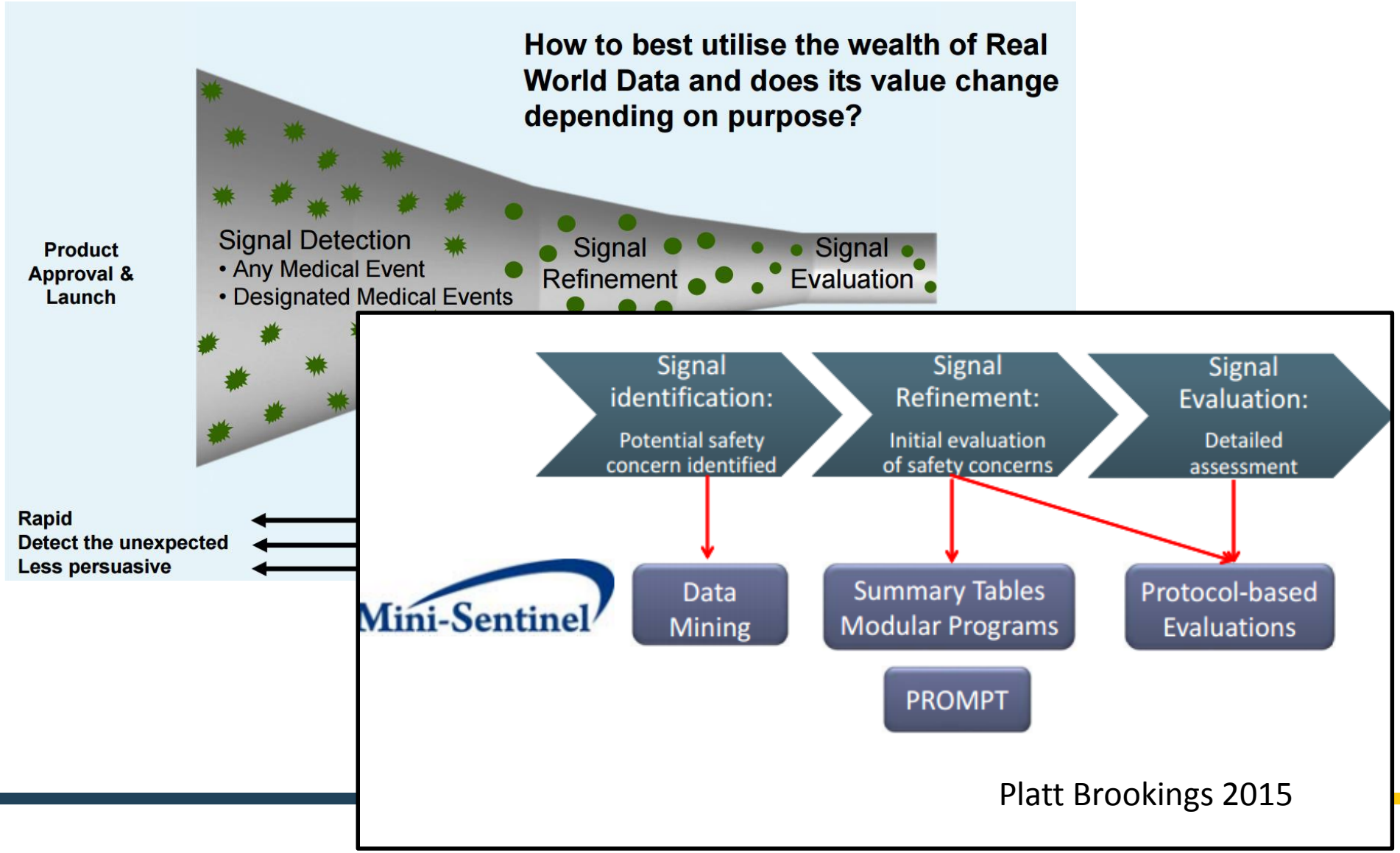
Applying Hill's criteria as a framework for causal inference in observational data

Patrick Ryan, PhD
Janssen Research and Development
Columbia University Medical Center
10 June 2015

Perspectives on the role of ‘signal detection’

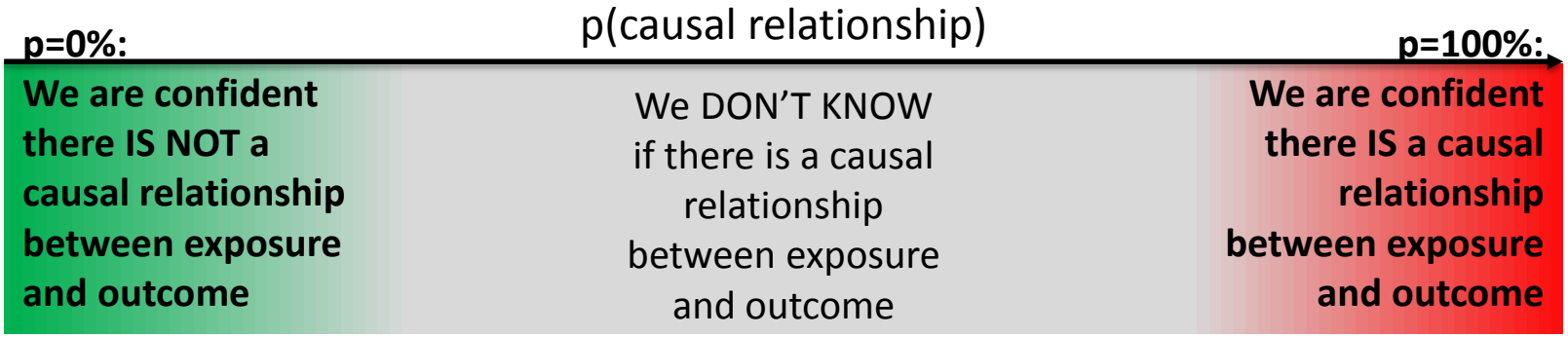


Platt Brookings 2015

Another perspective on ‘signal detection’

http://www.independent.co.uk/news/world/europe/sven-sachsalber-the-artist-literally-looking-for-a-needle-in-a-haystack-9859728.html

Alternative perspective: Generate evidence to determine the nature of a causal relationship



fluticasone-bleeding

warfarin-bleeding

terazosin-hepatoxicity

troglitazone – hepatotoxicity

Penicillin-acute myocardial infarction

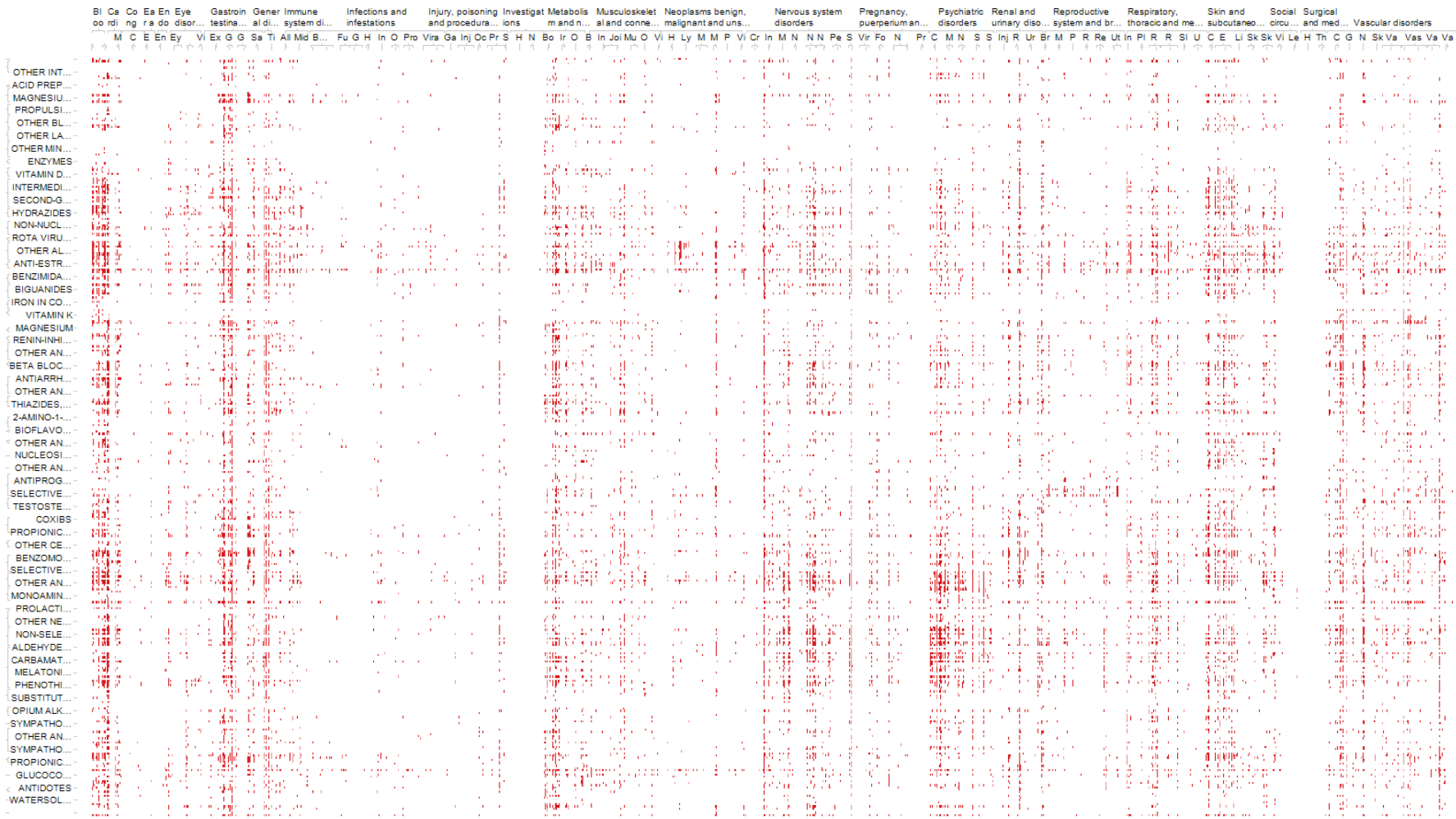
rosiglitazone – acute myocardial infarction

rofecoxib – acute myocardial infarction

How much evidence do we currently have?

All health outcomes of interest

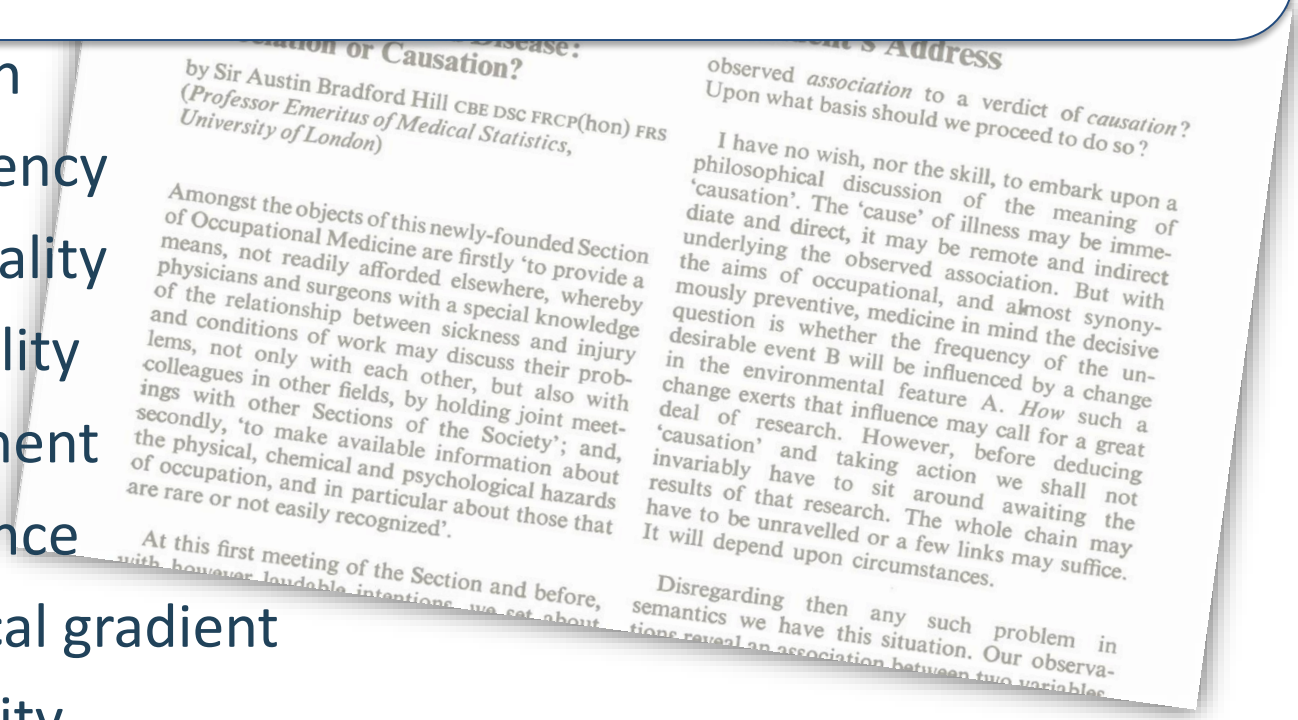
All drugs



To go forward, we must go back

"What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?"

- Strength
- Consistency
- Temporality
- Plausibility
- Experiment
- Coherence
- Biological gradient
- Specificity
- Analogy



or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before,

's Address

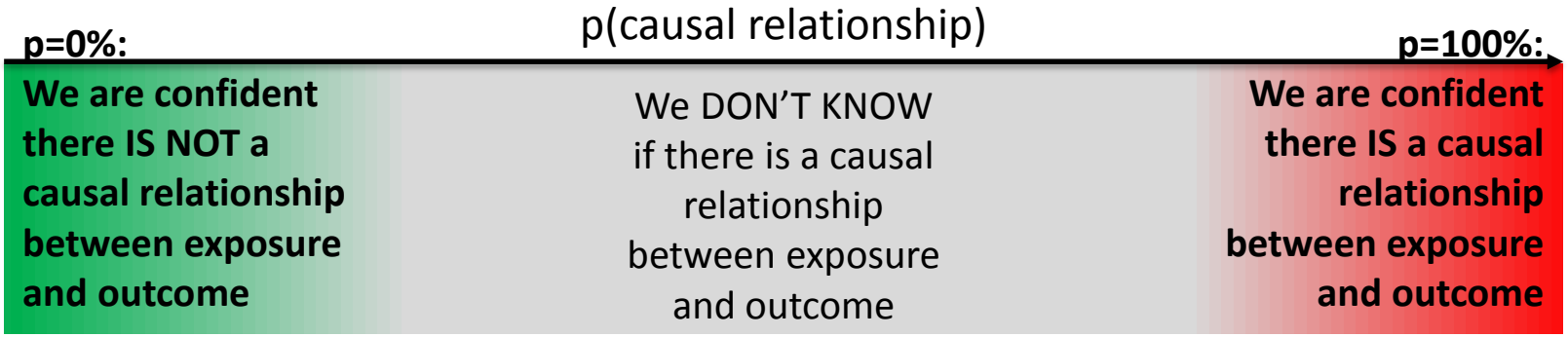
observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observa-

Austin Bradford Hill, "The Environment and Disease: Association or Causation?," *Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.

Role of randomized clinical trials in evaluating a causal relationship



Randomized clinical trials

(for trials with powered safety endpoints)

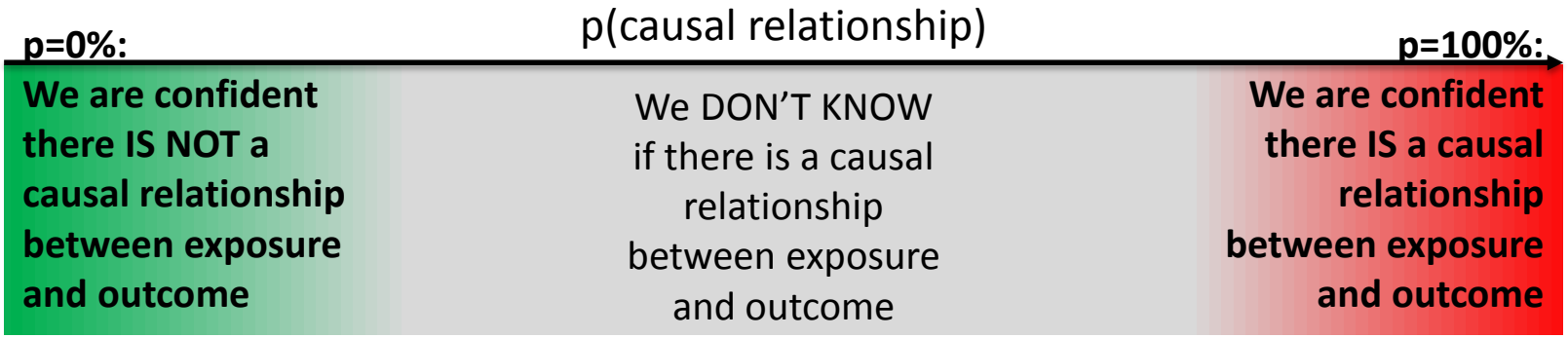
- Strength
- Experiment
- Biological gradient

Why we don't know:

- Insufficient number of persons exposed
- Insufficient length of exposure
- Inadequate coverage of exposed population

- Strength
- Consistency
- Temporality
- Plausibility
- Experiment
- Biological gradient
- Specificity

Role of spontaneous adverse event data in evaluating a causal relationship



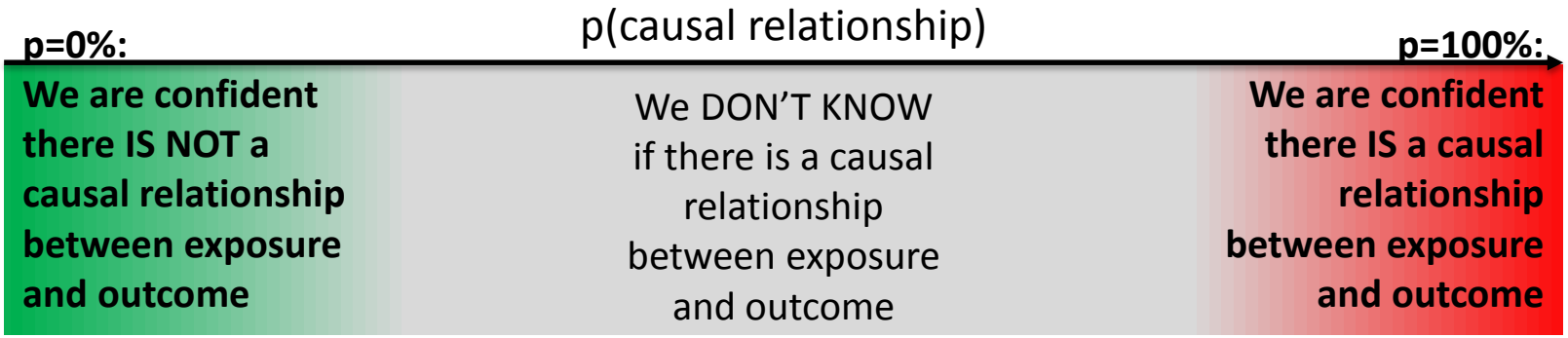
Spontaneous adverse event reporting

Why we don't know:

- Differential underreporting

- Strength: Disproportionality analysis
- Temporality: cases where exposure before outcome
- (Natural) Experiment: Dechallenge/rechallenge

Role of observational data in evaluating a causal relationship



- Strength
- Consistency
- Temporality
- Plausibility
- (Natural) Experiment
- Biological gradient
- Specificity
- Analogy

Why don't we know:

- Incomplete and biased data capture process
- Non-random treatment assignment
- Insufficient number of persons exposed
- Inadequate length of exposure

- Strength
- Consistency
- Temporality
- Plausibility
- (Natural) Experiment
- Biological gradient
- Specificity
- Analogy

Introducing OHDSI

- The Observational Health Data Sciences and Informatics (OHDSI) program is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics
- OHDSI has established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University

OHDSI Communities

Community: a social unit of any size that shares common values

--http://en.wikipedia.org/wiki/Community

OHDSI's communities:

- Research
- Open-source software development
- Data network

OHDSI: a global community

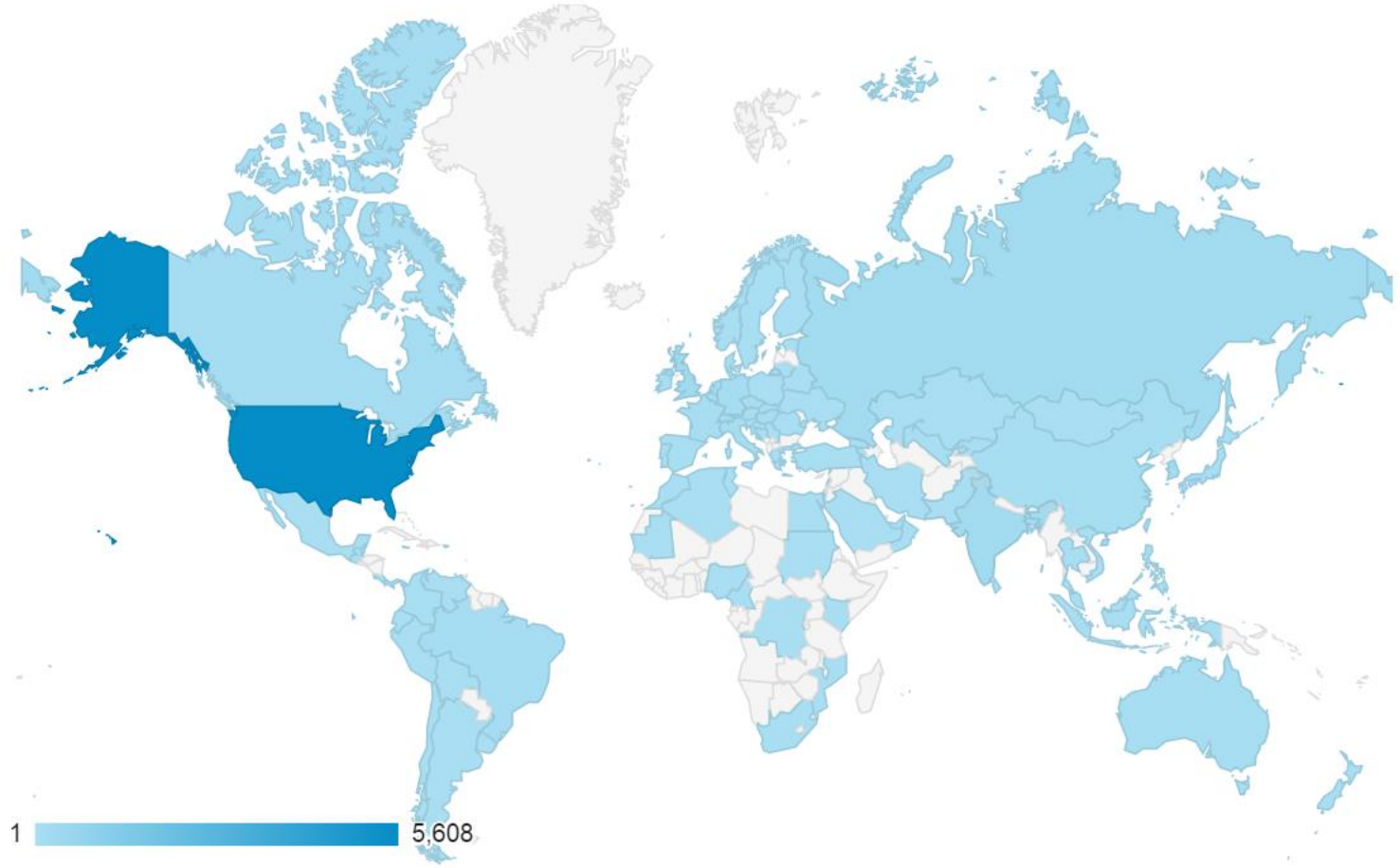
OHDSI Collaborators:

- >140 researchers in academia, industry and government
- >10 countries

OHDSI Data Network:

- >40 databases standardized to OMOP common data model
- >500 million patients

Global reach of ohdsi.org



- >4600 distinct users from 96 countries in 2015

Evidence OHDSI seeks to generate from observational data

- Clinical characterization:
  - Natural history: Who are the patients who have diabetes? Among those patients, who takes metformin?
  - Quality improvement: what proportion of patients with diabetes experience disease-related complications?
- Population-level estimation
  - Safety surveillance: Does metformin cause lactic acidosis?
  - Comparative effectiveness: Does metformin cause lactic acidosis more than glyburide?
- Patient-level prediction
  - Given everything you know about me and my medical history, if I start taking metformin, what is the chance that I am going to have lactic acidosis in the next year?

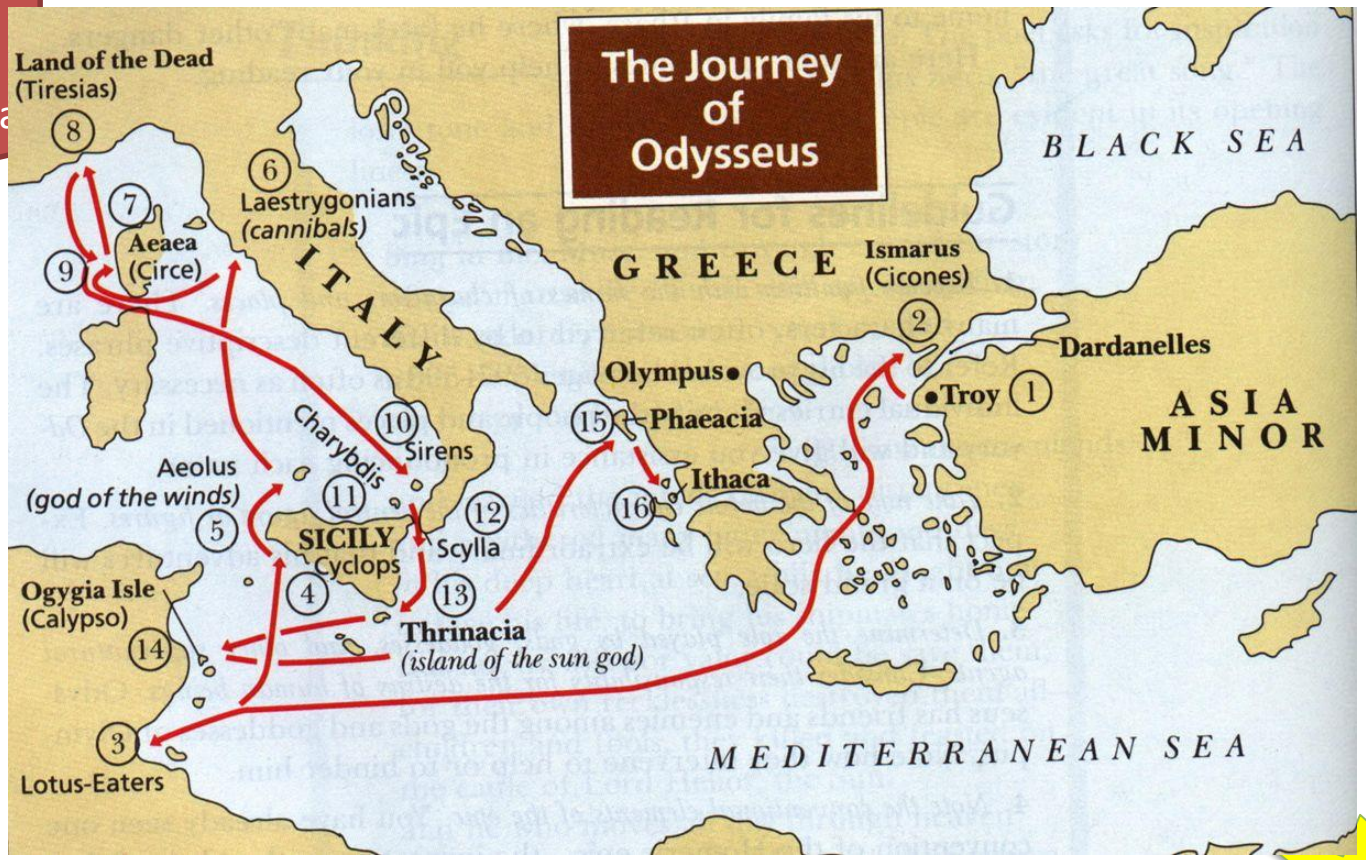
Opportunities for standardization in the evidence generation process

Protocol

- **Data structure** : tables, fields, data types
- **Data content** : vocabulary to codify clinical domains
- **Data semantics** : conventions about meaning
- **Cohort definition** : algorithms for identifying the set of patients who meet a collection of criteria for a given interval of time
- **Covariate construction** : logic to define variables available for use in statistical analysis
- **Analysis** : collection of decisions and procedures required to produce aggregate summary statistics from patient-level data
- **Results reporting** : series of aggregate summary statistics presented in tabular and graphical form

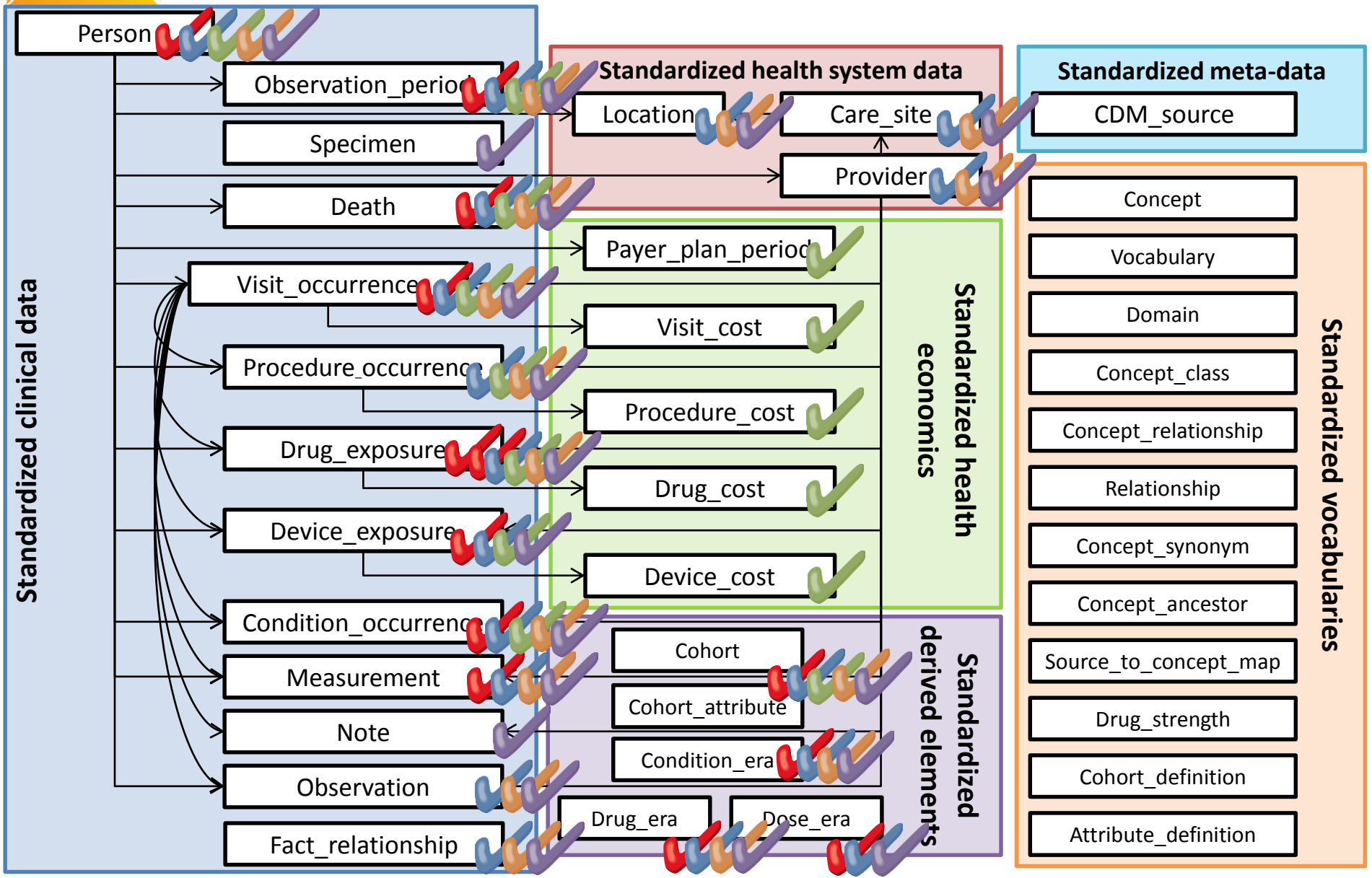
The odyssey to evidence generation

Patient-level data in source system/ schema

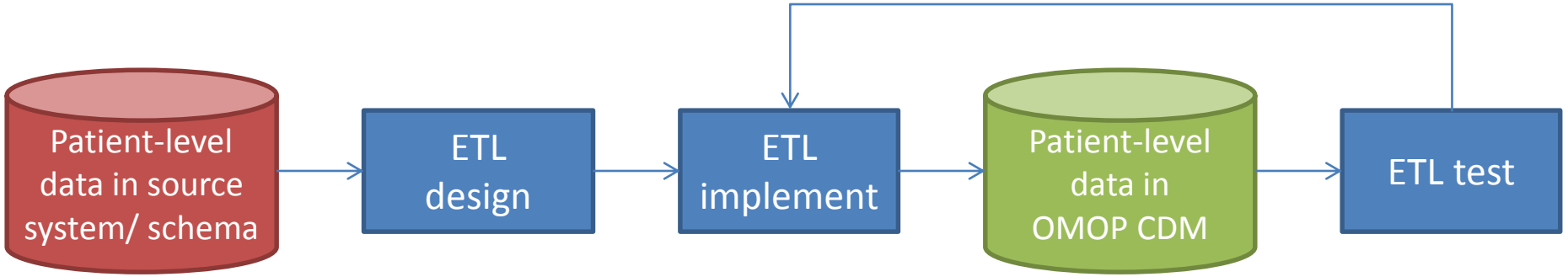


evidence

One model, multiple use cases



Preparing your data for analysis



OHDSI tools built to help

WhiteRabbit: profile your source data

RabbitInAHat: map your source structure to CDM tables and fields

ATHENA: standardized vocabularies for all CDM domains

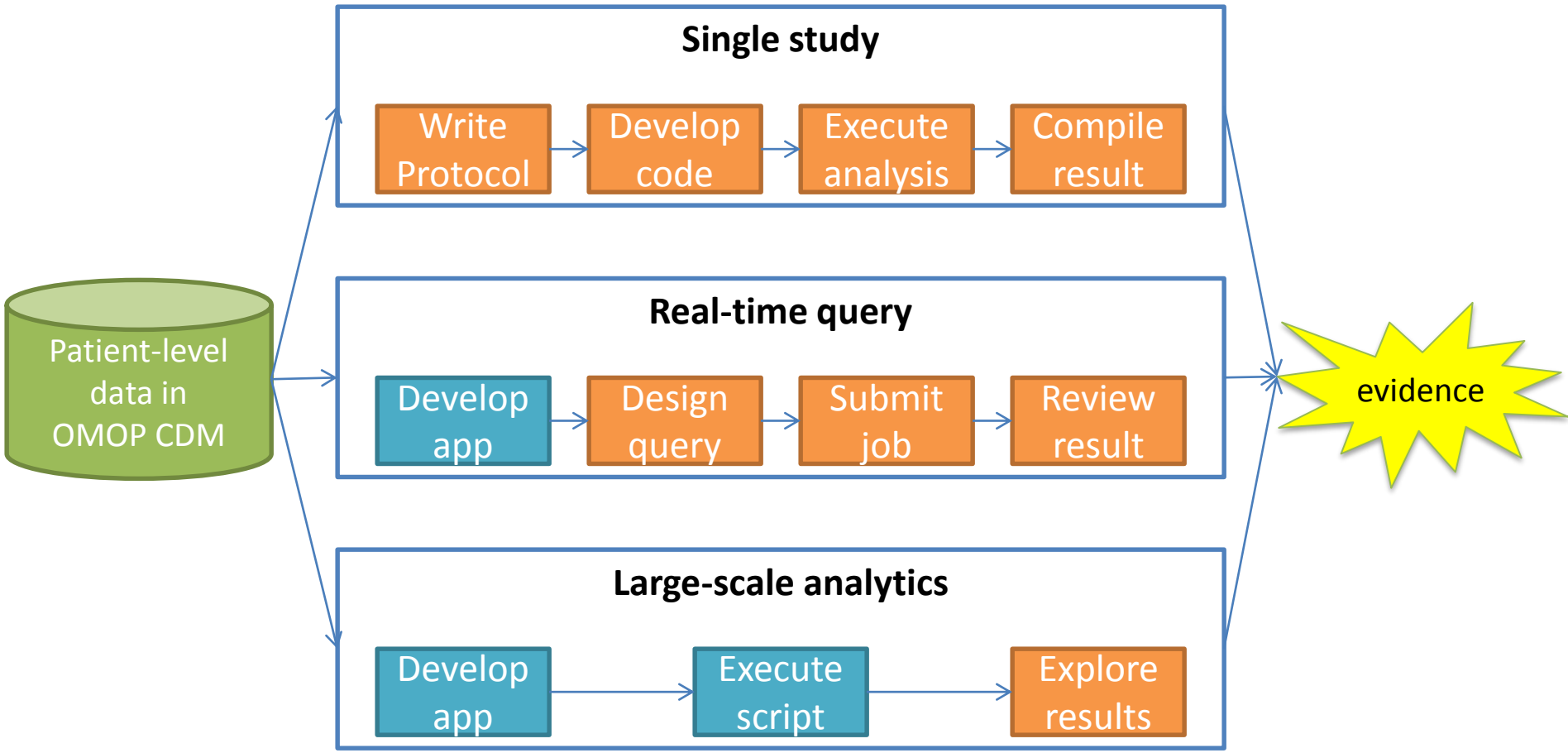
Usagi: map your source codes to CDM vocabulary

CDM: DDL, index, constraints for Oracle, SQL Server, PostgresQL; Vocabulary tables with loading scripts

ACHILLES: profile your CDM data; review data quality assessment; explore population-level summaries

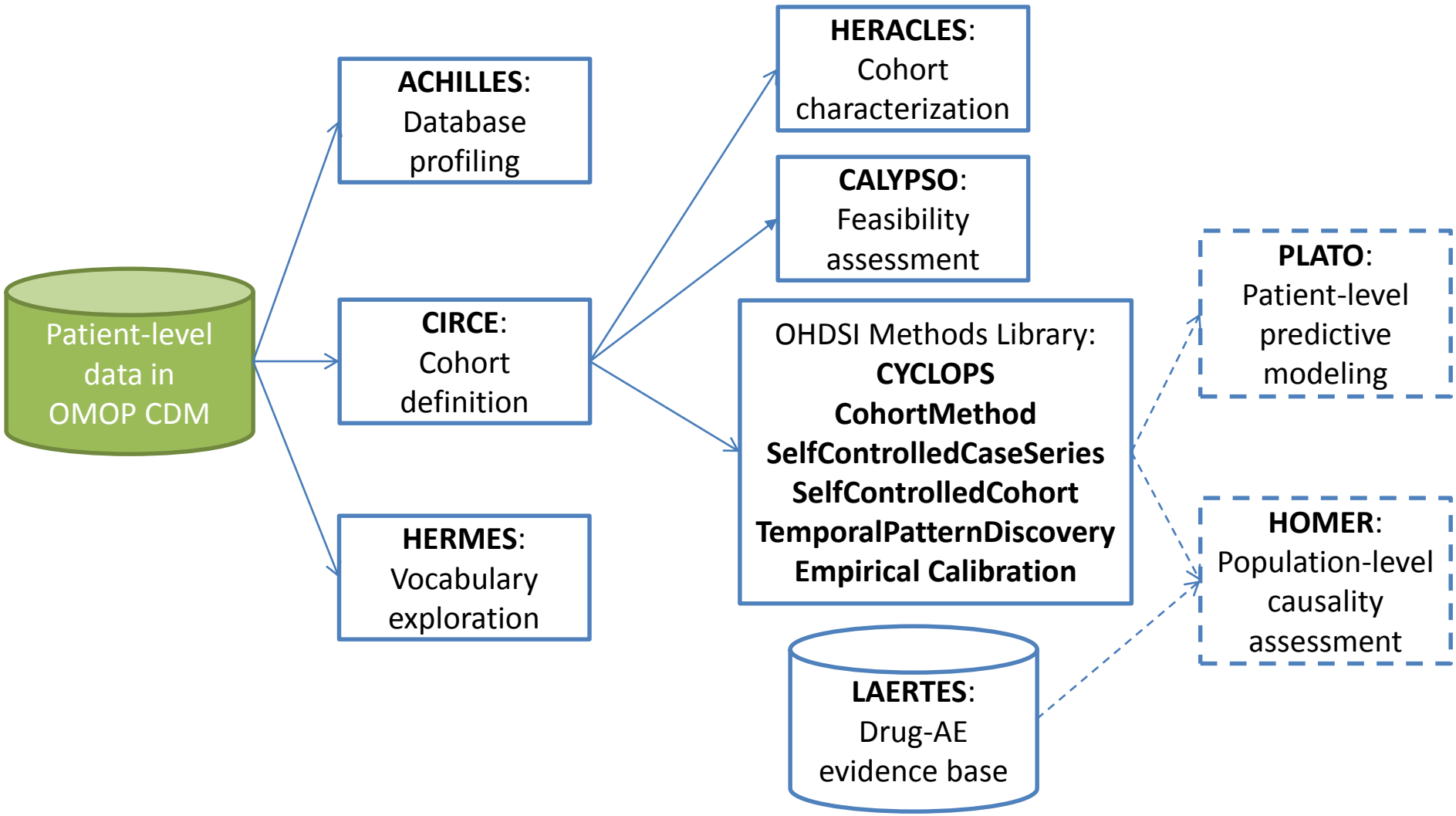
OHDSI Forums: Public discussions for OMOP CDM Implementers/developers

~~Data~~ Evidence sharing paradigms



One-time Repeated

Standardized large-scale analytics tools under development within OHDSI



HOMER implementation of Hill's viewpoints

http://omop.org/2013Symposium

Motivating example to see the OHDSI tools in action

Mini-Sentinel

MINI-SENTINEL MEDICAL PRODUCT ASSESSMENT

A PROTOCOL FOR ASSESSMENT OF DABIGATRAN

Version 3

March 27, 2015

Prior versions:
Version 1: December 31, 2013
Version 2: March 18, 2014

Prepared by: Alan S. Go, MD[1], Daniel Singer, MD[2], T. Craig Cheetham, PharmD MS[3], Darren Toh, ScD[4], Marsha Reichman, PhD[5], David Graham, MD MPH[5], Mary Ross Southworth, PharmD[6], Rongmei Zhang PhD[7], Monika Houstoun, PharmD[5], Yu-te Wu PhD[7], Katrina Mott MS[5], Joshua Gagne, PharmD ScD[8]

Author Affiliations: 1. Division of Research, Kaiser Permanente Northern California, Oakland, CA. 2. General Medicine Division, Massachusetts General Hospital, Boston, MA. 3. Kaiser Permanente Southern California, Downey, CA. 4. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA. 5. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, MD. 6. Division of Cardiovascular and Renal Products, Office of New Drugs, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, MD. 7. Division of Biometric VII, Office of Biostatistics, Office of

III. PROTOCOL DETAILS

A. ASSESSMENT DESIGN

This one-time assessment will employ a "new user" parallel cohort design.[12]

B. COHORT IDENTIFICATION

1. Target Population

We will focus on the identification of **adult (age ≥21 years) patients with diagnosed nonvalvular atrial fibrillation and who are new users of dabigatran or warfarin**.

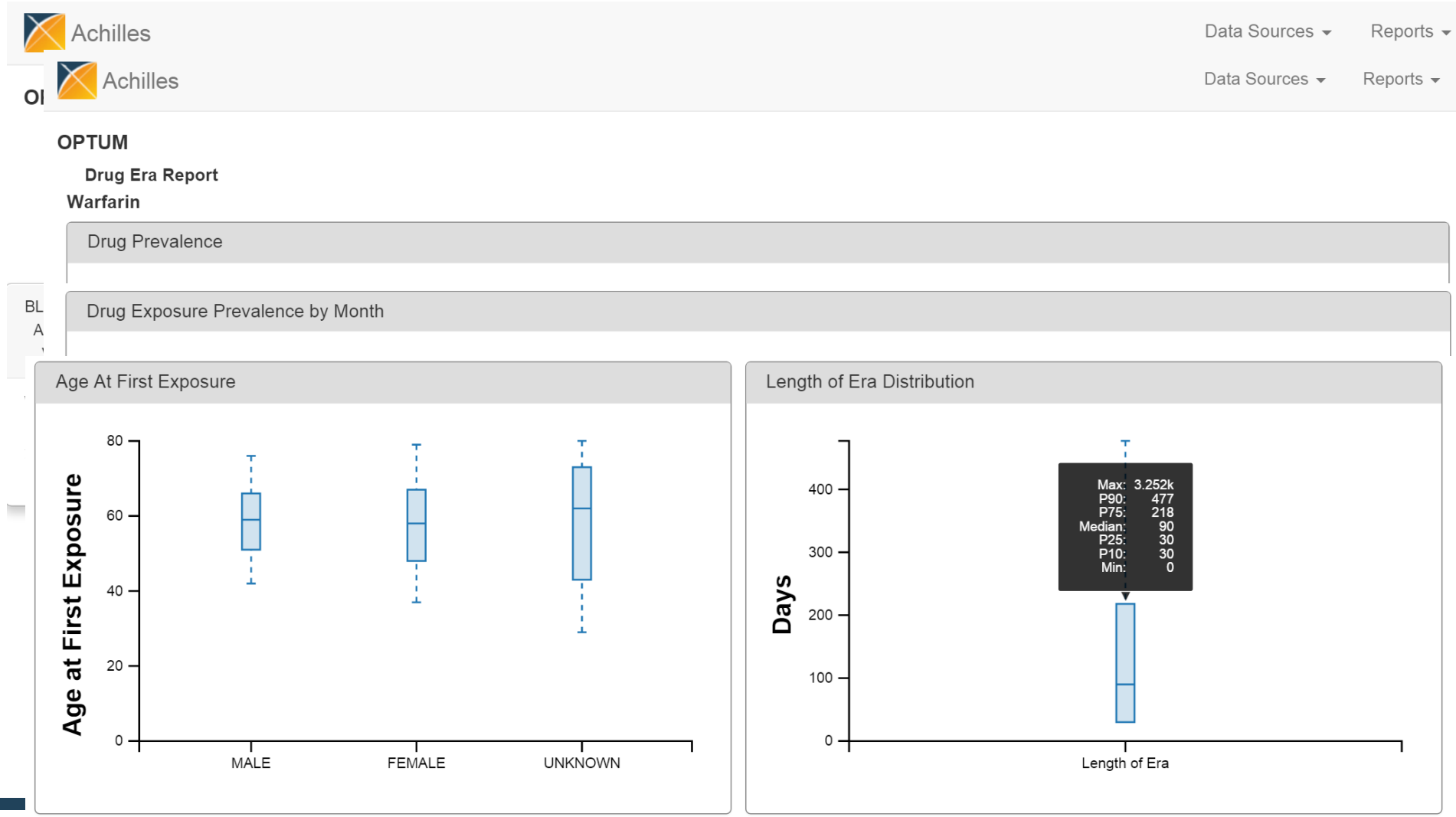
2. Sample Inclusion and Exclusion Criteria

The target sample inclusion and exclusion criteria are summarized in **Table 1** below. Please see **Appendix A** and *Section D* for additional details, definitions and rationale.

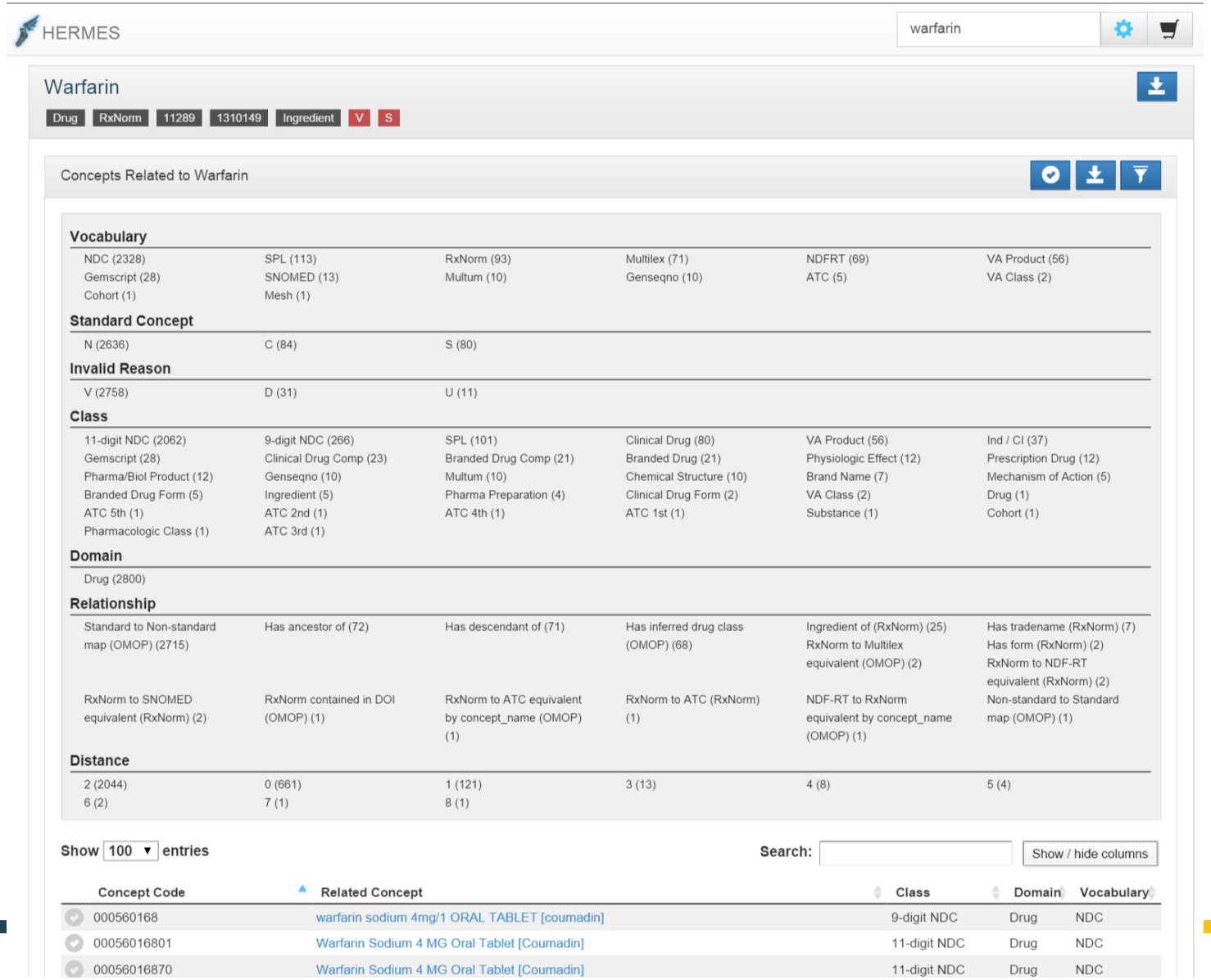
Table 1. Inclusion and exclusion criteria for comparison of adults with atrial fibrillation who are new users of dabigatran or warfarin in the MSDD.

Inclusion Criteria	Exclusion Criteria
• First dispensing of dabigatran or warfarin therapy from November 1, 2010 to the most recent data available in the MSDD from participating Data Partners *	• Less than 180 days of continuous enrollment with prescription and medical coverage immediately preceding the date of the index dispensing (i.e., index date)
• Age 21 years or older at the first dispensing of dabigatran or warfarin therapy	• Any prior dispensing for warfarin, dabigatran, rivaroxaban or apixaban during the 180 days before index date **
• One or more diagnoses of atrial fibrillation or atrial flutter based on ICD-9-CM codes (ICD-9-CM 427.31, 427.32) from any practice setting (inpatient or outpatient) any time before the first identified prescription for dabigatran or warfarin therapy during the study period *	• Known mechanical heart valve or diagnosed mitral stenosis at index date based on corresponding administrative diagnosis and/or procedure codes • Chronic hemodialysis or peritoneal dialysis at index date based on corresponding administrative diagnosis and/or procedure codes • History of kidney transplant at index date based on corresponding administrative diagnosis and/or procedure codes • At a skilled nursing facility or nursing home at index date

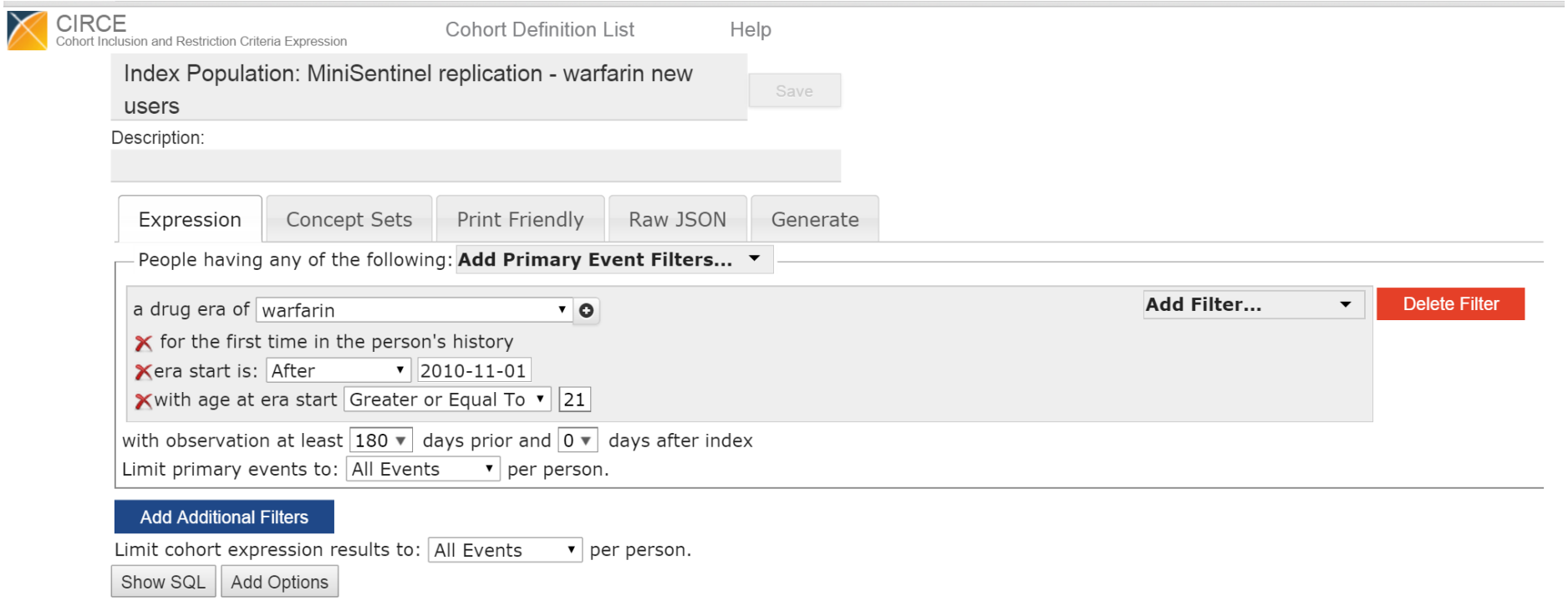
ACHILLES: Database characterization to examine if the data have the elements required for the analysis



HERMES: Explore the standardized vocabularies to define exposures, outcomes, and covariates



CIRCE: Define cohorts of interest



CALYPSO: Conduct feasibility assessment to evaluate the impact of study inclusion criteria

CAL
Criteria A
Populatio

Index Rule | Inclusion Rules | Concept Sets | Results

Source	Name	Dialect	
TRUVENCCAE	Truven CCAE (APS)	pdw	Generate
TRUVENMDCR	Truven MDCR (APS)	pdw	Generate
TRUVENMDCD	Truven MDCD (APS)	pdw	Generate
OPTUM	Optum (APS)	pdw	Generate
CPRD	CPRD (APS)	pdw	Generate
PREMIER	Premier (APS)	pdw	Generate
JMDC	JMDC (APS)	pdw	Generate
NHANES	NHANES (APS)	pdw	Generate
VOCAB	Default Vocabulary	sql server	Generate
LAERTES	Laertes	postgresql	Generate

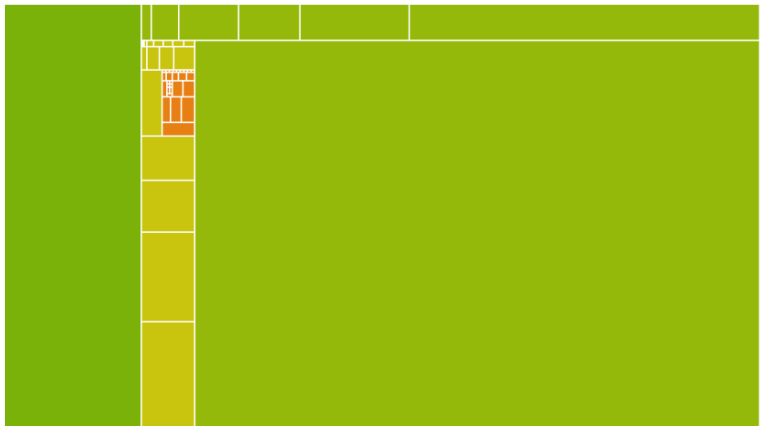
Consistency

Overview | Reports

	Match Rate	Matching Persons	Total Persons
Summary Statistics:	18.15%	12061	66443

Inclusion Rule	% Satisfied	% To-Gain
1. Prior atrial fibrillation	23.31%	71.19%
2. No prior warfarin ever	100.00%	0.00%
3. No prior dabigatran ever	98.80%	0.17%
4. No prior anticoagulants in past 183 days	98.05%	0.38%
5. No mechanical heart value or mitral stenosis	94.99%	2.23%
6. No dialysis in last 30 days	98.97%	0.39%
7. No history of kidney transplant	99.61%	0.06%
8. Not at long-term care visit	97.29%	0.70%

Population Visualization



HERACLES: Characterize the cohorts of interest

OHDSI Heracles

«Back

Refresh

Truven MDCD (APS)

Heracles Runner

Cohort Specific

Condition

Condition Eras

Conditions by Index

Dashboard

Data Density

Death

Drug Eras

Drug Exposures

Drugs by Index

Heracles Heel

Matching Population: MiniSentinel replication - warfarin new users

Condition Prevalence

Treemap | Table

Specificity

Box Size: Prevalence, Color: Log of Relative Risk (Red to Green = Negative to Positive), Use Ctrl-Click to Zoom, Alt-Click to Reset Zoom

Conditions by Index

Dashboard

Data Density

Death

Drug Eras

Drug Exposures

Drugs by Index

Heracles Heel

Measurements

Observation Periods

Observations

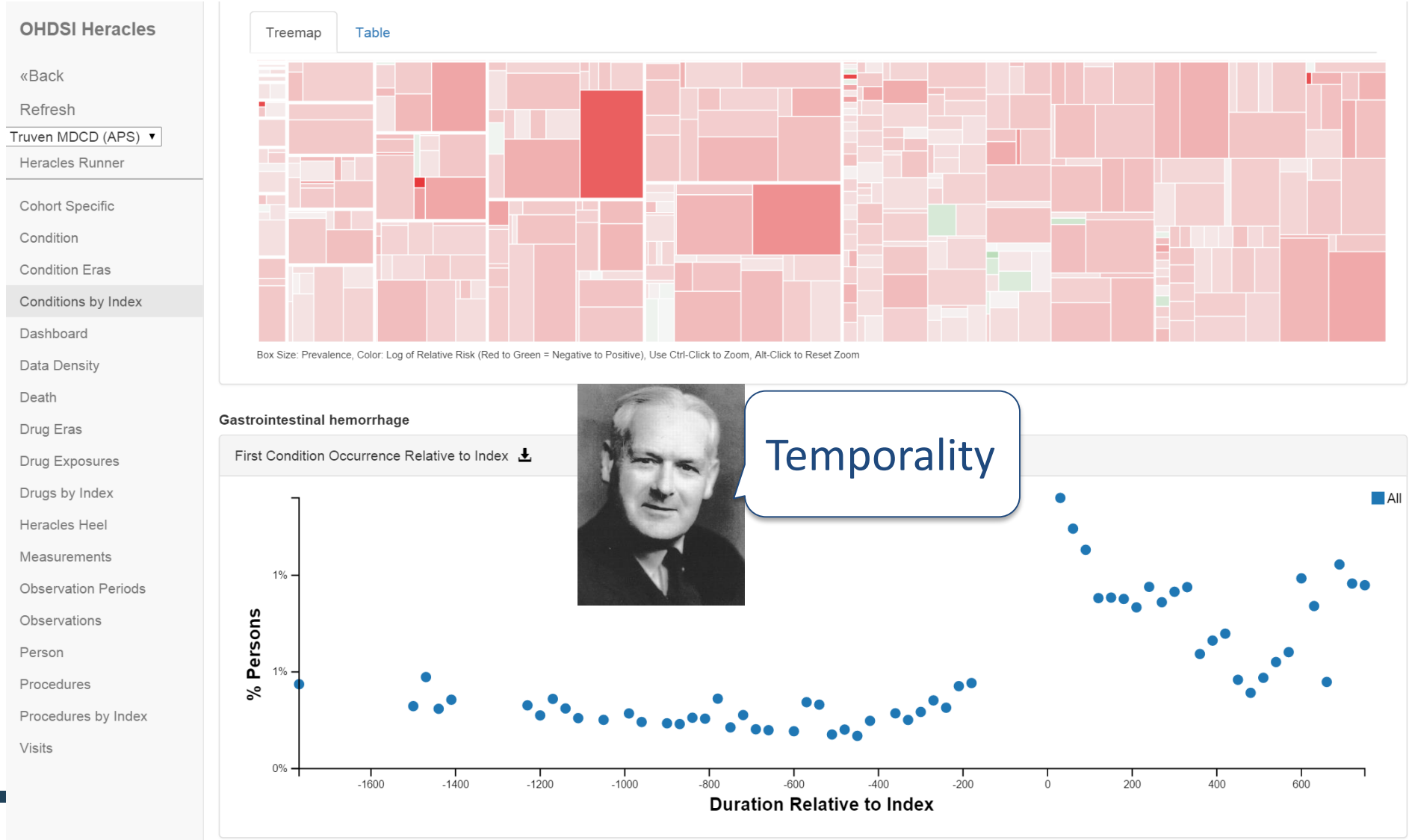
Person

Concept Id	SOC	HLT	SNOMED	Person Count	Prevalence	Relative Risk per Person
434894	NA	Vascular haemorrhagic disorders	Acute posthemorrhagic anemia	550	11.05%	-0.23
192671	Vascular disorders	Haemorrhages NEC	Gastrointestinal hemorrhage	451	9.06%	0.24
197925	NA	Vascular haemorrhagic disorders	Hemorrhage of rectum and anus	312	6.27%	-0.09
201322	Vascular disorders	Gastrointestinal varicosities and haemorrhoids	Internal hemorrhoids without complication	233	4.68%	-0.63
435141	Vascular disorders	Haemorrhages NEC	Hemorrhage AND/OR hematoma complicating procedure	113	2.27%	-0.19

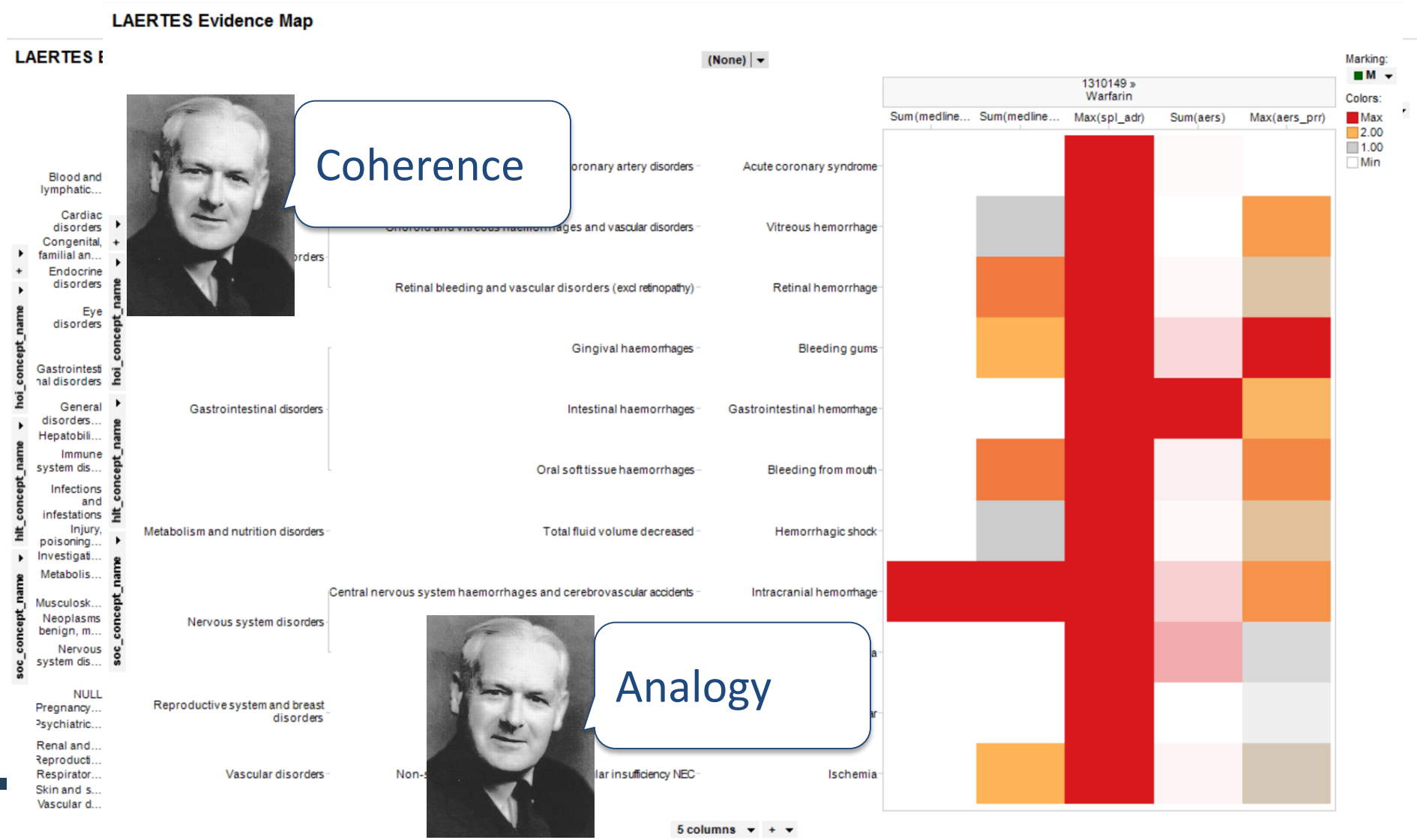
Showing 1 to 5 of 13 entries (filtered from 791 total entries)

Previous 1 2 3 Next

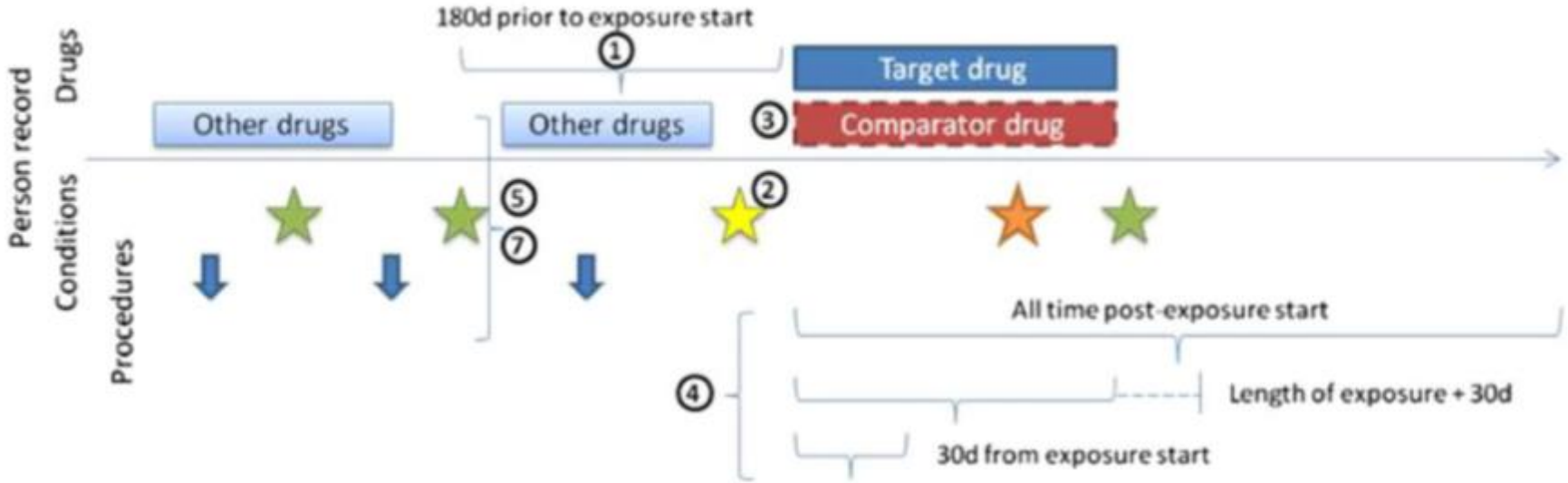
HERACLES: Characterize the cohorts of interest



LAERTES: Summarizing evidence from existing data sources: literature, labeling, spontaneous reporting



Standardizing analytic decisions in cohort studies

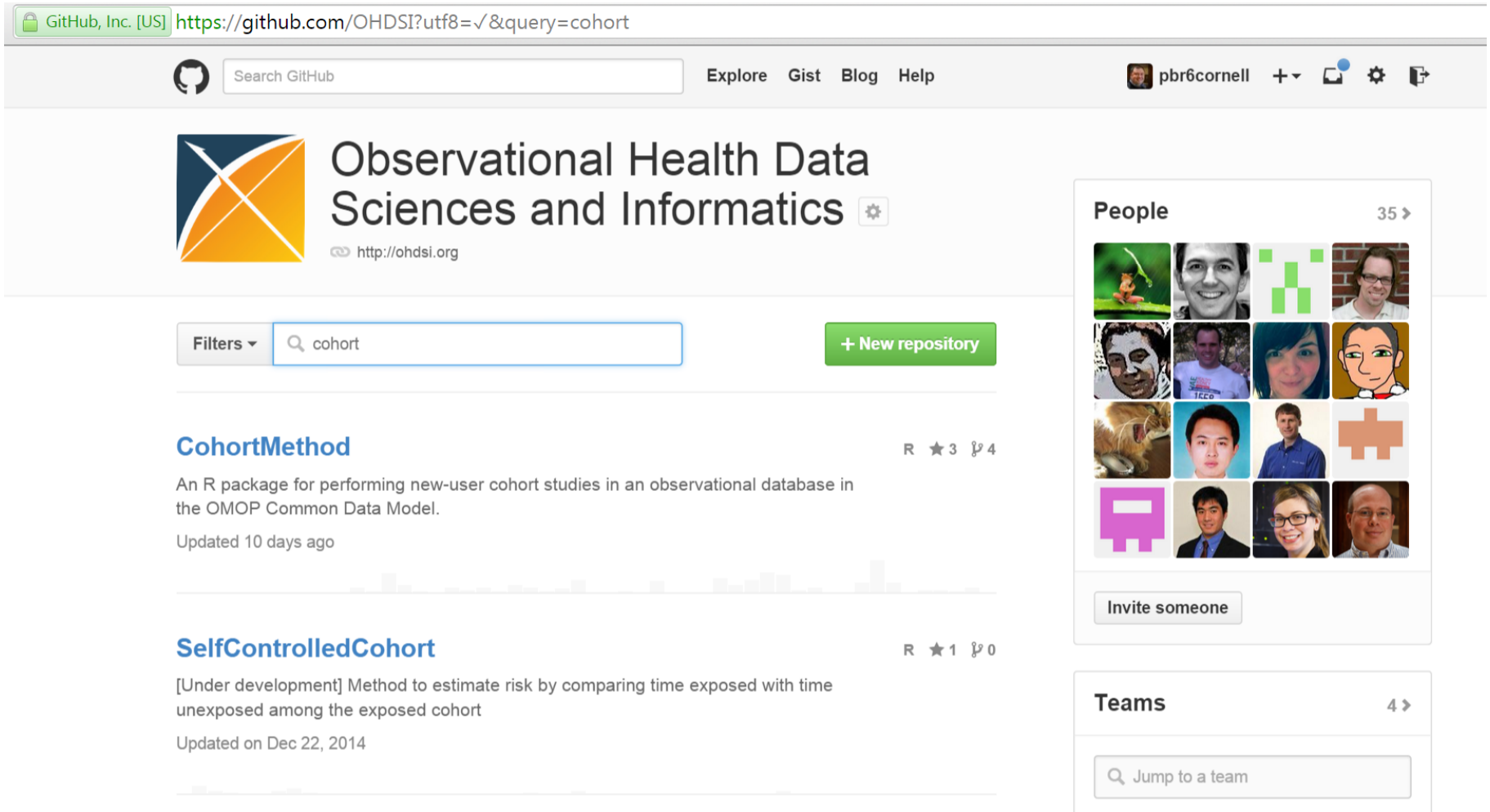


Decisions a researcher needs to make

→ parameters a standardized analytic routine needs to accommodate:

1. Washout period length
2. Nesting cohorts within indication
3. Comparator population
4. Time-at-risk
5. Propensity score covariate selection strategy
6. Covariate eligibility window
7. Propensity score adjustment strategy (trimming, stratification, matching)
8. Outcome model

Standardized analytics to enable reproducible research



http://github.com/OHDSI

Open-source large-scale analytics through R

Package 'CohortMethod'

February 23, 2015

Type Package

Title New-user cohort method with large scale propensity and outcome models

Version 1.0.0

Date 2015-02-02

Author Martijn J. Schuemie [aut, cre],Marc A. Suchard [aut],Patrick B. Ryan [aut]

Maintainer Martijn J. Schuemie <schuemie@ohdsi.org>

Description CohortMethod is an R package for performing new-user cohort studies in an observational database in the OMOP Common Data Model. It extracts the necessary data from a database in OMOP Common Data Model format, and uses a large set of covariates for both the propensity and outcome model, including for example all drugs, diagnoses,procedures, as well as age, comorbidity indexes, etc. Large scale regularized regression is used to fit the propensity and outcome models. Functions are included for trimming,stratifying and matching on propensity scores, as well as diagnostic functions, such as propensity score distribution plots and plots showing covariate balance before and after matching and/or trimming. Supported outcome models are (conditional) logistic regression,(conditional) Poisson regression, and (conditional) Cox regression.

License Apache License 2.0

VignetteBuilder knitr

Depends R (>= 3.1.0),bit,DatabaseConnector,Cyclops (>= 1.0.0)

Imports ggplot2,ff,ffbase,plyr,Rcpp (>= 0.11.2),RJDBC,SqlRender (>= 1.0.0),survival

Suggests testthat,pROC,gnm,knitr,rmarkdown

LinkingTo Rcpp

NeedsCompilation yes

Why is this a novel approach?

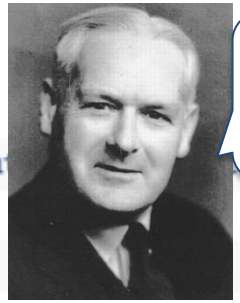
- Large-scale analytics, scalable to 'big data' problems in healthcare:
  - millions of patients
  - millions of covariates
  - millions of questions
- End-to-end analysis, from CDM through evidence
  - No longer de-coupling 'informatics' from 'statistics' from 'epidemiology'

Standardize covariate construction

```
#Load data:
cohortData <- getDbCohortData(connectionDetails,
                              cdmDatabaseSchema = cdmDatabaseSchema,
                              resultsDatabaseSchema = resultsDatabaseSchema,
                              targetDrugConceptId = 1,
                              comparatorDrugConceptId = 2,
                              indicationConceptIds = c(),
                              washoutWindow = 183,
                              indicationLookbackWindow = 183,
                              studyStartDate = "",
                              studyEndDate = "",
                              exclusionConceptIds = nsaids,
                              outcomeConceptIds = 3,
                              outcomeConditionTypeConceptIds = c(),
                              exposureDatabaseSchema = resultsDatabaseSchema,
                              exposureTable = "coxibVsNonselVsGiBleed",
                              outcomeDatabaseSchema = resultsDatabaseSchema,
                              outcomeTable = "coxibVsNonselVsGiBleed",
                              useCovariateDemographics = TRUE,
                              useCovariateConditionOccurrence = TRUE,
                              useCovariateConditionOccurrence365d = TRUE,
                              useCovariateConditionOccurrence30d = TRUE,
                              useCovariateConditionOccurrenceInpt180d = TRUE,
                              useCovariateConditionEra = TRUE,
                              useCovariateConditionEraEver = TRUE,
                              useCovariateConditionEraOverlap = TRUE,
                              useCovariateConditionGroup = TRUE,
                              useCovariateDrugExposure = TRUE,
                              useCovariateDrugExposure365d = TRUE,
                              useCovariateDrugExposure30d = TRUE,
                              useCovariateDrugEra = TRUE,
                              useCovariateDrugEra365d = TRUE,
                              useCovariateDrugEra30d = TRUE,
                              useCovariateDrugEraEver = TRUE,
                              useCovariateDrugEraOverlap = TRUE,
                              useCovariateDrugGroup = TRUE,
                              useCovariateProcedureOccurrence = TRUE,
                              useCovariateProcedureOccurrence365d = TRUE,
                              useCovariateProcedureOccurrence30d = TRUE,
```

Standardize model diagnostics

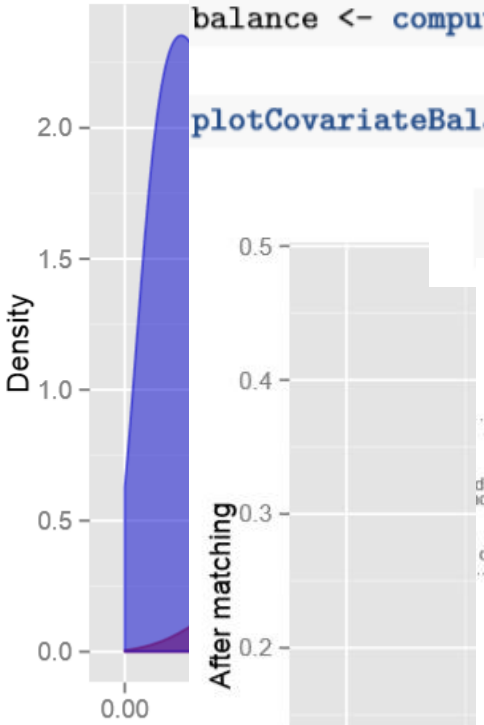
```
plotPs(ps, scale = "preference")
```



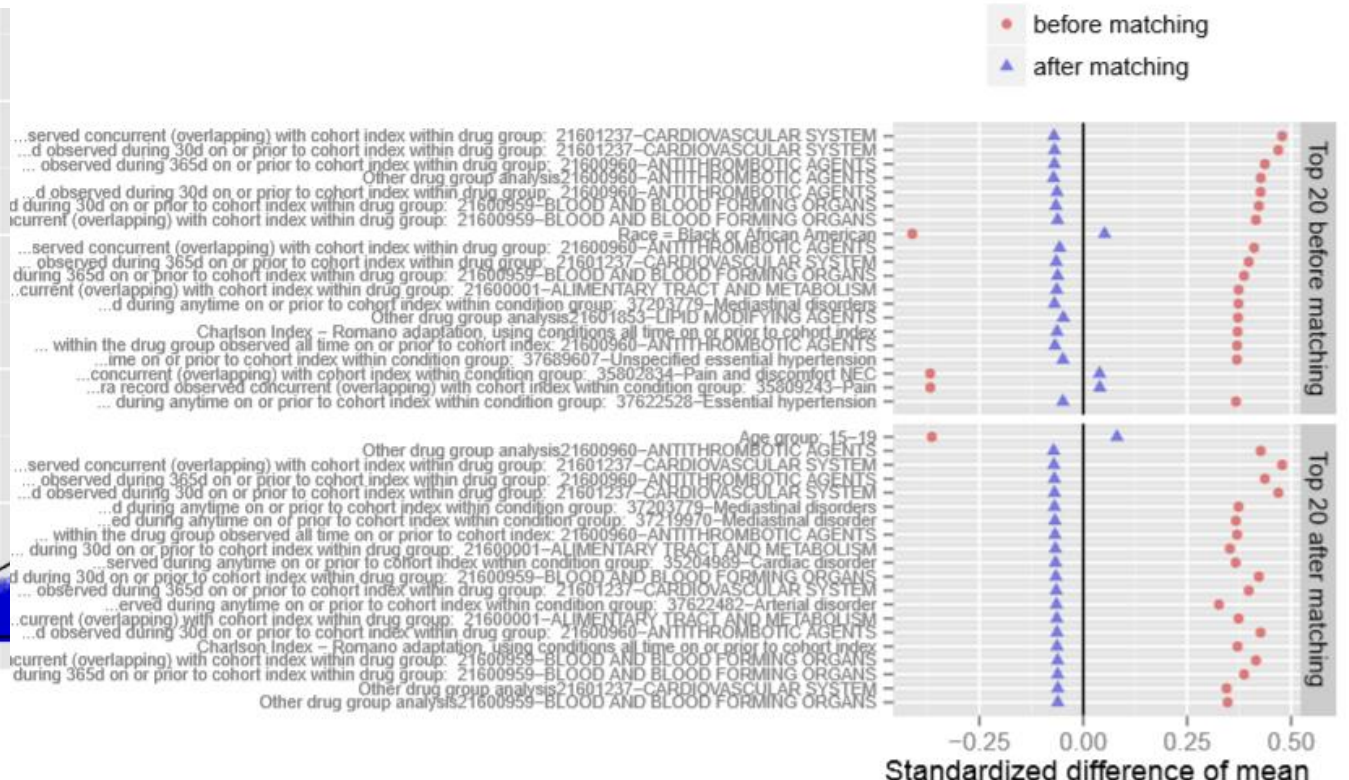
Plausibility

```
balance <- computeCovariateBalance(strata, cohortData, ou
```

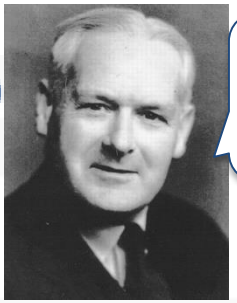
```
plotCovariateBalanceScatterPlot(balance)
```




```
plotCovariateBalanceOfTopVariables(balance)
```



Standardize analysis and results reporting



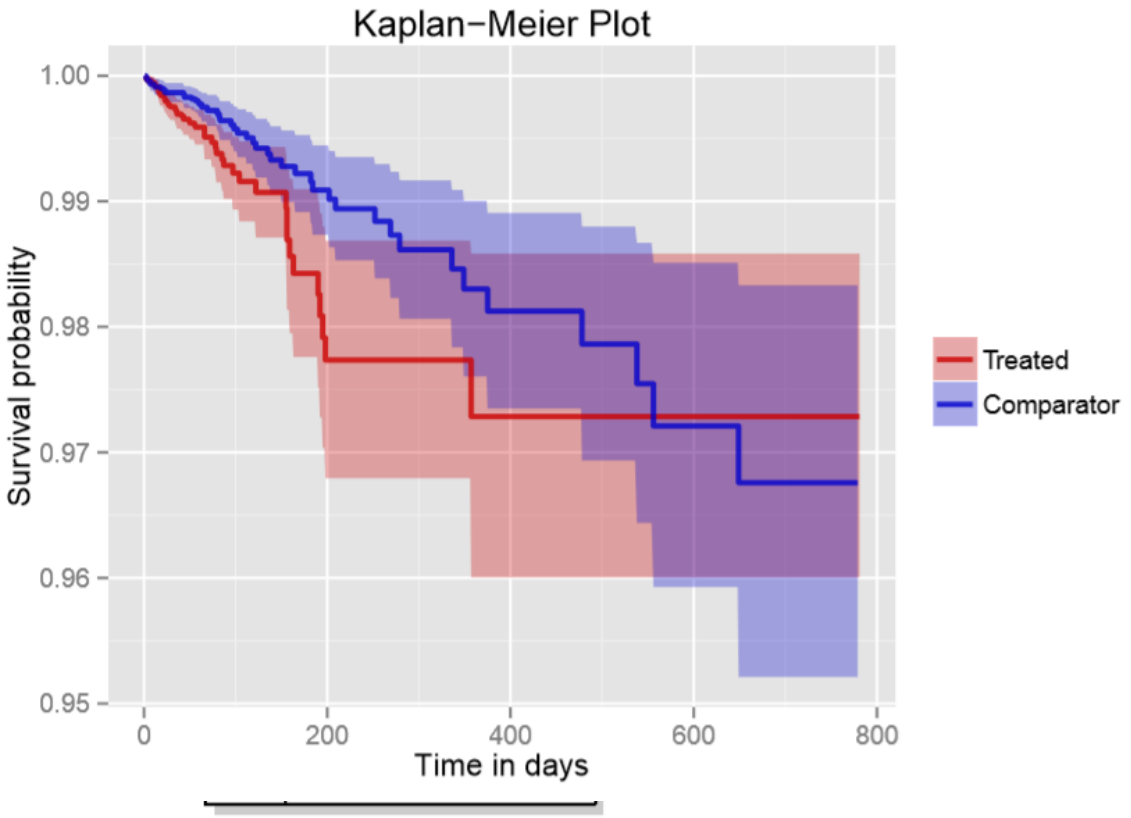
Strength

```
drawAttritionD
```

```
summary(outcomeModel)
```

```
#> Model type: cox
#> Status: OK
#>
#> Counts
#>                       Comparatc
#> Nr. of persons              90(
#> Nr. of events                5
#> Person time (days)       77054
#>
#> Model
#>           Nr. of betas Nr. of
#>                  16572
#>
#> Coefficients
#>             Estimate lower .95
#> treatment    0.52576   0.28105
#>
#> Prior variance: 0.0057675850
```

```
plotKaplanMeier(outcomeModel, includeZero = FALSE)
```



Concluding thoughts

- Our goal shouldn't just "signal detection": we need to enable reliable, scalable evidence generation for population-level estimation for all medical products and all outcomes of interest
- Hill's causal viewpoints can provide a valuable framework and logical bridge to connect observational evidence with clinical expertise
- Open-source large-scale analytics on a common data platform are required to facilitate efficient, transparent, and reproducible science
- A multi-disciplinary, community approach can greatly accelerate the research and development of shared solutions

Join the journey

Interested in OHDSI?

Questions or comments?

Contact:

ryan@ohdsi.org