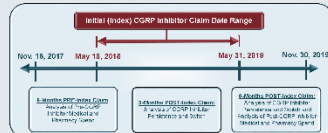


## Methods

### Inclusion Criteria



### Data Timeline



## Objectives

- To evaluate the persistence of switch patterns of CGRP inhibitors for the treatment of migraine.
- To evaluate the effect of CGRP inhibitors on migraine-related medical utilization and costs.

## Demographics

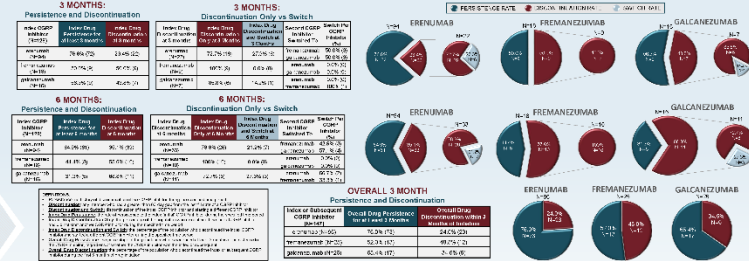
Race/Ethnicity	Participants
Don't know	127 (79.3%)
African American	7 (4.3%)
Hispanic/Latino	7 (4.3%)
Asian/Pacific Islander	4 (2.5%)
Others	8 (5.0%)

**Disclosure:**

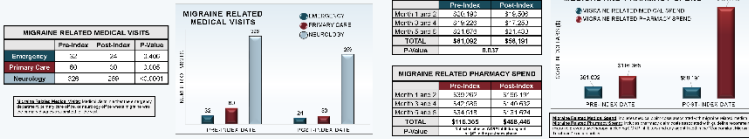
- References:**
1. Ruchir P. Dasgupta, D. Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends from Government Health Studies. *Headache* 2010; 50: 385-393.
  2. Haqqani K, Viano S, Roseman M. Headache disorders among insured US employees with migraine. *Headache* 2008; 48(4): 553-563.
  3. American Headache Society Position Statement on Integrating New Migraine Treatments Into Clinical Practice. *Headache* 2010; 50: 1-18.

## Results

### CGRP Inhibitor Persistence, Discontinuation, and Switch



### CGRP Inhibitor Migraine Related Utilization and Expenses



### Concomitant Migraine Treatment

[illegible]

## Limitations

- ▶ The population size was limited due to the relatively recent approval of the CGRP<sup>1</sup> inhibitors at the time of the study.
- ▶ Encumbrance was utilized on average 5.5 times more than the other CGRP<sup>1</sup> inhibitors, which may be a result of its first to market status.
- ▶ This study focuses on the Medicaid population only; future studies can be designed to include the commercial and/or Medicare populations.
- ▶ Due to lack of visibility into medical charts, this study does not evaluate the logic behind the decision to discontinue or switch to another CGRP<sup>1</sup> inhibitor.

## Conclusion

- Erenumab had the highest conversion rate at the 3-month endpoint; the 5-month endpoint and overall.
- Erenumab had the highest discontinuation rate at the 3-month endpoint and overall, while galcanezumab had the highest discontinuation rate at the 5-month endpoint.
- Erenumab had the highest safety rate at the 3-month endpoint and galcanezumab had the highest safety rate at the 5-month endpoint. No participants reported a subsequent CGRP-related headache after discontinuation of the treatment.
- Claims analysis concerning the 3-month pre- and post-treatment timeframe demonstrated that overall migraine re- and therapy success rates increased with the number of medical visits and overall headache success rates.
- Galcanezumab and eptinezumab were the most utilized non-injectable therapies along with a CGRP inhibitor during the study period.

## Follow Up

- ▶ Further investigation to identify the reason for the discontinued drugs and the selection of its second agent.
- ▶ Continue to monitor the overall change in medical and pharmacy spend over time.
- ▶ Future comparisons to the new FDA approved COX2 inhibitor, celecoxib, for the prevention/treatment of migraine.



# RWE and the Managed Care Pharmacy Research Agenda

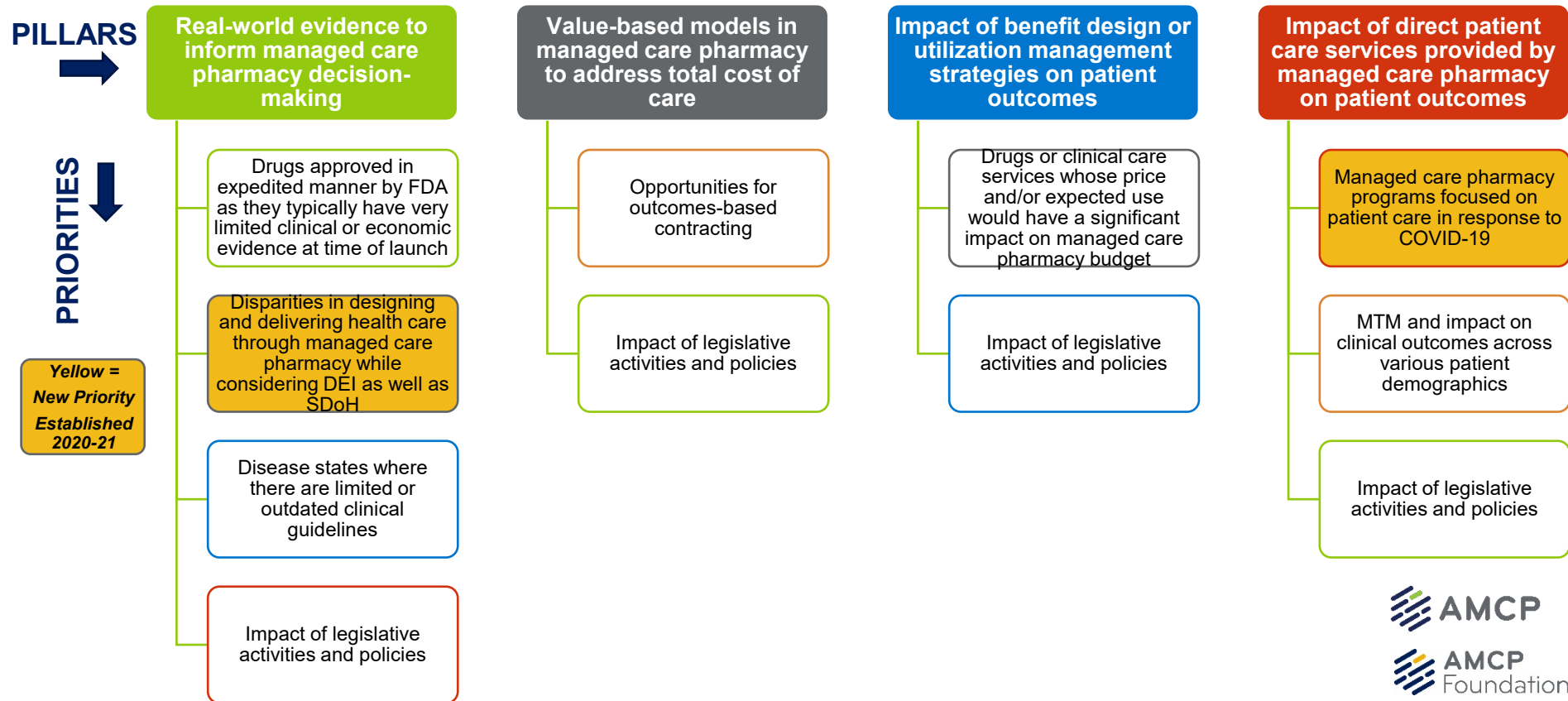


# The Future of Real-World Evidence

- RWE is becoming more widely accepted by providers and payers in patient care and decision making.
- Regulatory agencies are increasingly considering the use of RWE in approval and in validation of efficacy, effectiveness, and safety of NMEs.
- Follow-up studies are increasingly being used to:
  - Confirm RCT data from approval
  - Confirm reimbursement decisions
  - Validate patient outcomes
- Real-world evidence is a **STRATEGIC INITIATIVE** in drug development and life-cycle management.

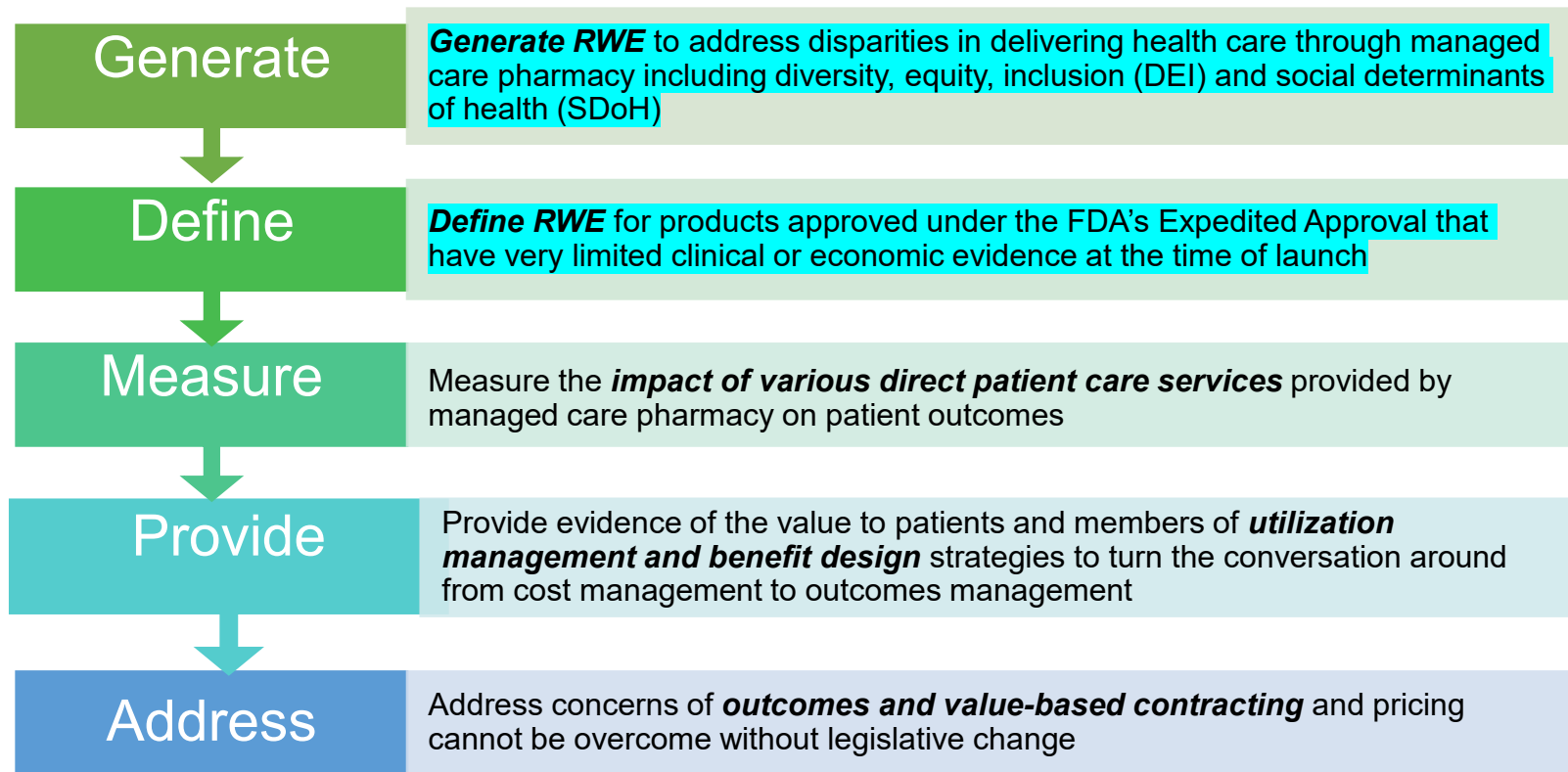


# Managed Care Pharmacy Agenda





# RWE in Research Agenda





# Future Directions for Our Research Agenda



Images:  
[KOTESOL](#)  
[The Intrepid Catalyst](#)





# Speaker Q&A



**Diana Brixner**



**Laura Happe**





# Additional References

## *References Noted on Slides*

### *Additional Background*

- [“A Primer for Managed Care Residents: How to Conduct Research Using Live Medical and Pharmacy Claims Data.”](#) J Manag Care Spec Pharm, 2019 May;25(5):538-543.
- [“Concept Series: What Is Outcomes Research?”](#) AMCP, 2019 Jul.
- [“Top Evidentiary Gaps in Managed Care Pharmacy: A Research Agenda.”](#) J Manag Care Spec Pharm, 2020 Apr;26(4):375-381.
- [“Advancing the Managed Care Pharmacy Research Agenda via Mapping of Research Pillars and Priorities.”](#) Poster presented at: AMCP 2021; April 12-16, 2021; Virtual.

### *Sample Studies*

- [“Real-world disease response to second-line pomalidomide for relapsed/refractory multiple myeloma: A US, multisite, retrospective chart review study.”](#) Poster presented at AMCP 2021; April 12-16, 2021; Virtual.
- [“Evaluation of persistence, switch patterns, and costs among migraine patients utilizing calcitonin gene-related peptide \(CGRP\) inhibitors in a U.S. Medicaid population.”](#) Poster presented at AMCP eLearning Days; April 20-24, 2020; Virtual.



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- AMCP Senior Manager, Educational Programs, Julia Veeder





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# **Thank You**