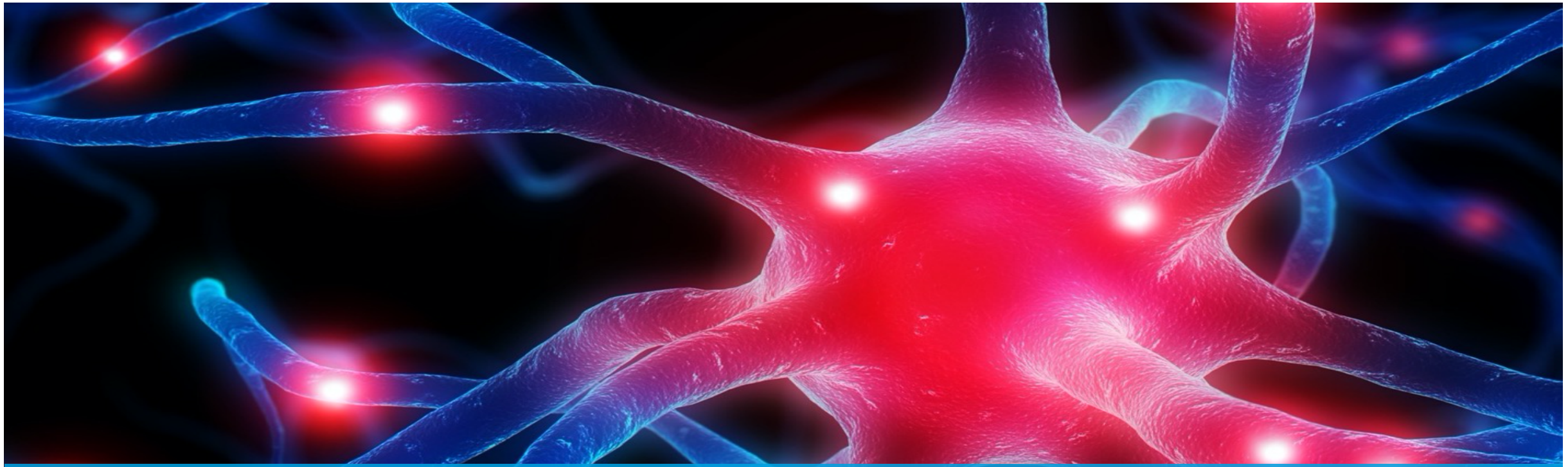


Real World Assessment and Research of Drug performance (REWARD)

Software demonstration

James Gilbert PhD

OHDSI Community Call 8th December 2020

Active neuron

Co-authors: Rachel Teneralli, Chris Knoll, Dave Kern, Soledad Cepeda, Patrick Ryan

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Introduction

REWARD Enables the discovery of **unknown effects of existing medications**

This is currently achieved through:

Exploiting OMOP CDM compliant databases using standardized vocabularies

Self-controlled cohort designs

Empirical calibration to minimize systematic error

Data Visualization and Exploration in Shiny Dashboards

The problem

Where does knowledge about drugs come from?

- Mechanistic understanding and compound discovery
- *In silico* simulation and *in vitro* lab studies
- *In vivo* animal model testing
- Clinical trials
- **Still have only a limited idea of what happens when you expose a population at large**

Real World Assessment and Research of Drug performance (REWARD)

Skin cells at 20x magnification

REWARD Mission

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.

Real World Evidence

Population level estimation provides **evidence** on what happens to **real people** exposed to **real medicines**.

This can be exploited to **generate new hypotheses** about any existing medications

How can we apply this at the scale of ***all exposures by all outcomes***?

Claims Databases currently used for REWARD

Source Name	Persons	Average Person-years	Years covered
Optum SES	84,310,086	2.97	May 1, 2000 to Dec 31, 2019
IBM CCAE	152,963,555	2.73	Jan 1, 2000 to Feb 29, 2020
IBM MDCD	28,917,265	3.35	Jan 1, 2006 to June 30, 2019
IBM MDCR	10,115,120	3.93	Jan 1, 2000 to Jan 31, 2020
Total	**276,306,026**	**3.25**	**Jan 1, 2000 to Feb 29, 2020**

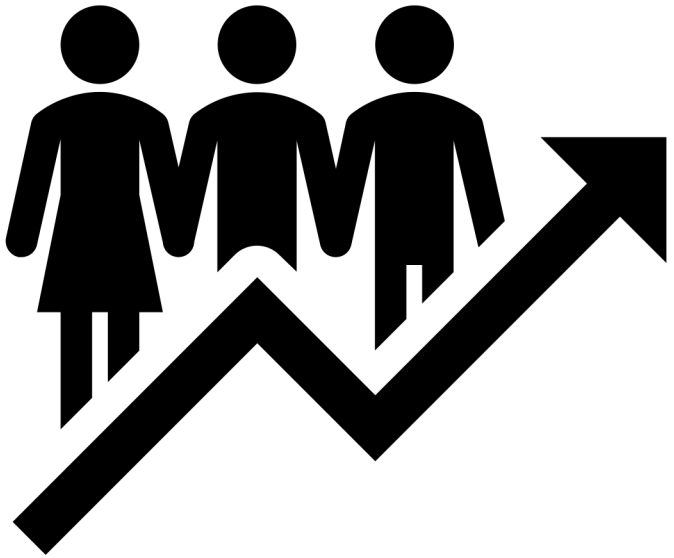
janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Cohort construction

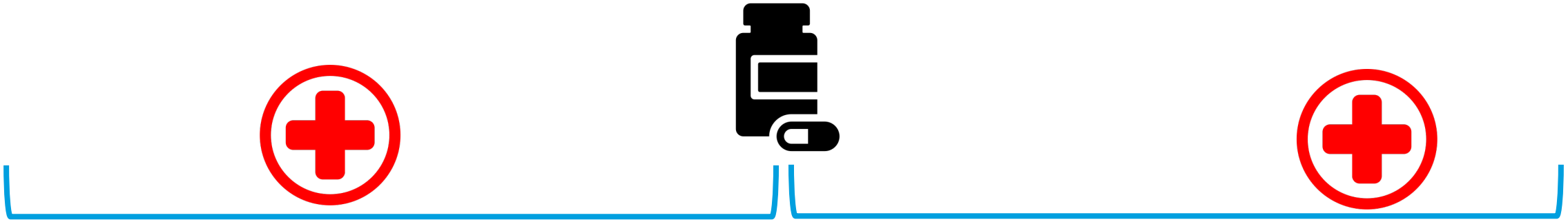
Exposure Cohorts:
- Rx Norm Ingredient
- New user cohort with 365 day washout period
- Custom cohorts defined in ATLAS e.g. drug classes
- ~2500 ingredient exposures (prescribed drugs)

Outcome cohorts:
- SNOMED standard concepts
- First occurrence of condition record
- Custom cohorts defined in ATLAS, e.g. phenotype library
- ~13,000 outcomes

Resulting combination of exposures and outcomes:
  - 32,500,000 exposure-outcome combinations
  - Sparse, heavy tailed distribution – most exposures have no outcomes.



Self-controlled cohort studies



Time prior to treatment

Equal in length to time on treatment

Time on treatment

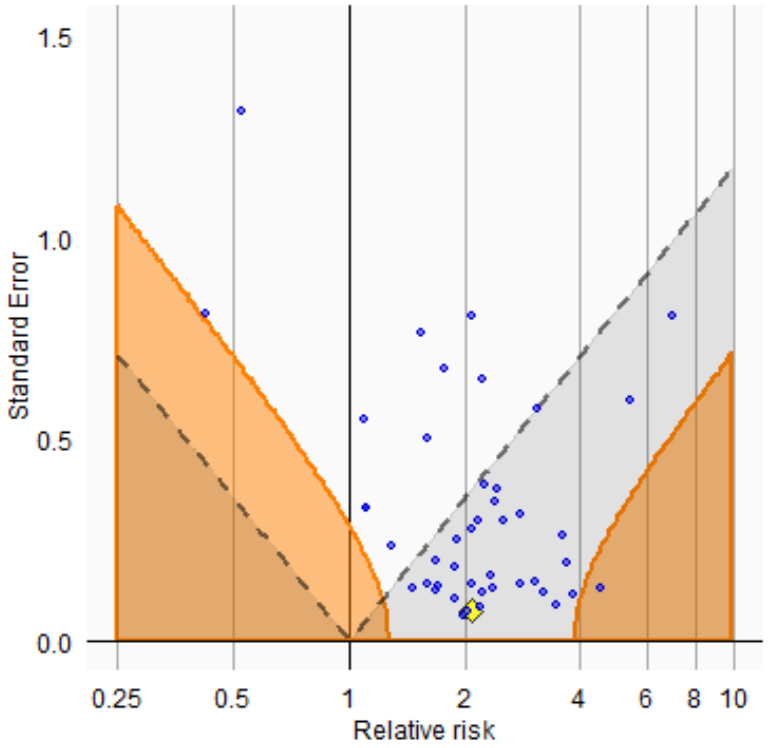
First diagnosis of condition:

can occur prior to treatment, during treatment, or neither

- Individual serves as own control
- Identify occurrence of condition for all patients with drug exposure
- Post-exposure and pre-exposure incidence rates are calculated, rate ratio is calculated
- Note: Drugs indicated for the condition would look protective
  - Condition occurs before exposure

Empirical calibration

Adjusting for systematic bias



- Systematic bias occurs because any study design is inherently imperfect
- Controlling for bias is achieved through using negative controls i.e. medications and diseases that do not interact.
- Estimate an empirical null distribution
- Allows adjustment of p-values and confidence intervals
- Achieved using EmpiricalCalibration package in R

https://ohdsi.github.io/EmpiricalCalibration/

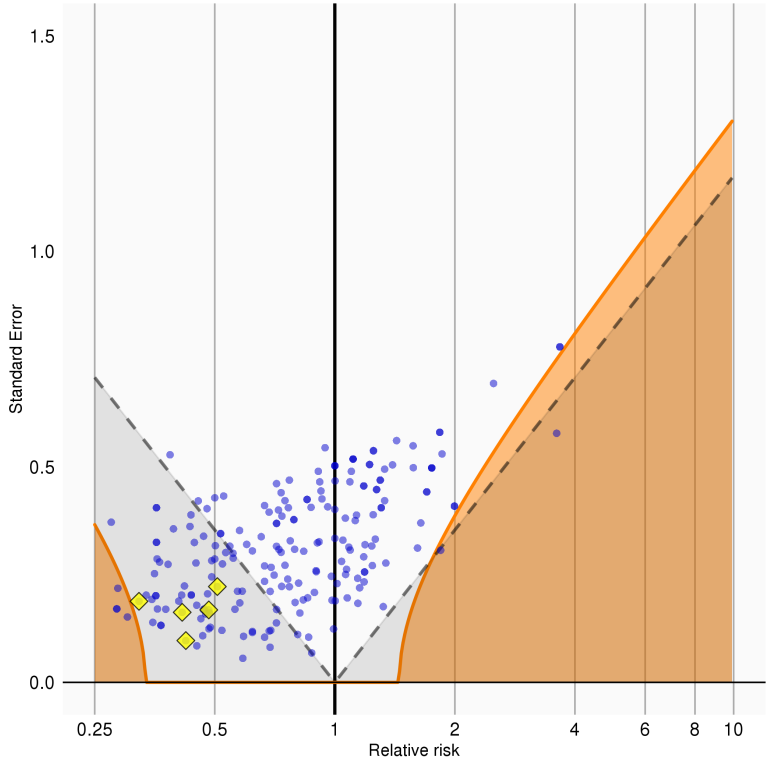
Automated negative control selection

- Adapted from Voss *et al*
- Scaled of all diseases by all treatments
- Use Common Evidence Model to construct map of drug-disease associations
- Based on Spontaneous Reports, PubMed MESH literature terms and Product Labels
- Mapping drugs to conditions in data-set is straightforward
- Mapping conditions to drugs requires looking up the concept hierarchy
- Initial validation performed on Depression data (Teneralli et al)

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

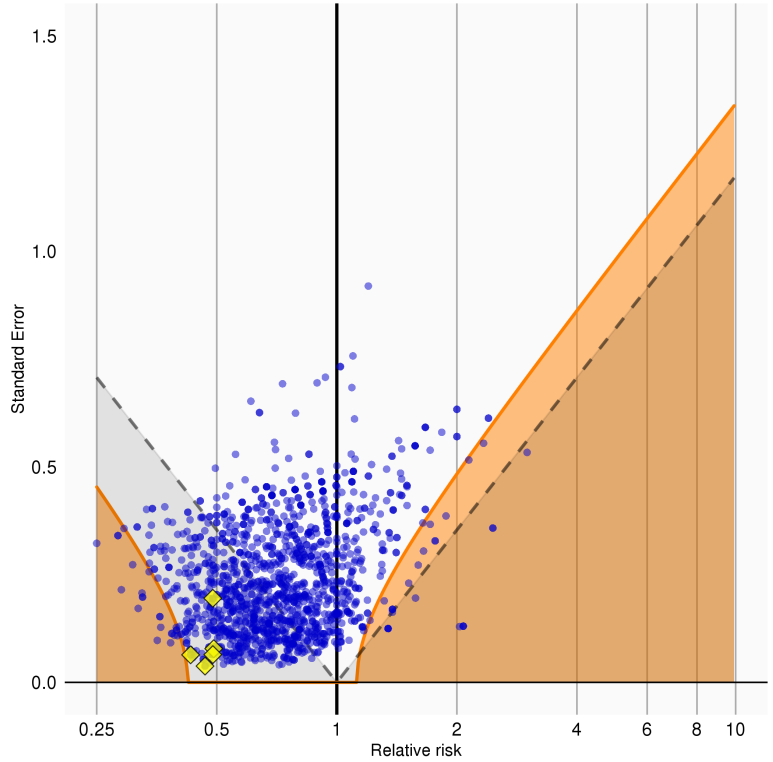
Examples - False positives

Lactulose for outcome of impaired cognition



Null distribution mean is IRR = 0.697 SD = 1.454.

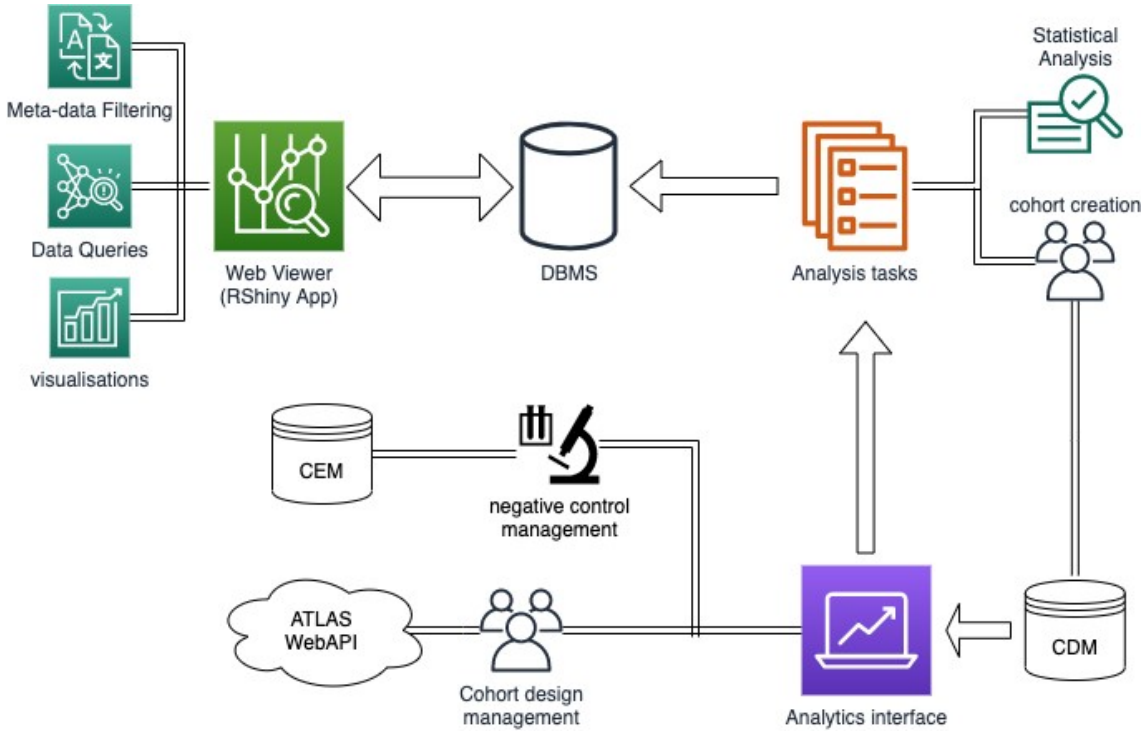
Metformin for bipolar disorder



Null distribution mean is IRR = 0.689 SD = 1.282

Calibration plot shows that the null distribution of negative controls is heavily biased to the left. Blue dots show negative controls. Yellow dots show **uncalibrated** IRR effect estimates for exposure, outcome pairs. Orange shaded area indicates significant results after calibration.

System overview



- Central Postgresql database for cohort references
- Integration with ATLAS – cohorts and concept sets
- Aims to be platform independent[1]
- Cohort references exported in a zip file
- Based on OHDSI R packages
- Shiny Application for visualization and exploration of results based on study areas

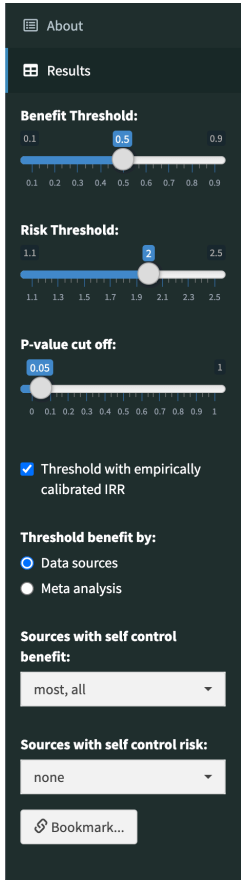
1. Currently built on MS PDW, Redshift under development.

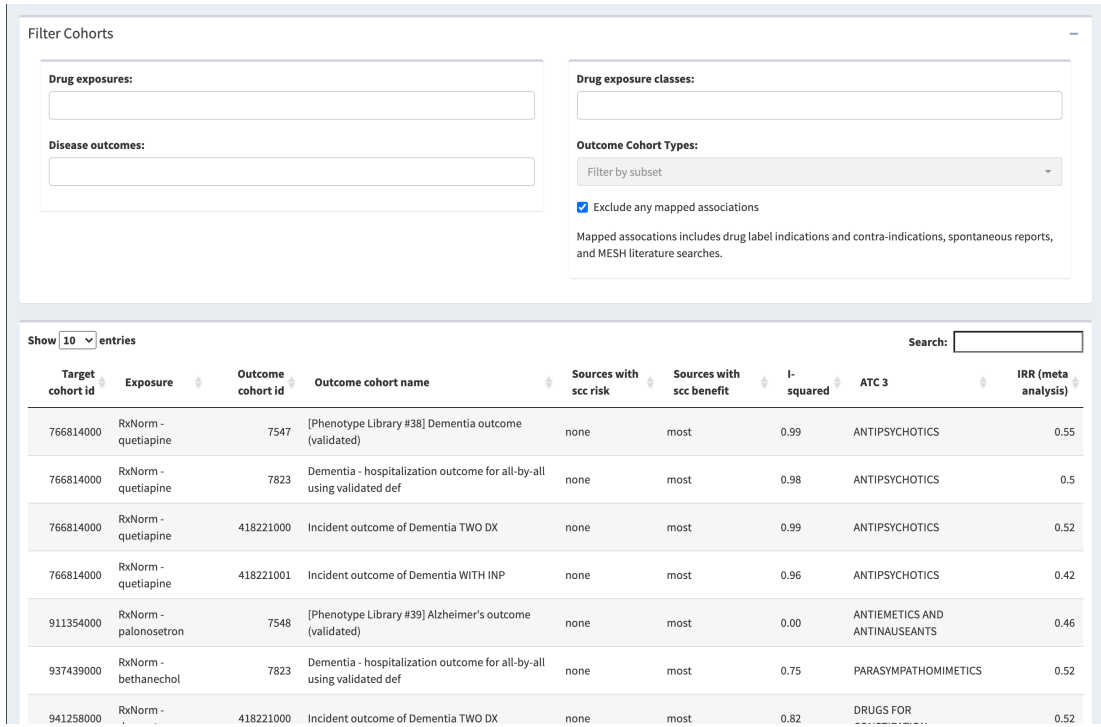
Shiny Dashboard

Skin cells at 20x magnification

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Demo





Target cohort id	Exposure	Outcome cohort id	Outcome cohort name	Sources with scc risk	Sources with scc benefit	I-squared	ATC 3	IRR (meta analysis)
766814000	RxNorm - quetiapine	7547	[Phenotype Library #38] Dementia outcome (validated)	none	most	0.99	ANTIPSYCHOTICS	0.55
766814000	RxNorm - quetiapine	7823	Dementia - hospitalization outcome for all-by-all using validated def	none	most	0.98	ANTIPSYCHOTICS	0.5
766814000	RxNorm - quetiapine	418221000	Incident outcome of Dementia TWO DX	none	most	0.99	ANTIPSYCHOTICS	0.52
766814000	RxNorm - quetiapine	418221001	Incident outcome of Dementia WITH INP	none	most	0.96	ANTIPSYCHOTICS	0.42
911354000	RxNorm - palonosetron	7548	[Phenotype Library #39] Alzheimer's outcome (validated)	none	most	0.00	ANTIEMETICS AND ANTINAUSEANTS	0.46
937439000	RxNorm - bethanechol	7823	Dementia - hospitalization outcome for all-by-all using validated def	none	most	0.75	PARASYMPATHOMIMETICS	0.52
941258000	RxNorm -	418221000	Incident outcome of Dementia TWO DX	none	most	0.82	DRUGS FOR	0.52

1. Or flat JSON files, e,g, from the Phenotype Library

Conclusions

- REWARD enables the discovery of unknown effects of existing medications
- One use case, providing clinical insights for drug development
- This software builds on the OMOP CDM and OHDSI Open-Source software tools
- Provides convenient mechanism for exploring results
- Set up to support multiple CDM compliant data sources
- Allows a quick test for clinical questions

Future work

- To include the phenotype library for well validated cohorts
- Self-controlled case series studies in addition to self-controlled cohort
- True all-by all interface for fast hypothesis checking
- ”one click” cohort characterization through integration with CohortDiagnostics
- End to end unit and integration testing

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

References

Voss, E.A., et al., Accuracy of an automated knowledge base for identifying drug adverse reactions. J Biomed Inform, 2017. 66: p. 72-81.

Schuemie, M.J., et al., Interpreting observational studies: why empirical calibration is needed to correct p-values. Stat Med, 2014. 33(2): p. 209-18.

Schuemie, M.J., et al., Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. Proc Natl Acad Sci U S A, 2018. 115(11): p. 2571-2577.

Teneralli, R, et al., Evaluation of Negative Control Selection as Method to Control for Systematic Bias in REal-World Assessment of Drug Benefits (REWARD-B) Platform. Abstract, OHDSI Symposium 2020