

Real-World Assessment and Research of Drugs (REWARD)

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New publication in JAMIA

Details the REWARD framework and aims to increase global participation from researchers utilizing local data

Journal of the American Medical Informatics Association, 2026, 1–12

<https://doi.org/10.1093/jamia/ocag137>

Research and Applications

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REWARD—an open-source framework for identifying the unknown benefits of existing medications to inform drug discovery, development, and repurposing

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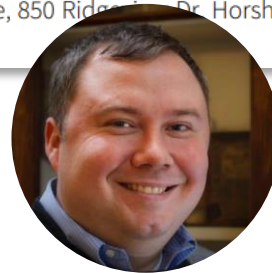
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REWARD Mission statement and objectives

Mission: To strengthen and expand J&J's existing observational health data analytics system by proactively providing **real-world evidence** via population-level effect estimation, enabling the exploration of **potential unknown benefits** of existing medical products



Typical Use Cases

Target identification for clinical development

Interested in a single indication, association with all medications

Indication expansion for existing products

Interested in a medication, association with all outcomes

REWARD Methodology

“All-by-All” framework leveraging the OMOP Common Data Model

Exposures: 14,466 unique drug ingredients according to the RxNorm vocabulary



Outcomes: 160,955 SNOMED conditions considered a “Clinical finding” (SNOMED ID 441840)



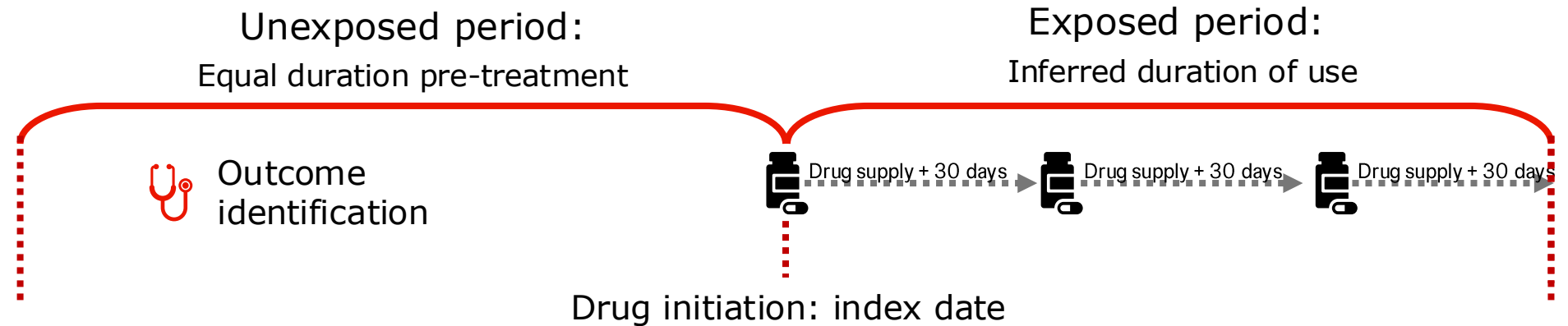
Total potential associations: 2+ BILLION, multiplied by 6 databases

When requiring at least 100 patients with a specific exposure or outcome, 61.9 million unique exposure-outcome pairs are in licensed data

The self-controlled cohort (SCC) design

To assess all combinations of exposures and outcomes

This design
scales to
“All-by-All”

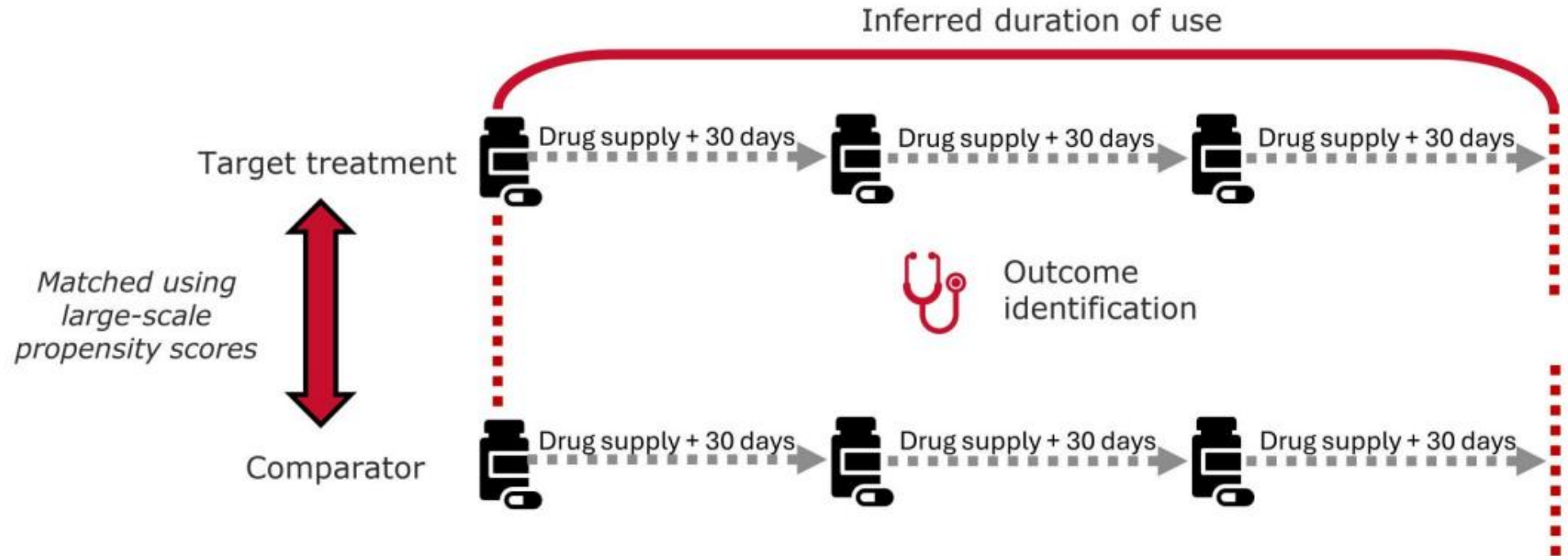


- All exposed patients contribute to analysis, contributing varying amount of person-time
- Pre-exposure follow-up is of equal length to duration of use
- Outcomes are identified from diagnoses, only first is used
- Incidence rates are calculated separately for pre- and post-index periods
- **Ratio of these rates is the measure of effect size**

The Active Comparator New-User (ACNU) design

When interested in a specific treatment

This design
DOES NOT
scale to
“All-by-All”



Key characteristics of the SCC and ACNU designs

Table 1. Key characteristics of the SCC and ACNU designs.

Feature	SCC	ACNU
Hypothesis tested	• Benefit of target drug use versus non-use	• Benefit of target drug versus alternative drug
Scale	• All-by-all	• One-by-all (selective)
Comparator	• Same patient, unexposed time	• Active new users of comparator drug
Confounding control	• Time-invariant confounders only • Empirical calibration	• LSPS matching, balancing all observed confounders • Empirical calibration
Key vulnerability	• Protopathic bias, time-varying confounding	• Unmeasured confounding
Computational burden	• Low	• High
Primary role in REWARD	• Hypothesis screening	• Hypothesis screening or refinement

Abbreviations: ACNU, active comparator new-user; LSPS, large-scale propensity score; REWARD: REal-World Evidence and Research of Drug; SCC, self-controlled cohort.

REWARD system architecture

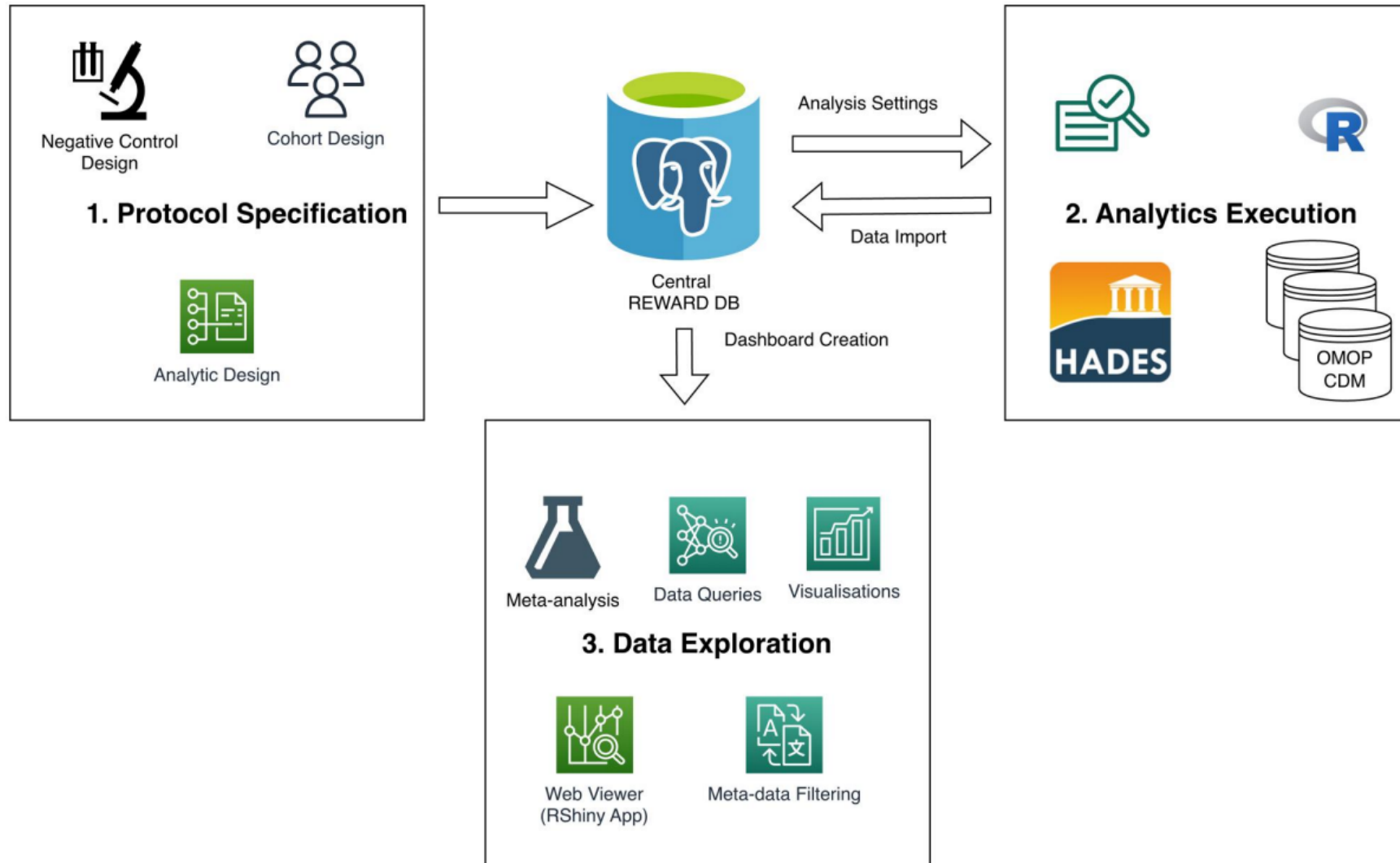


Figure 3. REWARD system architecture built around the central REWARD database. Protocol specifications inform analysis settings; the analytics execution produces raw data output; which is then meta-analyzed and used to build dashboards for data exploration.

REWARD Output

The REWARD results dashboard

The screenshot shows the REWARD results dashboard in a web browser. The browser address bar shows `rconnect.jnj.com/reward/doacs_feb_2023/`. The dashboard has a dark blue header with 'DOAC Exposures' and a hamburger menu icon. A sidebar on the left contains 'About' and 'Results' tabs, with 'Results' highlighted. The main content area has a title 'Real World Assessment and Research of Drug performance (REWARD)' and a description. Below this is a 'Data sources' table. On the right, there is a section 'About this dashboard - DOAC Exposures' with a description and two download buttons. The left-hand panel is highlighted with a yellow box and contains three sliders: 'Benefit Threshold' (set to 0.7), 'Risk Threshold' (set to 2), and 'P-value cut off' (set to 0.05). A checkbox 'Threshold with empirically calibrated IRR' is checked. Annotations with yellow arrows point to the 'Results' tab and the left-hand panel.

Results tab: click for interactive results viewer

Real World Assessment and Research of Drug performance (REWARD)

Reward aims to strengthen and expand our existing observational health data analytics system that proactively provides real-world evidence through the population-level effect estimation to enable exploration of performance of existing medical products.

Reward has been developed as an open-source tool and is released under the apache liscense 2.0. For more information about this dashboard please see our [github page](#).

Reward was built on top of the [OHDSI HADES library](#).

Data sources

Source Id	Source Name	Cdm Version
-99	Meta-analysis	
1	JMDC_v2129	
2	IBM MDCR V2183	
3	IBM CCAE v2182	
4	IBM MDCD V2128	
5	OPTUM SES	

About this dashboard - DOAC Exposures

DOAC exposures - custom cohort

Click the dashboard option to see the results. The sidebar options allow filtering of results based on risk and benift IRR thresholds

[Download filtered results as a csv](#) [Download full results](#)

Benefit Threshold:

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

Risk Threshold:

1.1 1.3 1.5 1.7 1.9 2.1 2.3 2.5

P-value cut off:

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

☒ Threshold with empirically calibrated IRR

Left-hand panel: set filtering criteria

Viewing detailed results

Page485

Sort by columnIRR

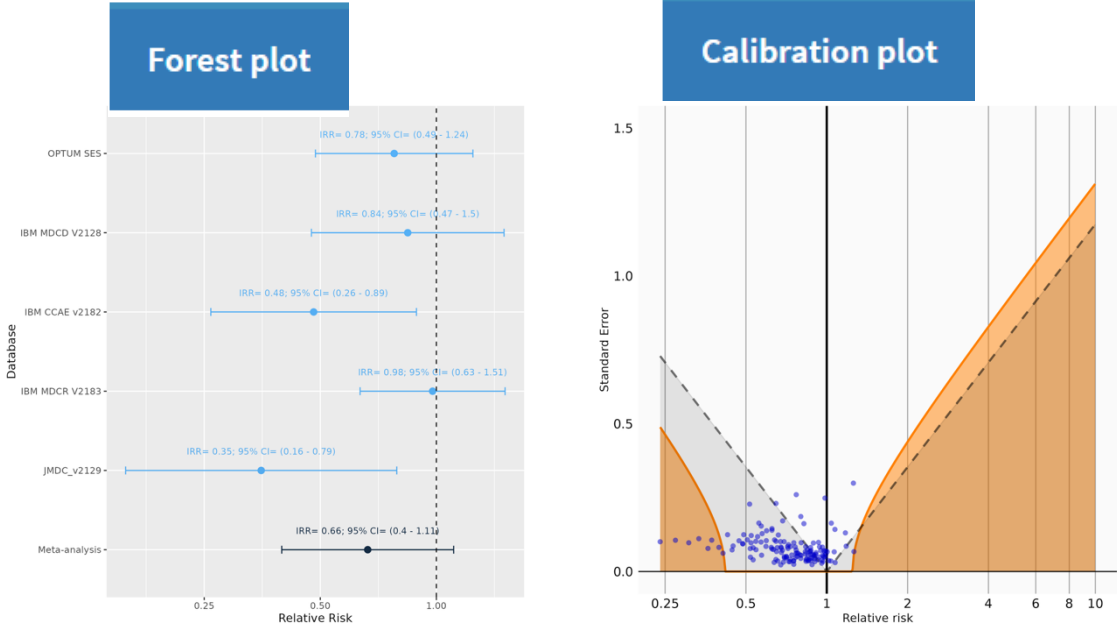
Ascending

Descending

Show per page10

Target Cohort Id	Target Cohort Name	Outcome Cohort Id	Outcome Cohort Name	Risk Count	Benefit Count	I2	Meta Rr
60	{REWARD} DOAC exposures, 60d grace period, all events	4154630000	Incident outcome of Malignant neoplasm of genitourinary organ- TWO DX	0	2	0.96	0.65
				0	3	0.97	0.65
				0	2	0.95	0.65
				0	2	0.75	0.66
60	{REWARD} DOAC exposures, 60d grace period, all events	4231941002	Incident outcome of Injury of ligament of knee- ONE DX	0	2	0.97	0.66

Clickable rows: clicking a row highlights a given result in blue and pulls up more granular results, shown below and at right



{REWARD} DOAC exposures, 60d grace period, all events - Incident outcome of Injury of ligament of knee- ONE DX

Detailed resultsForest plotCalibration plotTime on treatmentTime to outcome

* Indicates values after empirical calibration

Source Name	Rr	Ci 95	P Value	Calibrated Rr	Calibrated Ci 95	Calibrated P Value
Meta-analysis	0.55	0.41-0.74	0.00	0.66	0.40-1.11	0.12
JMDC_v2129	0.29	0.17-0.49	0.00	0.35	0.16-0.79	0.01
IBM MDCR V2183	0.90	0.77-1.05	0.19	0.98	0.63-1.51	0.92
IBM CCAE v2182	0.39	0.36-0.42	0.00	0.48	0.26-0.89	0.02
IBM MDCC V2128	0.65	0.57-0.73	0.00	0.84	0.47-1.50	0.56
OPTUM SES	0.61	0.57-0.66	0.00	0.78	0.49-1.24	0.29

Applied examples

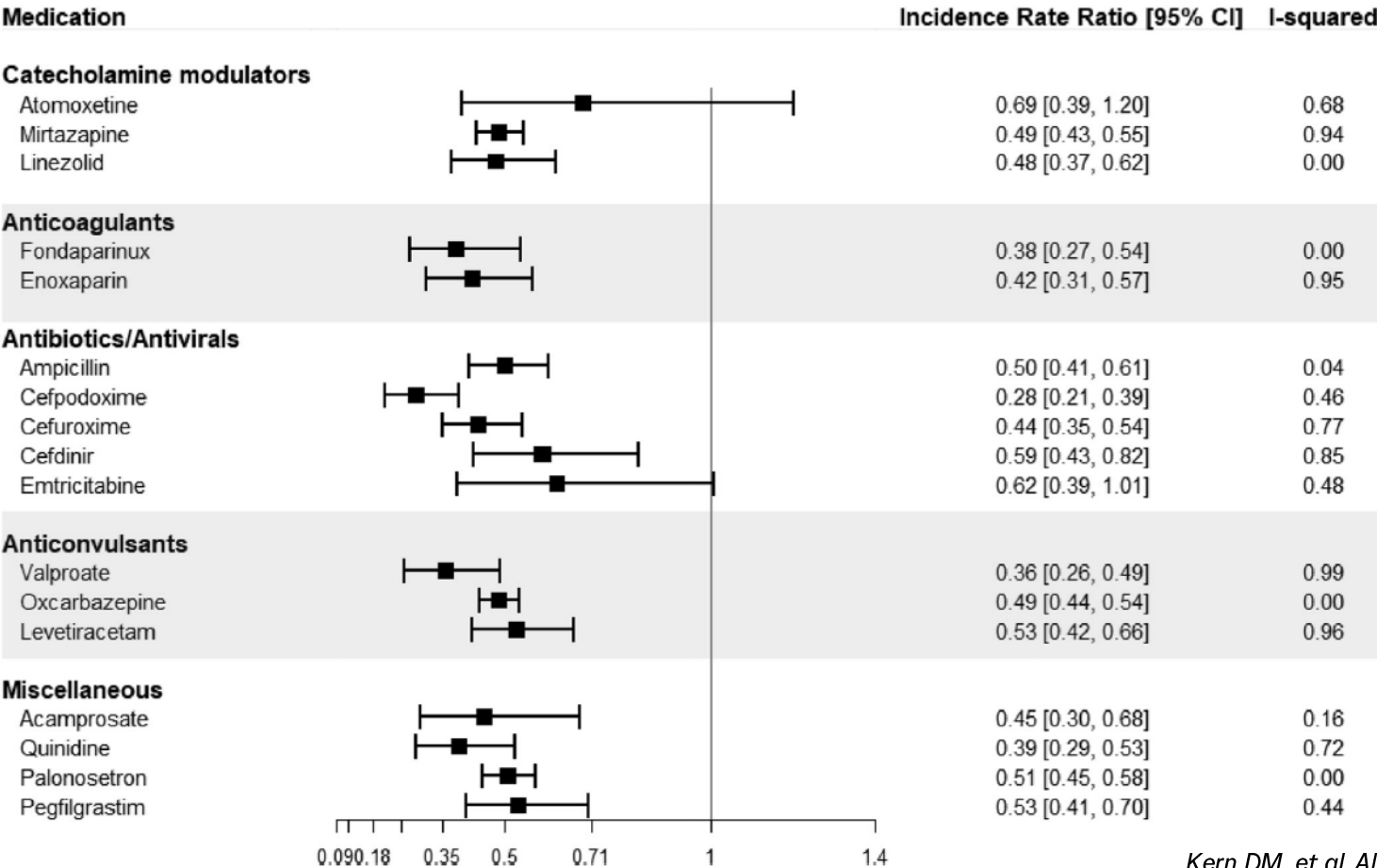
Aiding the discovery of new treatments for dementia by uncovering unknown benefits of existing medications

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^cJohnson & Johnson, Scientific Innovation, South San Francisco, CA, USA



Identified treatments that appear to be protective against dementia; results have been used to further investigate biologic pathways and genetic associations to inform future drug development.

Potential Targets for the repurposing of an ADHD medication

Assessed associations between medication and every SNOMED condition to inform potential expansion efforts

- 1. At least 30% reduction in incidence (IRR ≤ 0.7)
- 2. Statistically significant (p < 0.05 after calibration) in at least two databases
- 3. No contrary association (IRR > 2 and p < 0.05) in any database

Identified key alternative uses already present in literature, aiding expansion prioritization efforts

10,000+
outcomes
assessed



312
outcomes met
criteria



116
outcomes
remain

Outcomes meeting signaling criteria, by category	N	Range of Effects
Fatigue		
<i>Cancer</i>	61	IRR = 0.31 to 0.68
<i>Multiple sclerosis</i>	4	IRR = 0.42 to 0.59
Cognition		
<i>Cerebrovascular disease</i>	15	IRR = 0.29 to 0.61
<i>Dementia</i>	1	IRR = 0.68
<i>Traumatic brain injury</i>	35	IRR = 0.19 to 0.65

Assessing benefits of memantine to identify disease targets for new NMDA receptor antagonists

CNS Drugs (2021) 35:243–251
https://doi.org/10.1007/s40263-020-00789-3

ORIGINAL RESEARCH ARTICLE



Application of Real-World Data and the REWARD Framework to Detect Unknown Benefits of Memantine and Identify Potential Disease Targets for New NMDA Receptor Antagonists

David M. Kern¹ · M. Soledad Cepeda¹ · Christopher M. Flores¹ · Gayle M. Wittenberg¹

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Table 1 Results from the pooled meta-analyses across the four US claims databases, showing a maximum of three outcomes per condition group

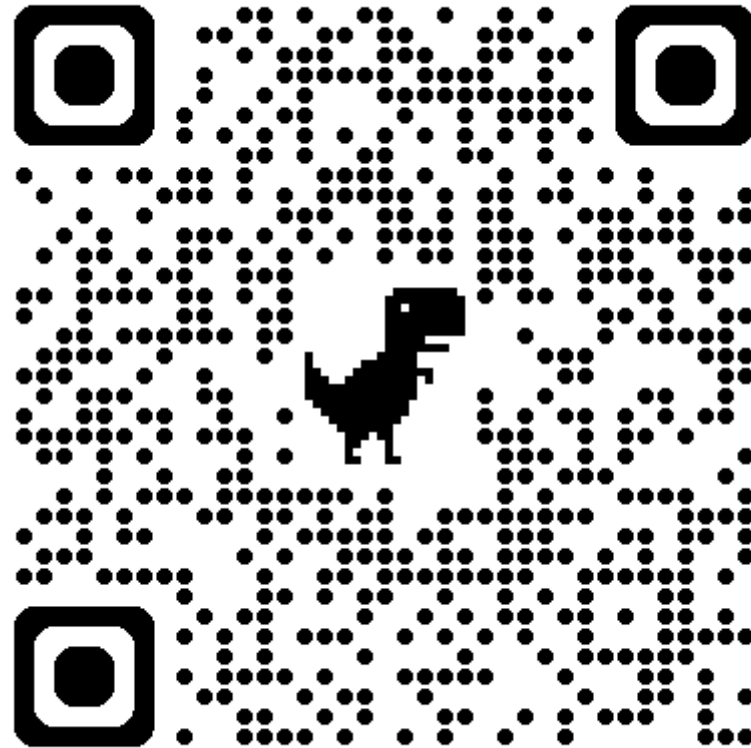
Condition group and outcome	Mean ± SD treatment time (days) ^a	Cases in the exposed period	Cases in the unexposed period	IRR	Lower 95% CI	Upper 95% CI	p value	I ²
Mental disorder								
Depressive disorder	480.4 ± 408.3	9603	15,017	0.53	0.45	0.61	< 0.01	0.96
Bipolar disorder	433.5 ± 395.5	853	1377	0.52	0.39	0.70	< 0.01	0.91
Psychotic disorder	443.6 ± 395.5	4475	8723	0.43	0.37	0.49	< 0.01	0.91
Alcohol and drug abuse								
Drug dependence	472.7 ± 416.3	1233	2418	0.48	0.41	0.57	< 0.01	0.78
Psychoactive substance use disorder	435.6 ± 398.0	576	1155	0.46	0.41	0.52	< 0.01	0.20
Alcoholism	439.7 ± 407.1	409	860	0.44	0.40	0.50	< 0.01	0.00
Pain								
Pain of truncal structure	529.0 ± 431.1	10,060	19,909	0.47	0.45	0.49	< 0.01	0.45
Idiopathic peripheral neuropathy	529.0 ± 434.0	1643	2805	0.55	0.47	0.64	< 0.01	0.76
Atypical facial pain	464.5 ± 388.7	29	79	0.35	0.23	0.54	< 0.01	0.00
GI/colon								
Diverticulosis of colon	622.7 ± 493.0	1307	2475	0.54	0.46	0.63	< 0.01	0.73
Stenosis of intestine	496.9 ± 439.6	8	29	0.27	0.12	0.59	< 0.01	0.00
Demyelinating disease								
Demyelinating disease of central nervous system	421.9 ± 363.5	109	279	0.36	0.24	0.54	< 0.01	0.67

SD standard deviation, IRR incidence rate ratio, CI confidence interval, GI gastrointestinal

^aTreatment duration calculated within patients who had the outcome in either the exposed or unexposed periods

REWARD is
publically
available

Location: <https://github.com/OHDSI/Reward>



Questions?

Shifting the Scientific Question: From prevention to treatment

Directly generate evidence for a treatment benefit rather than making the argument via the potential for prevention

	Original REWARD	REWARD 2.0
Core Research Question	“Does [DRUG] appear to reduce the incidence of [CONDITION]?”	“Among patients with [CONDITION], does [DRUG] appear to reduce the incidence of [KNOWN COMPLICATION of CONDITION]?”
Outcomes Assessed	All, bulk-defined from RxNorm/ATC	Indication-specific, deeply phenotyped
Exposures Assessed	All, bulk-defined from SNOMED	J&J-specific, deeply phenotyped
Study Designs Implemented	Self-controlled cohort Active comparator new user (ad-hoc)	Self-controlled cohort Self-controlled case series Active comparator new user

Overview of Real-World Data Sources

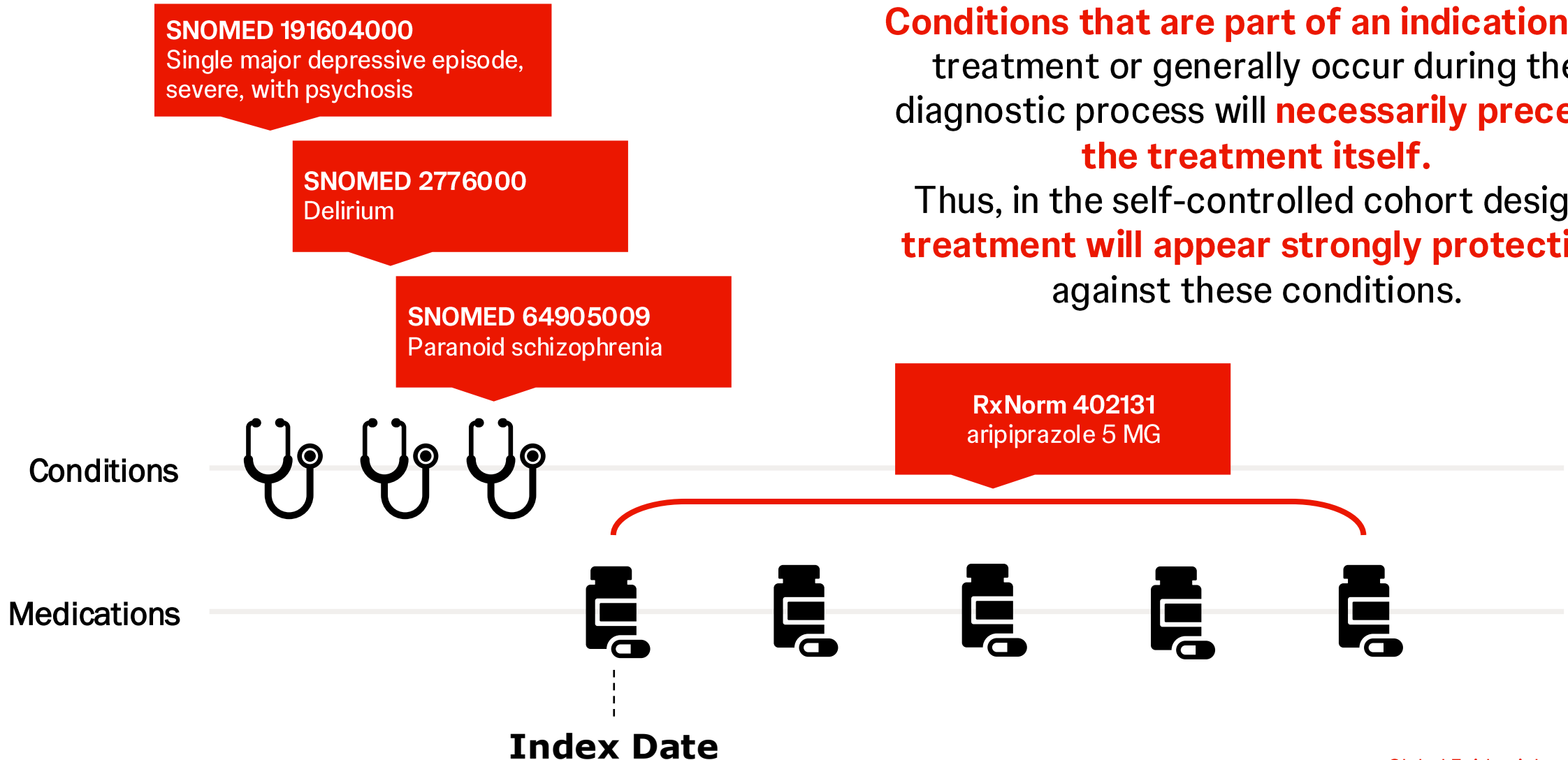
Data Source	Persons	Person-Years of Observation	Observation Min	Observation Max
HealthVerity CC	250,778,474	1,187,374,969	6/1/2009	5/26/2026
JMDC	22,775,462	106,782,639	1/1/2005	6/30/2025
Merative CCAE	181,577,850	518,801,805	1/1/2000	10/31/2025
Merative MDCD	33,986,684	130,114,932	1/1/2006	6/30/2025
Merative MDCR	11,473,320	46,855,050	1/1/2000	10/31/2025
Optum Clinformatics	104,873,480	353,204,677	5/1/2000	12/31/2025

CC, comprehensive claims; CCAE, commercial claims and encounters; MDCD, Medicaid; MDCR, Medicare

Protopathic bias: the need for manual review

Conditions that are part of an indication for treatment or generally occur during the diagnostic process will **necessarily precede the treatment itself.**

Thus, in the self-controlled cohort design, **treatment will appear strongly protective** against these conditions.



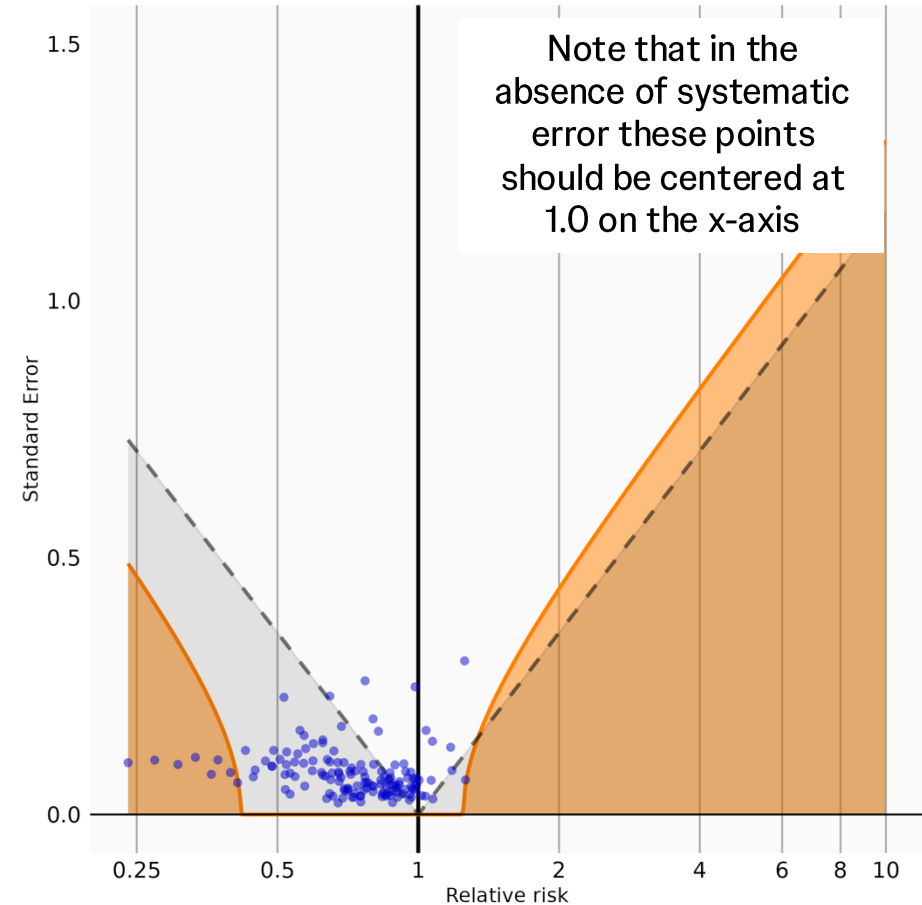
Empirical calibration

144 conditions not known to be associated with exposure were selected as negative controls

The self-controlled cohort analysis was run using these negative controls as outcomes

A log-normal distribution was fit to the negative control estimates, which showed substantial left-skew

Estimates for all other condition outcomes were then corrected based on this fitted empirical null distribution



Example data from REWARD analysis (Feb 2023)

Identifying relevant outcomes

