Public Sentinel Training at FDA: Day 2 of the Tenth Annual Sentinel Initiative Public Workshop

February 8, 2018

Housekeeping

- Wi-fi information
  - Network: FDA Public
  - Passcode: publicaccess
- Lunch details
  - Please pre-order at the food service kiosk in the foyer
  - Keep your receipt
  - Pick up your selection during the lunch break

Today's Schedule

- **9:00 – 9:10** – Welcome and Introduction (Robert Ball and Richard Platt)
- **9:10 – 9:20** – Knowledge Check (Tyler Coyle)
- **9:20 – 9:30** – Review of Sentinel Capabilities (Judy Maro)
- **9:30 – 10:20** – Propensity Score Analysis Tool (Jane Huang)
- **10:20 – 10:30** – Q&A
- **10:30 – 10:45** – Break
- **10:45 – 11:30** – Self-Controlled Risk Interval Tool (Justin Bohn)
- **11:30 – 11:40** – Q&A
- **11:40 – 12:30** – Lunch
- **12:30 – 1:30** – TreeScan (Judy Maro)
- **1:30 – 1:40** – Q&A
- **1:40 – 1:50** – Knowledge Check (Tyler Coyle)
- **1:50 – 2:00** – Closing Remarks (Michael Nguyen)

Welcome and Introduction

Robert Ball, MD, MPH, ScM[1]
Richard Platt, MD, MS[2]

[1]U.S. Food and Drug Administration, [2]Harvard Medical School and Harvard Pilgrim Health Care Institute

Knowledge Check

Website: www.zeetings.com/sentinel

Access code: Sentinel

Review of Sentinel Capabilities

Judith C. Maro, PhD[1]

[1]Harvard Medical School and Harvard Pilgrim Health Care Institute

COMMUNICATIONS

- FDA Safety Communications
- Publications and Presentations
- Sentinel Initiative Events
- Report Finder

Sentinel Initiative Events

The following table provides information about both international professional conferences and meetings hosted on behalf of FDA concerning development of active medical product surveillance methods and systems in the Sentinel Initiative. The Annual Sentinel Initiative Public Workshop is hosted by the Duke-Margolis Center for Health Policy at Duke University.

Keywords

Search | Show All

Public Sentinel Training at FDA

07/10/2017

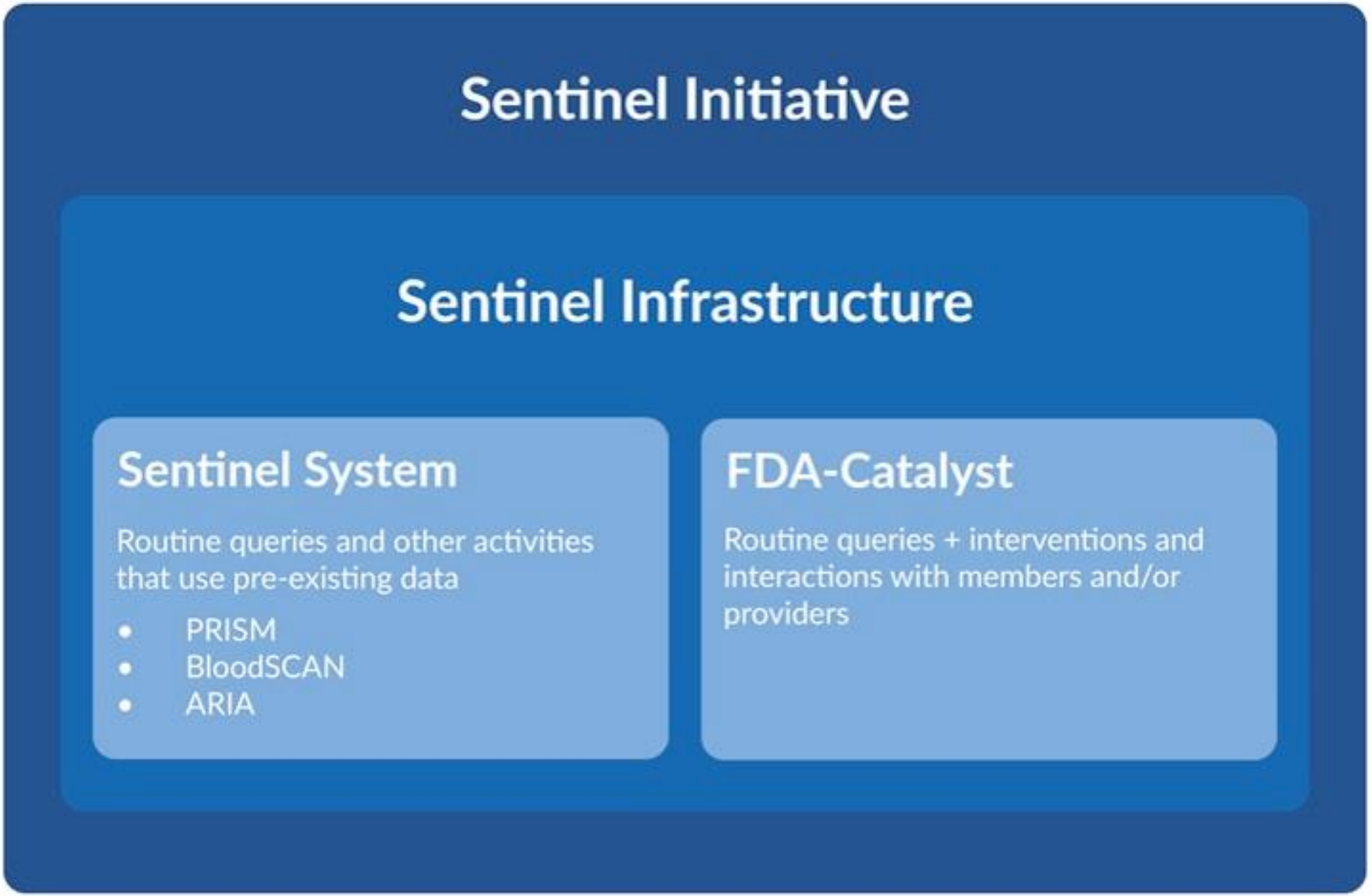
Recordings of the presentations are available via the following links:

Welcome, introduction, agenda, learning objectives
Introduction to the Sentinel Program and Sentinel Distributed Database *(skip ahead to 11:35)*
What Kind of Questions can the Sentinel Distributed Database Answer?
Tools to Answer Public Health Questions, Part 1
Tools to Answer Public Health Questions, Part 2

Recap

- What comprises the Sentinel Initiative
- Types of data available and patient populations captured in the Sentinel Infrastructure
- What the Sentinel Infrastructure can reliably capture
  - Guidance on the types of exposures, outcomes, and covariates that can be identified
- Present routine querying tools in the context of questions common to many product safety concerns

Sentinel Program Overview



The Sentinel Eco-System

Lead – HPHC Institute

DEPARTMENT OF POPULATION MEDICINE
HARVARD MEDICAL SCHOOL
Harvard Pilgrim Health Care Institute

Data and scientific partners

HealthCore Anthem
VANDERBILT SCHOOL OF MEDICINE
health care systems research network
MASSACHUSETTS
HUMANA
HCA Hospital Corporation of America
DukeMedicine
OPTUM
KAISER PERMANENTE
aetna

Scientific partners

IQVIA
Penn Medicine
UAB
DEPARTMENT OF MEDICINE BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL
AHIP America's Health Insurance Plans
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
UF College of Pharmacy UNIVERSITY of FLORIDA
UIC
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
RUTGERS

Sentinel Distributed Network and Available Data Elements

Sentinel Utilizes Secondary Data

- Patient interaction with the U.S. healthcare system generates data
- Why is data collected?
  - Payment/billing
  - Document clinical care
  - Physician decision support
  - Recordkeeping
  - Registries
- Data provide rich source of information for patient safety evaluations

Numerous Data Elements are Available

Administrative

Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure
Person ID	**Person ID**	**Person ID**	**Person ID**	**Person ID**	**Person ID**
Enrollment start & end dates	Birth date	Dispensing date	Service date(s)	Service date(s)	Service date(s)
Drug coverage	Sex	National drug code (NDC)	Encounter ID	Encounter ID	Encounter ID
Medical coverage	ZIP code	Days supply	Encounter type & provider	Encounter type & provider	Encounter type & provider
Medical record availability	Etc.	Amount dispensed	Facility	Diagnosis code & type	Procedure code & type
			Etc.	Principal discharge diagnosis	Etc.

Clinical

Lab Result	Vital Signs
Person ID	**Person ID**
Result and specimen collection dates	Measurement date and time
Test type, immediacy & location	Height and weight
Logical Observation Identifiers Names and Codes (LOINC ®)	Diastolic & systolic BP
Test result & unit	Tobacco use & type
Etc.	Etc.

Registry

Death	Cause of Death	State Vaccine
Person ID	**Person ID**	**Person ID**
Death date	Cause of death	Vaccination date
Source	Source	Admission Type
Confidence	Confidence	Vaccine code & type
Etc.	Etc.	Provider
		Etc.

Inpatient

Inpatient Pharmacy	Inpatient Transfusion
Person ID	**Person ID**
Administration date and time	Administration start and end date and time
Encounter ID	Encounter ID
National Drug Code (NDC)	Transfusion administration ID
Route	Transfusion product code
Dose	Blood Type
Etc.	Etc.

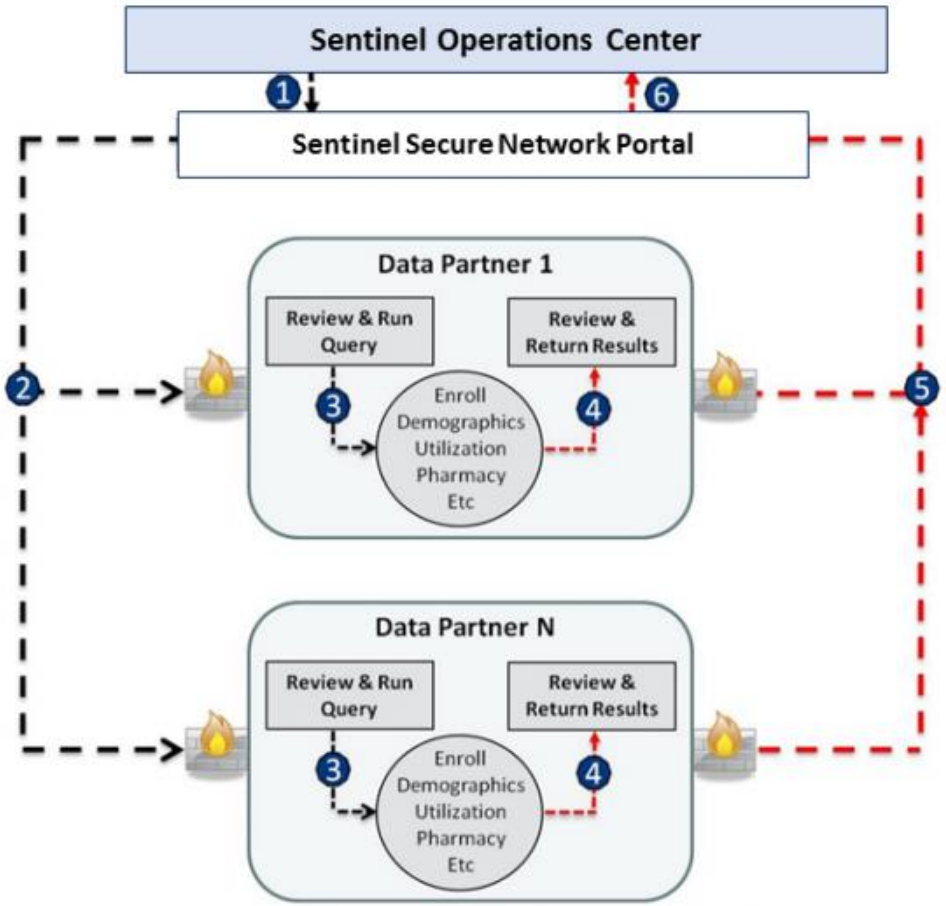
Snapshot of Database Statistics

	Traditional Sentinel	Medicare Fee-for-Service	Total
Unique Enrolled Patient Identifiers	239 million	53.5 million	292.5 million
People Accruing New Data	44.6 million	22.3 million	66.9 million
Pharmacy Dispensings	6.6 billion	7.7 billion	14.3 billion
Unique Medical Encounters	7.8 billion	5.5 billion	13.3 billion
Members with ≥1 Laboratory Test Result	45.6 million	Laboratory data unavailable	45.6 million

Sentinel Data Philosophy

- Data Partners maintain ownership of **all uses** of their data and have “opt out” privileges
- Minimum necessary data is transferred to Sentinel Operations Center (SOC)
  - Minimize use of de-identified patient-level data
- Data Partners do not transfer data to each other

Sentinel is a Distributed Data Network



1- FDA data request sent to Data Partners via FISMA-compliant secure network portal

2- Data Partners retrieve query

3- Data Partners review and run query against their local data behind their firewalls

4- Data Partners review results for accuracy and privacy compliance

5&6- Data Partners return results, stripped of direct identifiers, to SOC via secure portal

Sentinel Capabilities: Identifying Cohorts, Exposures, Outcomes and Covariates

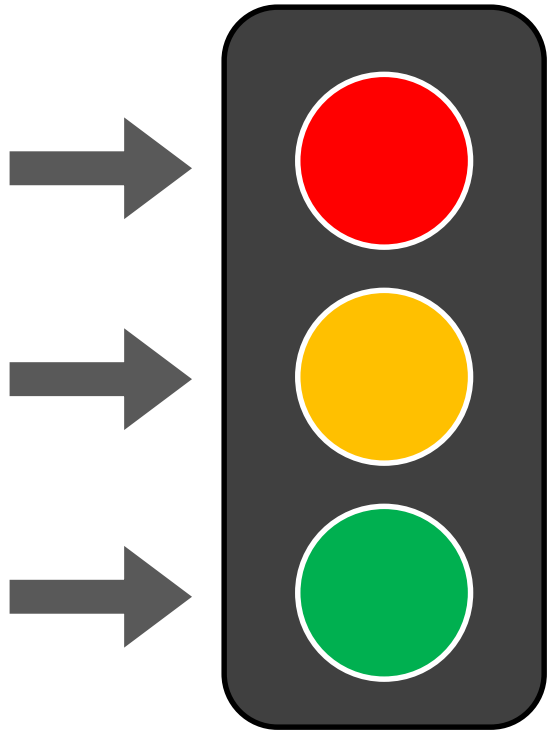
Framework for Discussion

- Stoplight provided as simple metric
- Describes Sentinel's current capabilities to support specific topics

Cannot currently support using existing data and tools

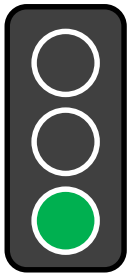
Possible, but warrants further discussion

Works well under most circumstances

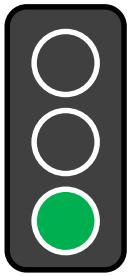


Rules of Thumb: Cohort Definitions

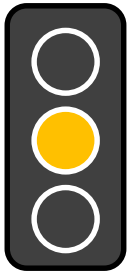
- Age reliably captured



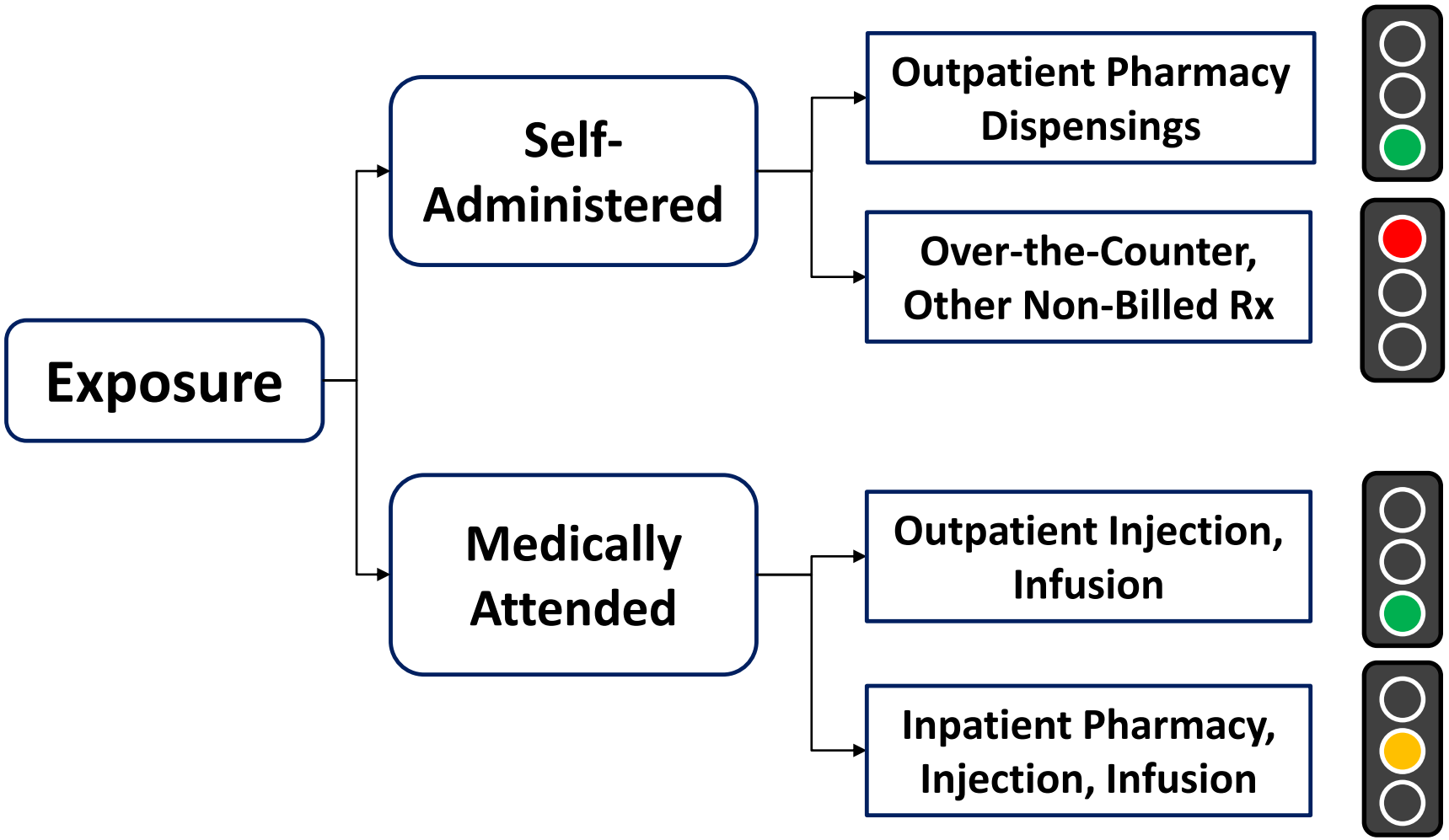
- Sex complete and reliably utilized



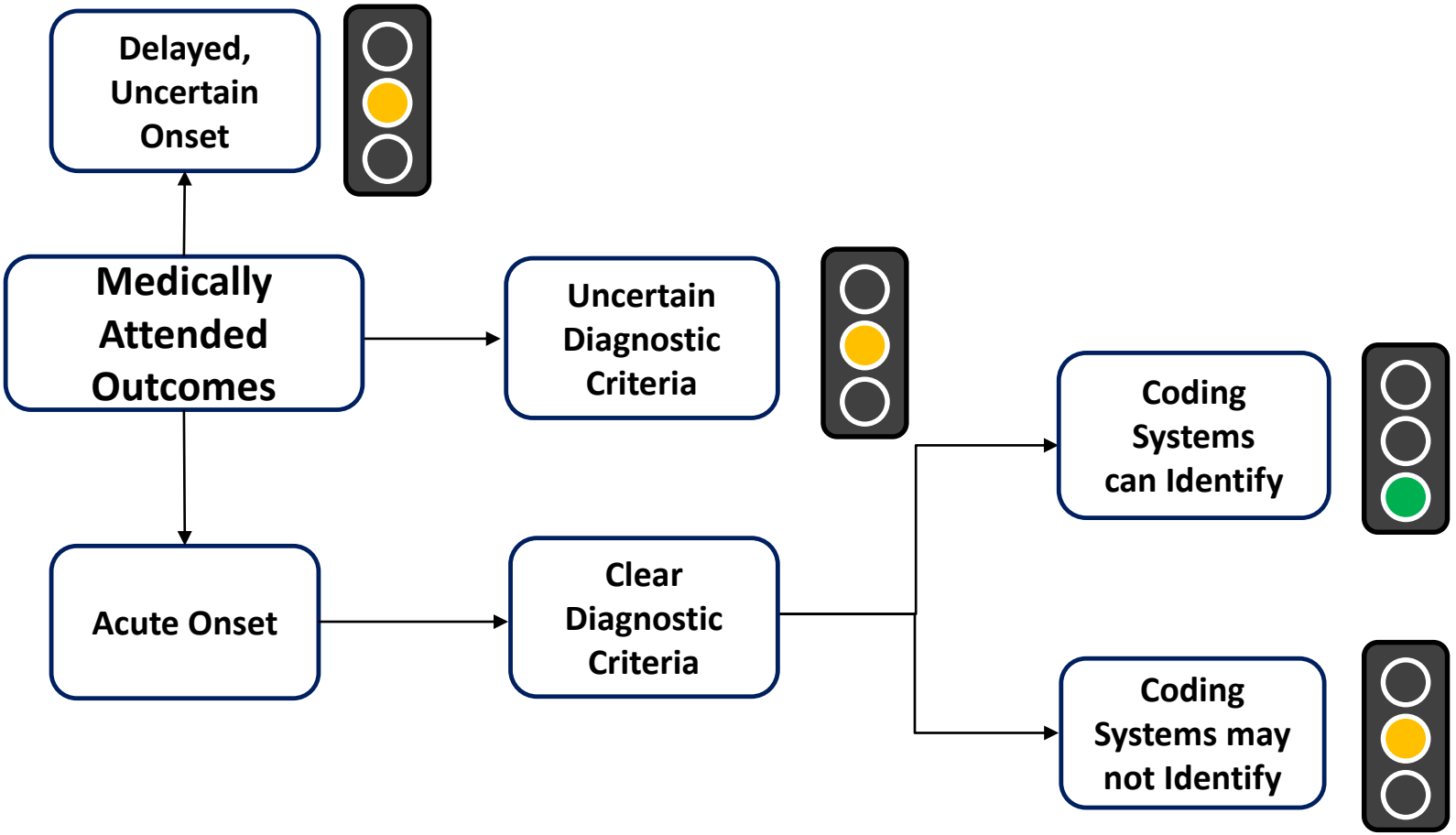
- Race/ethnicity available in some Data Partners, missingness and reliability remain a concern



Rule of Thumb: Exposures

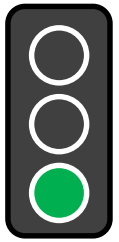


Rules of Thumb: Outcomes

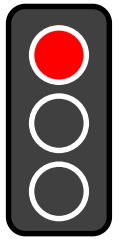


Rules of Thumb: Covariate Definitions

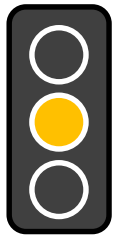
- Medical history/comorbidities, treatment history



- Lifestyle factors are not processed as part of administrative claims and are not reliable



- Clinical data: laboratory test results, vital signs



Takeaway Messages

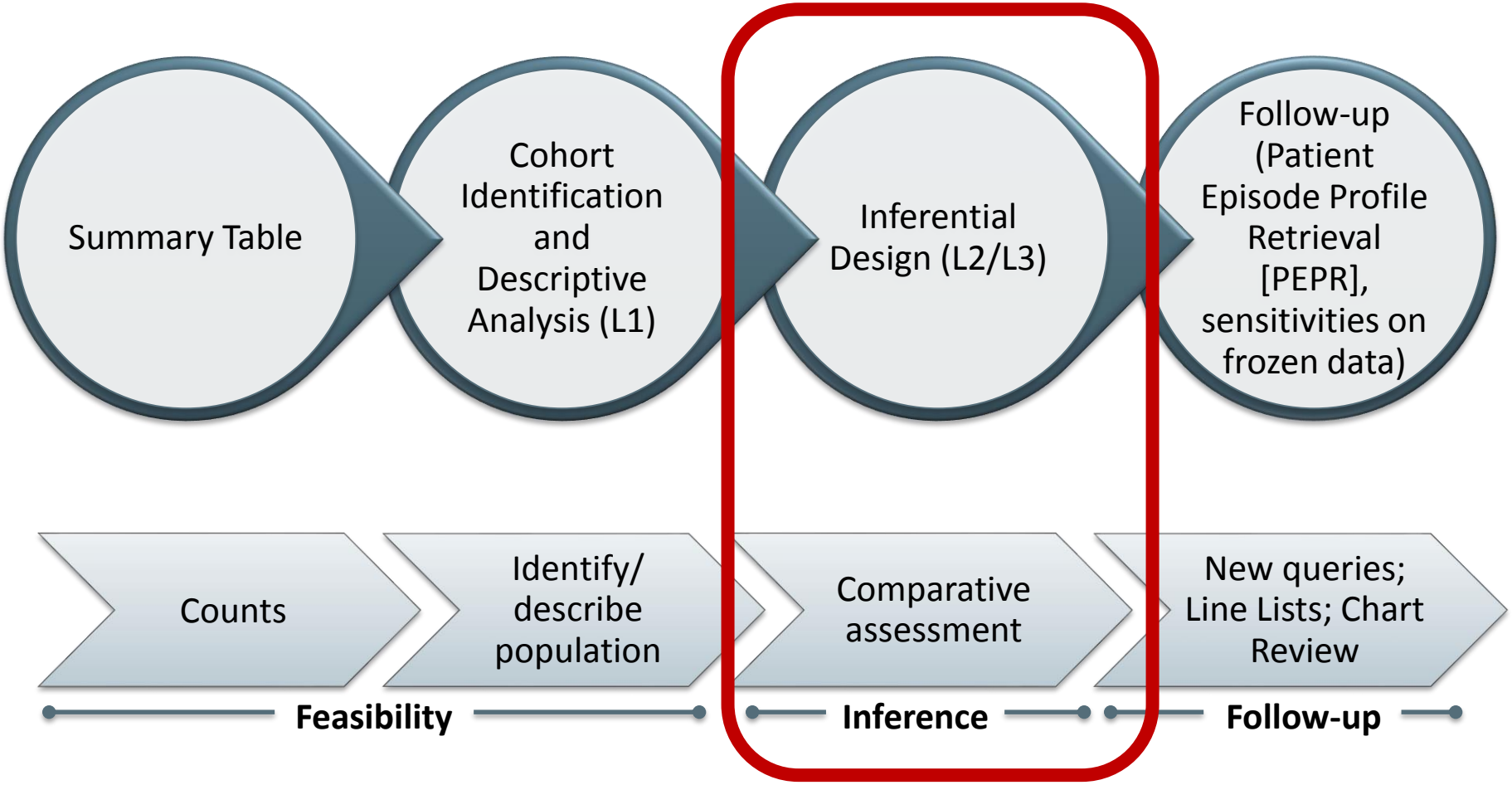
- Most outpatient exposures are reliably captured
- Most acute onset outcomes are reliably captured, provided there are clear diagnostic criteria and code(s) that can distinguish the outcome
- Over-the-counter medications are not captured
- Inpatient treatment capture requires discussion
- Non-medically attended events are not captured

Sentinel Data Queries: Routine Querying Tools

How Are Routine Queries Implemented?

- Query “templates” target types of common questions
  - Example: Profile medical product exposure time “at risk”
- Parameterized at program execution
  - Example medical product exposure: ACE inhibitors
- Pre-tested and validated (no custom programming)
  - Significantly shortens response time
- Standard output

Typical Query Sequence



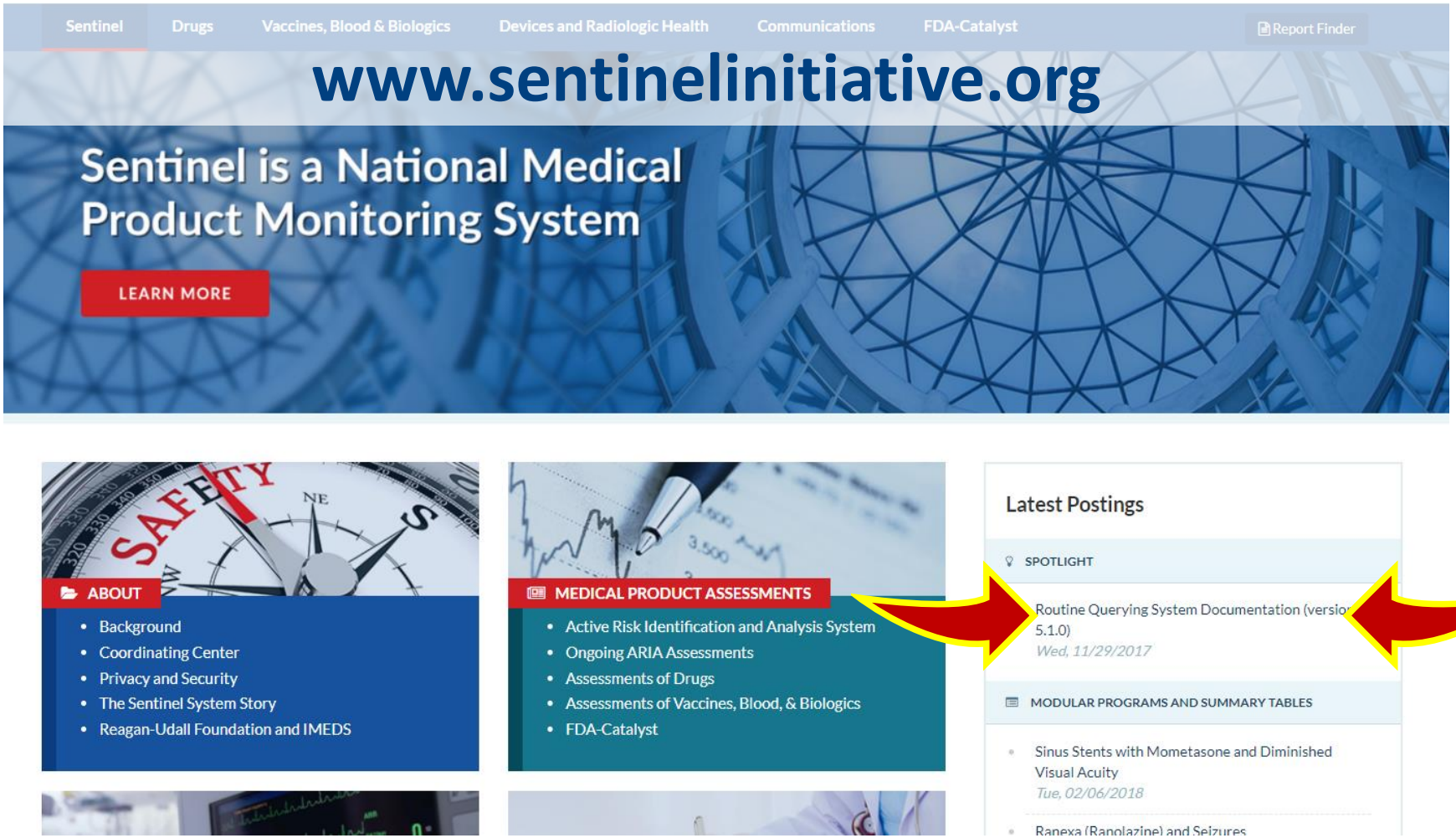
Questions?

Propensity Score Analysis Tool

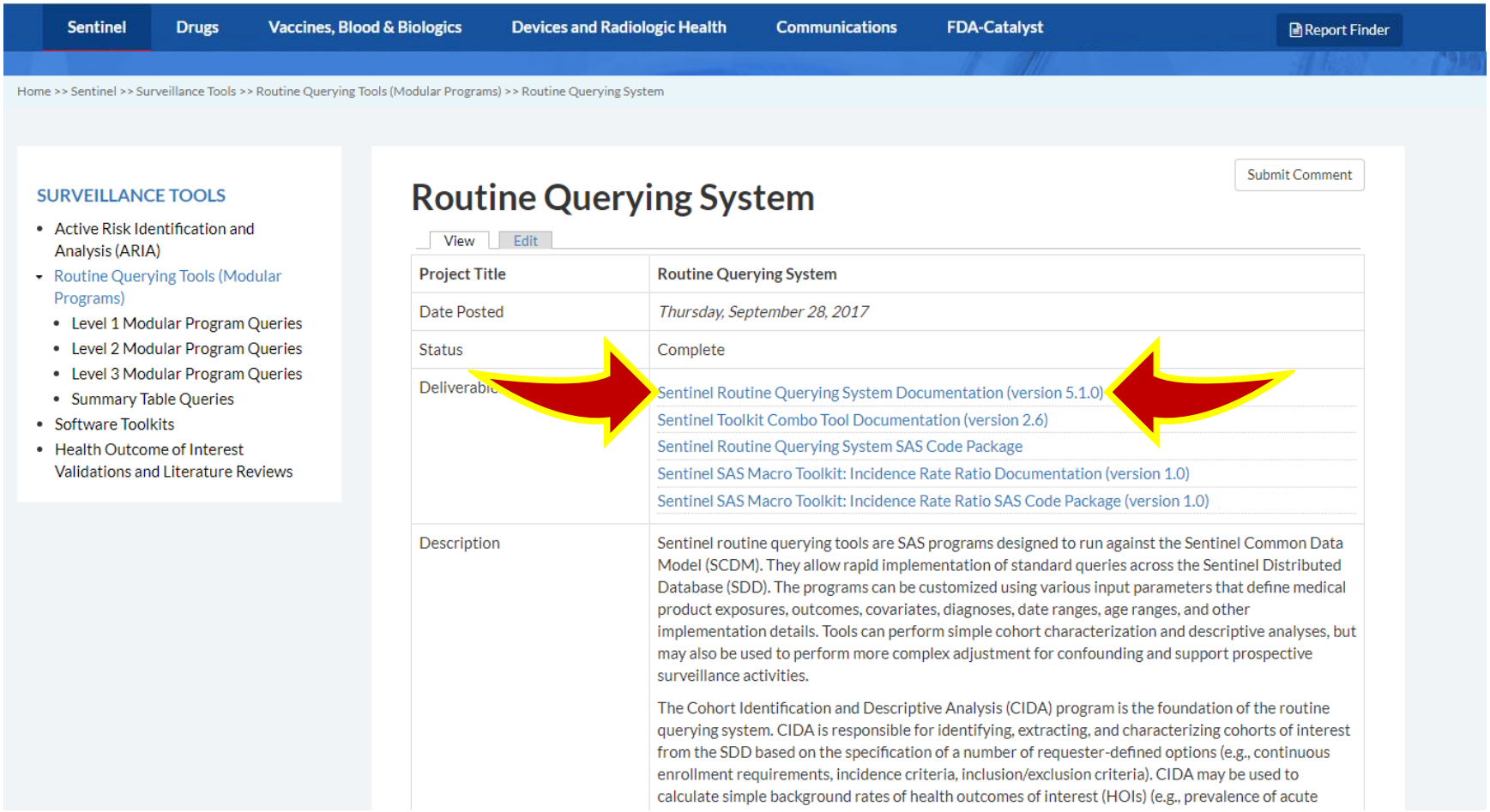
Ting-Ying (Jane) Huang, PhD[1]

[1]Harvard Medical School and Harvard Pilgrim Health Care Institute

How to Access the Routine Querying Tools



How to Access the Routine Querying Tools



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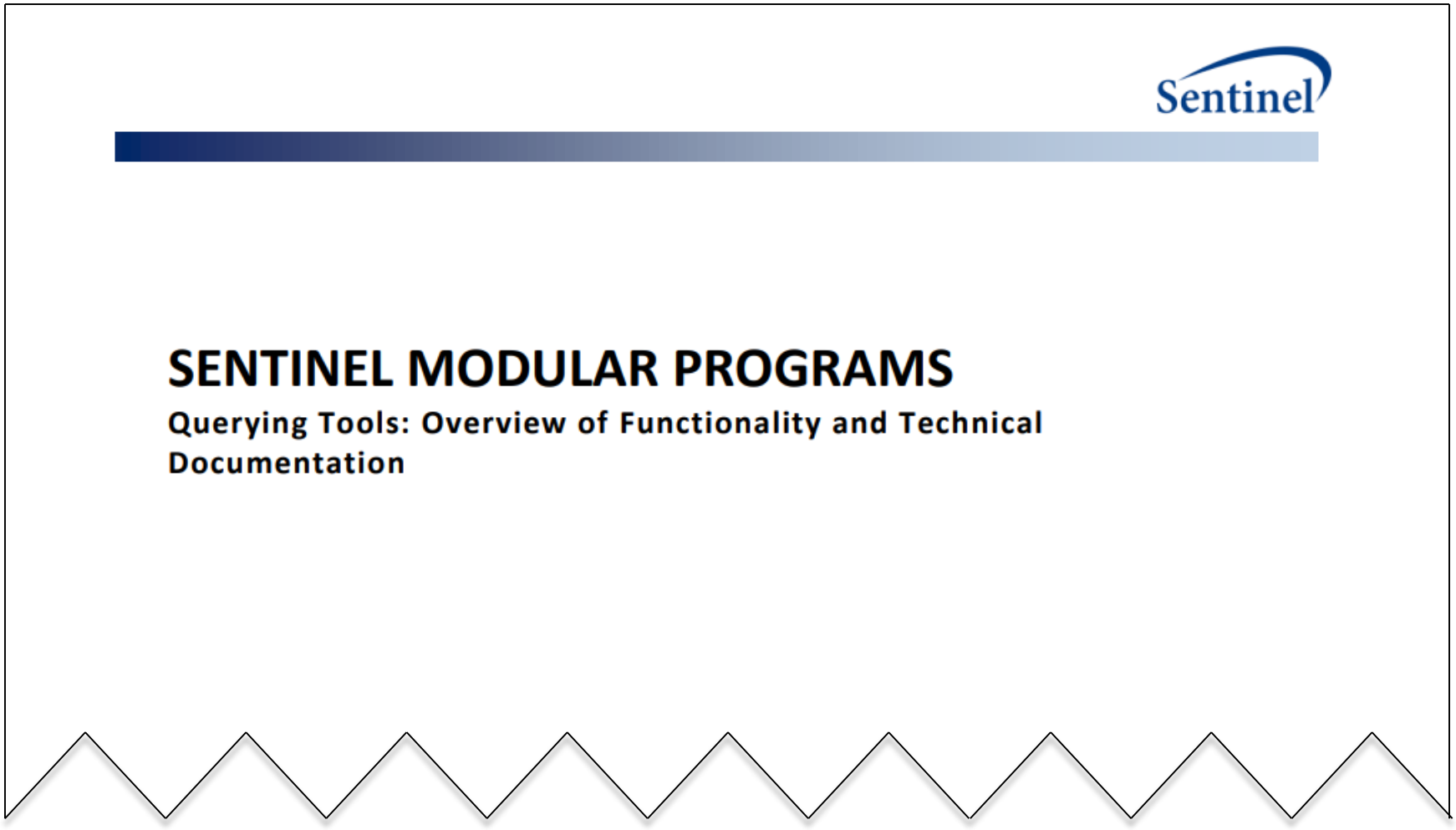


How to Access the Routine Querying Tools

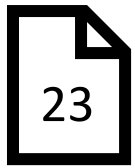
PROPENSITY SCORE ANALYSIS (PSA) TOOL

A. OVERVIEW

The PSA tool performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts. Propensity score estimation and matching are conducted within each Sentinel Data Partner site via distributed programming code; data are returned to the Sentinel Operations Center (SOC), aggregated, and used to calculate effect estimates.

Propensity scores may be estimated using requester-defined covariates and/or empirically identified covariates via a high dimensional propensity score (hdPS) approach. Patients in exposed and comparator cohorts are matched in 1:1 or variable 1:*n* ($n \leq 10$) ratios within a requester-defined caliper.

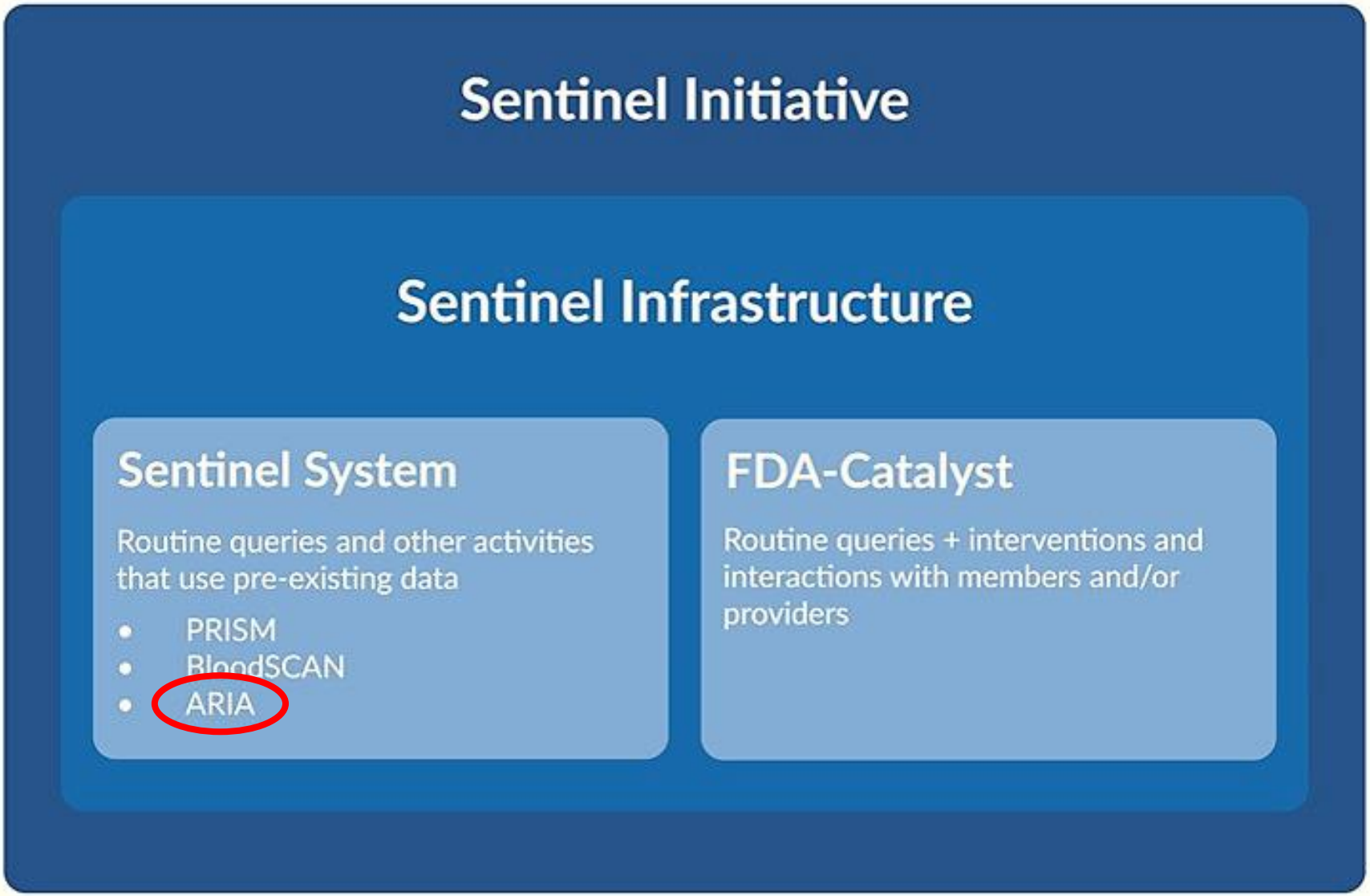
As the PSA tool functions in a distributed database environment, propensity scores are estimated at each Data Partner site separately. Additionally, as the PSA tool is designed to support sequential analysis, patients are matched in each monitoring period and propensity scores are estimated for each monitoring period.



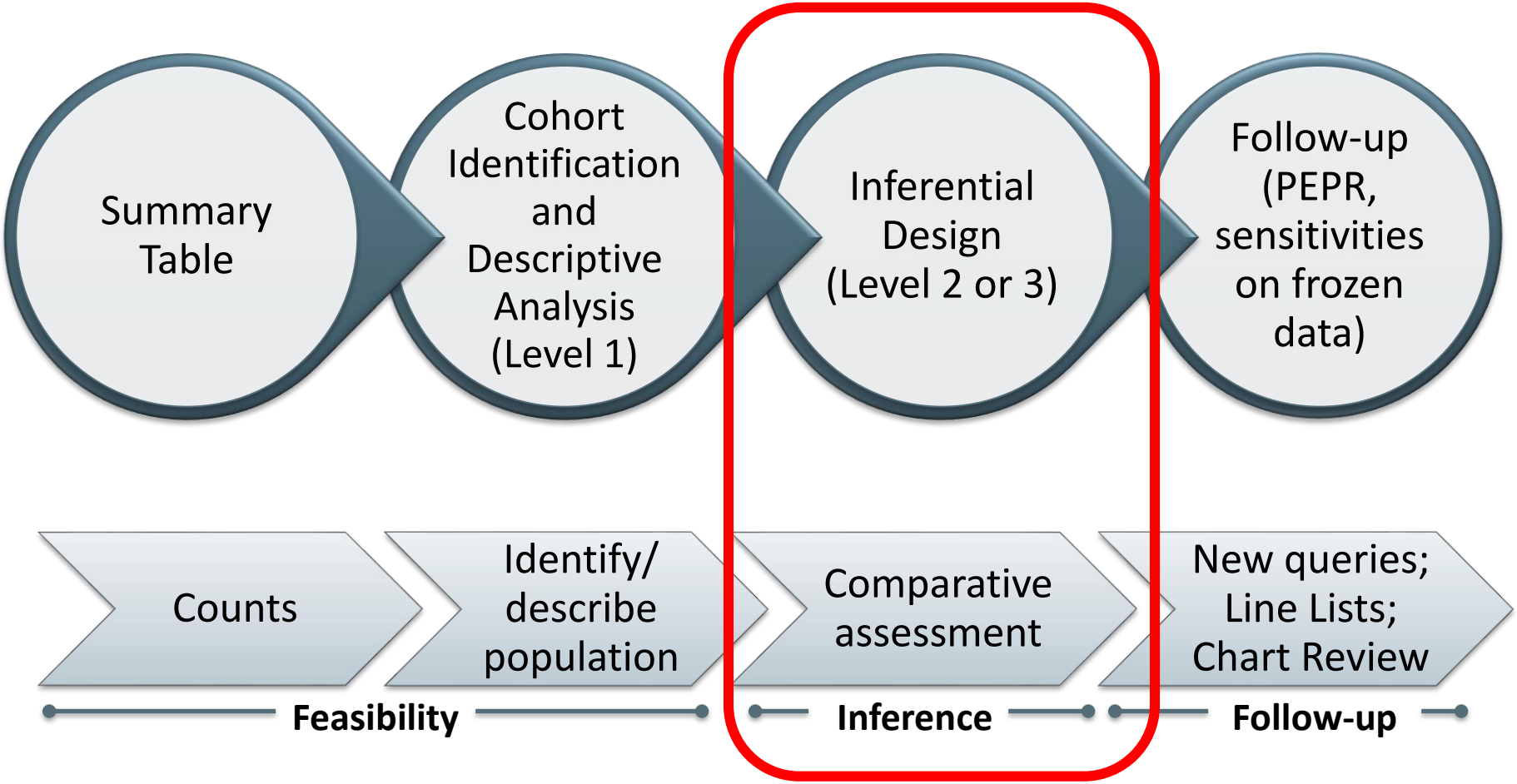
Agenda

- Active Risk Identification and Analysis (ARIA)
- Level 2 capabilities in ARIA
- Propensity score (PS) methods
- Case study: ACEI-angioedema
  - Identify treatment and comparator exposure cohorts
  - Extract covariate information
  - Estimate an exposure propensity score
  - Match treatment and comparator patients on PS, or
  - Stratify treatment and comparator patients by PS percentile
  - Generate effect estimates and create report

Active Risk Identification and Analysis



Typical Query Sequence



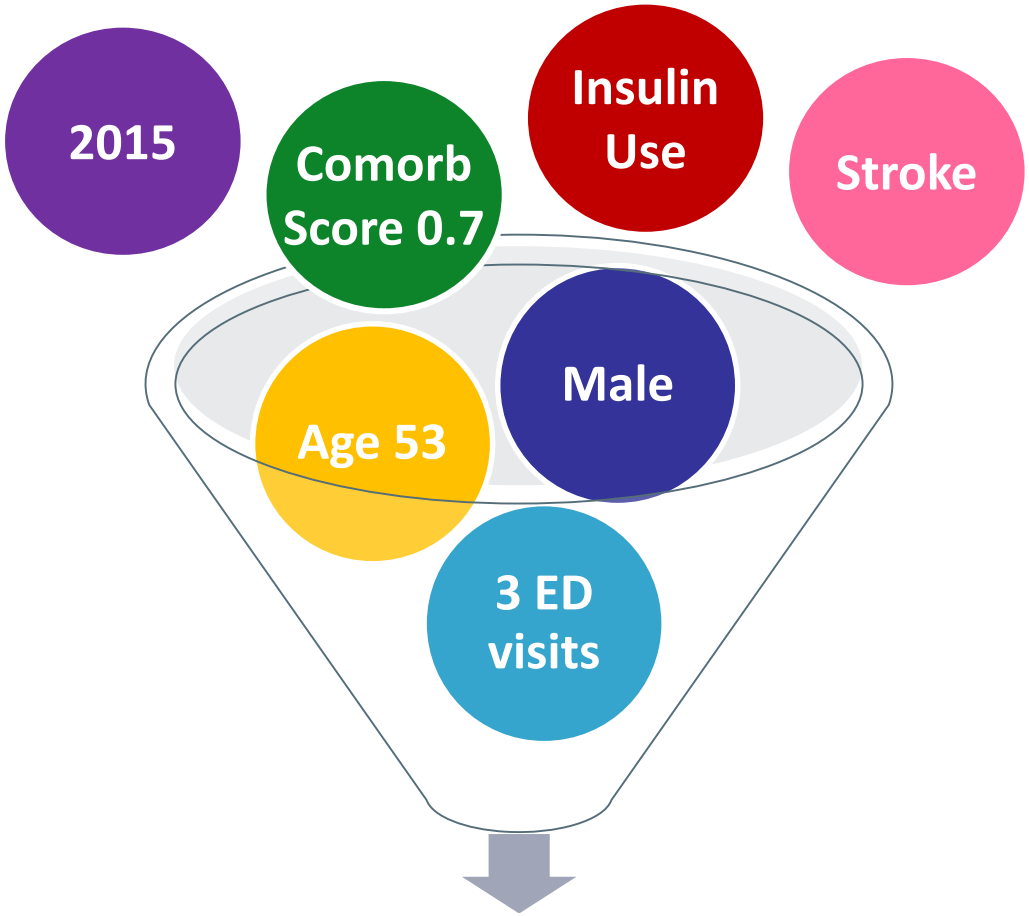
*PEPR= Patient Episode Profile Retrieval

Level 2 Capabilities in ARIA

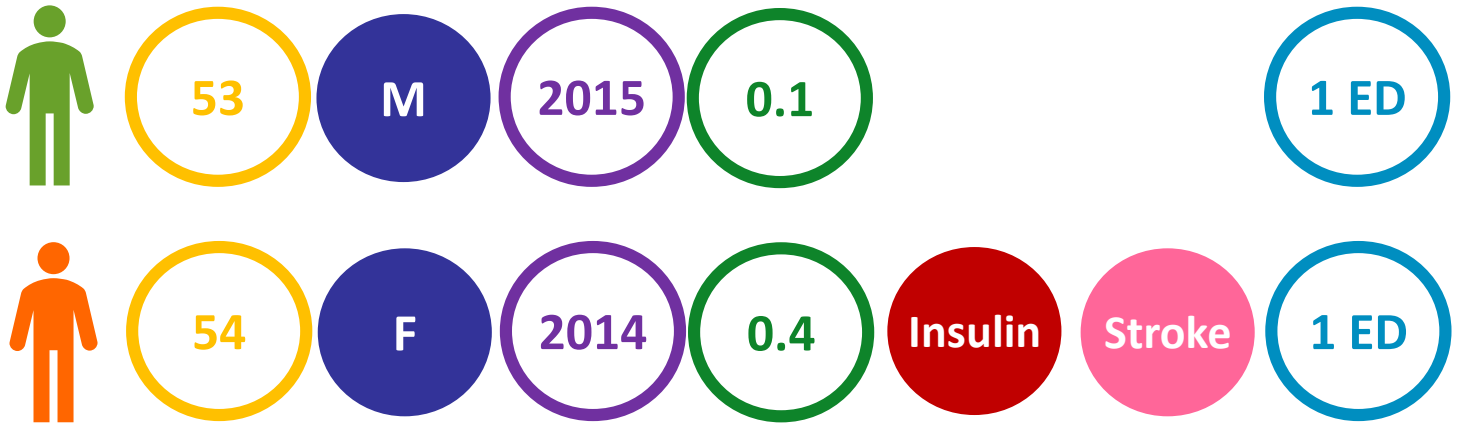
- Propensity score matching and stratification
  - New user cohort design
  - Explicit control of non-time-varying confounding
  - Observational analogue of RCT
  - Asks "*why does this happen to them?*"
- Self-controlled risk interval (SCRI)
  - New user, case-only design
  - Implicit control of non-time-varying confounding
  - Useful for studying acute effects of intermittent exposures
  - Asks "*why does this happen now?*"

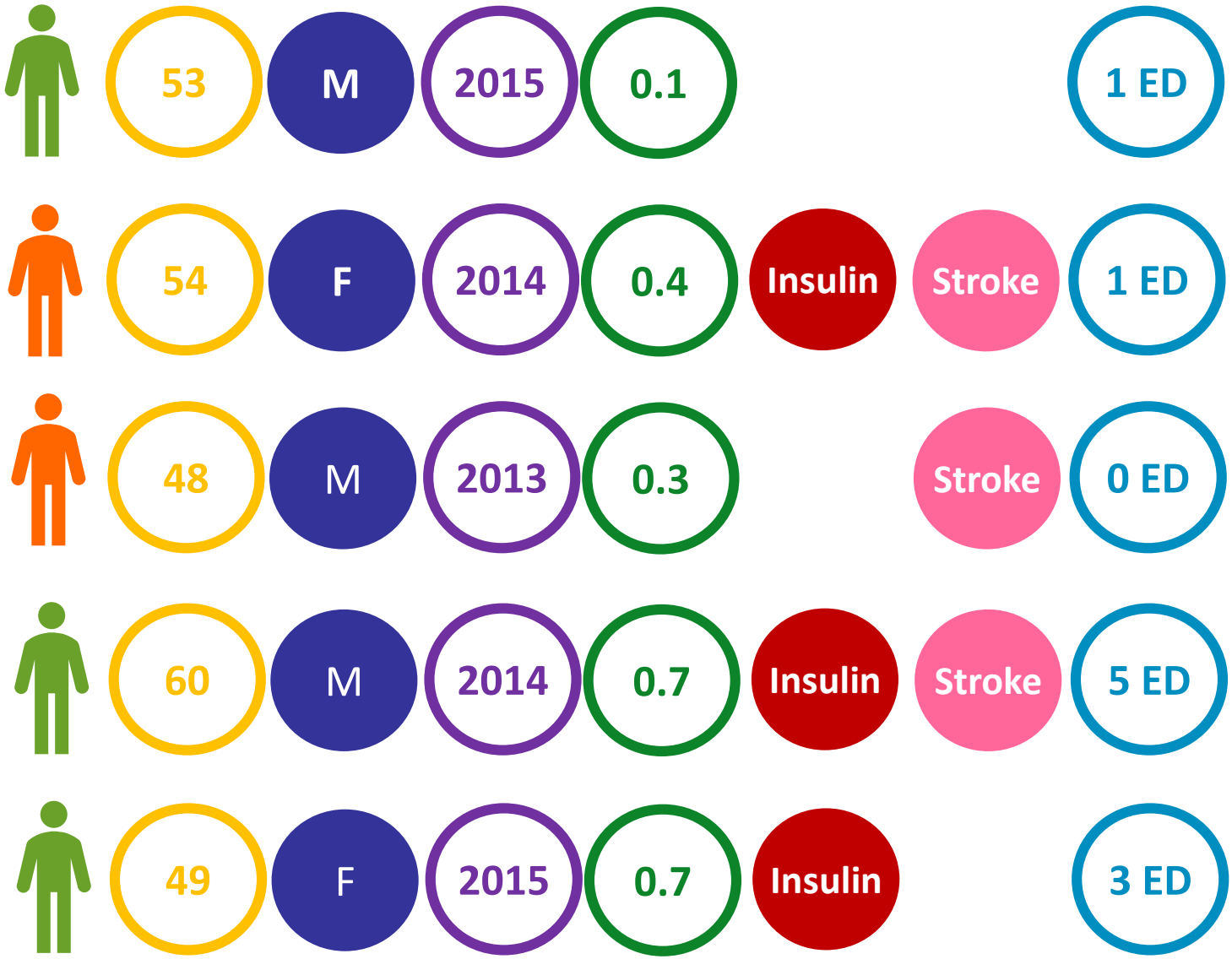
Propensity Score: A Brief Summary

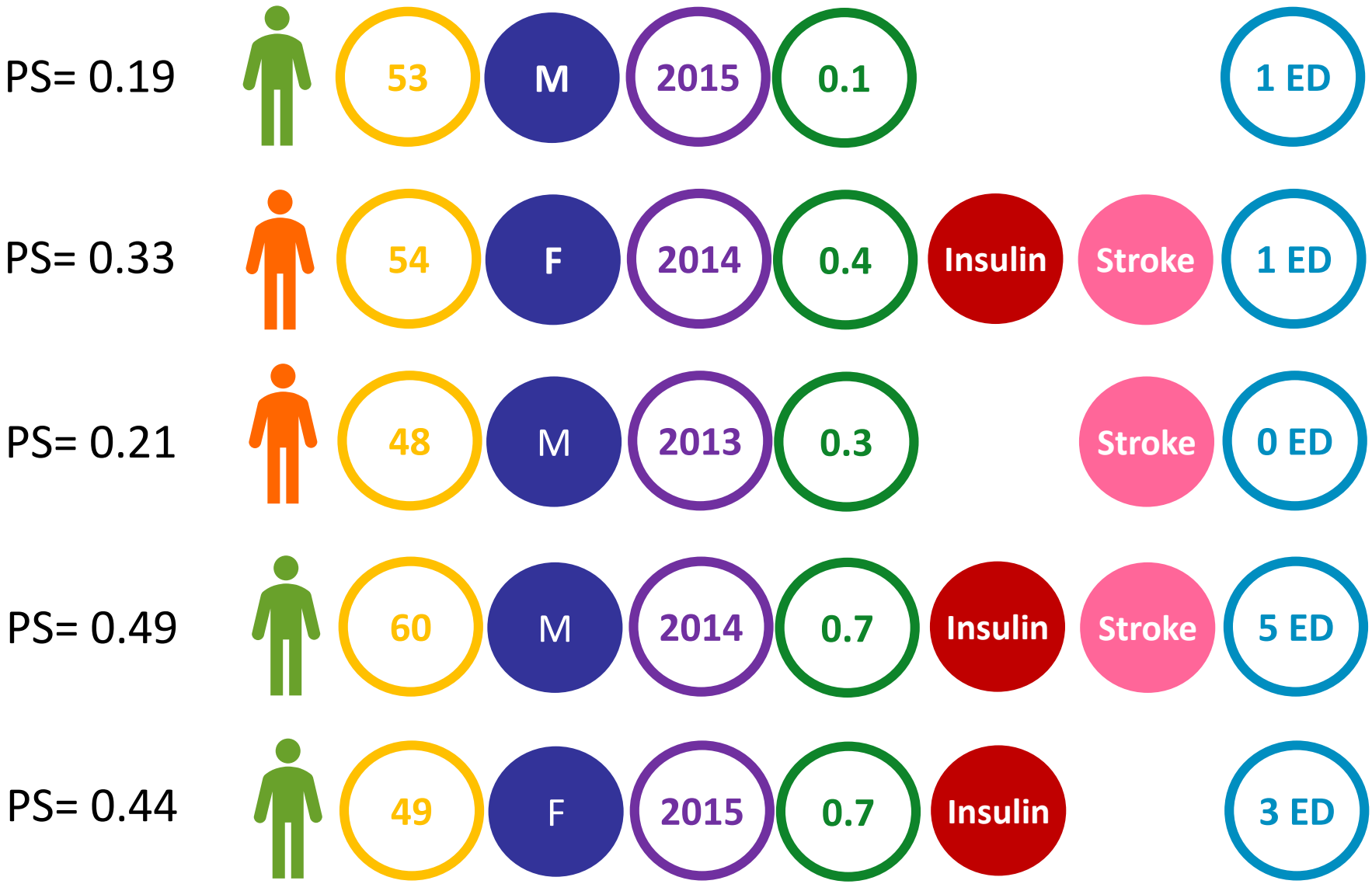
A Brief Summary



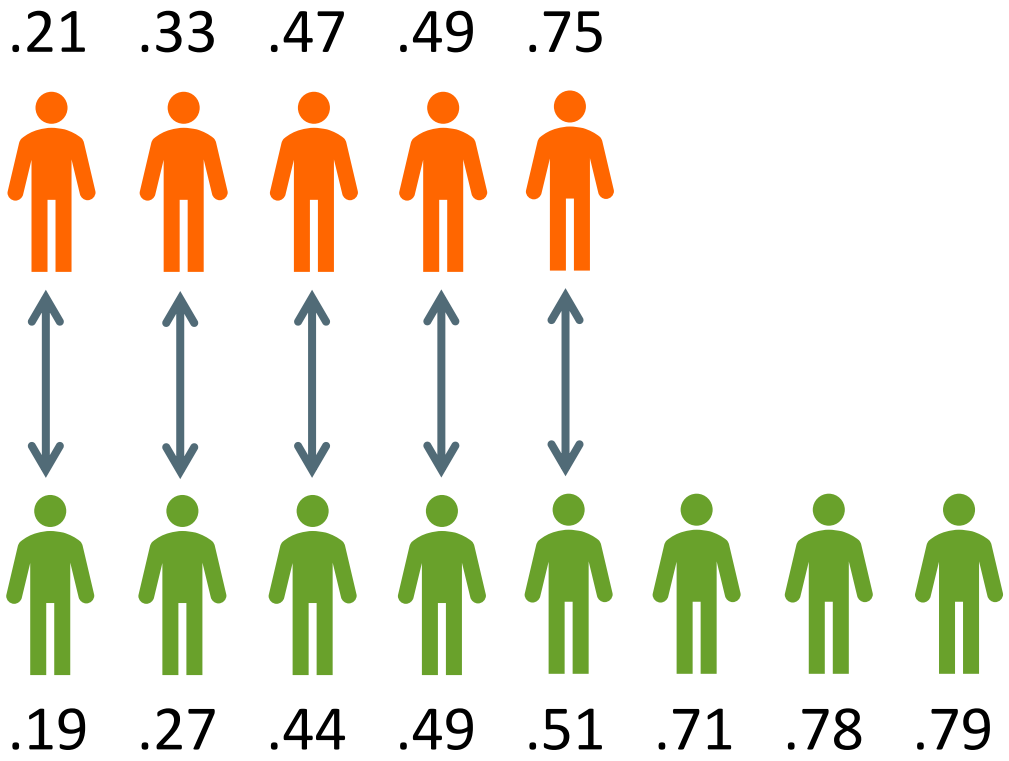
Rosenbaum, P.R. and Rubin, D.B., 1983. *Biometrika*, 70(1), pp.41-55.



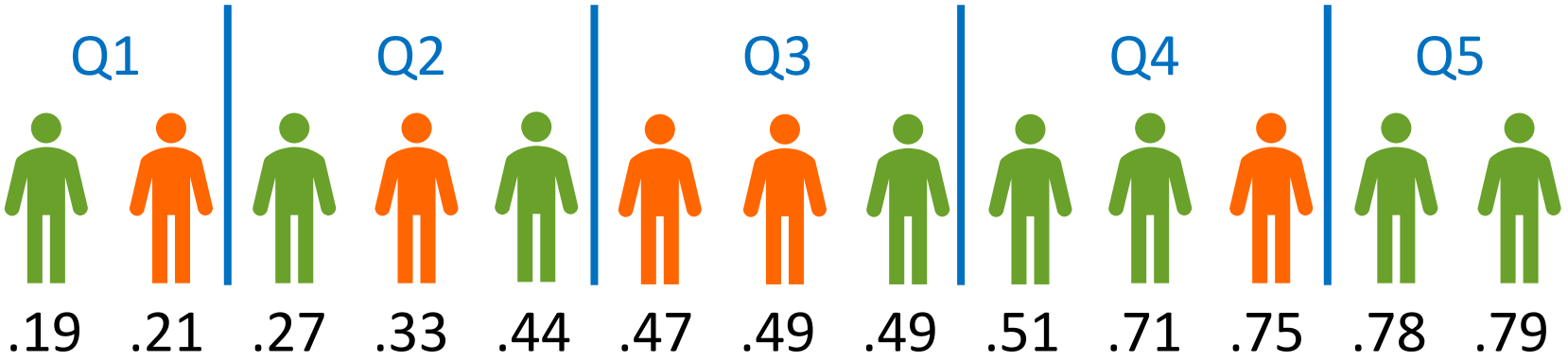




- PS matching
  - Nearest neighbor
  - 1:1
  - Caliper= 0.05



- PS stratification
  - Quintiles



Propensity Score Matching or Stratification

	Matching	Stratification
Strengths	• Widely used • Trim always-/never-treated • Bias reduction: balanced measured confounders	• Keep entire cohort • Retain precision • Generalizability
Limitations	• Keep matched cohort only • Lose precision • Generalizability	• Residual confounding within extreme strata • Characteristic tables (Table 1s) difficult to obtain or interpret

Case Study:
ACEIs and Angioedema

Query Intended to Mimic a Completed Protocol-Based Assessment for Testing Purposes

ORIGINAL INVESTIGATION

Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houstoun, PharmD; Mary Ross Southworth, PharmD; Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey, MD, MPH; Azadeh Shoaibi, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD

Background: Although certain drugs that target the renin-angiotensin-aldosterone system are linked to an increased risk for angioedema, data on their absolute and comparative risks are limited. We assessed the risk for angioedema associated with the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and the direct renin inhibitor aliskiren.

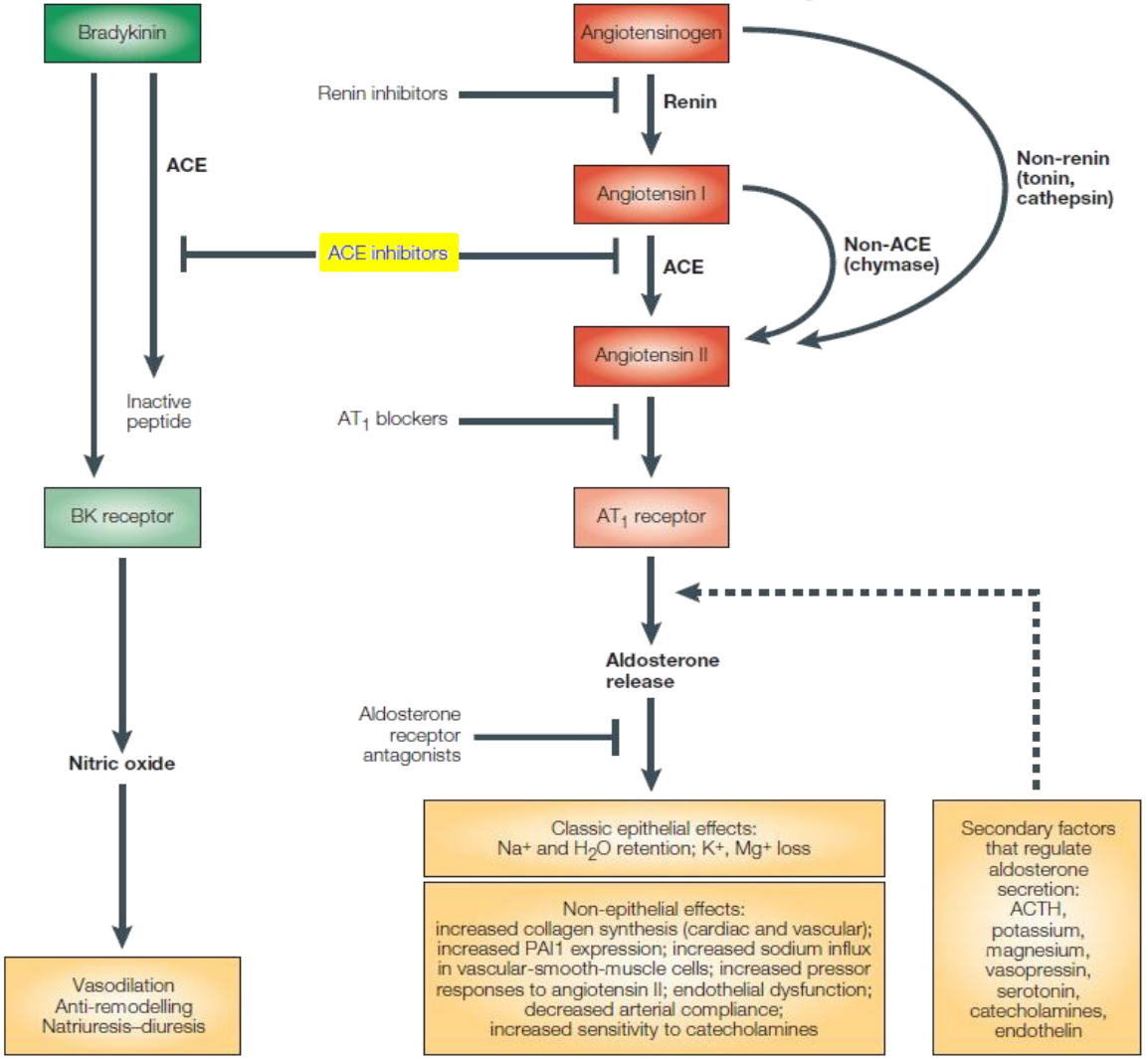
Methods: We conducted a retrospective, observational, inception cohort study of patients 18 years or older from 17 health plans participating in the Mini-Sentinel

Results: A total of 4511 angioedema events (3301 for ACEIs, 288 for ARBs, 7 for aliskiren, and 915 for β-blockers) were observed during the follow-up period. The cumulative incidences per 1000 persons were 1.79 (95% CI, 1.73-1.85) cases for ACEIs, 0.62 (95% CI, 0.55-0.69) cases for ARBs, 1.44 (95% CI, 0.58-2.96) cases for aliskiren, and 0.58 (95% CI, 0.54-0.61) cases for β-blockers. The incidence rates per 1000 person-years were 4.38 (95% CI, 4.24-4.54) cases for ACEIs, 1.66 (95% CI, 1.47-1.86) cases for ARBs, 4.67 (95% CI, 1.88-9.63) cases for aliskiren, and 1.67 (95% CI, 1.56-1.78) cases for β-blockers. Compared with the use of β-blockers, the adjusted hazard ratios were 3.04 (95% CI, 2.81-3.27) for ACEIs

Toh et al. Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System. *Arch Intern Med*. 2012;172:1582-1589

ACEIs Biologically Can Induce Angioedema

- **Red Box** Pathway: Mechanism to produce hypertension
- **Green Box** Pathway: Mechanism to produce angioedema
- Desired Effect: ACEI inhibitors interrupt the **Red Box** pathway
- Undesired Effect: ACEI inhibitors strengthen the **Green Box** pathway



Zaman et al, *Nat Rev Drug Discov* 2002;1:621-636

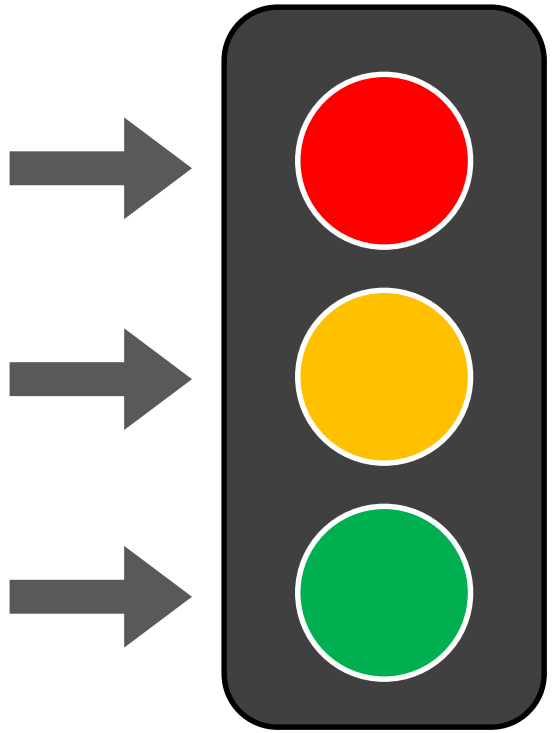
Recall the Framework

- Stoplight provided as simple metric
- Describes Sentinel's current capabilities to support specific topics

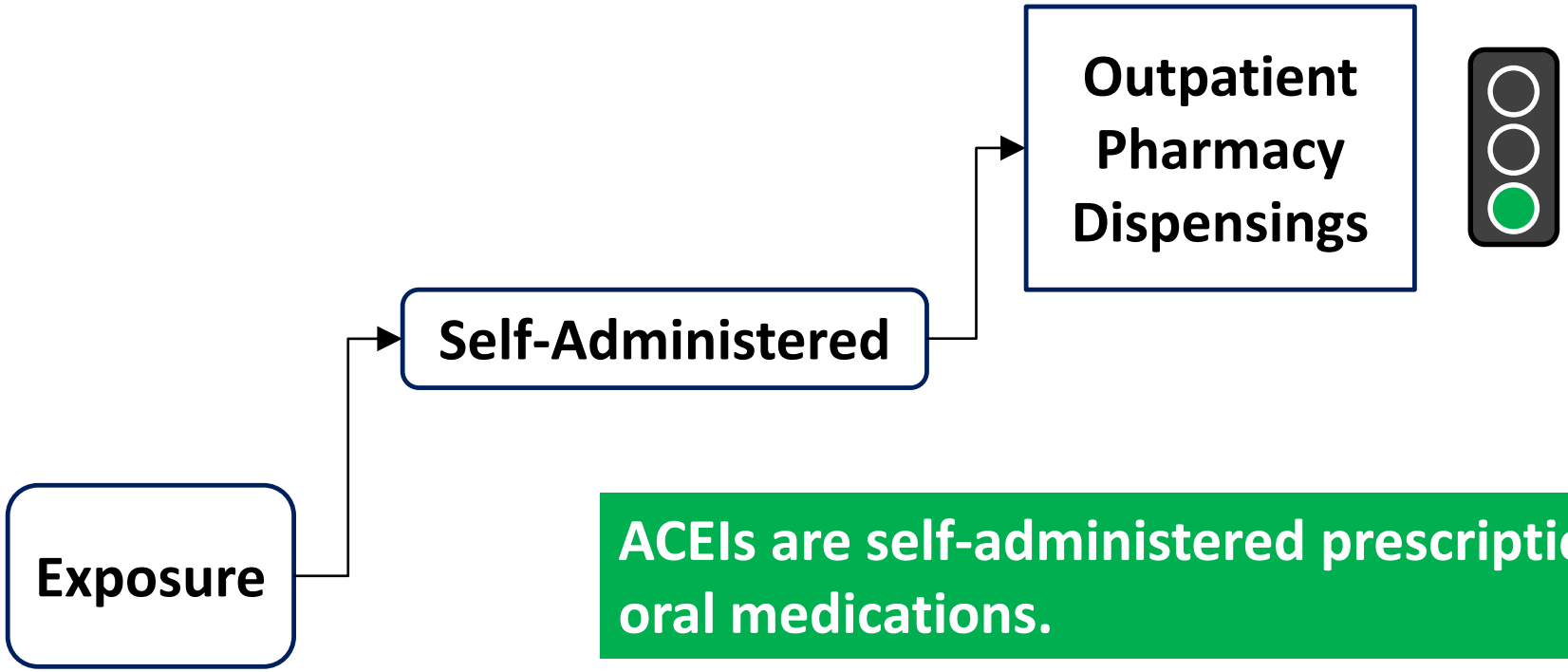
Cannot currently support using existing data and tools

Possible, but warrants further discussion

Works well under most circumstances

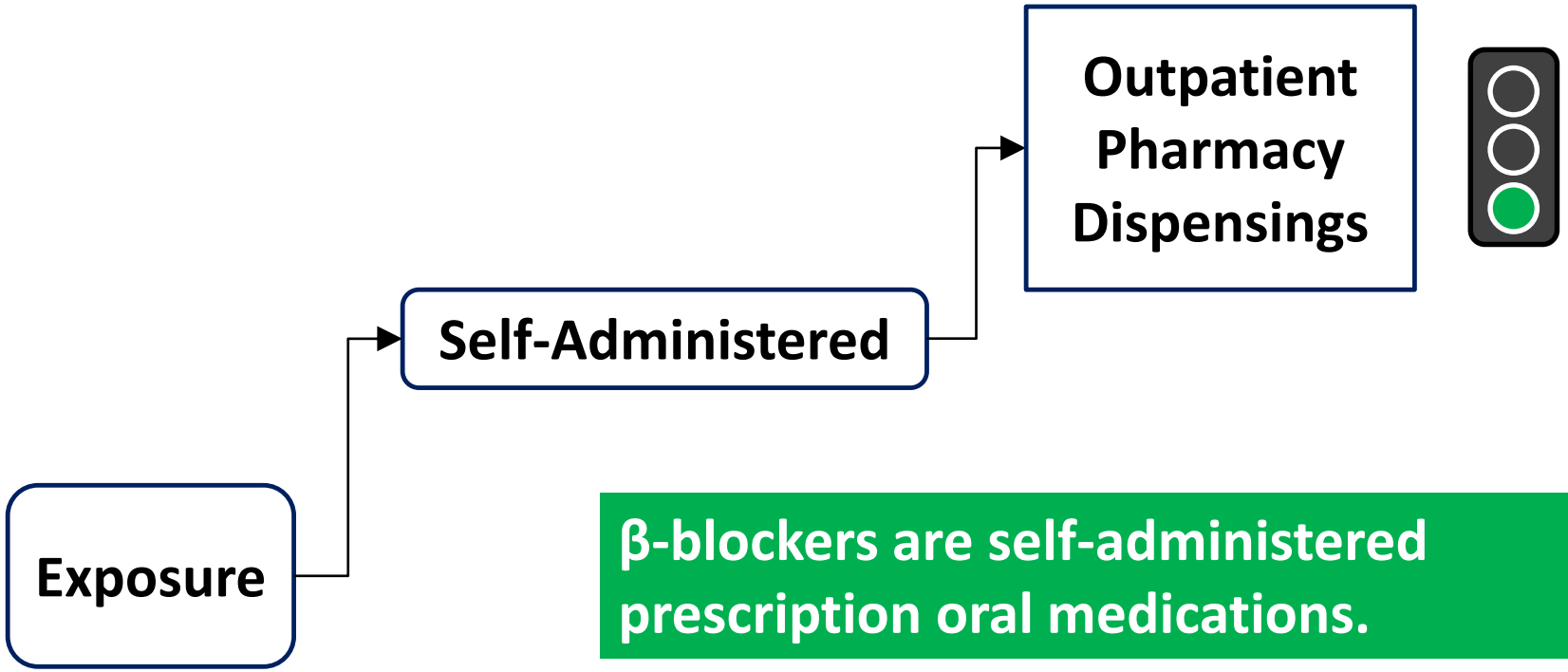


Is the Treatment Exposure Green (or Yellow)?



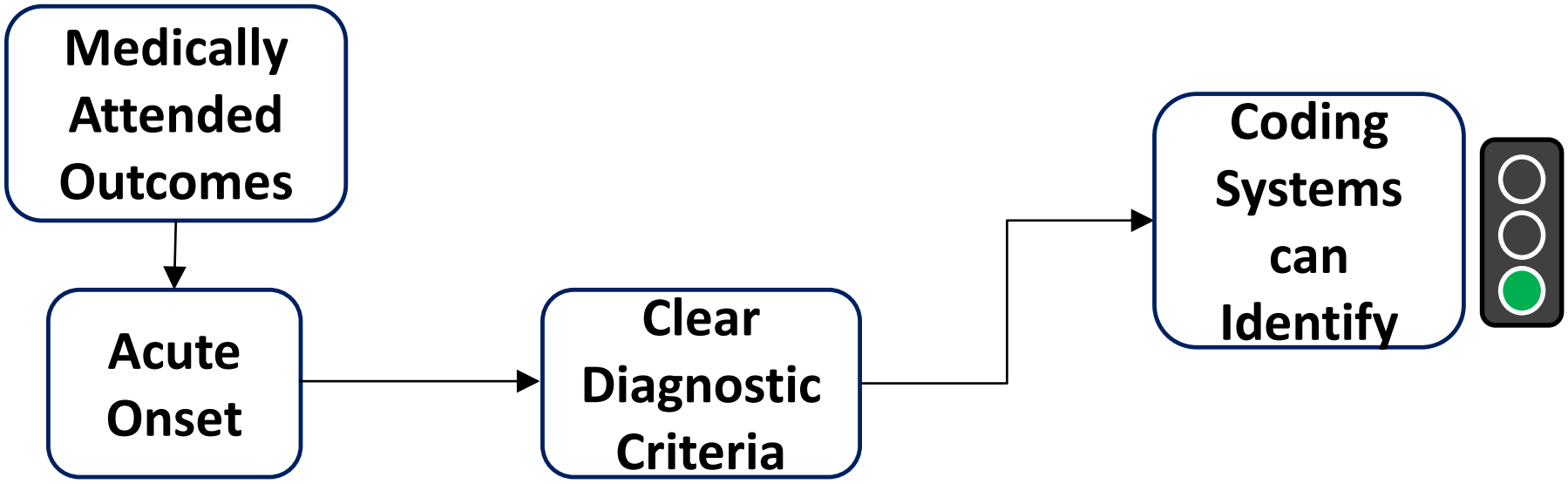
ACEIs are self-administered prescription oral medications.

Is the Comparator Exposure Green (or Yellow)?



β-blockers are self-administered prescription oral medications.

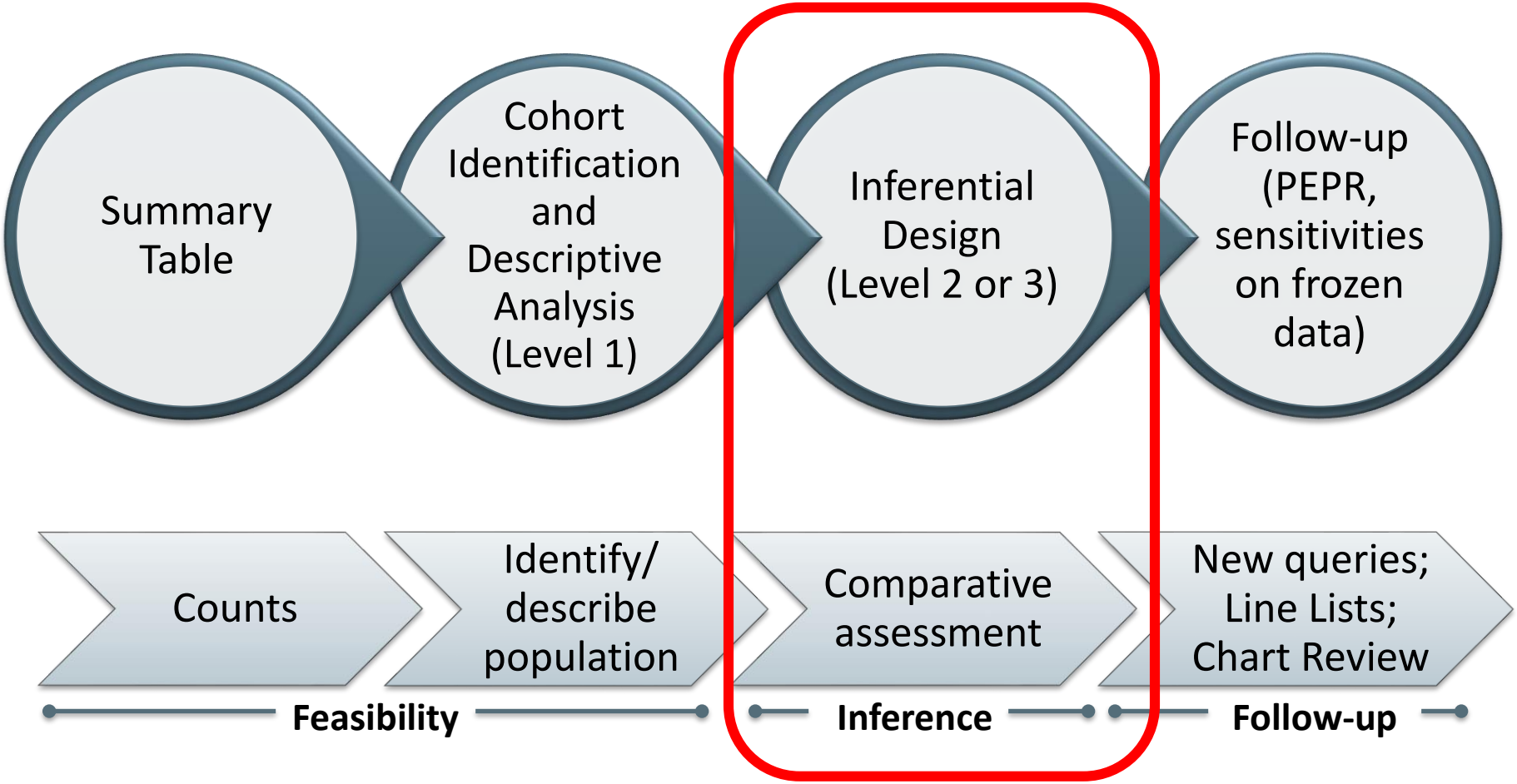
Is the Outcome Green (or Yellow)?



Angioedema* is an acute onset event with clear diagnostic criteria and administrative codes.

*Previously validated outcome definition

Typical Query Sequence



*PEPR= Patient Episode Profile Retrieval

Gather Descriptive Information?

- Could Level 1 queries provide useful information for a more sophisticated analysis?

User count

Exposure uptake

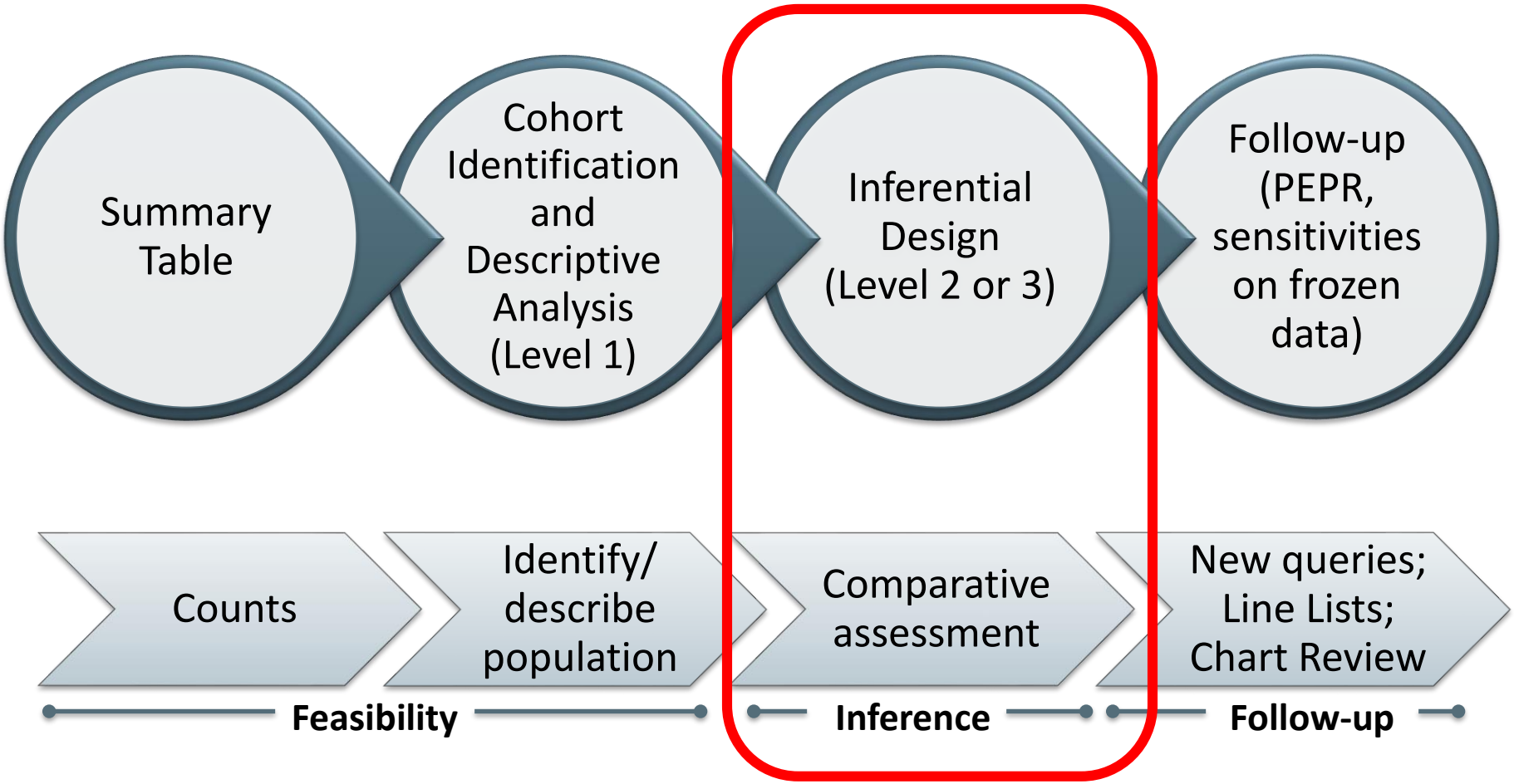
Exposure pattern

Event rate

Follow-up time

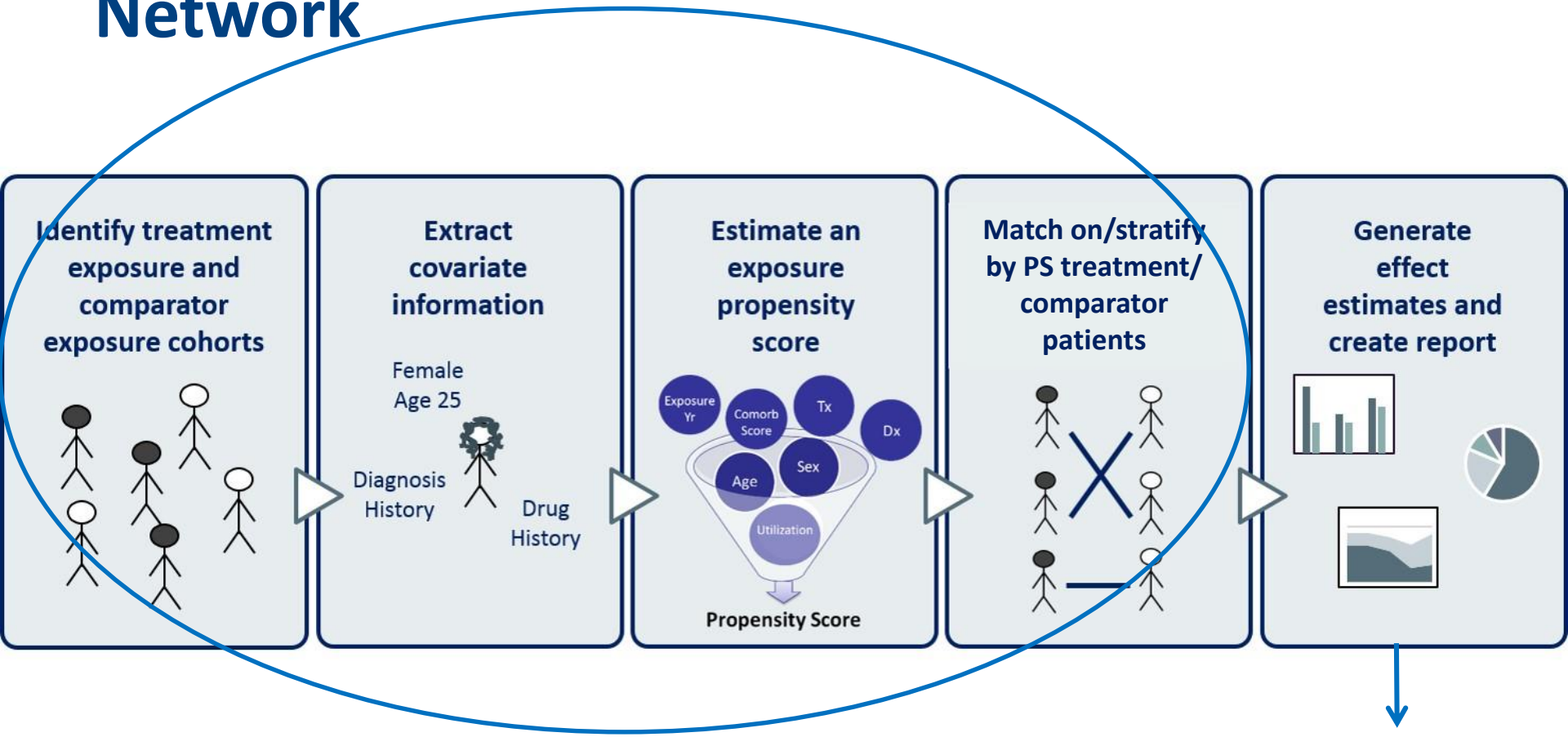
- Given the understanding and nature of the assessment (known positive relationship), we did not perform any Level 1 queries

Typical Query Sequence



*PEPR= Patient Episode Profile Retrieval

Propensity Score Analysis in the Distributed Network



Performed at Data Partner Site

Performed at SOC

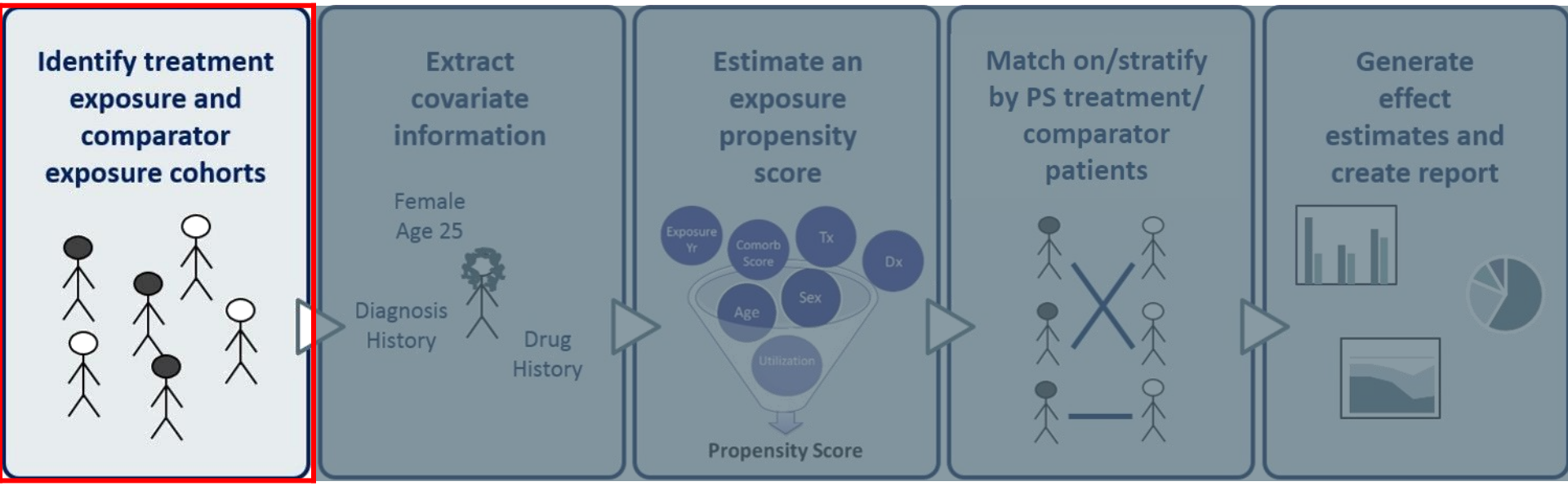
Objective, Design, and Data

- Evaluate the association between angiotensin converting enzyme inhibitors (ACEIs) and angioedema, with β-blockers as the comparison exposure
- Study design: retrospective, new-user cohort
- Data (formatted to Sentinel Common Data Model)
  - First test distributed to all data partners contributing to the Sentinel Distributed Database (2001-2010); 13 partners returned results
  - Recent test with newer data in the Truven Health MarketScan® Commercial Claims and Encounters Database (2010-2014; results shown in this training)

Analysis

- Evaluate risk of angioedema during active treatment with an ACEI as compared to β-blocker
  - Propensity score matching and stratification
  - Cox proportional hazards models
    - Maximum follow-up of 90 days

Identify Treatment and Comparator Exposure Cohorts



Define Treatment and Comparator Cohorts

- *Treatment exposure of interest:* ACEIs: benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, perindopril, ramipril, and tranolapril
- *Comparator exposure of interest:* β-blockers: acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, sotalol, penbutolol, pindolol, propranolol, and timolol

- Use evidenced by National Drug Codes recorded in outpatient pharmacy dispensings

Who is in the Cohort?

Washout/Lookback Duration

No evidence of ACEI or β-blocker use in prior 183 days

Translate Options into Specifications

Main Query and New User Parameters					
Product Name	**Query Period**	**Coverage**	**Age Groups**	**Washout/ Lookback Period**	**Products Defining New Use**
ACEIs	01/01/2011 -12/31/2014	Medical + Drug	18+	183 days	ACEIs, β-blockers
β-blockers	01/01/2011 -12/31/2014	Medical + Drug	18+	183 days	β-blockers, ACEIs

Define Inclusion/Exclusion Criteria

- Requesters may specify cohort inclusion and/or exclusion criteria
  - Specify a pre-exposure period to evaluate presence/absence of medical conditions or treatment of interest

- Requires enrollment during pre-exposure period
  - Evidence of continuous medical and/or drug coverage (requirements are requester-defined)

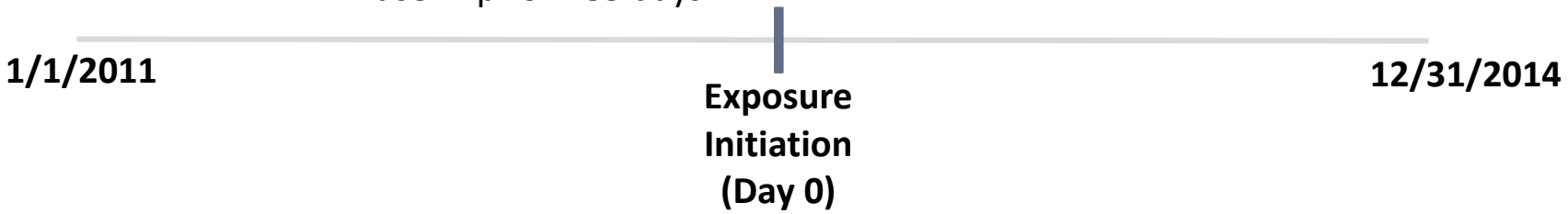
Who is in the Cohort?

Washout/Lookback Duration

No evidence of ACEI or β-blocker use in prior 183 days

Exclusion Criteria Assessment

No evidence of aliskiren or ARB use in prior 183 days



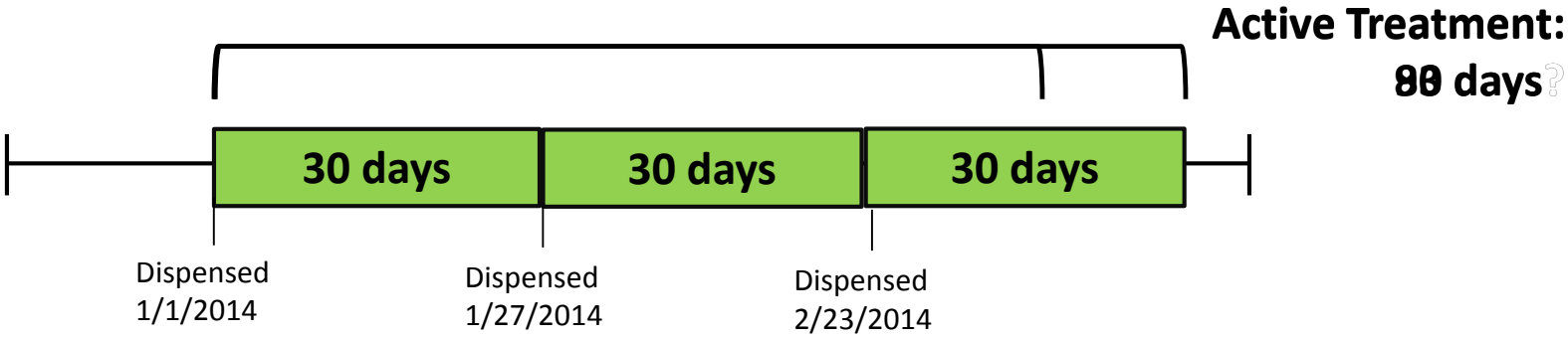
Translate Options into Specifications

Inclusion/Exclusion Criteria Parameters			
Cohort Name	**Include or Exclude**	**Criteria**	**Evaluation Window**
ACEIs	Exclude	Aliskiren, ARB	183 days before ACEI initiation
β-blockers	Exclude	Aliskiren, ARB	183 days before β-blocker initiation

ARB= angiotensin II receptor blocker

How to Define an Exposure Episode?

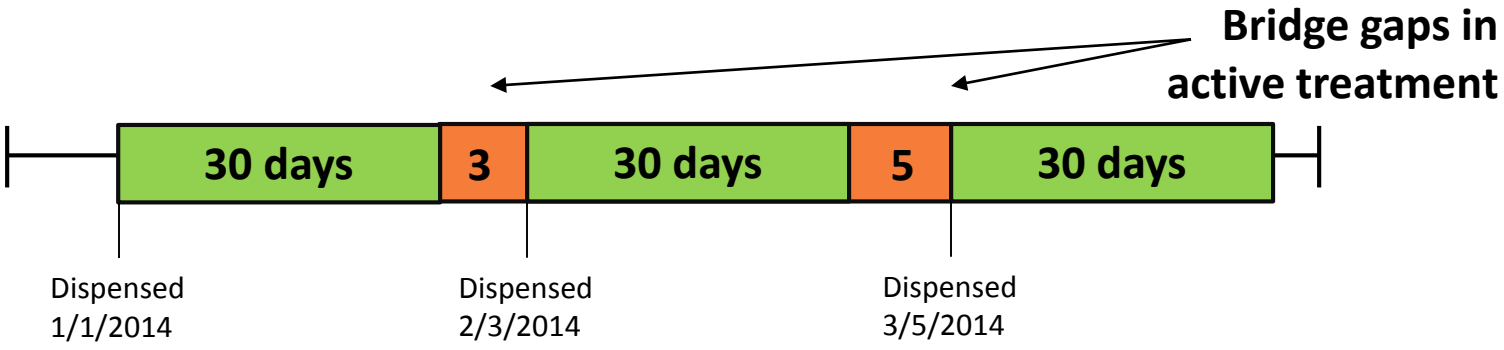
- Create episodes by observing outpatient pharmacy dispensing patterns
  - Uses dispensing date and days supply
  - Options
    - Adjust for **early refill patterns** with "stockpiling algorithm"



Dispensings

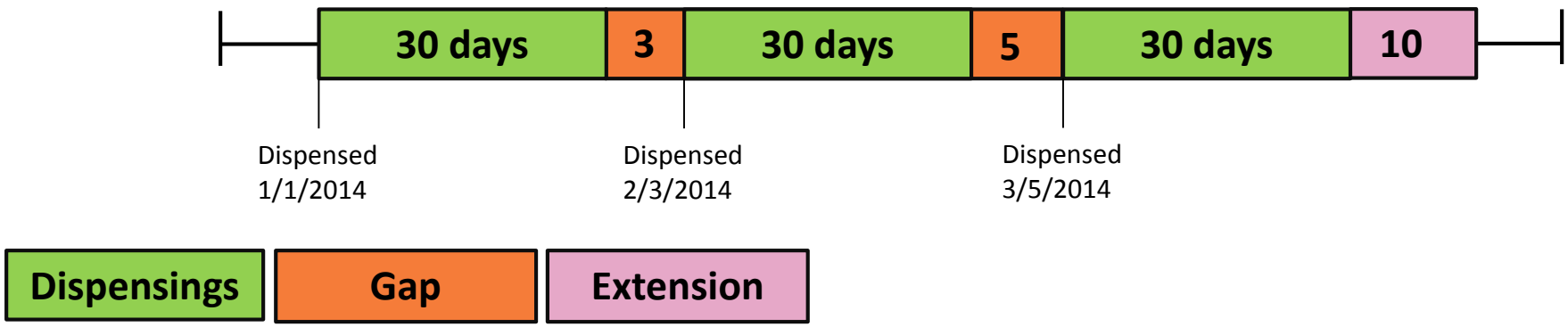
How to Define an Exposure Episode?

- Create episodes by observing outpatient pharmacy dispensing patterns
  - Uses dispensing date and days supply
  - Options
    - Adjust for **late refill patterns** with allowable gaps

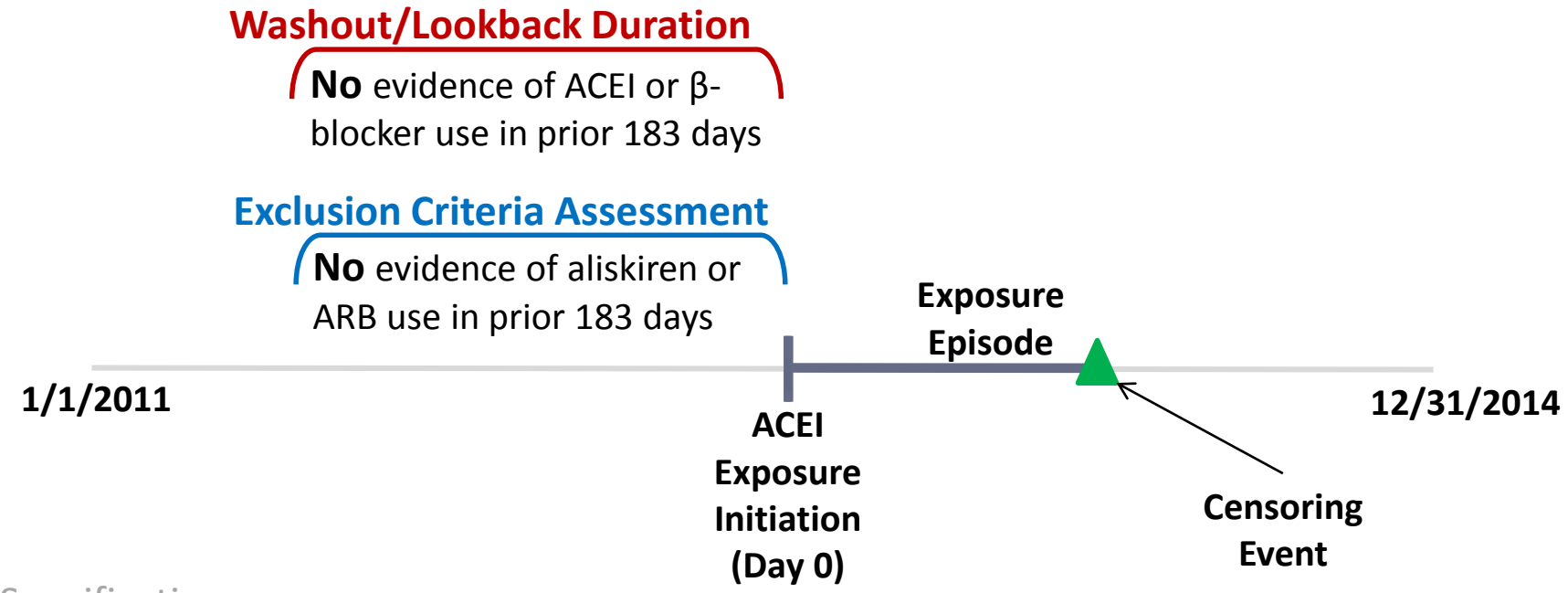


How to Define an Exposure Episode?

- Create episodes by observing outpatient pharmacy dispensing patterns
  - Uses dispensing date and days supply
  - Options
    - **Extend at-risk time beyond active treatment** with an exposure extension



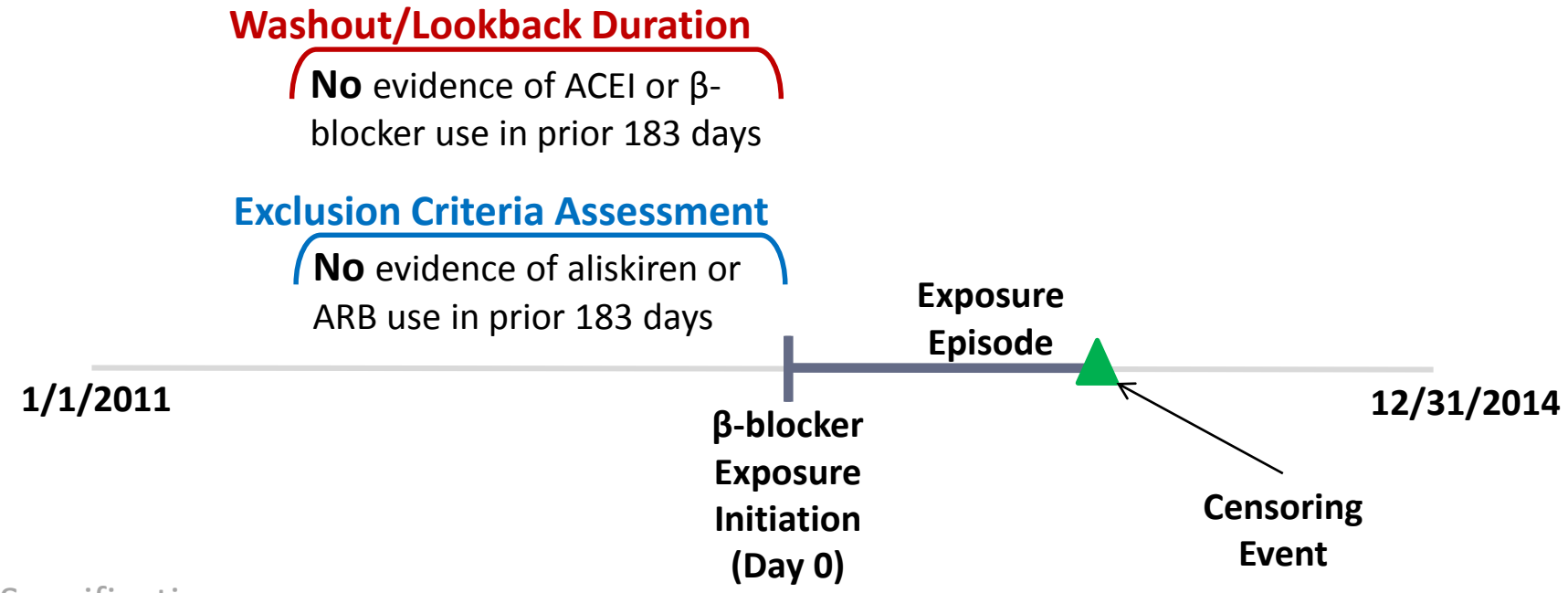
Who is in the ACEI New User Cohort?



Specifications

- Age 18+ at exposure initiation
- Continuous enrollment in medical and drug coverage during washout/lookback duration
- Exposure episode created using outpatient pharmacy dispensings' days supplied with 14-day episode gap and extension
- Censoring event can be 1) disenrollment, 2) data or query end; 3) β-blocker, ARB, aliskiren exposure; 4) death; 5) 90 days after index exposure

Who is in the β-blocker New User Cohort?



Specifications

- Age 18+ at exposure initiation
- Continuous enrollment in medical and drug coverage during washout/lookback duration
- Exposure episode created using outpatient pharmacy dispensings' days supplied with 14-day episode gap and extension
- Censoring event can be 1) disenrollment, 2) data or query end; 3) ACEI, ARB, aliskiren exposure; 4) death; 5) 90 days after index exposure

Translate Options into Specifications

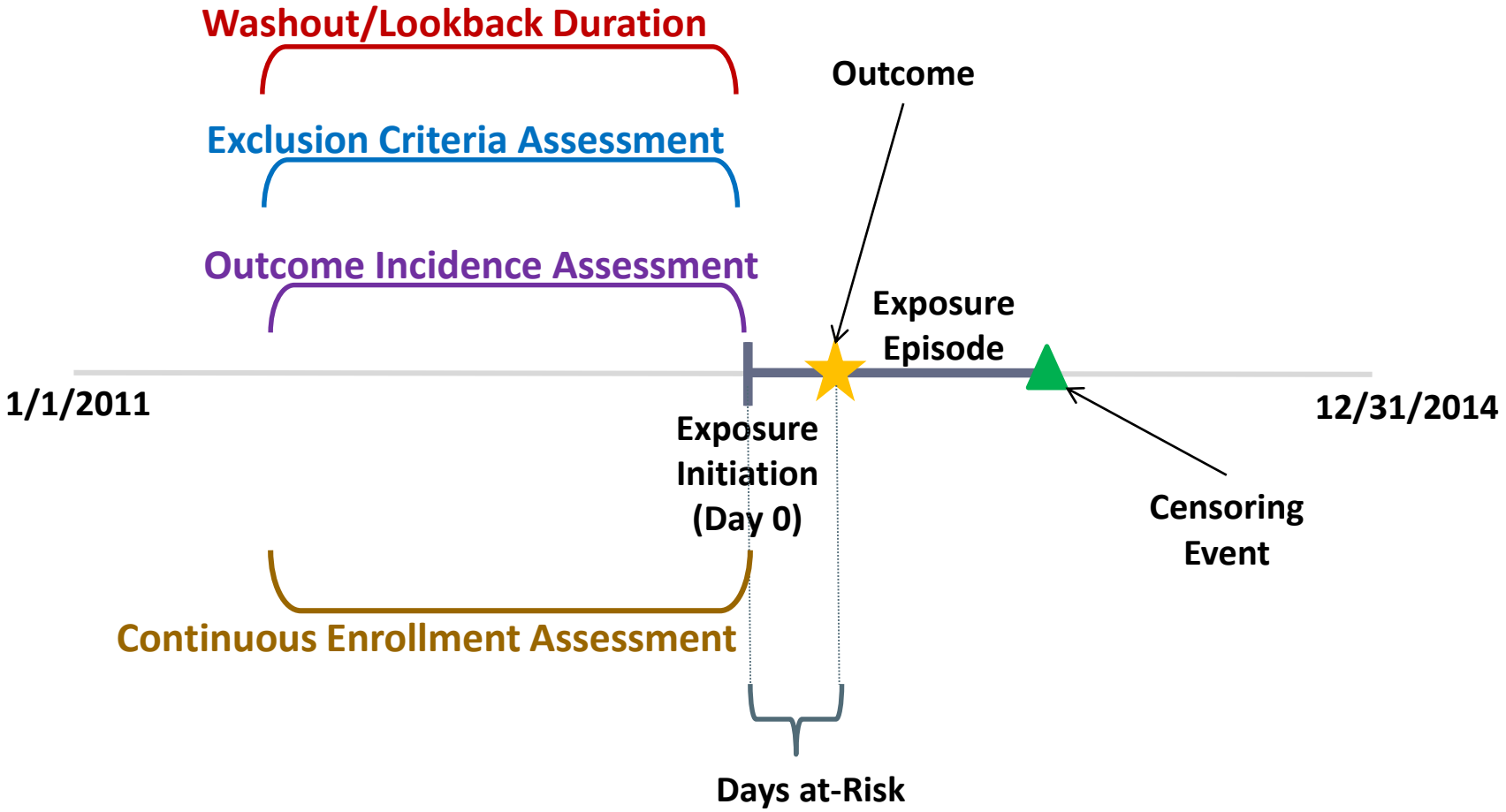
Exposure Episode Parameters				
Product Name	**Early Refill Pattern Approach**	**Late Refill Pattern Approach**	**Exposure Extension**	**Episode Censoring Criteria**
ACEIs	Standard "stockpiling" algorithm	14-day allowable episode gap	14 days	1) Disenrollment 2) Data or query end; 3) β-blocker, ARB, aliskiren exposure; 4) Death 5) 90 days of follow-up
β-blockers	Standard "stockpiling" algorithm	14-day allowable episode gap	14 days	1) Disenrollment 2) Data or query end; 3) ACEI, ARB, aliskiren exposure; 4) Death 5) 90 days of follow-up

Define Outcome of Interest

- Define the outcome using any combination of codes in the distributed database
  - Outcomes can be required to occur in specific care settings (e.g., inpatient, outpatient)
  - Inpatient diagnosis codes used to define outcomes can be required in a specific position (e.g., principal discharge diagnosis, secondary)

- New, or incident, outcomes defined as no prior occurrence in requester-defined pre-exposure period

Who is in the Cohort?



Complex Algorithms Can be Used to Define Outcomes

- Outcomes are sometimes defined with single codes
  - Angioedema: any inpatient, outpatient, or ED with ICD-9-CM diagnosis of 995.1
- But can use **AND** and/or **OR** operators to require two or more codes to occur **within a pre-specified window**
  - Serious angioedema: inpatient diagnosis **PLUS** intensive care unit admission, intubation, tracheostomy, or laryngoscopy **within 2 days of** hospital admission

Translate Options into Specifications

Outcome Parameters		
Outcome	**Definition**	**Incidence Criteria**
Angioedema*	Angioedema, as identified by ICD-9-CM code 995.1 recorded in any position during an outpatient, inpatient, or emergency department encounter	183 days

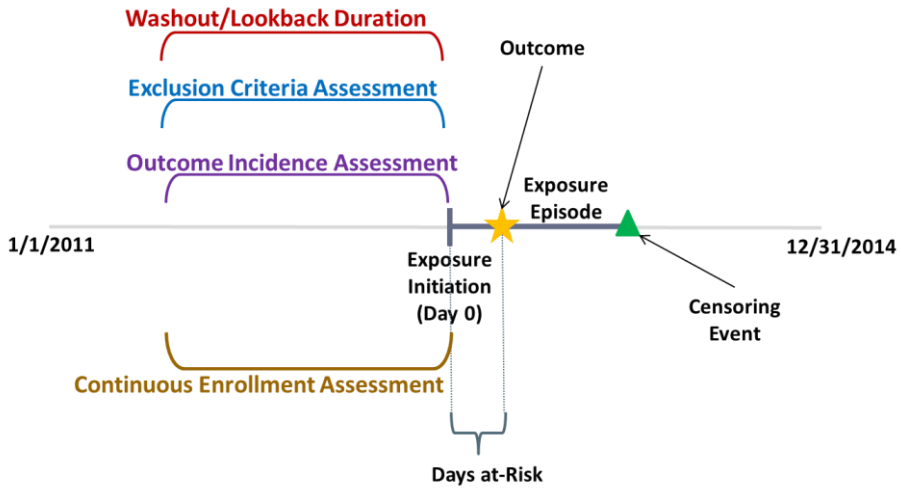
* Previously validated outcome definition

Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension*. 2008;51(6):1624-163

Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor–associated angioedema. *JAMA*. 1997;278(3):232-233

Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor–associated angioedema. *Clin Pharmacol Ther*. 1996;60(1):8-13

Cohort Identification Summary



- Treatment: ACEIs
- Comparator: β-blockers
- Included: age 18+ years with an exposure washout of ≥183 days
- Excluded: patients with the following during washout: 1) study drug of the other class; 2) aliskiren; 3) ARBs; 4) angioedema
- Follow-up: began on exposure initiation and continued until first occurrence of 1) angioedema; 2) death; 3) disenrollment; 4) cessation of study drug use; 5) initiation of aliskiren, another study drug of a different class, or an ARB; 6) query end; 7) data end; 8) 90 days after exposure
- Outcome: angioedema

Original Report

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger[1,], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]*

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Italy

Original Report

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2,], Sebastian Schneeweiss[1,2], Marc L. Berger[3], Jeffrey Brown[4], Frank de Vries[5], Ian Douglas[6], Joshua J. Gagne[1,2], Rosa Gini[7], Olaf Klungel[8], C. Daniel Mullins[9], Michael D. Nguyen[10], Jeremy A. Rassen[11], Liam Smeeth[6], Miriam Sturkenboom[12], on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making*

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, MA, USA; [2]Department of Medicine, Harvard Medical School, MA, USA; [3]Pfizer, NY, USA; [4]Department of Population Medicine, Harvard Medical School, MA, USA; [5]Department of Clinical Pharmacy, Maastricht UMC+, The Netherlands; [6]London School of Hygiene and Tropical Medicine, England, UK; [7]Agenzia regionale di sanità della Toscana, Florence, Italy; [8]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [9]Pharmaceutical Health Services Research Department, University of Maryland School of Pharmacy, MA, USA; [10]FDA Center for Drug Evaluation and Research, USA; [11]Aetion, Inc., NY, USA; [12]Erasmus University Medical Center Rotterdam, Netherlands

Propensity Score Analysis Pre-Processing: Evaluate Overlap in ACEI and β-blocker Users

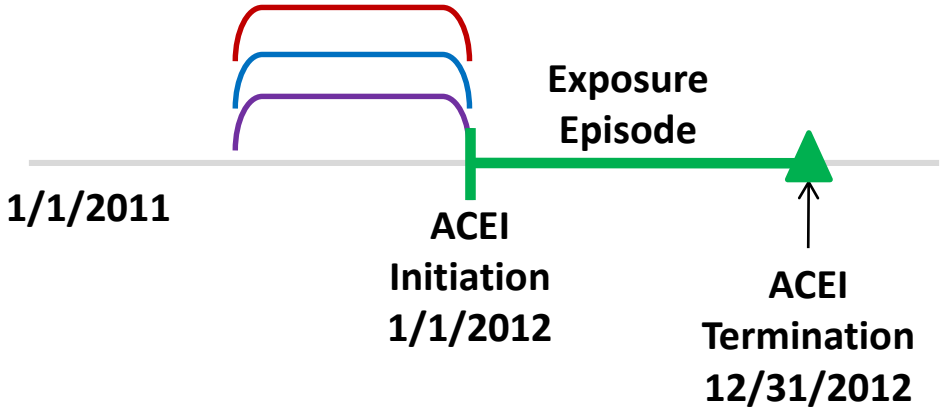
- If the same patient initiates treatment and comparator exposures on the same day, the patient is removed from analysis

- If the same patient is identified in the exposure and comparator cohorts, the patient is retained in the cohort of earliest exposure

How is it Possible to be in Both Cohorts?

Patient "A"

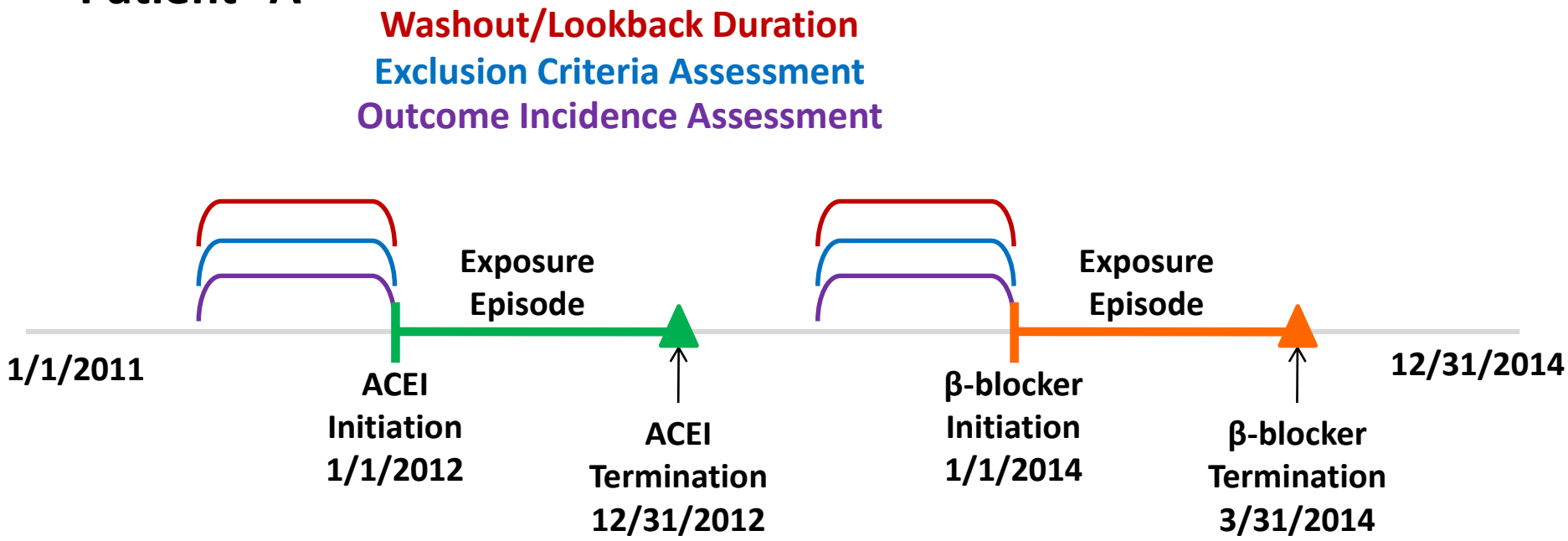
Washout/Lookback Duration
Exclusion Criteria Assessment
Outcome Incidence Assessment



Patient "A" will be included in ACEI cohort

How is it Possible to be in Both Cohorts?

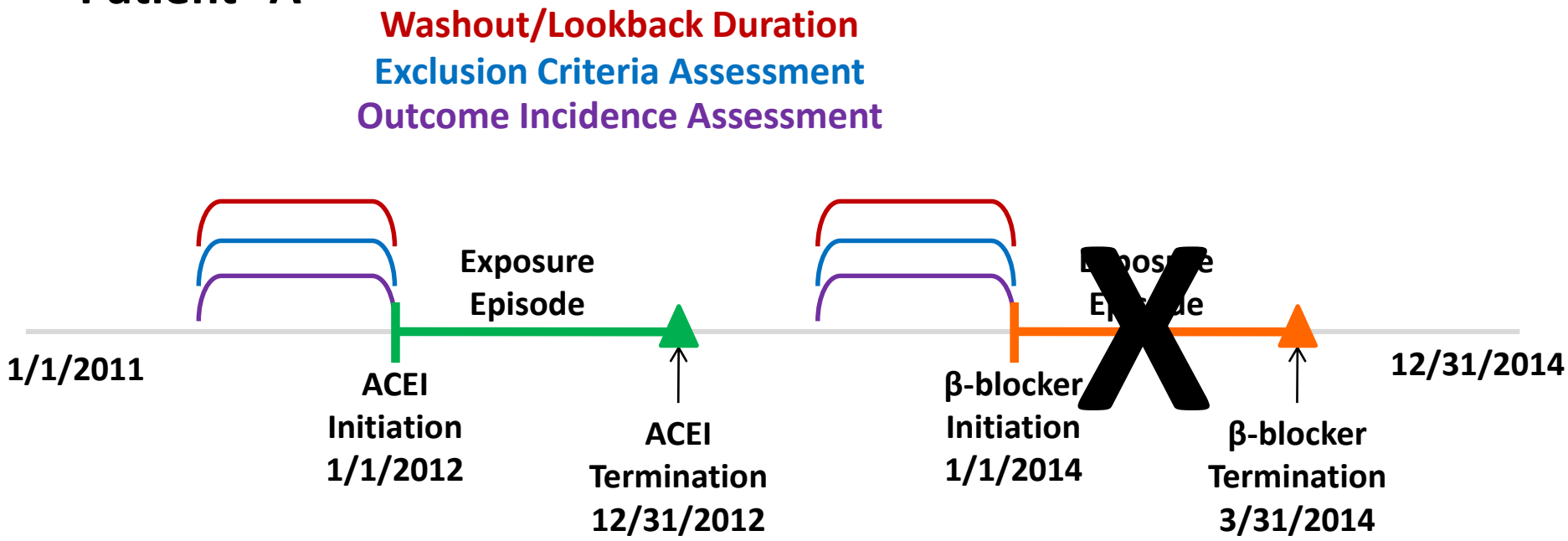
Patient "A"



Patient "A" will be included in ACEI cohort

How is it Possible to be in Both Cohorts?

Patient "A"

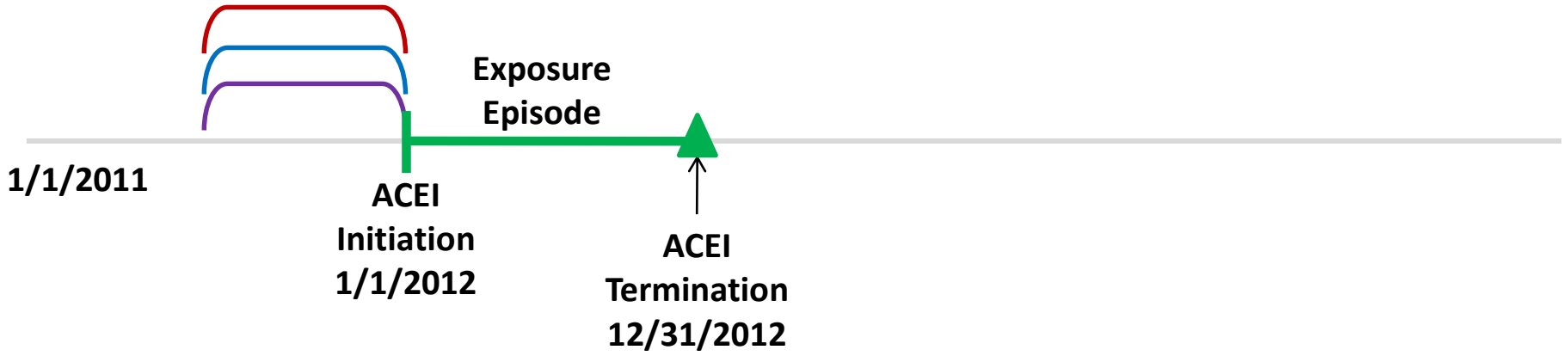


Patient "A" will be included in ACEI cohort

How is it Possible to be in Both Cohorts?

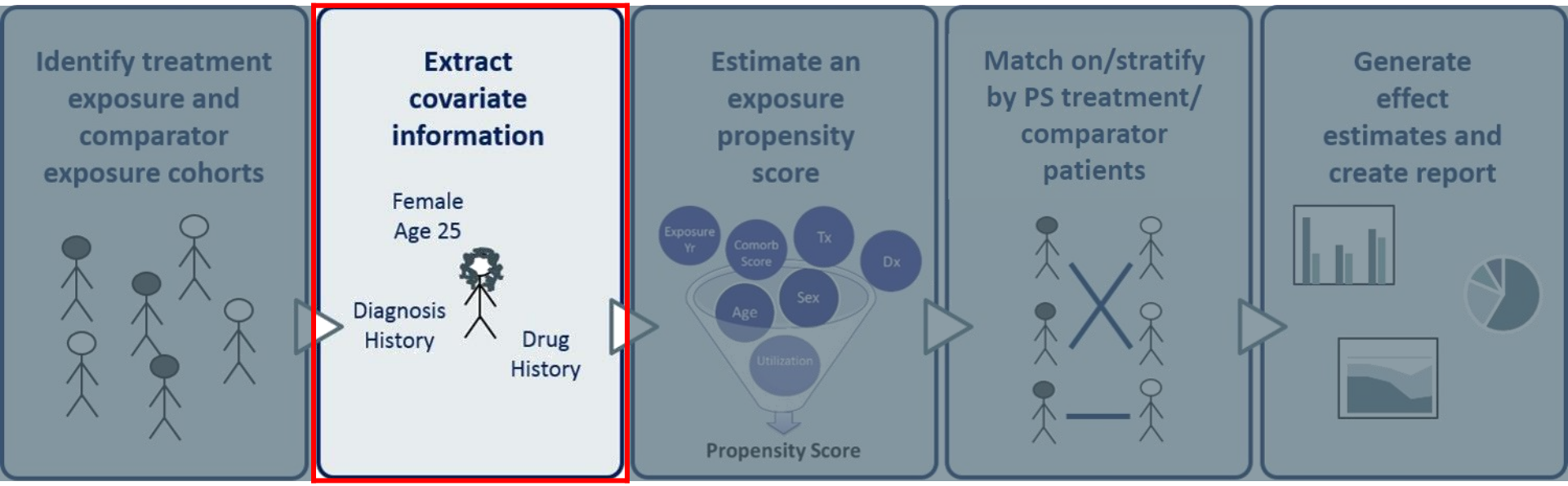
Patient "A"

Washout/Lookback Duration
Exclusion Criteria Assessment
Outcome Incidence Assessment



Patient "A" will be included in ACEI cohort

Extract Covariates (Risk Factors)



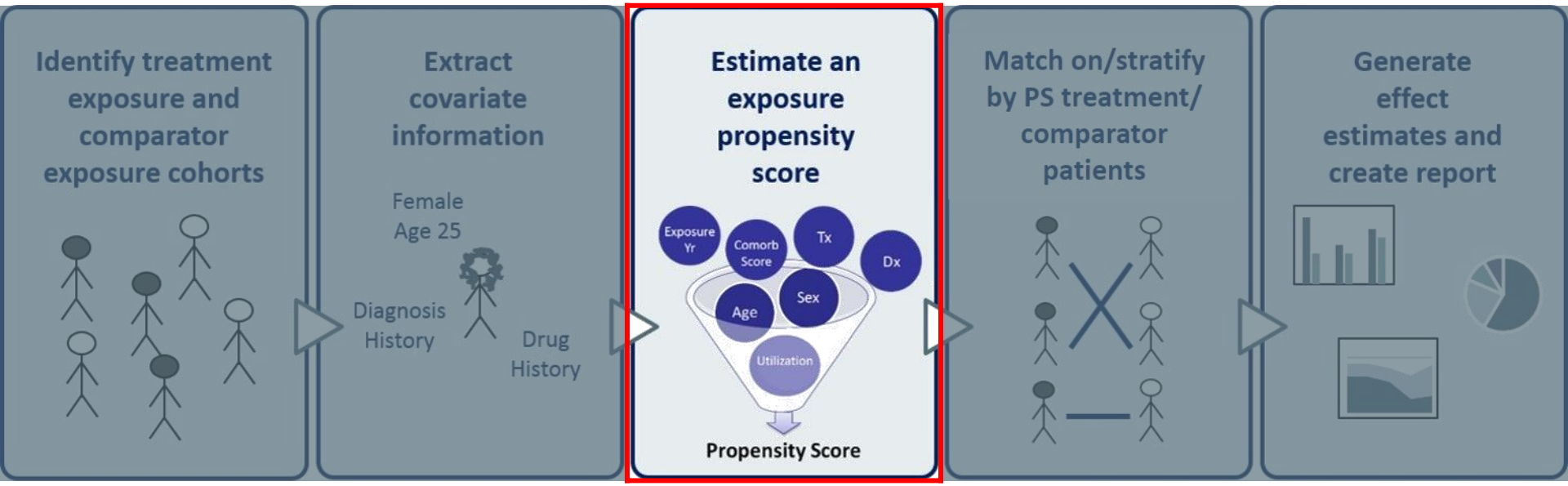
Define Covariates of Interest for PS Estimation

- Requesters specify covariates for inclusion in the propensity score estimation model
  - Age, sex, year of exposure initiation
  - Any clinical concept that can be defined using a list of codes available in the distributed database
  - Healthcare utilization metrics
    - E.g., number of inpatient, outpatient, emergency dept. encounters
  - Drug utilization metrics
    - E.g., number of dispensings, unique generics dispensed
- Lookback period for covariate assessment defined by requester

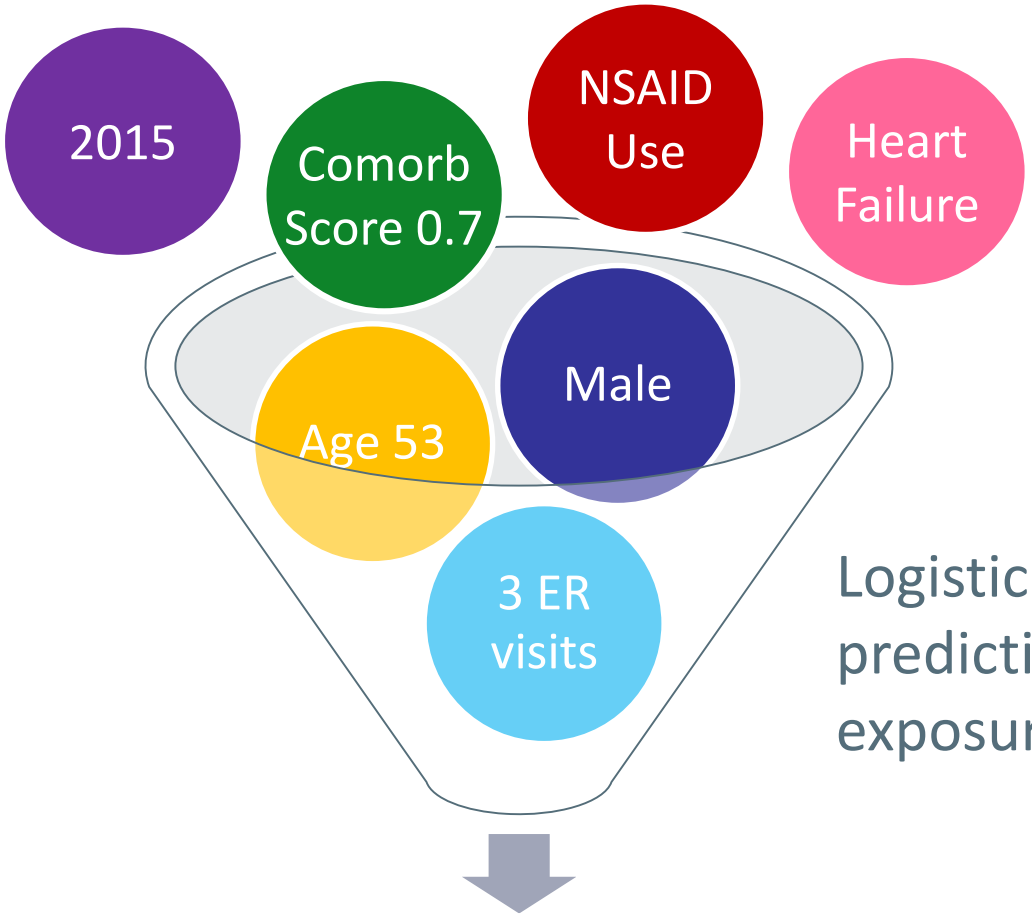
Translate Options into Specifications

Propensity Score Estimation Parameters	
Covariates	**Evaluation Window**
Age (continuous)	183 days before exposure initiation
Sex (M/F)	
Year of exposure (4 variables)	
Comorbidity score (continuous)	
Healthcare utilization (5 continuous variables)	
Drug utilization (3 continuous variables)	
History of allergic reactions (Y/N)	
History of diabetes mellitus (Y/N)	
History of heart failure (Y/N)	
History of ischemic heart disease (Y/N)	
Use of prescription NSAIDs (Y/N)	

Estimate an Exposure Propensity Score

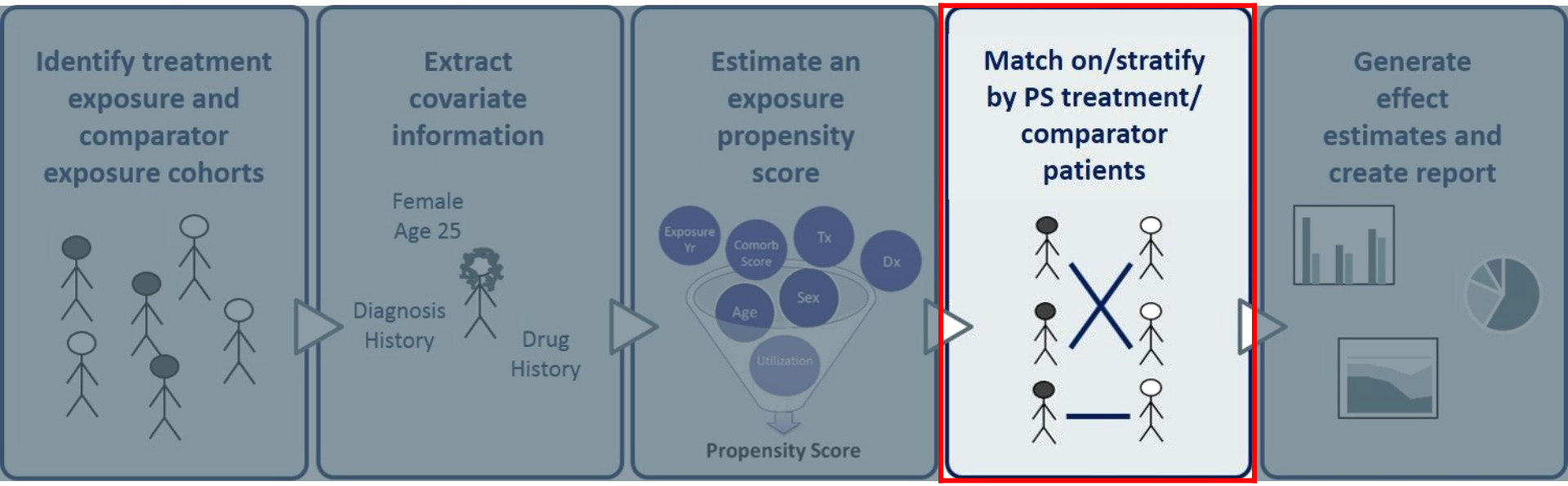


Estimate a Propensity Score at Data Partner

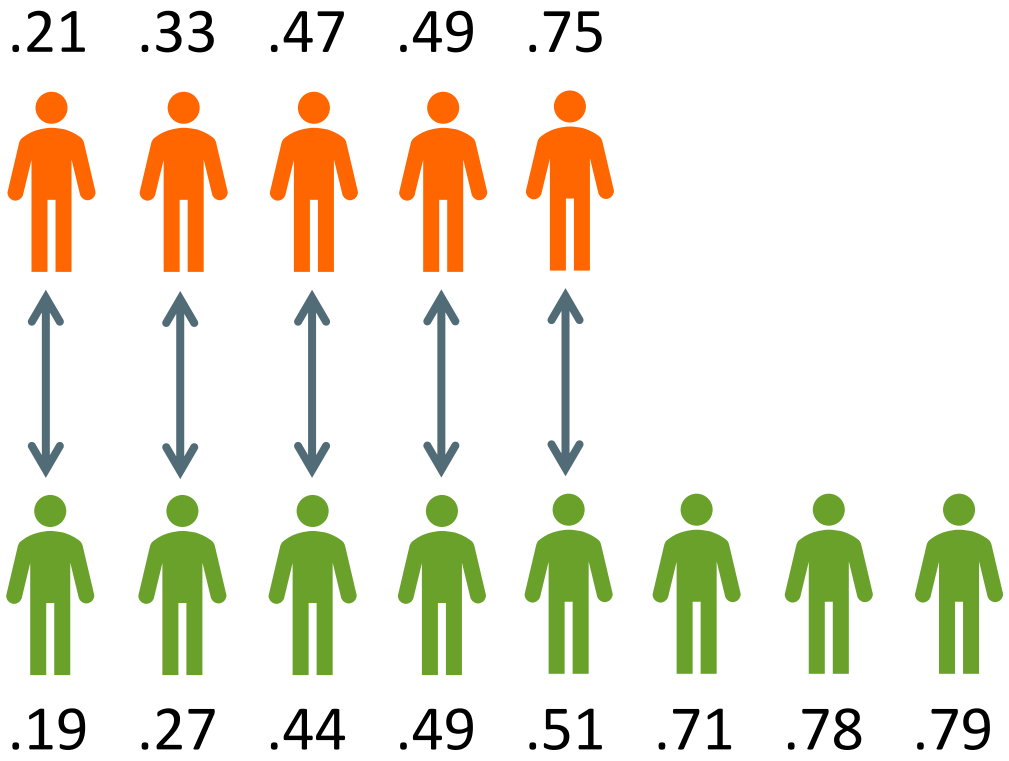


Logistic regression predicting treatment exposure

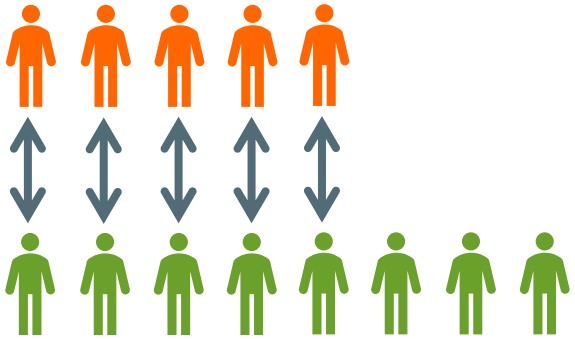
Match on or Stratify by Propensity Score Treatment and Comparator Patients



- PS matching
  - Nearest neighbor
  - 1:1
  - Caliper= 0.05

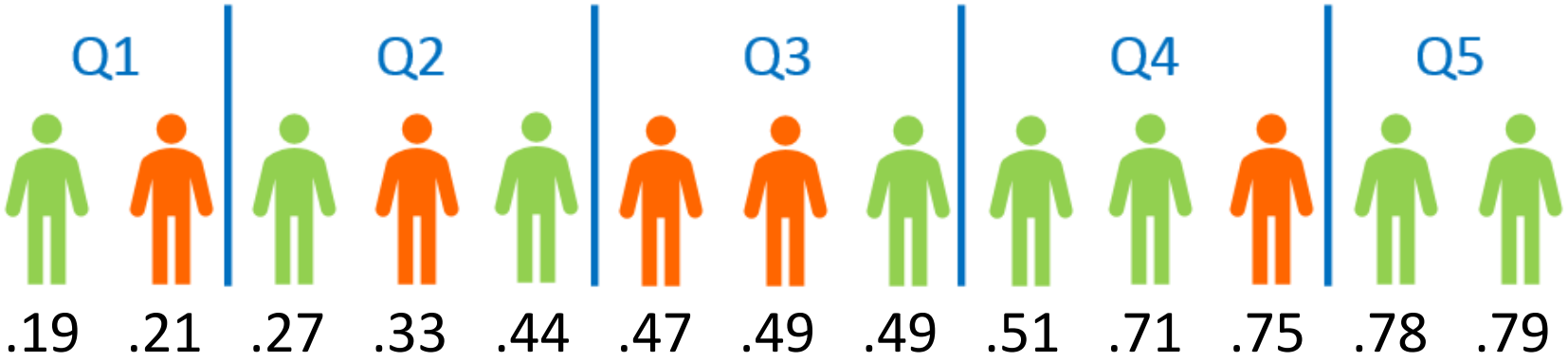


Matching: Ratio and Caliper



- Nearest neighbor
  - Algorithm aims to reduce the absolute difference in propensity scores across all matched sets
- Ratio
  - 1:1 matching, without replacement
  - Option= 1:*n* (*n*≤ 10)
- Caliper: can be set as any value 0-1
  - Maximum distance allowed between two matched patients' PS
  - Natural scale of PS (e.g., 0.01, 0.05)

- PS stratification
  - Quintiles

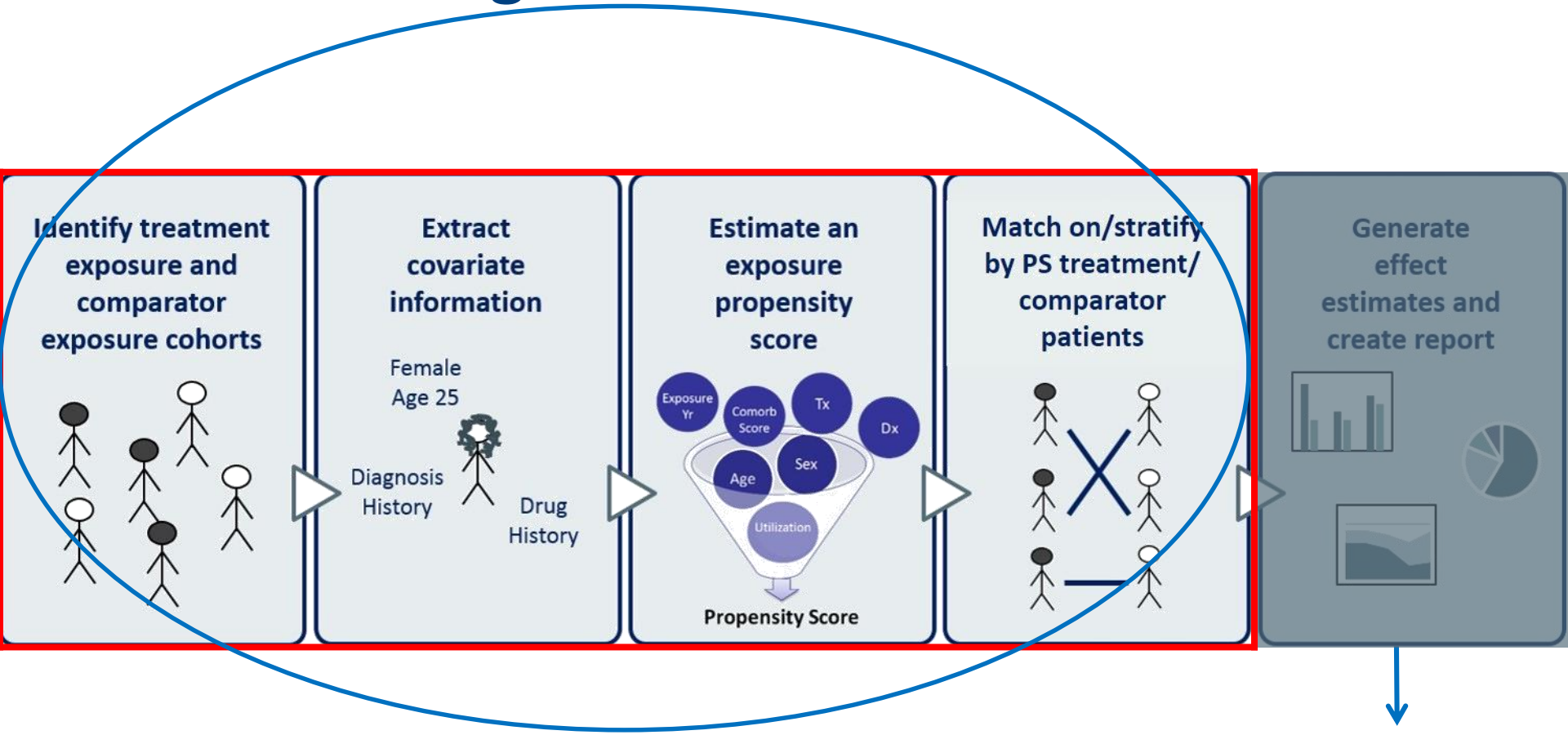


Stratification: Percentiles

- Divide treatment and comparator exposure cohorts into requester-defined PS percentiles

- Percentile: can be set as any value 1-100
  - E.g., 10= deciles, 5= quintiles

Before Package Distribution …



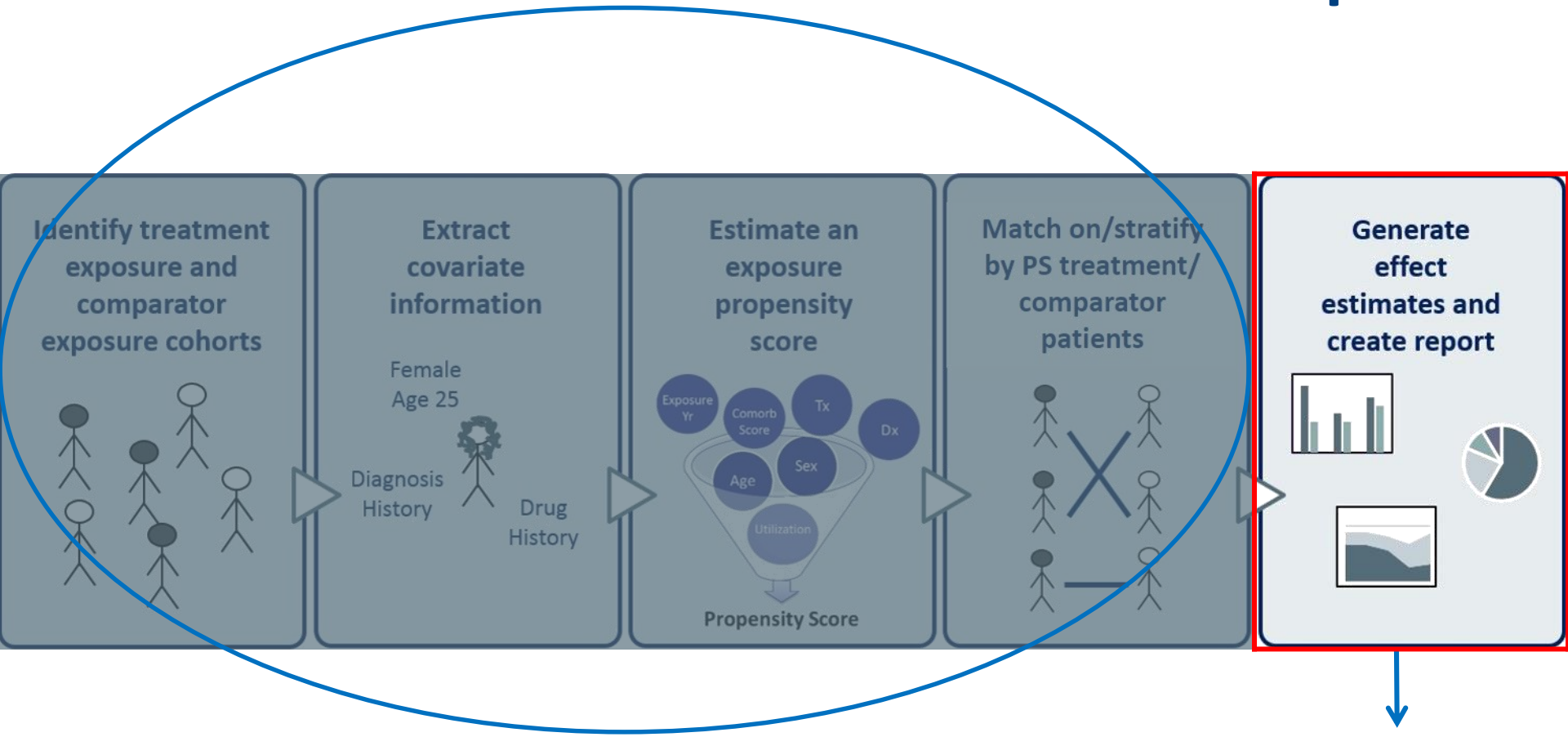
Performed at Data Partner Site

Performed at SOC

Conduct Sensitivity Analyses?

- Options include:
  - New user criteria (e.g., 183 versus 365-day washout period)
  - Inclusion/exclusion criteria
  - Exposure episode creation parameters (extensions, gaps, stockpiling)
  - Algorithms to define the outcome
  - Lookback windows for inclusion/exclusion and covariates
  - Follow-up to as-treated, or various maximum period
  - Matching ratio/caliper
  - Stratification percentiles

Generate Effect Estimates and Create Report



Performed at Data Partner Site

Performed at SOC

Specify Cox Proportional Hazards Model

- Effect estimation performed via Cox proportional hazards model
- Requesters may specify PS-adjusted analysis
  - Matched unconditional analysis
    - Option= matched conditional (stratified by matched set) analysis
  - Stratified analysis

- Outcome models also stratified by Data Partner
- Unmatched results output by default

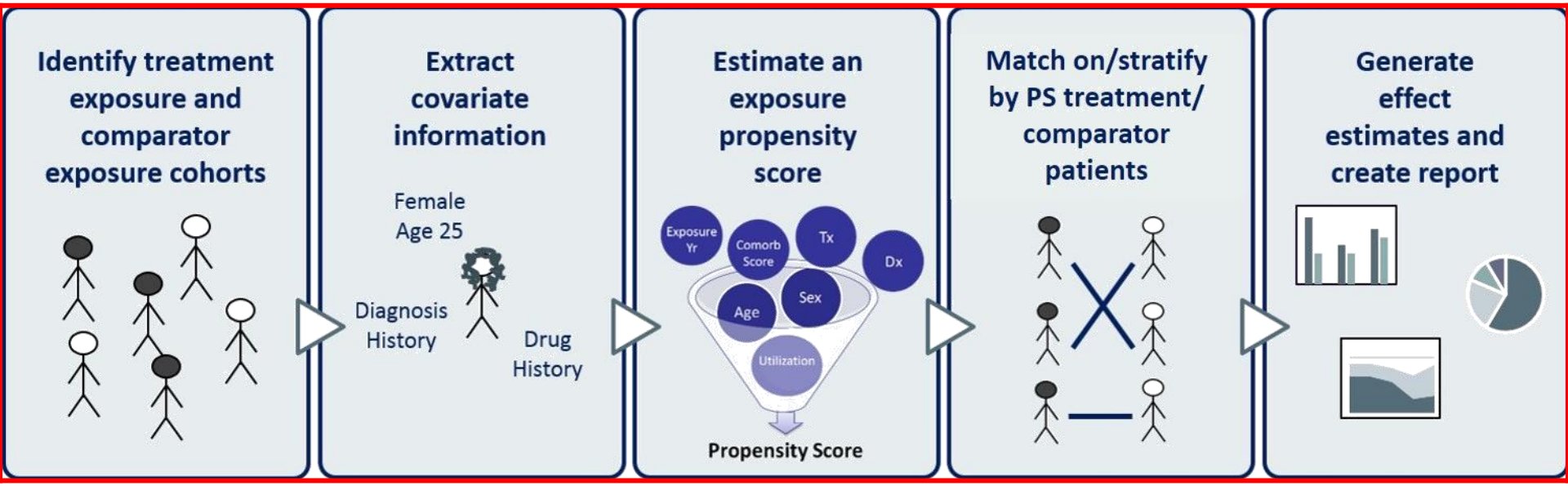
Specify Subgroup Analyses (Matching Only)

- Evaluate treatment effects by subsets of the population
  - May use levels of any requester-defined covariates
- Current capability:
  - Rematch patients within subgroup levels and perform effect estimation
- Future capability:
  - Match on PS *and* subgroup level(s)
    - Rematching will not be necessary before effect estimation

Translate Options into Specifications

Propensity Score Analysis Parameters	
Matching ratio	1:1
Matching caliper	0.025
Stratification percentile	5 (quintile)
Cox model	Unmatched Matched unconditional Stratified
Subgroup analysis	No

Evaluate Results

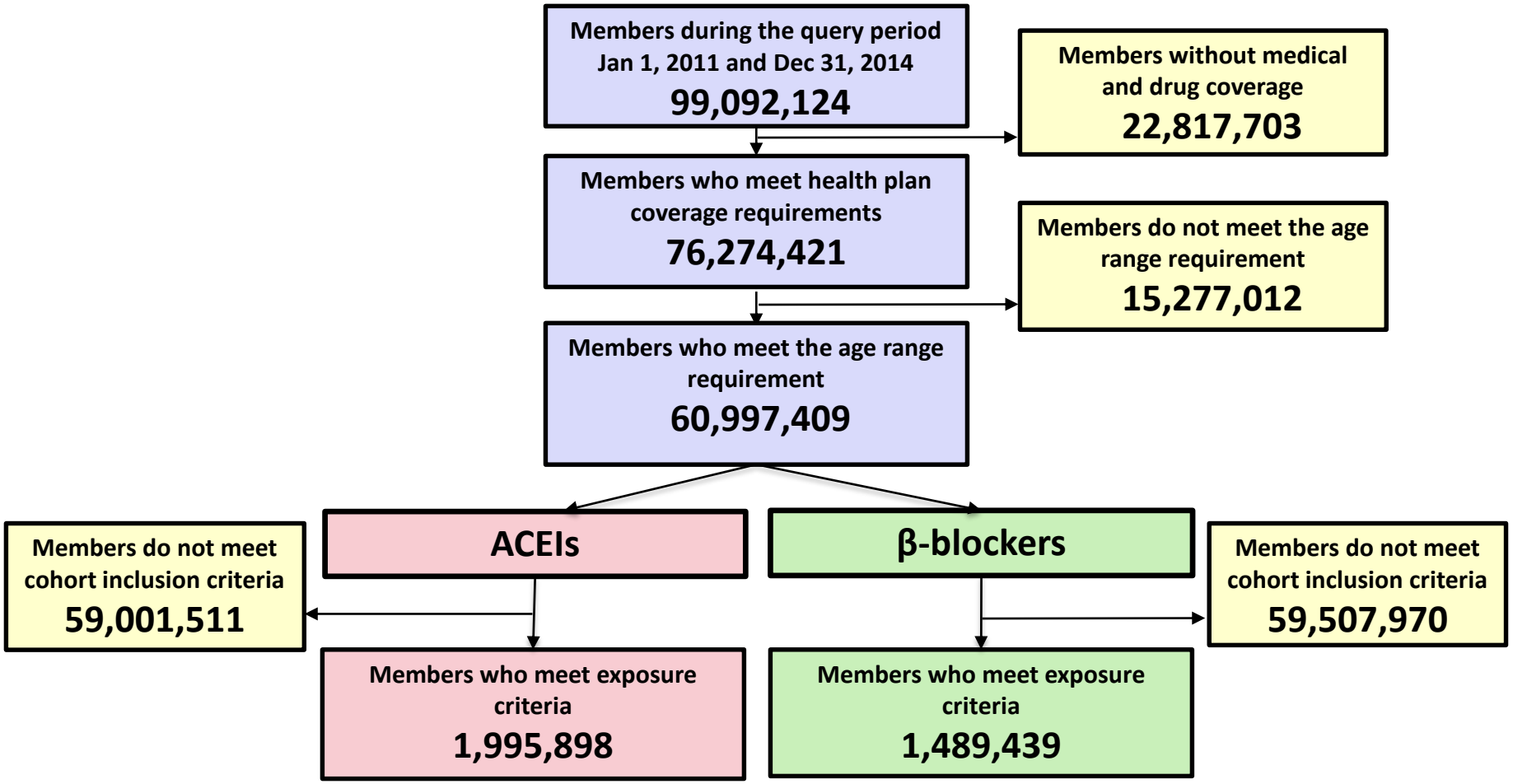


Output Includes Diagnostics, Effect Estimates

- By Data Partner
  - Cohort attrition table
  - Cohort censoring table
    - Number of episodes by censored time and censoring reasons (e.g., disenrollment, episode end, data end, or death)
  - Propensity score distributions, pre/post matching
- Aggregate
  - Cohort baseline characteristics, pre/post matching
  - Kaplan-Meier plots
  - Effect estimates and 95% confidence intervals

User can choose output to receive (e.g., evaluate diagnostics before evaluating frequency of outcomes)

Review Cohort Attrition for Treatment and Comparator Exposure Cohorts



Evaluate Baseline Characteristics: Unmatched Cohort

	Medical Product				Covariate Balance	
Characteristic	ACE Inhibitors		Beta Blockers		Difference	
	N	%	N	%	Absolute	Standardized
Patients	1,838,853	100.0%	1,330,298	100.0%	-	-
Demographics						
Age (mean, std)	53.4	12.9	52.5	16.4	0.91	0.062
Gender (female)	832,867	45.3%	778,726	58.5%	-13.25	**-0.267**
Recorded history of						
Allergic reactions	77,685	4.2%	77,787	5.8%	-1.62	-0.074
Diabetes	365,640	19.9%	137,309	10.3%	9.56	**0.269**
Heart failure	22,613	1.2%	56,455	4.2%	-3.01	**-0.186**
Ischemic heart disease	68,552	3.7%	165,536	12.4%	-8.72	**-0.324**
NSAIDs	268,443	14.6%	201,748	15.2%	-0.57	-0.016
Selected Health Service Utilization Intensity						
Ambulatory encounters (mean, std)	4.9	6.6	7.2	9.1	-2.37	**-0.297**
Emergency room encounters (mean, std)	0.2	0.7	0.4	1.0	-0.17	**-0.202**
Inpatient hospital encounters (mean, std)	0.1	0.3	0.2	0.5	-0.15	**-0.328**
Filled prescriptions (mean, std)	9.2	9.6	11.1	11.2	-1.84	**-0.177**
Unique drug classes (mean, std)	4.7	3.2	5.7	3.8	-0.99	**-0.279**

NSAIDs= nonsteroidal anti-inflammatory drugs

Evaluate Baseline Characteristics: Unmatched Cohort

Characteristic	Medical Product				Covariate Balance	
	ACE Inhibitors		Beta Blockers		Difference	
	N	%	N	%	Absolute	Standardized
Patients	1,838,853	100.0%	1,330,298	100.0%	-	-
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Ischemic heart disease	68,552	3.7%	165,536	12.4%	-8.72	**-0.324**
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Ambulatory encounters (mean, std)	4.9	6.6	7.2	9.1	-2.37	**-0.297**
Emergency room encounters (mean, std)	0.2	0.7	0.4	1.0	-0.17	**-0.202**
Inpatient hospital encounters (mean, std)	0.1	0.3	0.2	0.5	-0.15	**-0.328**
Filled prescriptions (mean, std)	9.2	9.6	11.1	11.2	-1.84	**-0.177**
Unique drug classes (mean, std)	4.7	3.2	5.7	3.8	-0.99	**-0.279**

NSAIDs= nonsteroidal anti-inflammatory drugs

Evaluate Baseline Characteristics: Unmatched Cohort

Characteristic	Medical Product				Covariate Balance	
	ACE Inhibitors		Beta Blockers		Difference	
	N	%	N	%	Absolute	Standardized
Patients	1,838,853	100.0%	1,330,298	100.0%	-	-
Demographics						
Age (mean, std)	53.4	12.9	52.5	16.4	0.91	0.062
Gender (female)	832,867	45.3%	778,726	58.5%	-13.25	**-0.267**
Recorded history of						
Allergic reactions	77,685	4.2%	77,787	5.8%	-1.62	-0.074
Diabetes	365,640	19.9%	137,309	10.3%	9.56	**0.269**
Heart failure	22,613	1.2%	56,455	4.2%	-3.01	**-0.186**
Ischemic heart disease	68,552	3.7%	165,536	12.4%	-8.72	**-0.324**
NSAIDs	268,443	14.6%	201,748	15.2%	-0.57	-0.016
Selected Health Service Utilization Intensity						
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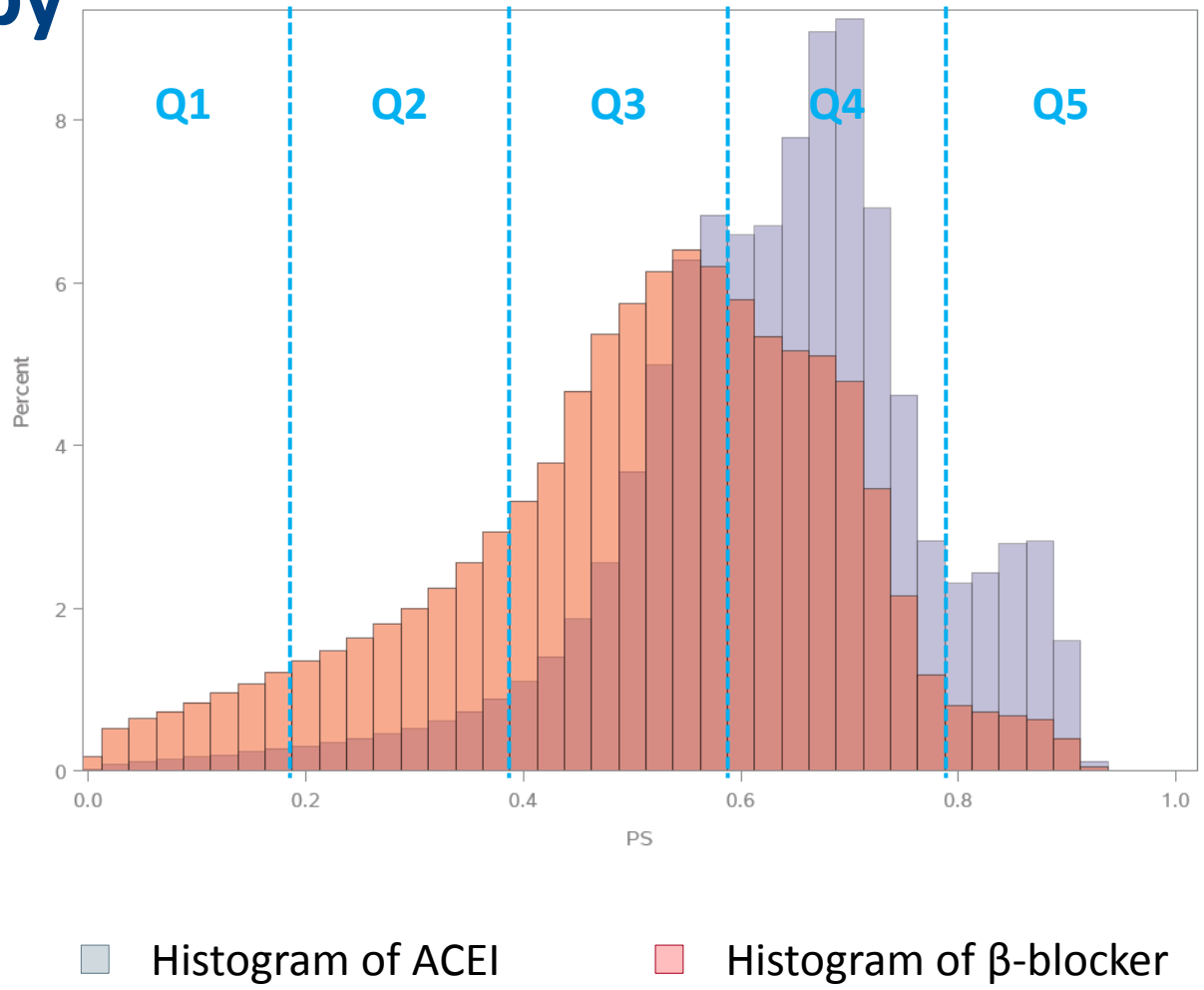
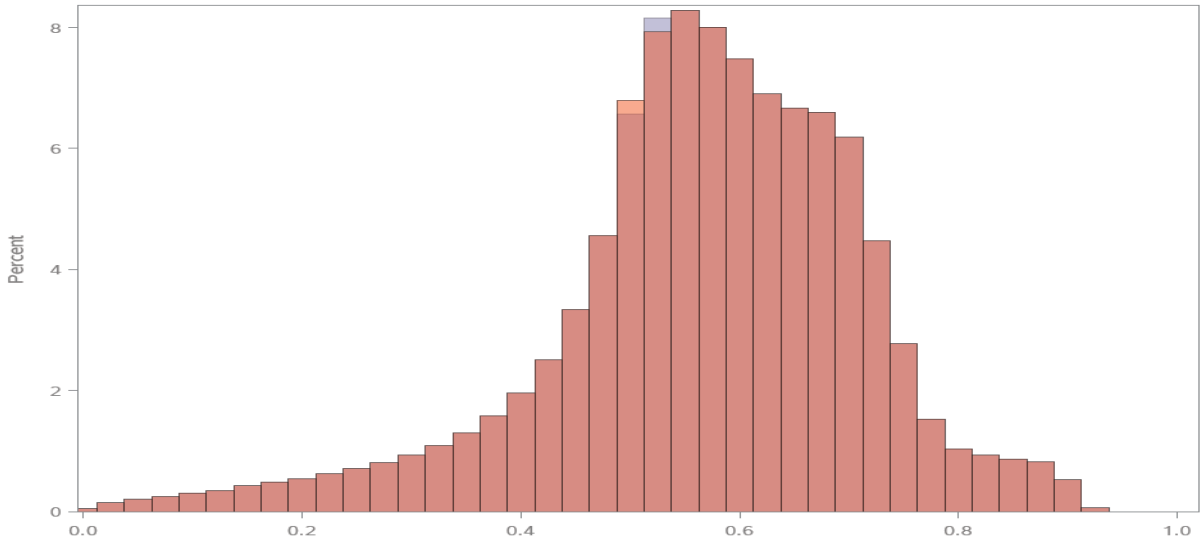
Evaluate Pre-Matching Propensity Score Distributions by Data Partner

- Whether the two cohorts can reasonably be compared (no complete discrimination)
- Analytic cohort for PS stratification



Evaluate Post-Matching Propensity Score Distributions by Data Partner

- Whether matching performs well



Evaluate Baseline Characteristics: Matched Cohort

Characteristic	Medical Product: ACE Inhibitors N	ACE Inhibitors %	Beta Blockers N	Beta Blockers %	Covariate Balance: Difference Absolute	Difference Standardized
Patients (N)	1,029,223	56.0%	1,029,223	77.4%	-	-
Demographics						
Age (mean, std)	52.6	13.3	53	15.6	-0.36	-0.025
Gender (female)	589,675	57.3%	564,570	54.9%	2.44	0.049
Recorded history of						
Allergic reactions	51,720	5.0%	50,639	4.9%	0.11	0.005
Diabetes	114,890	11.2%	113,886	11.1%	0.10	0.003
Heart failure	20,162	2.0%	23,927	2.3%	-0.37	-0.025
Ischemic heart disease	64,070	6.2%	67,646	6.6%	-0.35	-0.014
NSAIDs	153,261	14.9%	151,741	14.7%	0.15	0.004
Selected Health Service Utilization Intensity						
Ambulatory encounters (mean, std)	5.8	7.9	5.8	7.0	0.03	0.004
Emergency room encounters (mean, std)	0.3	0.8	0.3	0.7	-0.01	-0.009
Inpatient hospital encounters (mean, std)	0.1	0.4	0.1	0.4	-0.01	-0.028
Filled prescriptions (mean, std)	9.9	10.2	9.9	10.1	0.08	0.008
Unique drug classes (mean, std)	5.1	3.5	5.1	3.4	0.01	0.004

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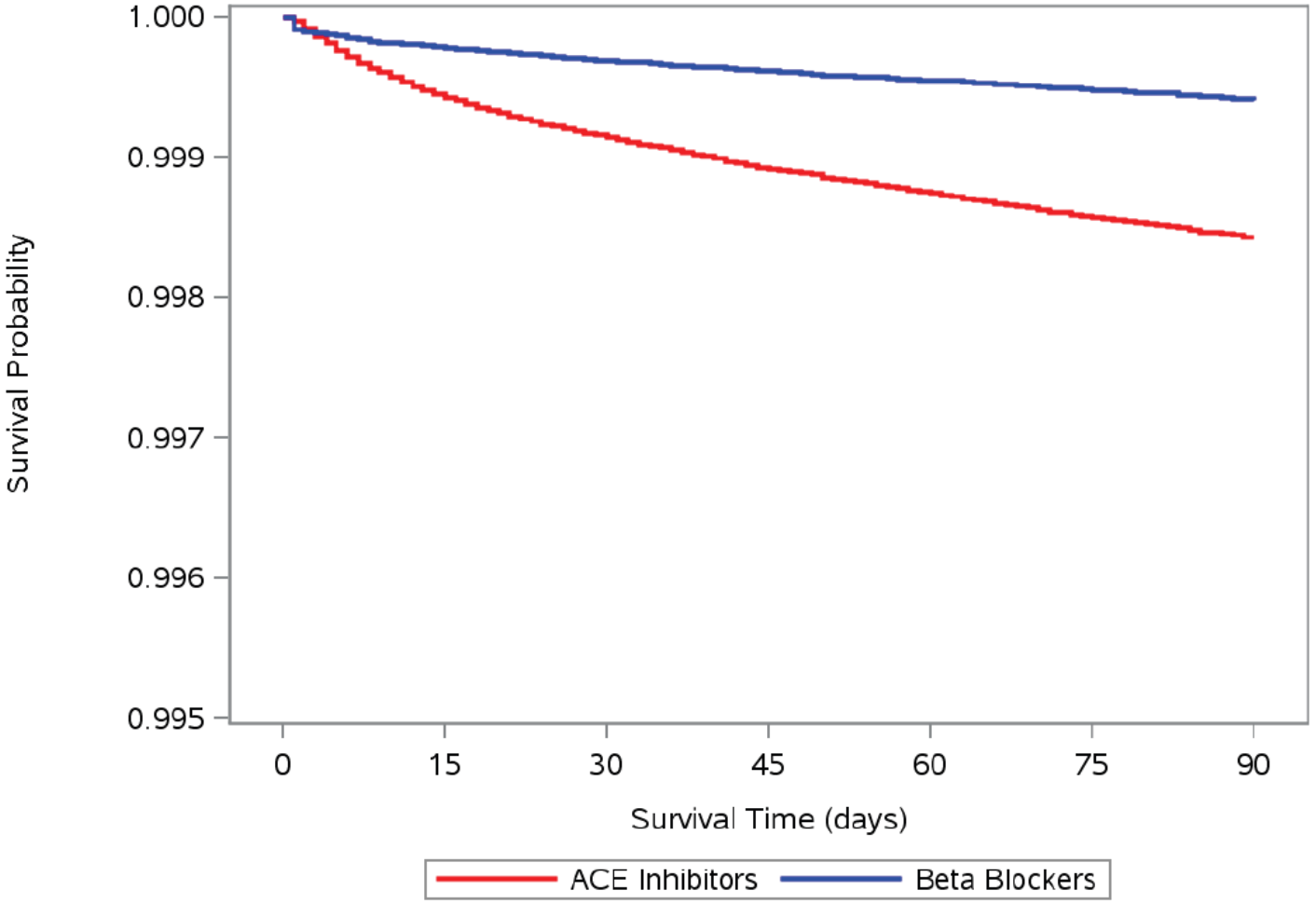
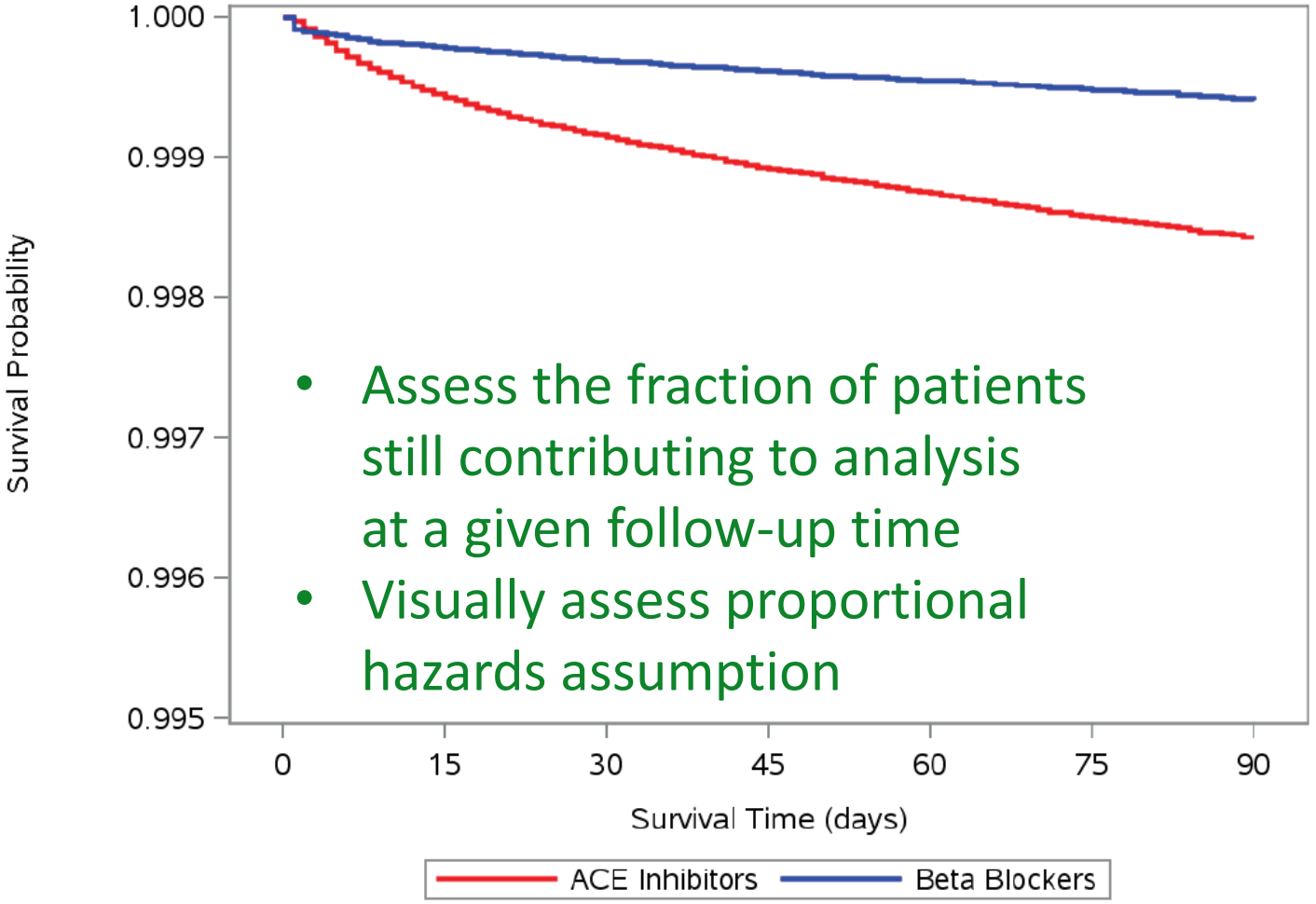
Evaluate Kaplan-Meier Survival Curves

Matched cohort, unconditional



Evaluate Kaplan-Meier Survival Curves

Matched cohort, unconditional



- Assess the fraction of patients still contributing to analysis at a given follow-up time
- Visually assess proportional hazards assumption

What do We Have for PS Strata?

- Pre-matching distributions tell us
  - Distribution of the treatment and comparator exposure groups within each stratum

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Quantile	ACEI	β blocker	Event_ACEI	Event_βblocker	FUTime_ACEI	FUTime_βblocker
Overall	1,838,853	1,330,298	2,345	619	127,413,153	82,500,727
1	181,582	452,248	338	242	11,871,783	27,662,205
2	320,632	313,198	605	130	21,690,394	19,380,254
3	391,912	241,919	499	106	27,078,032	15,185,315
4	448,589	185,242	449	77	31,369,197	11,553,511
5	496,138	137,691	454	64	35,403,747	8,719,442

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- More outputs are in development, including stratum-specific cohort characteristic tables (Table 1s)

Propensity Score Analysis Effect Estimates

Medical Product	New Users	PY at Risk	Average PY at Risk	Events	IR per 1000 PY	Risk per 1000 New Users	IRD per 1000 PY	RD per 1000 New Users	Hazard Ratio (95% CI)	Wald P-Value
Unmatched Analysis (DP Site-adjusted only)										
ACEIs	1,838,853	348,838	0.19	2,345	6.72	1.28	3.98	0.81	**2.54**	<.0001
β-Blockers	1,330,298	225,875	0.17	619	2.74	0.47			**(2.33, 2.78)**	
1:1 Matched Unconditional Analysis										
ACEIs	1,029,223	192,920	0.19	1,530	7.93	1.49	5.34	1.04	**3.15**	<.0001
β-Blockers	1,029,223	175,437	0.17	455	2.59	0.44			**(2.83, 3.49)**	
Stratified Percentile Analysis										
ACEIs	1,838,853	348,838	0.19	2,345	6.72	1.28	3.98	0.81	**3.05**	<.0001
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1:1 Ma										
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Stratif										
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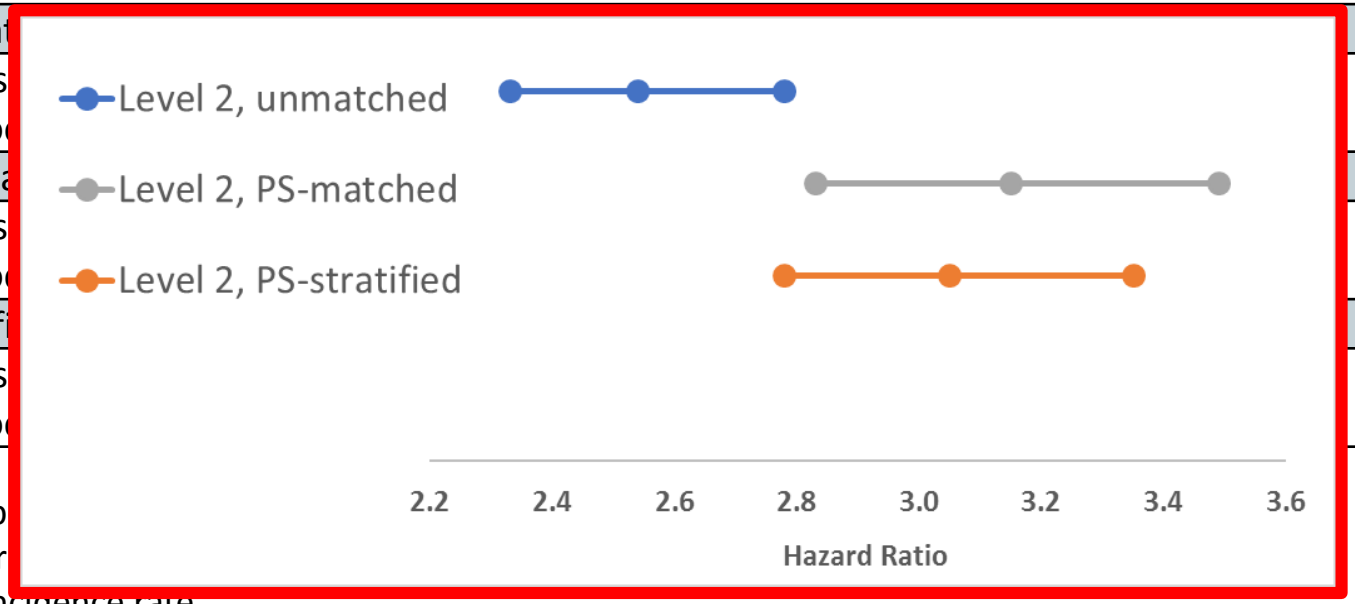

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Effect Estimates with Tool Comparable to Previous Studies

Table 2. Angioedema and Serious Angioedema Events by Study Drug Use During a Maximal Follow-up Period of 365 Days, 2001-2010

Drug	No. of Events	No. of Exposed Persons	No. of Exposed Person-Years	Value (95% CI)		HR (95% CI)	
				Cumulative Incidence per 1000 Persons	Incidence Rate per 1000 Person-Years	Site Adjusted	Propensity Score Adjusted
Angioedema							
ACEIs	3301	1 845 138	753 105.4	1.79 (1.73-1.85)	4.38 (4.24-4.54)	2.77 (2.57-2.98)	3.04 (2.81-3.27)
ARBs	288	467 313	173 437.9	0.62 (0.55-0.69)	1.66 (1.47-1.86)	1.11 (0.97-1.28)	1.16 (1.00-1.34)
Candesartan	4	12 286	4177.0	0.33 (0.09-0.83)	0.96 (0.26-2.45)	0.91 (0.34-2.43)	0.95 (0.35-2.55)
Eprosartan	0	1165	392.3				
Irbesartan	24	44 094	15 997.7	0.54 (0.35-0.81)	1.50 (0.96-2.23)	1.05 (0.70-1.58)	1.11 (0.73-1.67)
Losartan potassium	94	106 522	41 230.2	0.88 (0.71-1.08)	2.28 (1.84-2.79)	1.48 (1.20-1.84)	1.53 (1.23-1.90)
Olmesartan	39	92 973	30 170.1	0.42 (0.30-0.57)	1.29 (0.92-1.77)	0.84 (0.60-1.16)	0.88 (0.63-1.22)
Telmisartan	11	26 530	8177.9	0.42 (0.21-0.74)	1.35 (0.67-2.41)	0.83 (0.45-1.50)	0.86 (0.47-1.56)
Valsartan	110	183 743	69 397.0	0.60 (0.49-0.72)	1.59 (1.30-1.91)	1.04 (0.85-1.28)	1.08 (0.88-1.34)
Aliskiren	7	4867	1498.1	1.44 (0.58-2.96)	4.67 (1.88-9.63)	2.75 (1.30-5.81)	2.85 (1.34-6.04)
β-Blockers	915	1 592 278	548 684.3	0.58 (0.54-0.61)	1.67 (1.56-1.78)	1 [Reference]	1 [Reference]
Serious Angioedema							
ACEIs	326	1 845 138	753 581.4	0.18 (0.16-0.20)	0.43 (0.39-0.48)	4.42 (3.29-5.96)	4.91 (3.62-6.65)
ARBs	10	467 313	173 511.8	0.02 (0.01-0.04)	0.06 (0.03-0.11)	0.52 (0.26-1.05)	0.56 (0.28-1.14)
Candesartan	0	12 286	4178.5				
Eprosartan	0	1165	392.3				
Irbesartan	0	44 094	16 002.4				
Losartan	3	106 522	41 255.2	0.03 (0.01-0.08)	0.07 (0.02-0.21)	0.97 (0.30-3.18)	1.01 (0.31-3.34)
Olmesartan	1	92 973	30 179.7	0.01 (0.00-0.06)	0.03 (0.00-0.19)	0.80 (0.10-6.20)	0.83 (0.11-6.57)
Telmisartan	0	26 530	8180.2				
Valsartan	6	183 743	69 425.1	0.03 (0.01-0.07)	0.09 (0.03-0.19)	1.05 (0.43-2.56)	1.14 (0.46-2.82)
Aliskiren	1	4867	1499.4	0.21 (0.01-1.14)	0.67 (0.03-3.72)	8.67 (1.11-67.62)	8.84 (1.13-69.41)
β-Blockers	51	1 592 278	548 953.6	0.03 (0.02-0.04)	0.09 (0.07-0.12)	1 [Reference]	1 [Reference]

Toh et al. Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System. *Arch Intern Med*. 2012;172:1582-1589

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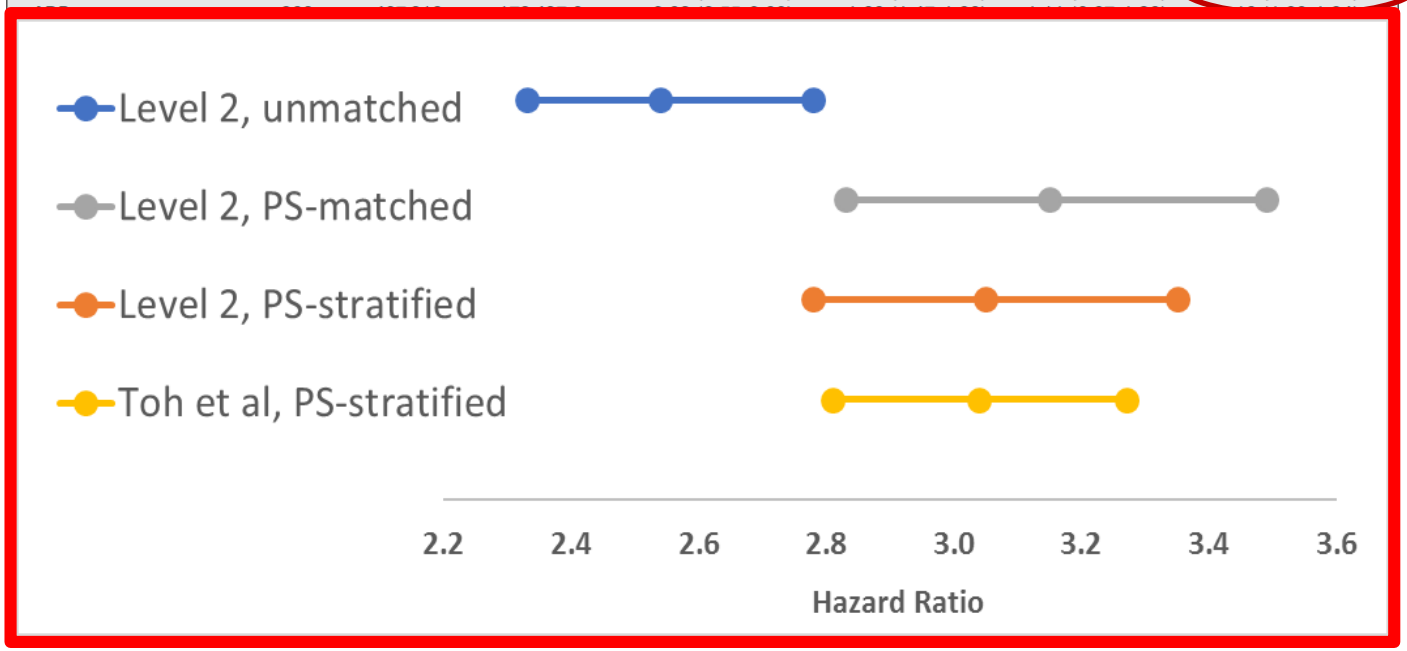

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Summary

- The Sentinel Propensity Score Analysis Tool builds in two propensity score methods – matching and stratification
  - Generalizability: matched versus entire user cohorts
  - Precision in effect estimates
- Standard outputs include
  - Simple diagnostics
  - Hazard ratios and 95% confidence intervals
- Always ready to use in data formatted to Sentinel Common Data Model
- Program packages are publicly available

ARTICLES

Successful Comparison of US Food and Drug Administration Sentinel Analysis Tools to Traditional Approaches in Quantifying a Known Drug-Adverse Event Association

JJ Gagne[1], X Han[2], S Hennessy[2], CE Leonard[2], EA Chrischilles[3], RM Carnahan[3], SV Wang[1], C Fuller[4], A Iyer[4], H Katcoff[4], TS Woodworth[4], P Archdeacon[5], TE Meyer[6], S Schneeweiss[1] and S Toh[4]

The US Food and Drug Administration's Sentinel system has developed the capability to conduct active safety surveillance of marketed medical products in a large network of electronic healthcare databases. We assessed the extent to which the newly developed, semiautomated Sentinel Propensity Score Matching (PSM) tool could produce the same results as a customized protocol-driven assessment, which found an adjusted hazard ratio (HR) of 3.04 (95% confidence interval [CI], 2.81–3.27) comparing angioedema in patients initiating angiotensin-converting enzyme (ACE) inhibitors vs. beta-blockers. Using data from 13 Data Partners between 1 January 2008, and 30 September 2013, the PSM tool identified 2,211,215 eligible ACE inhibitor and 1,673,682 eligible beta-blocker initiators. The tool produced an HR of 3.14 (95% CI, 2.86–3.44). This comparison provides initial evidence that Sentinel analytic tools can produce findings similar to those produced by a highly customized protocol-driven assessment.

Gagne et al. *Clin Pharmacol Ther.* 2016 Nov; 100(5):558-564.

Questions?

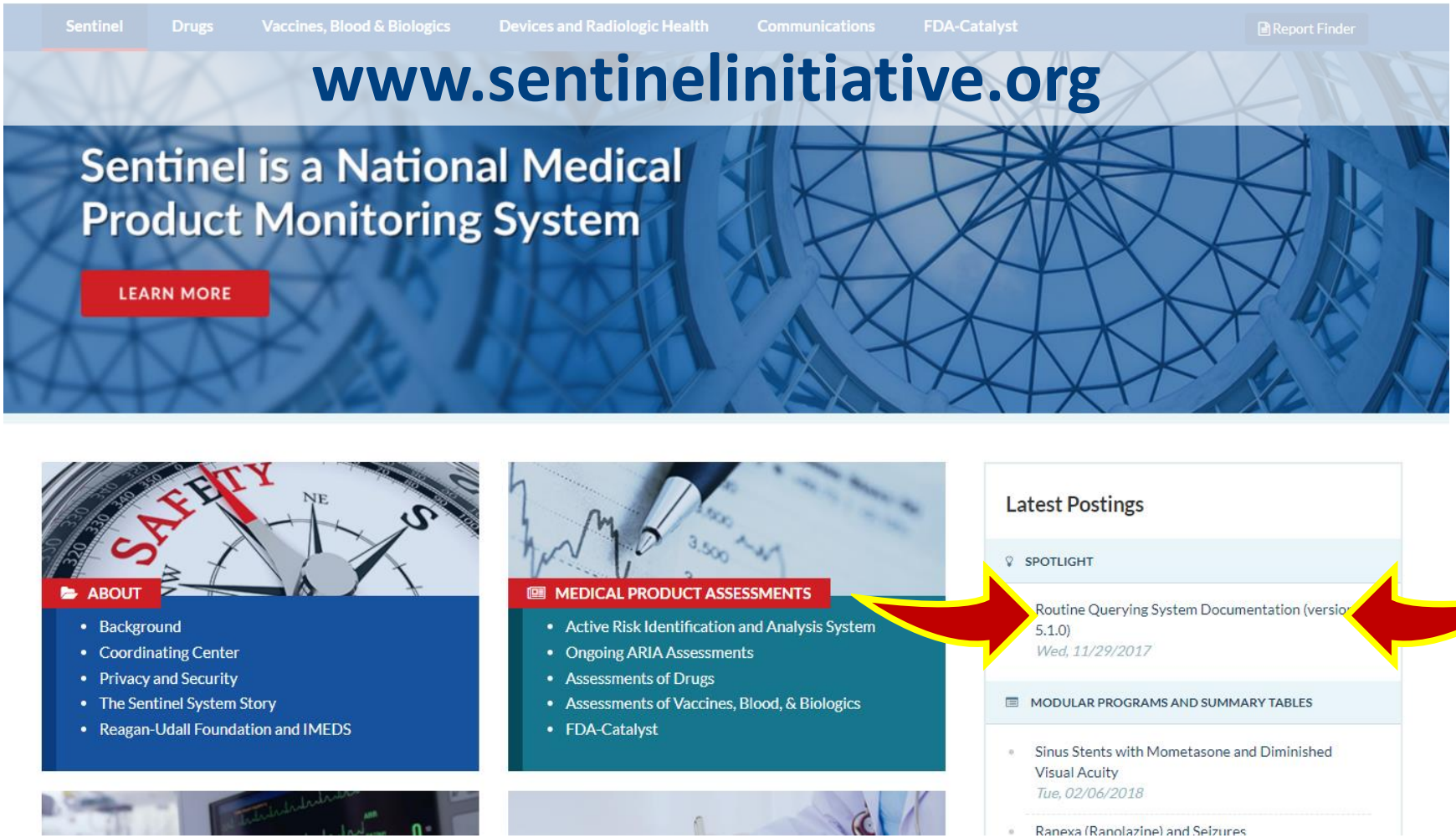
Break

Self-Controlled Risk Interval Tool

Justin Bohn, ScD[1]

[1]Harvard Medical School and Harvard Pilgrim Health Care Institute

How to Access the Routine Querying Tools



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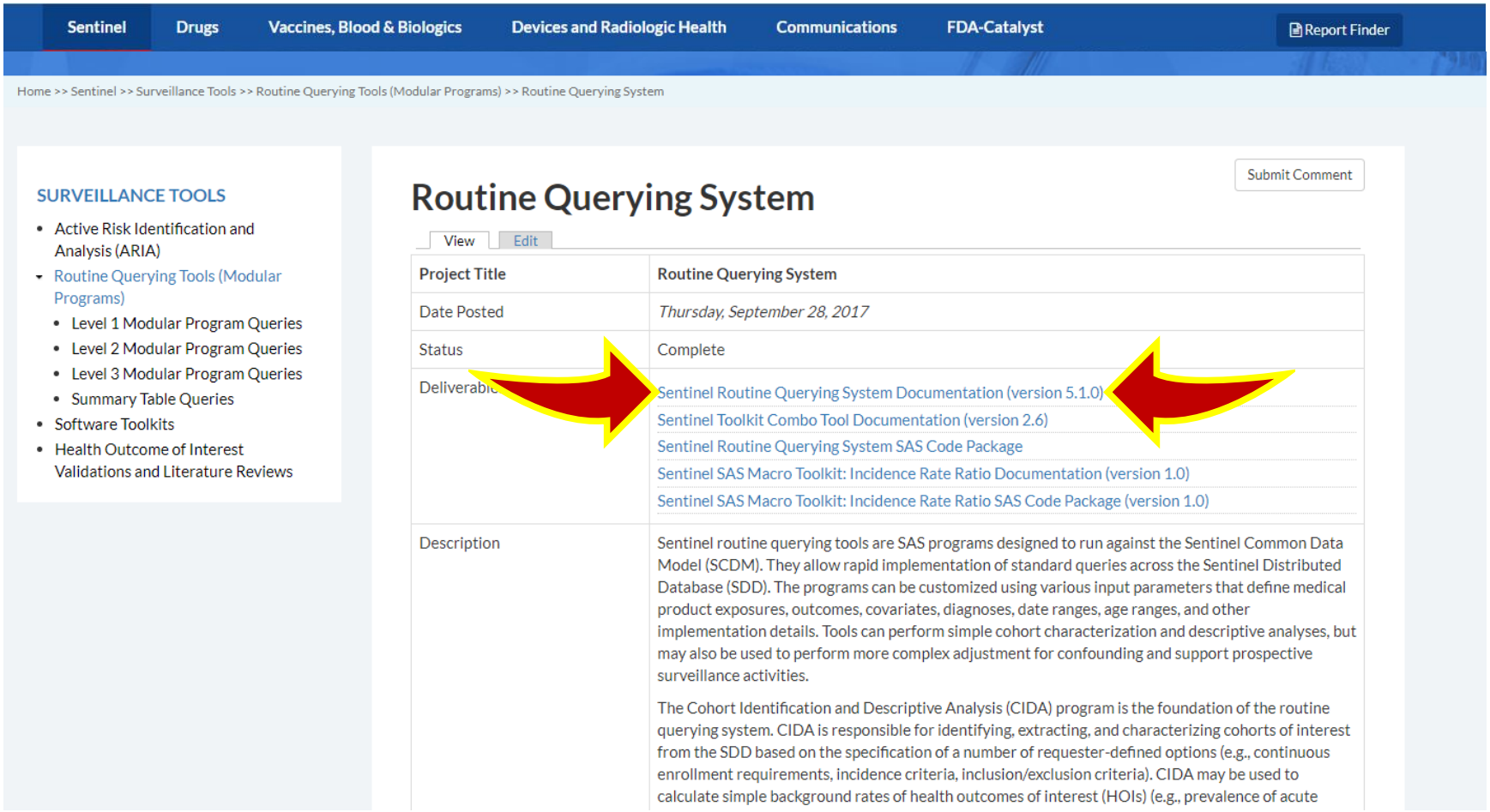

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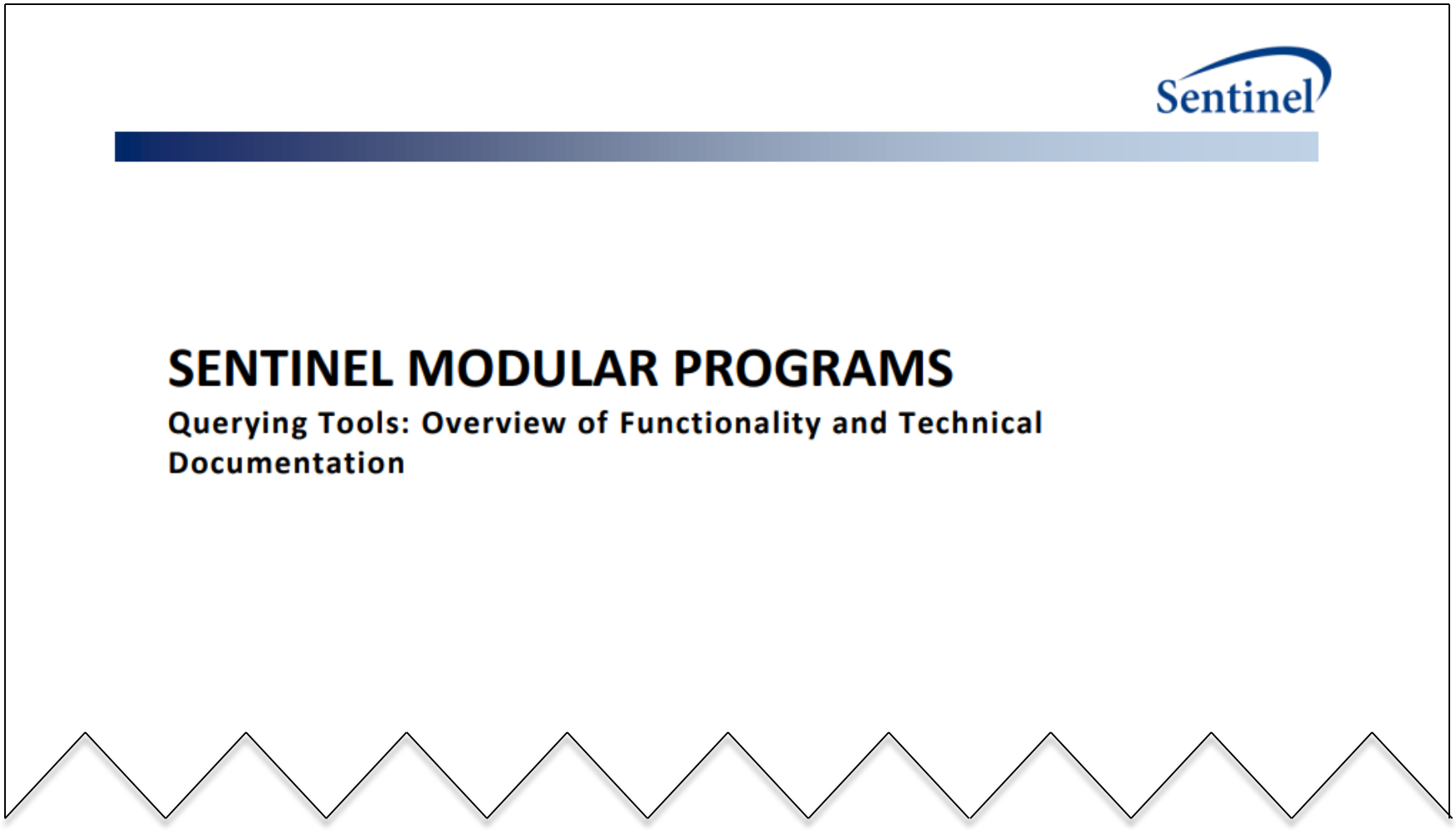


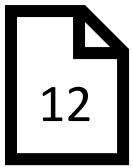
How to Access the Routine Querying Tools

means that if an individual has 5 index dates in step (1), and the first 3 aren't valid (no inclusion criteria, doesn't meet enrollment requirements, etc.), the 4th index date is still eligible for inclusion when only the first valid index date per individual during the query period is requested.

SELF-CONTROLLED RISK INTERVAL (SCRI) DESIGN COHORT IDENTIFICATION STRATEGY

The self-controlled risk interval (SCRI) design cohort identification strategy defines new use of a medical product of interest, identifies a risk and control window relative to exposure, and examines the occurrence of HOIs. Risk and control windows may be of the same or different duration, and the control window may be specified before exposure or after the risk window. To avoid bias by contraindication, requesters specifying a control window before exposure should have confidence that the occurrence of an HOI does not influence receipt of treatment.[3]

Two cohorts are identified using the self-controlled design: an exposure cohort and an analytic cohort. The exposure cohort includes patients with the exposure of interest that meet cohort inclusion criteria; the analytic cohort is a subset of the exposure cohort that includes patients that also have an HOI during the risk and/or control windows and sufficient post-exposure continuous enrollment.



Agenda

- ARIA workflow
- Level 2 capabilities in ARIA
- Case study: Contrast MRI/MRA and seizure
- SCRI design
  - Defining a cohort
  - Choosing risk and control windows
  - Analysis
- Differentiating case-only designs

ARIA Workflow

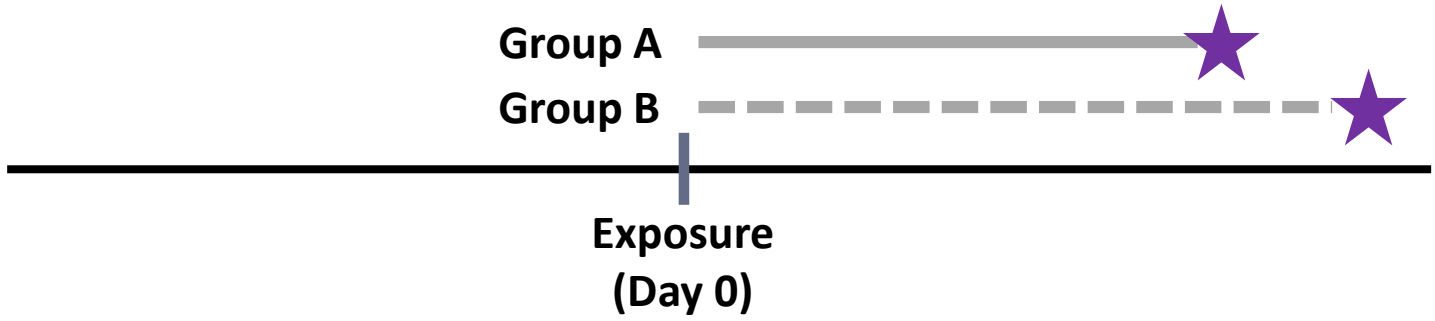
- ARIA is Sentinel's routine query/analysis framework
  - **A**ctive **R**isk **I**dentification and **A**nalysis
  - Modular SAS programs identify populations of interest, characterize them, and perform comparative assessments
  - No *new* code needs to be written
- ARIA performs three levels of analysis
  - **Level 1:** descriptive or comparative without adjustment
  - **Level 2:** comparative, with adjustment
  - **Level 3:** comparative, with adjustment and sequential monitoring

Level 2 Capabilities in ARIA

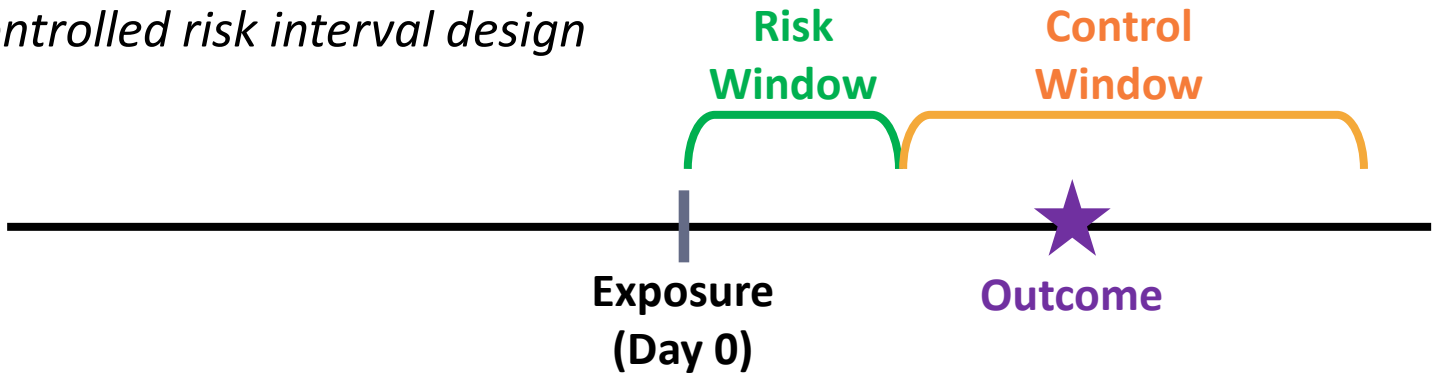
- Propensity score matching and stratification
  - New user cohort design
  - Explicit control of non-time-varying confounding
  - Observational analogue of RCT
  - Asks "*why does this happen to them?*"
- Self-controlled risk interval (SCRI)
  - New user, case-only design
  - Implicit control of non-time-varying confounding
  - Useful for studying acute effects of intermittent exposures
  - Asks "*why does this happen now?*"

Motivating the SCRI Design

New user cohort design



Self-controlled risk interval design



Motivating the SCRI Design

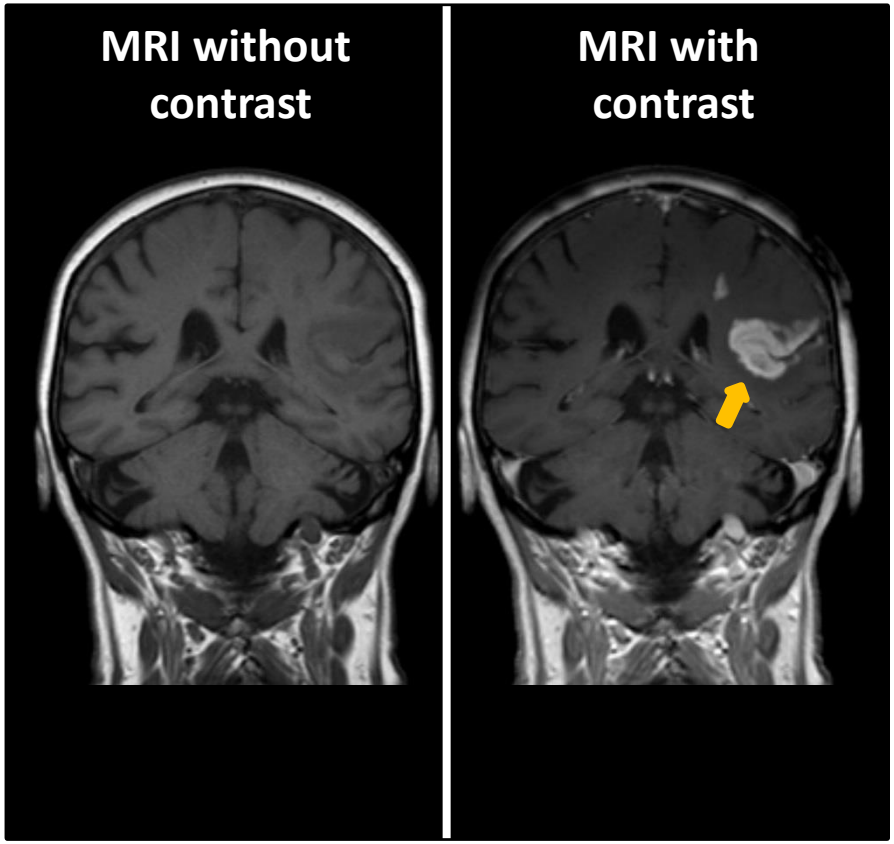
- **S**elf-**C**ontrolled **R**isk **I**nterval
  - Created to study vaccine safety
  - Special case of Self-Controlled Case Series method
- Several relevant issues
  - Lack of appropriate comparator group
  - Events are rare
  - Pooling of multiple data sources may be required
- Need a design that is
  - **Self-controlled**: no between-person confounding
  - **Efficient**: does not require follow-up of large # of patients
  - **Privacy-preserving**: can be performed on aggregated data from multiple sources without identifying patients

Case Study:
Contrast MRI/MRA* and Seizure

*Magnetic resonance imaging/angiography

Contrast MRI

- Gadolinium (Gd) is a rare earth metal
  - Paramagnetic at room temperature
- Commonly used in MRI contrast agents to enhance images
  - "Picture Juice"
- Contrast agent injected prior to scan



P. Hellerhoff (2010)

Contrast MRI and Seizures

- Concern about seizure triggering
  - Biologically plausible[1]
  - Evidence from animal studies[2]
  - Limited clinical evidence[3-4]
  - Series of 183 FDA Adverse Event Reporting System (FAERS) reports of seizure within one hour of contrast MRI[5]
    - Some seizures were fatal

1 Montagne A et al. JAMA Neurol 2016;73(1):13-14.
2 Muldoon LL et al. Radiology 2015;277(3):925-6.
3 Ray DE et al. AJNR Am J Neuroradiol 1996;17(2):365-73.
4 Kapoor R et al. Pain Physician 2010;13(5):E321-6.
5 Safriel Y et al. AJNR Am J Neuroradiol 2006;27(6):1194-7.

Radiology. 2015 Jun;275(3):772-82. doi: 10.1148/radiol.15150025. Epub 2015 Mar 5.

Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging.

McDonald RJ[1], McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ.

Author information

Abstract

PURPOSE: To determine if repeated intravenous exposures to gadolinium-based contrast agents (GBCAs) are associated with neuronal tissue deposition.

MATERIALS AND METHODS: In this institutional review board-approved single-center study, signal intensities from T1-weighted magnetic resonance (MR) images and postmortem neuronal tissue samples from 13 patients who underwent at least four GBCA-enhanced brain MR examinations between 2000 and 2014 (contrast group) were compared with those from 10 patients who did not receive GBCA (control group). Antemortem consent was obtained from all study participants. Neuronal tissues from the dentate nuclei, pons, globus pallidus, and thalamus of these 23 deceased patients were harvested and analyzed with inductively coupled plasma mass spectrometry (ICP-MS), transmission electron microscopy, and light microscopy to quantify, localize, and assess the effects of gadolinium deposition. Associations between cumulative gadolinium dose, changes in T1-weighted MR signal intensity, and ICP-MS-derived tissue gadolinium concentrations were examined by using the Spearman rank correlation coefficient (ρ).

RESULTS: Compared with neuronal tissues of control patients, all of which demonstrated undetectable levels of gadolinium, neuronal tissues of patients from the contrast group contained 0.1-58.8 μg gadolinium per gram of tissue, in a significant dose-dependent relationship that correlated with signal intensity changes on precontrast T1-weighted MR images (ρ = 0.49-0.93). All patients in the contrast group had relatively normal renal function at the time of MR examination. Gadolinium deposition in the capillary endothelium and neural interstitium was observed only in the contrast group.

CONCLUSION: Intravenous GBCA exposure is associated with neuronal tissue deposition in the setting of relatively normal renal function. Additional studies are needed to investigate the clinical significance of these findings and the generalizability to other GBCAs. Online supplemental material is available for this article.

Assessing ARIA Sufficiency for SCRI

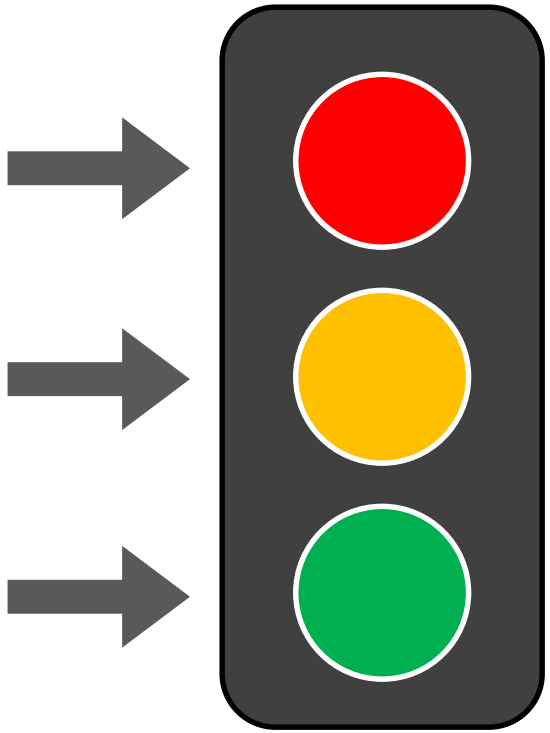
Recall the Framework

- Stoplight provided as simple metric
- Describes Sentinel's current capabilities to support specific topics

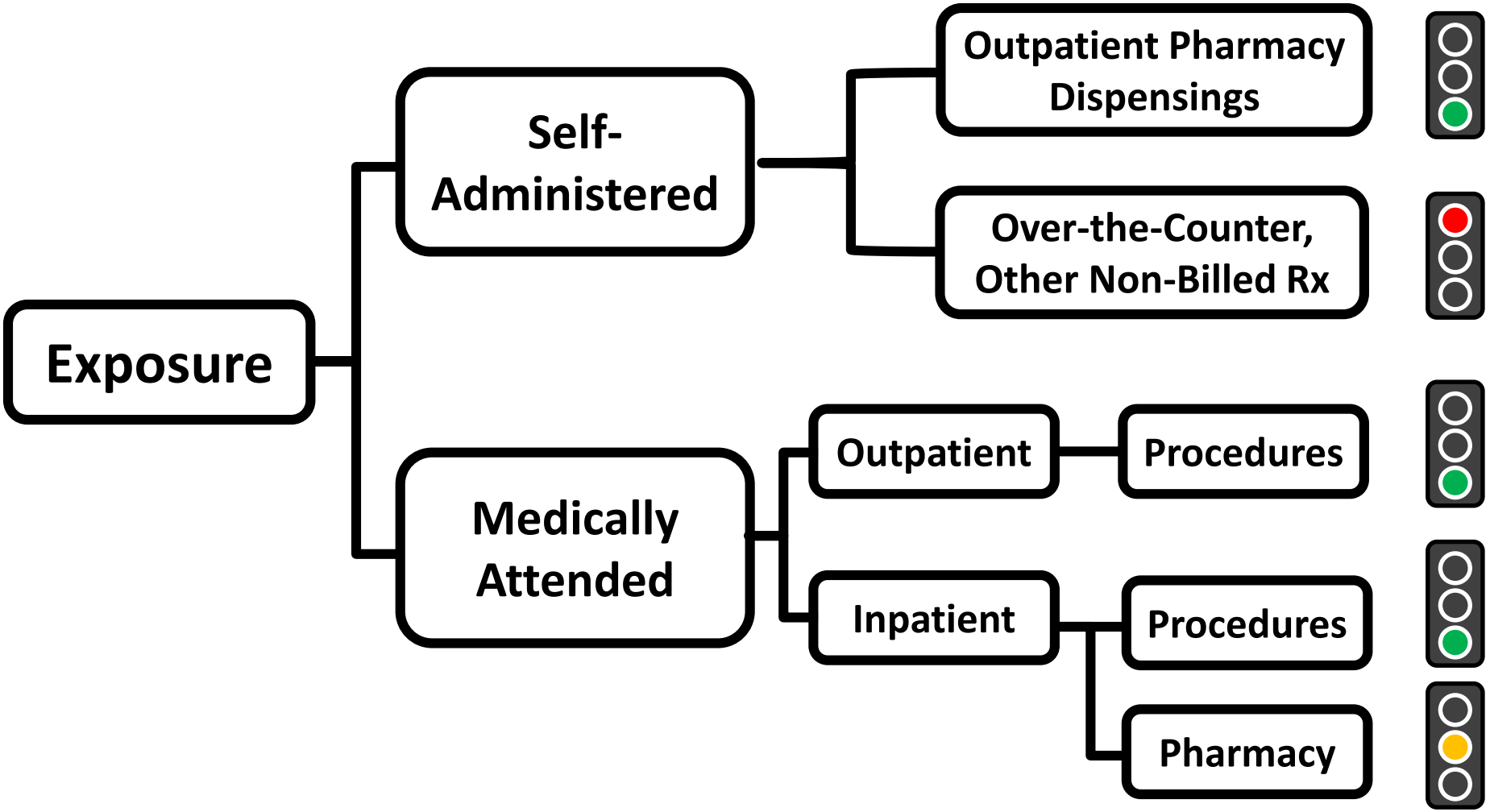
Cannot currently support using existing data and tools

Possible, but warrants further discussion

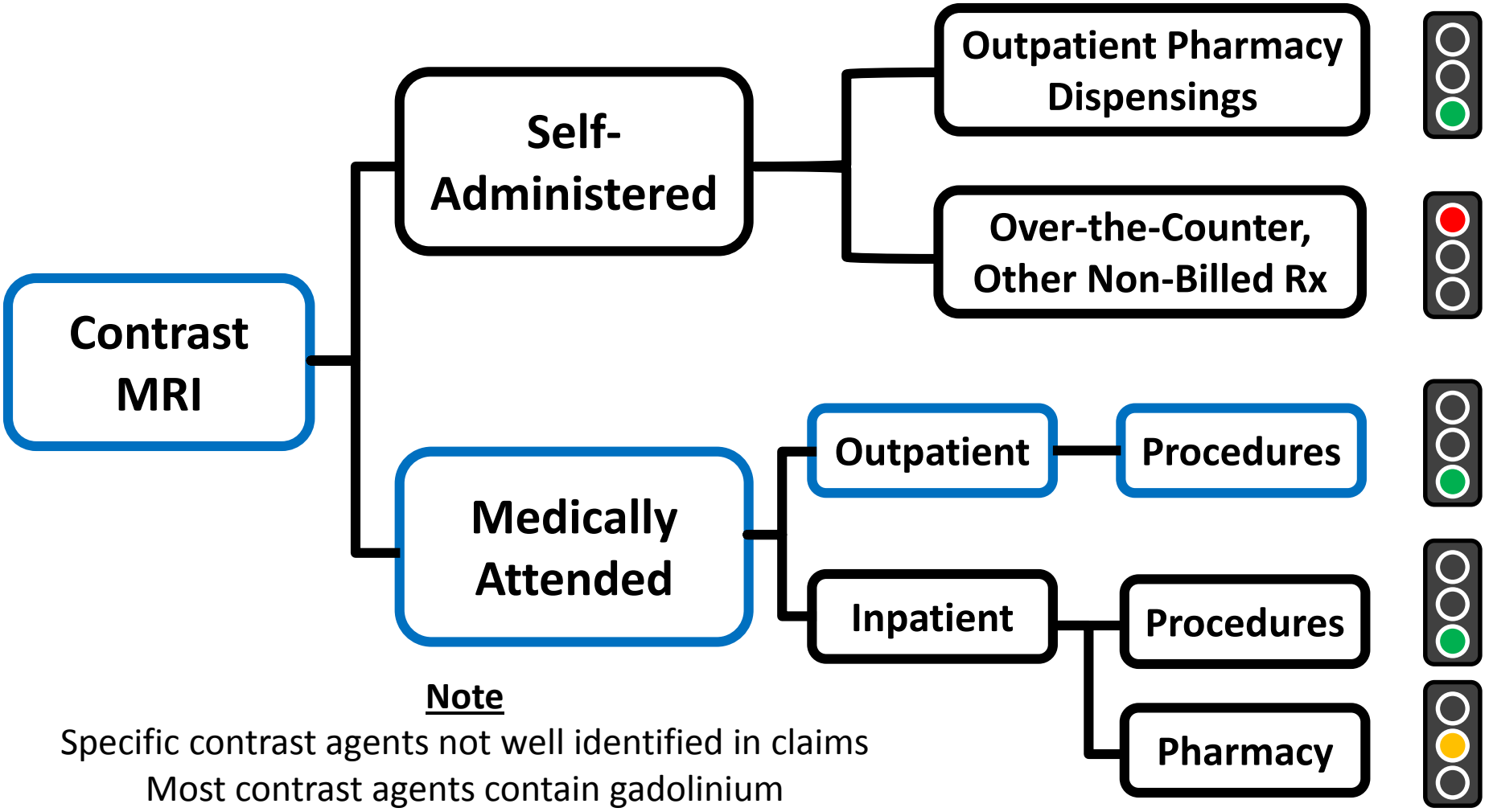
Works well under most circumstances



Exposure Sufficiency



Contrast MRI is a medically-attended outpatient procedure with well-defined administrative codes



Note

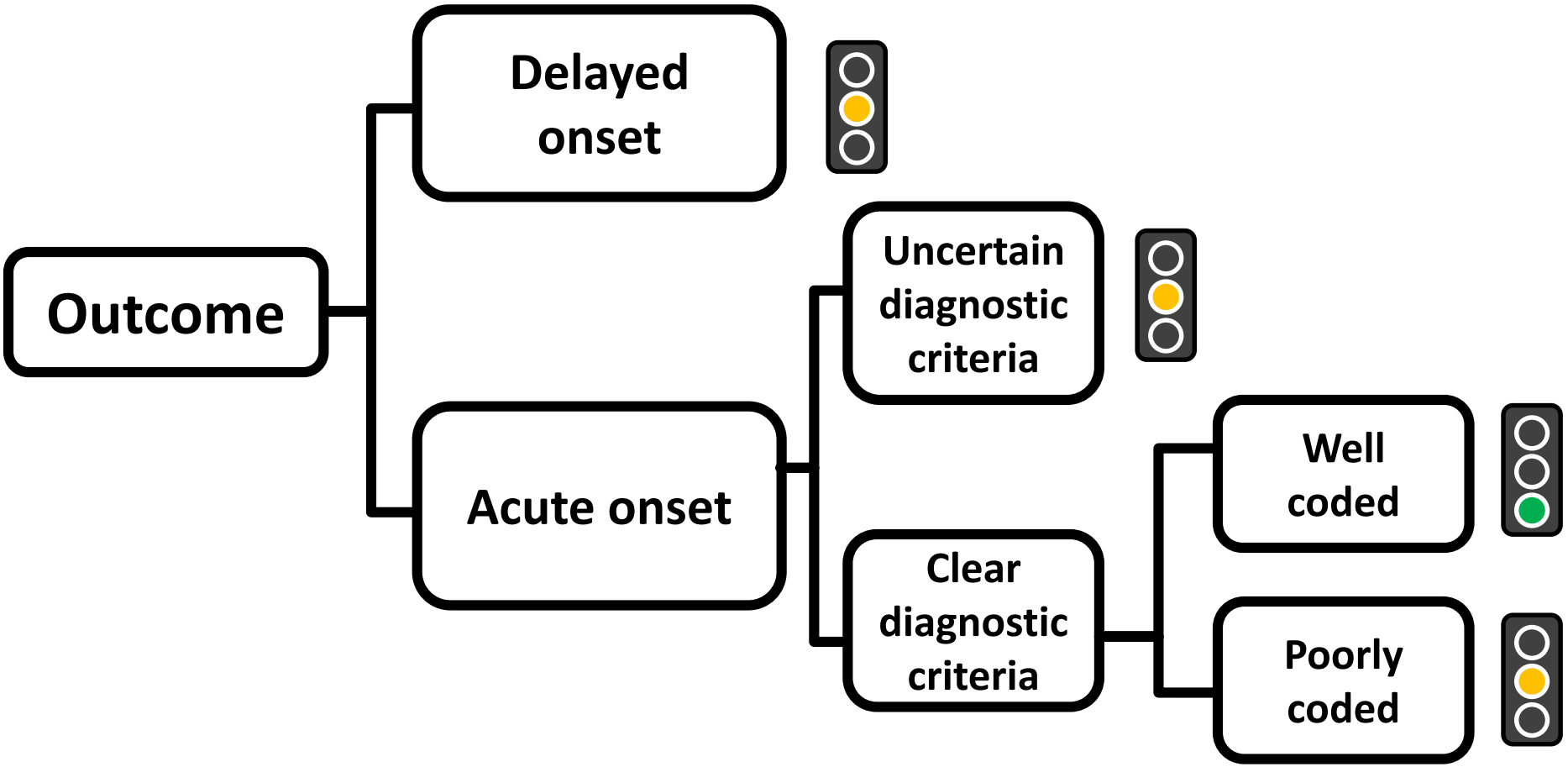
Specific contrast agents not well identified in claims

Most contrast agents contain gadolinium

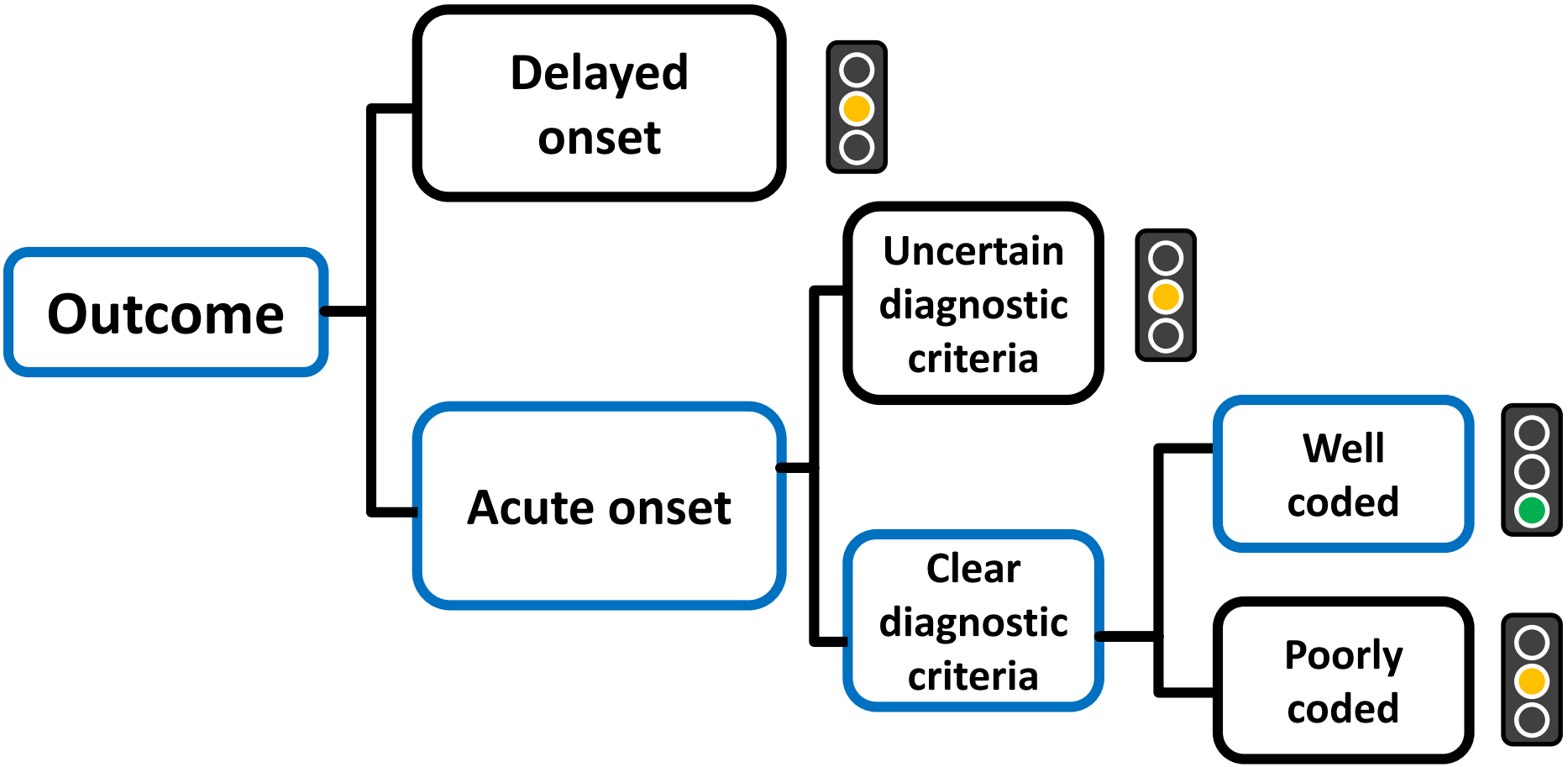
Case Study: Cohort-Defining Exposure

- Four exposures categories of interest
  - **Contrast MRI/MRA** during ambulatory visit
    - Any type
    - Non-extremity (e.g., pelvis, torso, head/neck)
    - Extremity (e.g., arm, leg)
  - **Non-contrast MRI/MRA** during ambulatory visit
    - Negative control exposure
- All defined by procedure codes during an ambulatory visit
- SCRI analysis run separately for each category

Outcome Sufficiency



Seizure is an acute-onset event with clear diagnostic criteria and well-defined administrative codes



Case Study: Outcome Definition

- Seizure, defined in ICD as:
  - Epilepsy (345, 345.X, 345.XX, some ICD-10 G40 codes), or
  - Convulsion (780.3, 780.3X, R56.00, R56.01, R56.9)
- In either of two care settings
  - Emergency department visit
  - Inpatient stay (as primary diagnosis)
- PPV for confirmed seizure 79%-99%
- First in prior 183 days
  - Outcome incidence relative to itself, <u>not exposure</u>

When to Use a SCRI Design

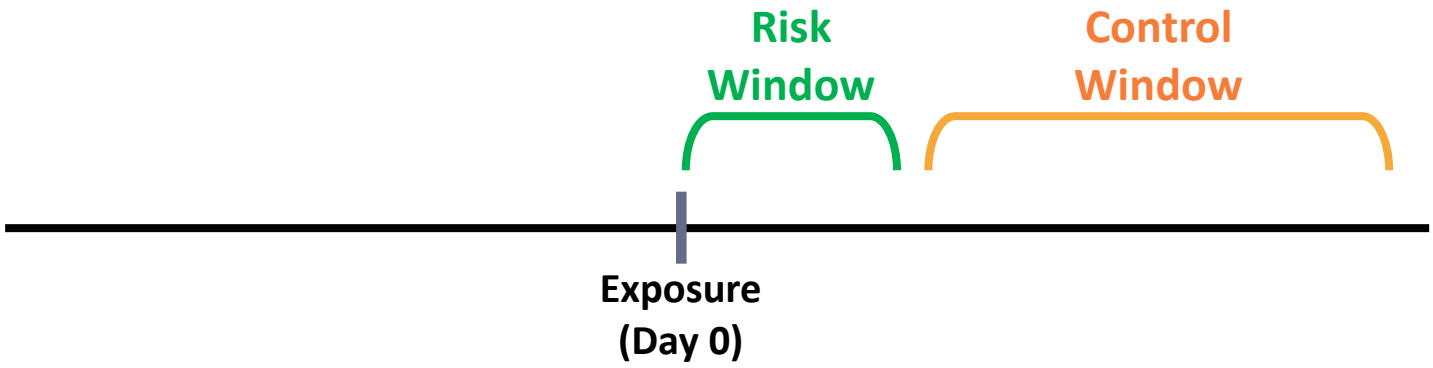
- Exposure **must** be
  - Fixed event
  - Identifiable in claims
  - Accurately dated
- Outcome **must** be
  - Acute onset
  - Identifiable in claims
  - Accurately dated

Bad Examples

- Continuous use of a drug
- OTC products
- Procedure/diagnosis during hospitalization
- Parkinson's disease
- Cause-specific mortality
- Procedure/diagnosis during hospitalization

SCRI Design

Specifying a SCRI Study



Identify exposed individuals

Define biologically relevant **risk** and **control** windows

Restrict to those experiencing outcome in either window

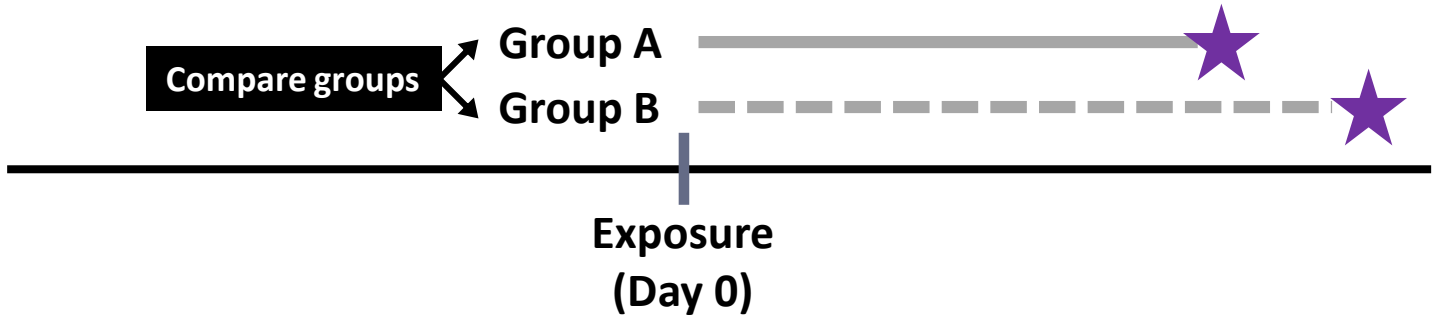
Compare outcome frequency in risk window to control window

SCRI and Confounding

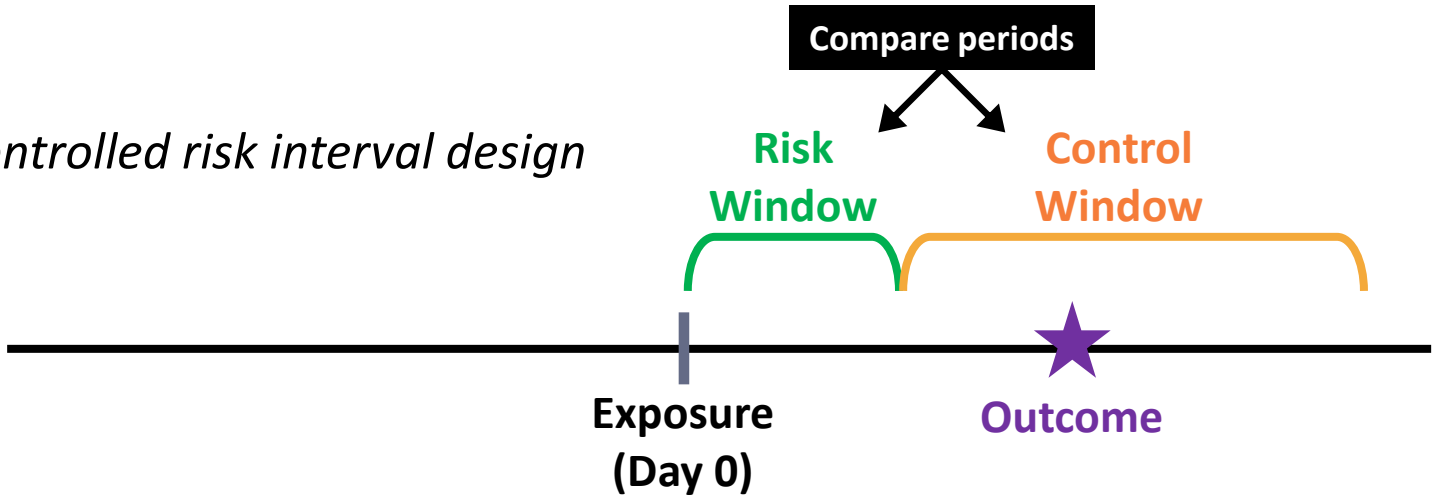
- Comparison is between *periods*, not *persons*
- Each patient serves as own control
  - Adjusts for measured and unmeasured confounders *that don't vary over time*
- Susceptible to time-varying confounding
  - Seasonality in exposure and outcome
  - Relatively small changes in age among children
  - Common triggers of exposure and outcome
    - E.g., PPSV before splenectomy

SCRI and Confounding

New user cohort design



Self-controlled risk interval design



Contrast MRI and Seizure: Why SCRI?

- Want to know if contrast MRI **triggers** seizures
  - Acute outcome occurrence
  - Risk window → day of MRI
- Issues identifying comparator group
  - In cohort, who would serve as unexposed?
  - Comparison to non-scanned not possible in ARIA
- If contrast MRI is triggering, should see higher incidence soon after scan

Defining a Cohort

Traditional components

- *Study period*
- *Cohort-defining exposure* ✓
  - Washout period
- *Baseline period*
  - Inclusion criteria
  - Exclusion criteria
- *Outcome definition* ✓
  - Incidence criteria

SCRI-specific components

- *Risk window*
  - Start
  - End
- *Control window*
  - Start
  - End

Case Study: Inclusion/Exclusion Criteria

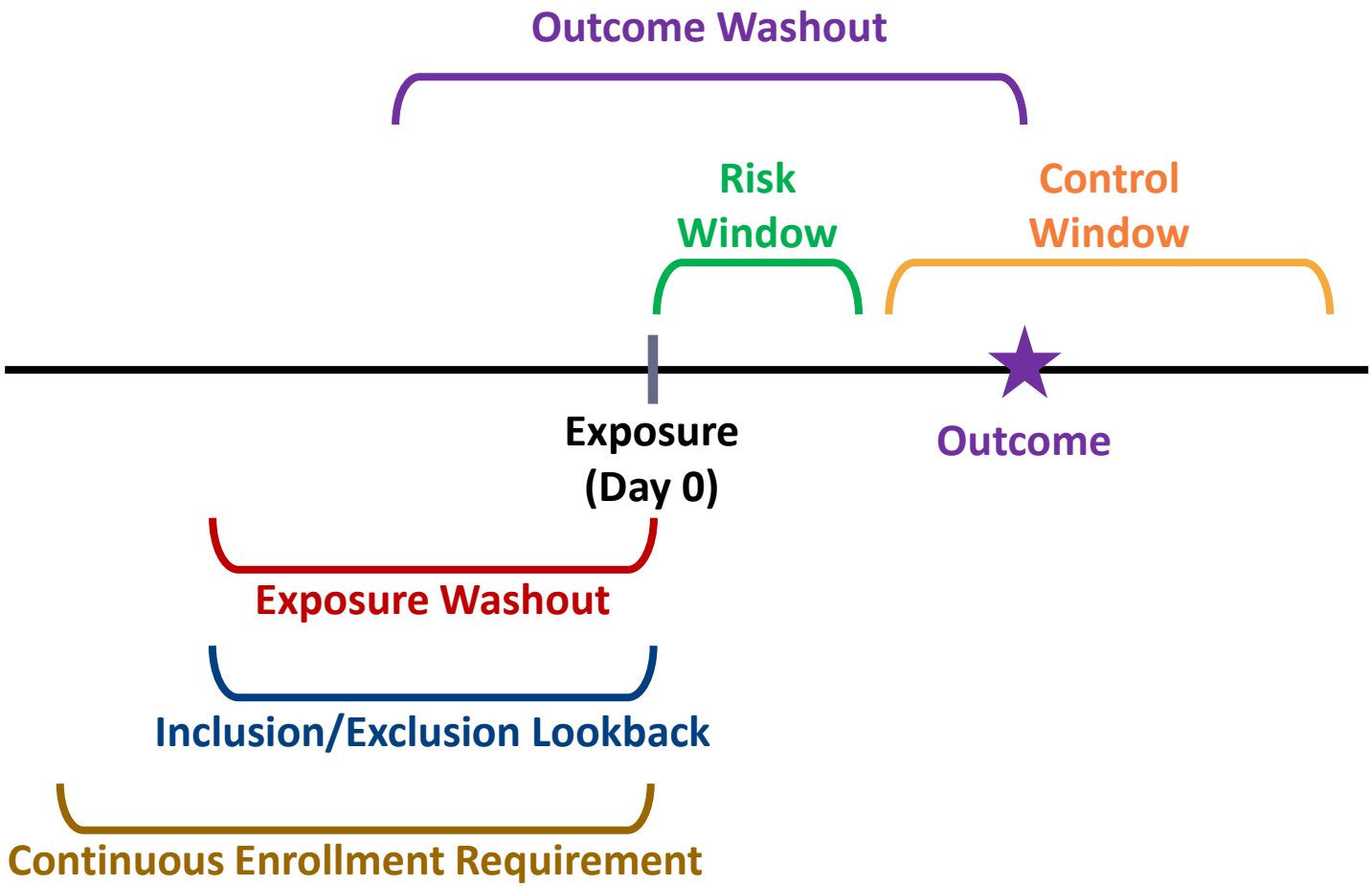
Inclusion

- Cohort-defining exposure (MRI/MRA) during 2008-2016
- Age ≥ 2 years at MRI/MRA
- Continuous enrollment for ≥ 183 days before MRI/MRA

Exclusion

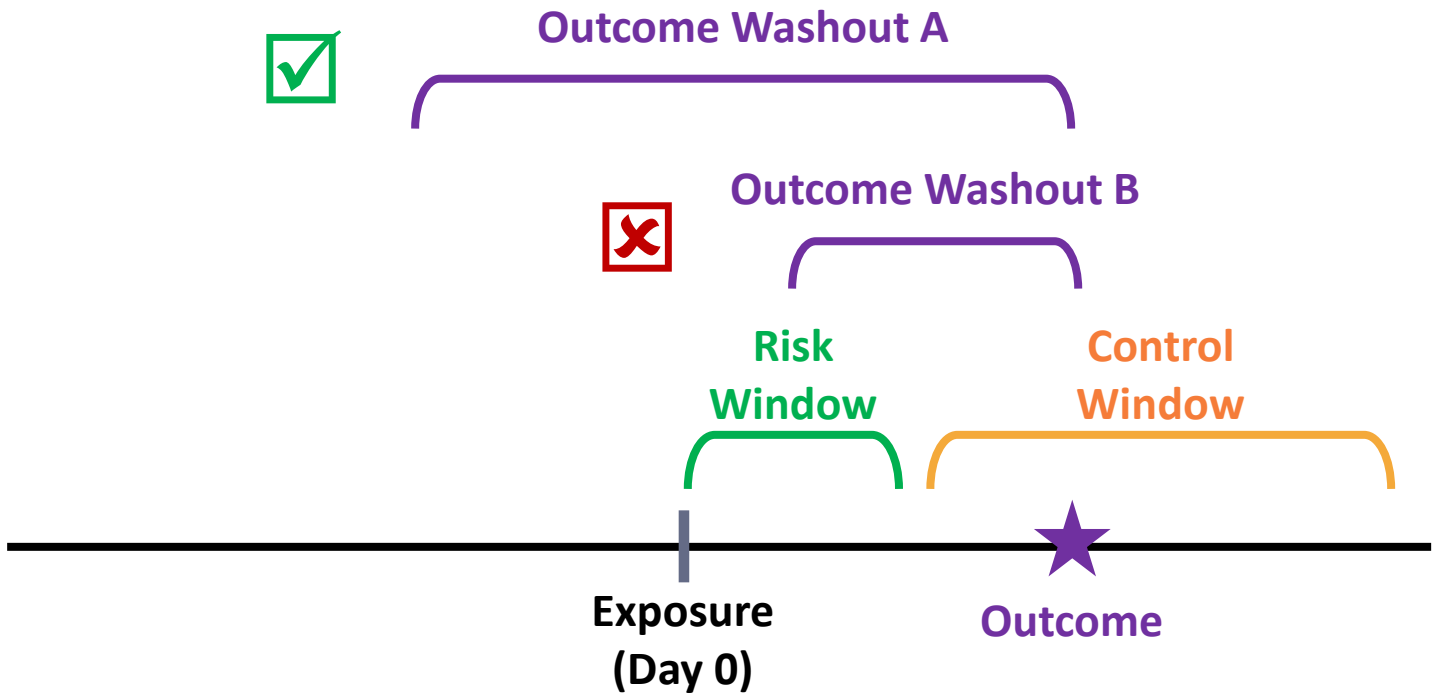
- Same day scan
  - Head MRI or head CT
- History in 183 days MRI/MRA of:
  - MRI/MRA, seizures, epilepsy, antiepileptic drug use, myocardial infarction, stroke, syncope, brain tumor, Alzheimer's, Autism, overdose, head injury, brain compression, kidney disease, or drug dependency

Defining SCRI Input Parameters in ARIA



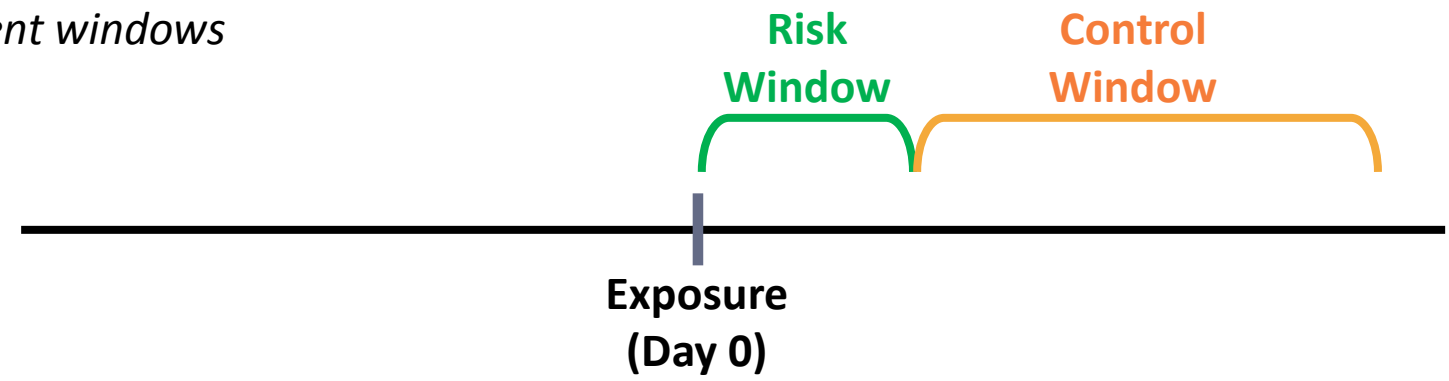
Minimum Outcome Washout Periods

- In order to prevent patients from contributing events in both the risk and control windows, need appropriate washout

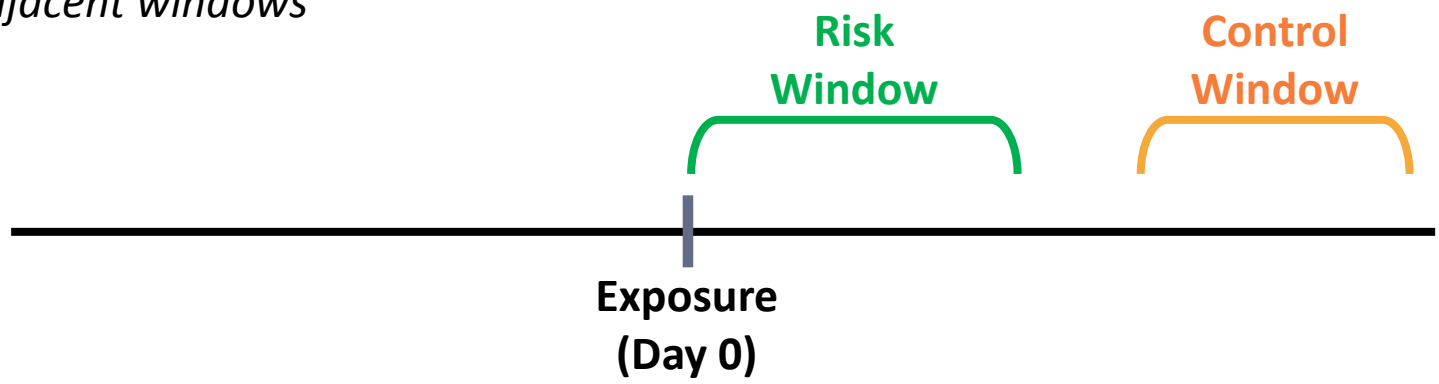


Window Placement

Adjacent windows

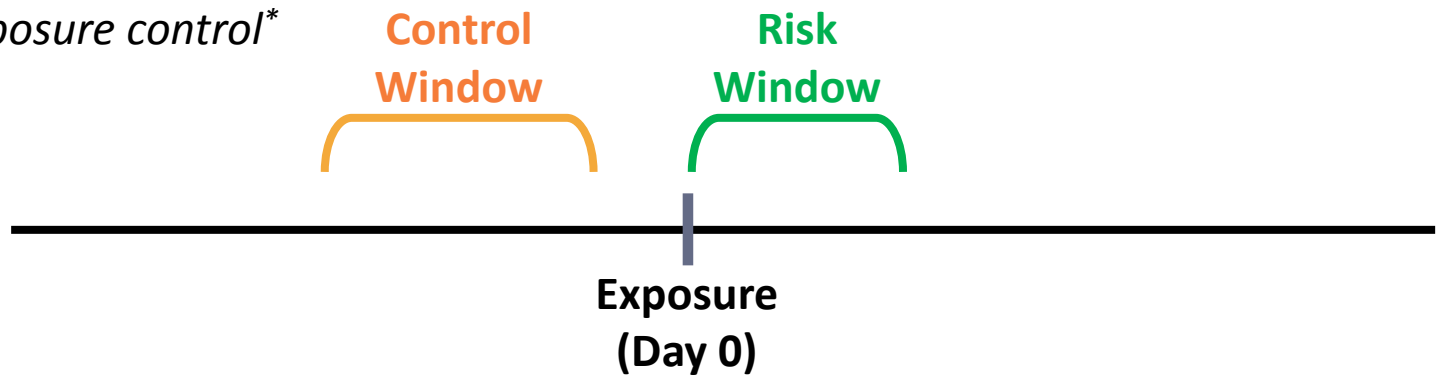


Non-adjacent windows

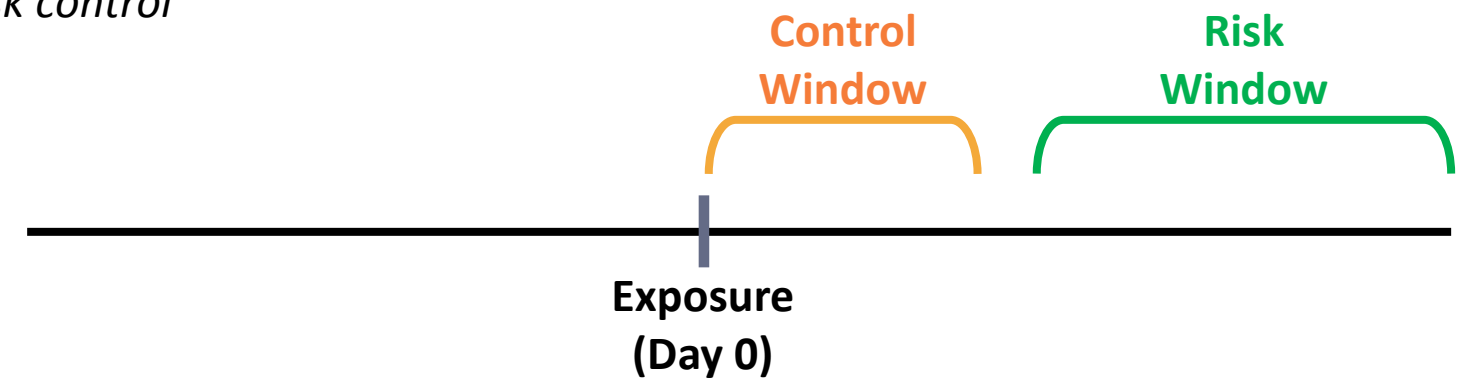


Window Placement

*Pre-exposure control**

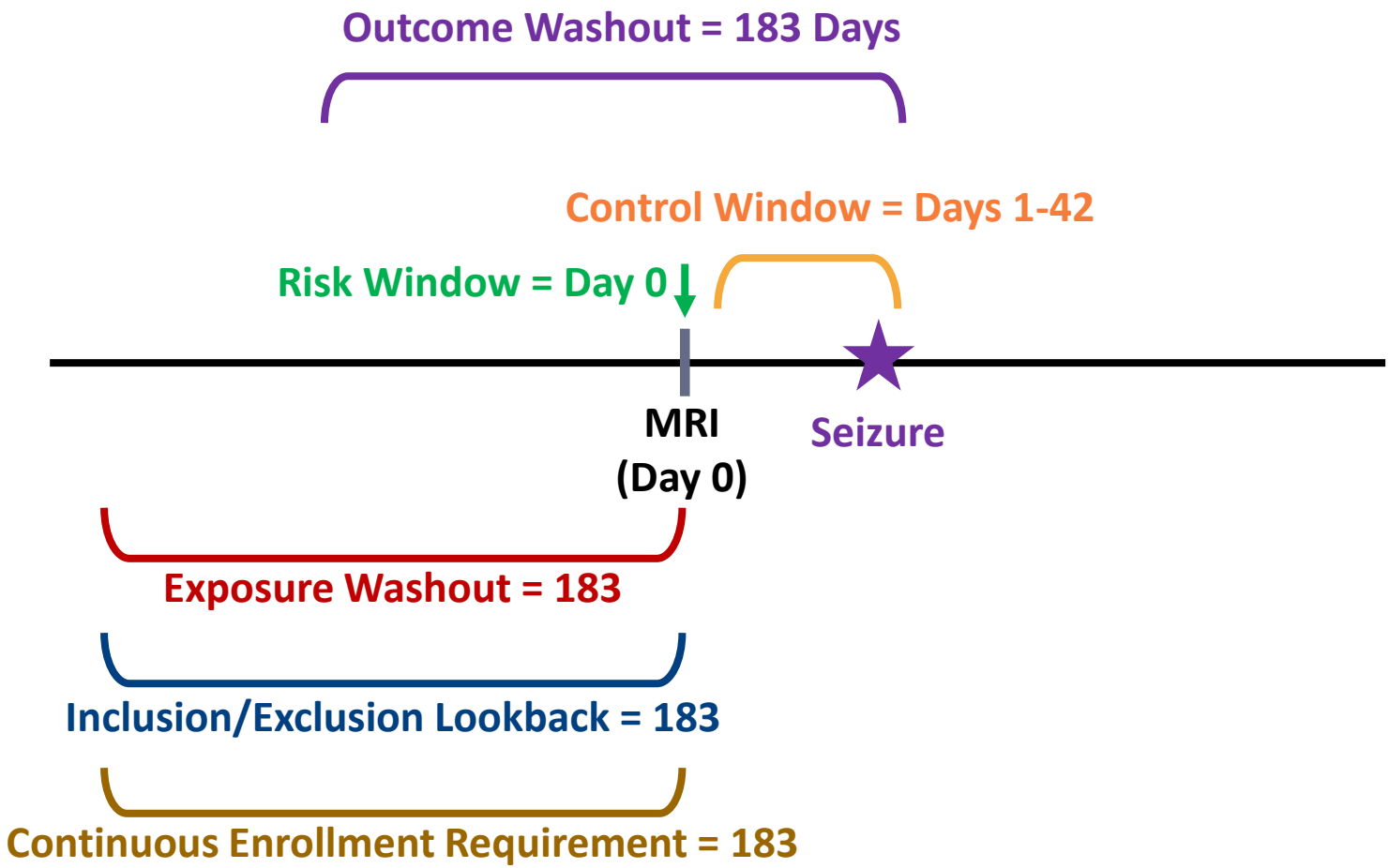


Pre-risk control



**Must ensure outcome doesn't affect probability of subsequent exposure*

Input Parameters for our SCRI Study



Results of SCRI Analysis

- For each exposure level, output data on two cohorts
- An **exposure cohort** for characterization
  - All patients meeting inclusion/exclusion/exposure criteria
  - "Table 1" of pre-exposure baseline characteristics
- An **analytic cohort** for effect estimation
  - Patients from exposure cohort with outcome in risk or control window
  - Event counts and incidence rate ratio estimates
  - Histogram of event times

Characterizing the Exposure Cohort

Single "Table 1" returned per exposure group

Characterizes *all* exposed patients meeting eligibility criteria

Only a subset of these will be included in SCRI analysis

Characteristic	Contrast MRI/ MRA	
	N/Mean	%/Std Dev
Number of unique patients	1,708,779	100.0%
Patient Characteristics		
Mean age	49.5	16
Gender (Female)	1,030,234	60.3%
Recorded History of		
Diabetes Mellitus	175,123	10.2%
Hypertension	463,701	27.1%
Major Surgery	54,308	3.2%
History of Use		
Antihypertensive Medications	351,479	20.6%
Diuretics	147,038	8.6%
Oral Antidiabetic Medications	107,862	6.3%
Health Service Utilization Intensity		
Mean number of ambulatory encounters	8.6	7.9
Mean number of filled prescriptions	9.3	10.5

Assessing the Analytic Cohort

	Exposure Cohort		Analysis Cohort		Number of Events		
	Patients	Index Dates	Patients	Index Dates	Risk Window	Control Window	Relative Risk (95% CI)
Contrast MRI/MRA							
Extremity or Non-Extremity	1,708,779	1,991,158	316	317	25	292	3.49 (2.32, 5.25)
Non-Extremity	1,210,037	1,445,364	245	246	21	225	3.85 (2.46, 6.03)
Extremity	507,944	535,838	70	70	4	66	2.35 (0.86, 6.47)
Non-Contrast MRI/MRA							
Extremity or Non-Extremity	6,714,901	7,955,932	1,150	1,152	87	1,065	3.35 (2.69, 4.16)

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Incidence = 317/1,991,158 = 0.015%

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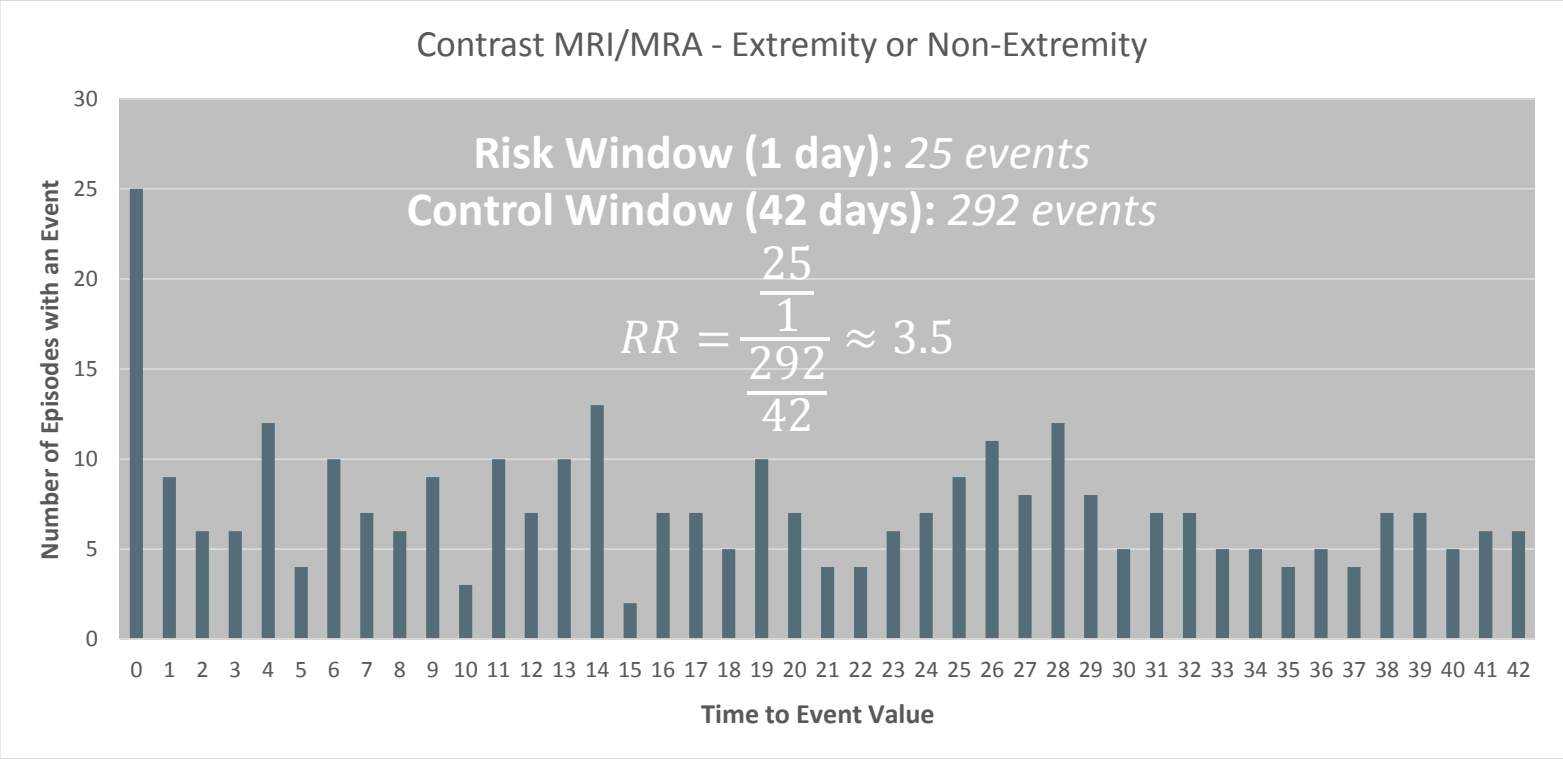
Incidence = 317/1,991,158 = 0.015%

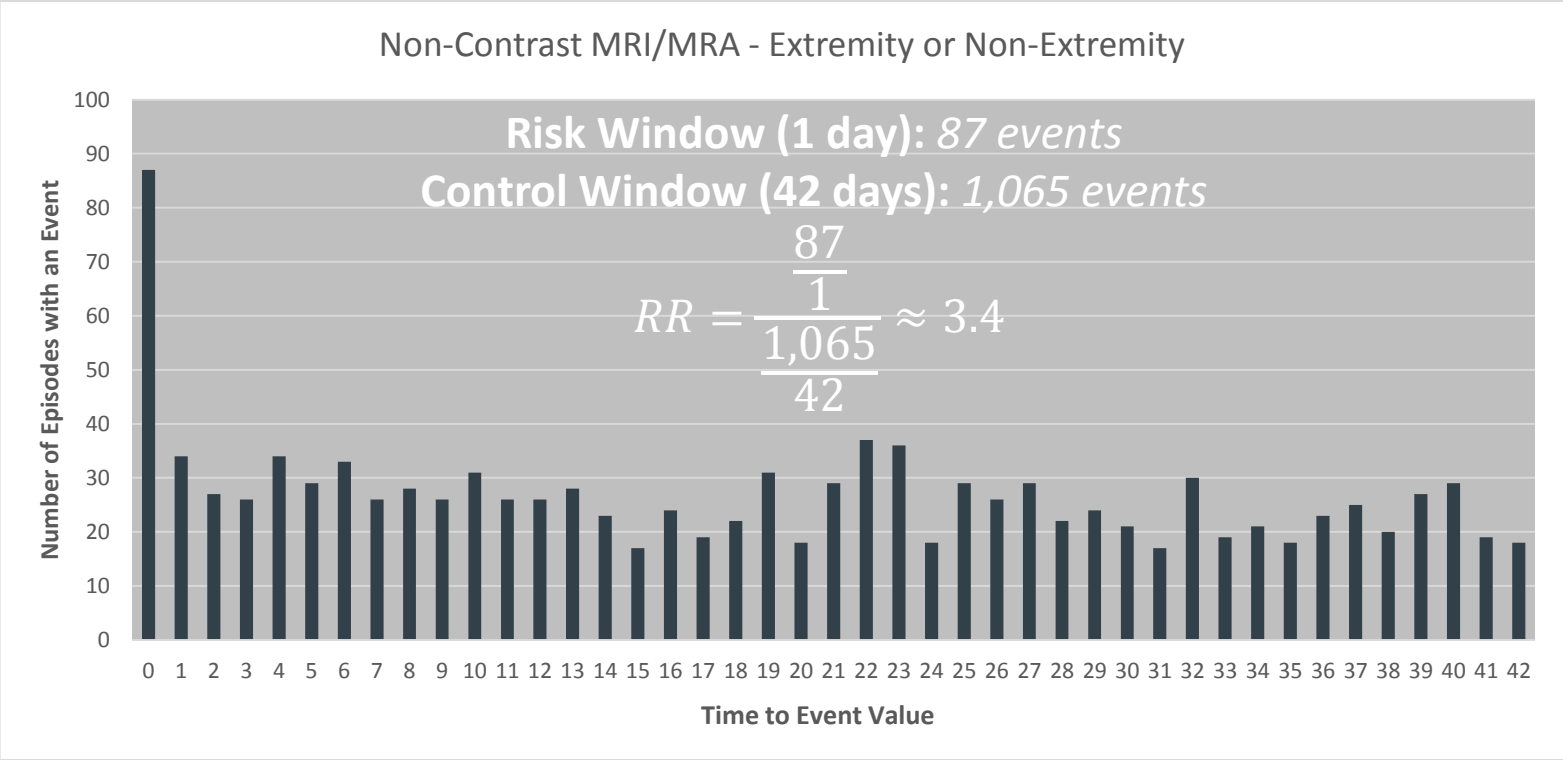
RR = (25/1)/(292/42) = 3.49

Distribution of Events



Contrast MRI/MRA associated with
3.5-fold increase in rate of seizure

Distribution of Events



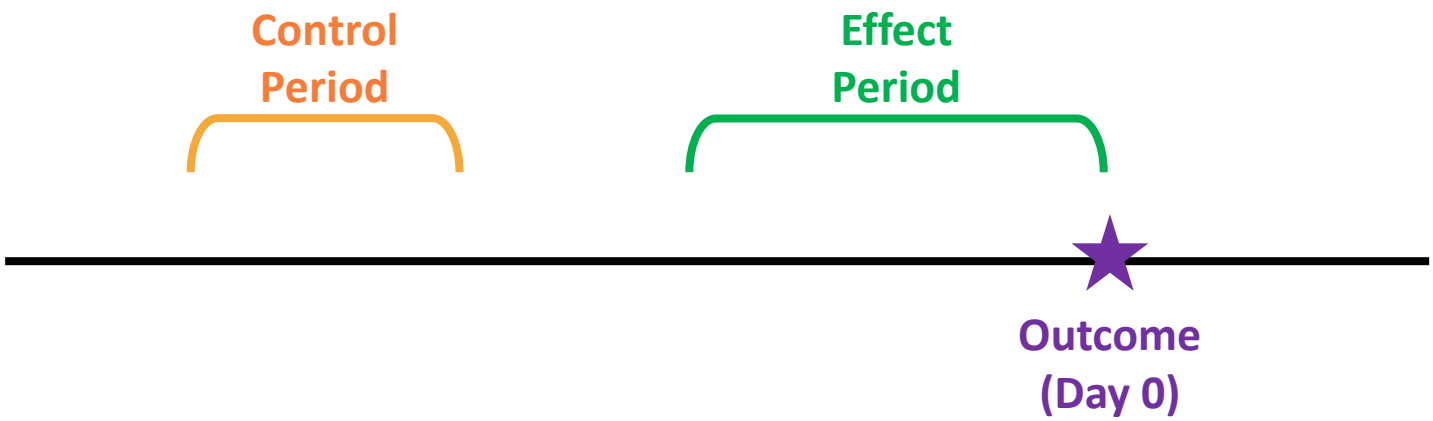
Non-contrast MRI/MRA associated with
3.4-fold increase in rate of seizure

Case Study Summary

- Outcome is very rare → SCRI advantageous
- Rate of seizure 3.5x higher on day of contrast MRI/MRA than in following 42 days
  - Effect nearly same for non-contrast MRI/MRA
- Suggests gadolinium-based contrast agents not primary driver of increase in seizure rate

Differentiating Case-Only Designs

Case-Crossover Design



Step 1: Identify all individuals experiencing the **outcome** during the study period

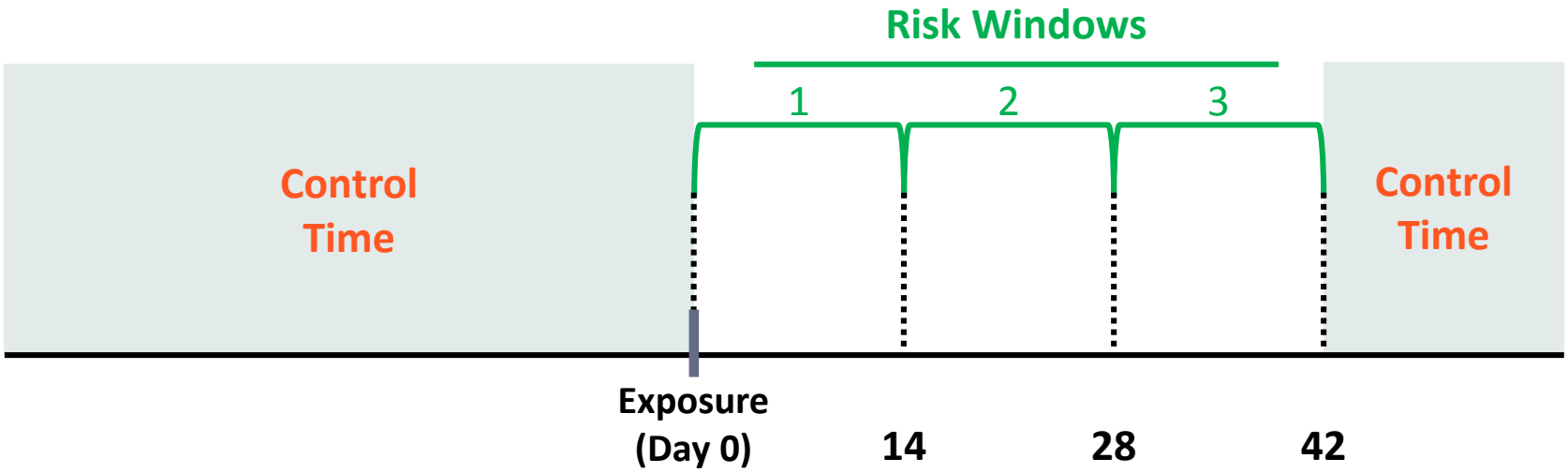
Step 2: Define an **effect period** preceding the outcome

Step 3: Define a **control period** relative to the outcome

Step 4: Compare the exposure statuses in the effect period to that in the control period

RR = OR comparing odds of exposure in effect period to that in control period

Self-Controlled Case Series Design



Step 1: Define 1 or more **risk windows** relative to exposure, when patients are at risk for an exposure-related outcome

Step 2: Assign all other observation time to a control "window", which need not be continuous

Step 3: Compare the outcome incidence in the risk window(s) to that in the control window (i.e., all other observed time)

Closing Remarks

- SCRI design is a simple analytic method
- Compares *periods*, not *persons*
  - Identifies windows of elevated risk associated with common medical interventions
- Results very sensitive to risk and control window choices
  - Can be mitigated with sensitivity analysis
- Rapid implementation in ARIA

Questions?

Lunch

TreeScan Analyses

Judith C. Maro, PhD, MS[1]

[1]Harvard Medical School and Harvard Pilgrim Health Care Institute

TreeScan 101

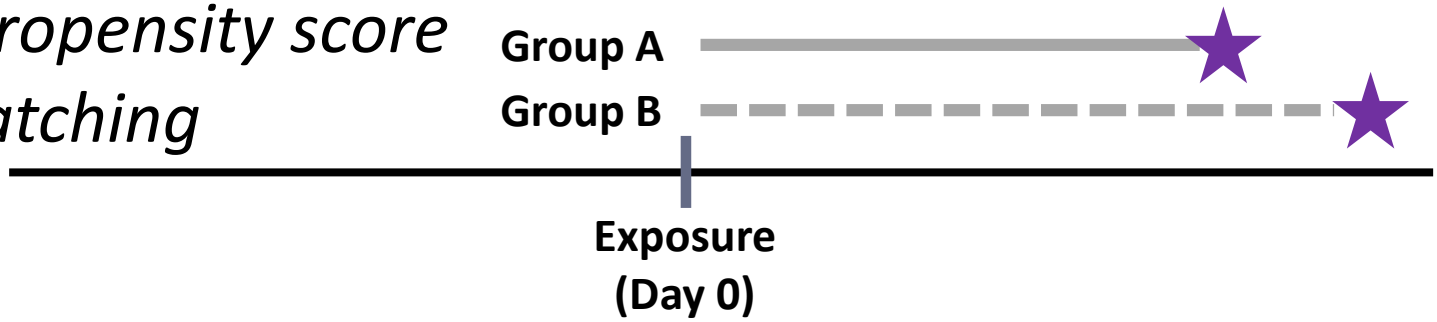
What is

- A signal detection / data-mining method
- Automatically adjusts for multiple hypothesis testing
- Scans electronic health data that are grouped into hierarchical tree structures

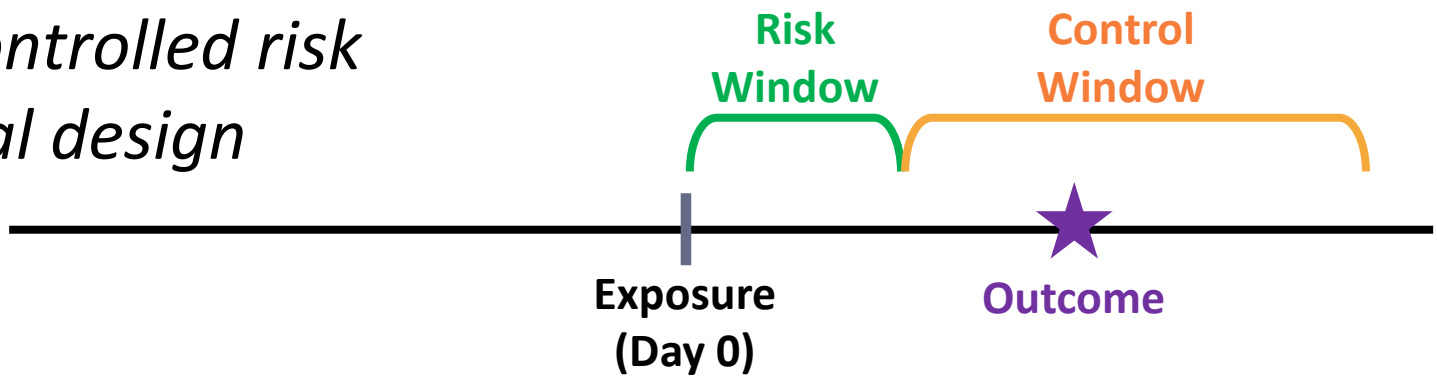
http://www.treescan.org

TreeScan: Adding Multiple Outcomes to Designs for Exposure-Outcome Pairs

New user cohort design with propensity score 1:1 matching



Self-controlled risk interval design



Data-Mining Designs with TreeScan

- Exposure-Oriented - 1 Exposure: N Outcomes
  - Uses Multi-Level Clinical Classification System (MLCCS) where N=~8000
- Outcome-Oriented - M Exposures: 1 Outcome
  - Uses Medi-Span Therapeutic Classification System (Drug Tree) where M=300,000+
- *Future - M Exposures: N Outcomes*

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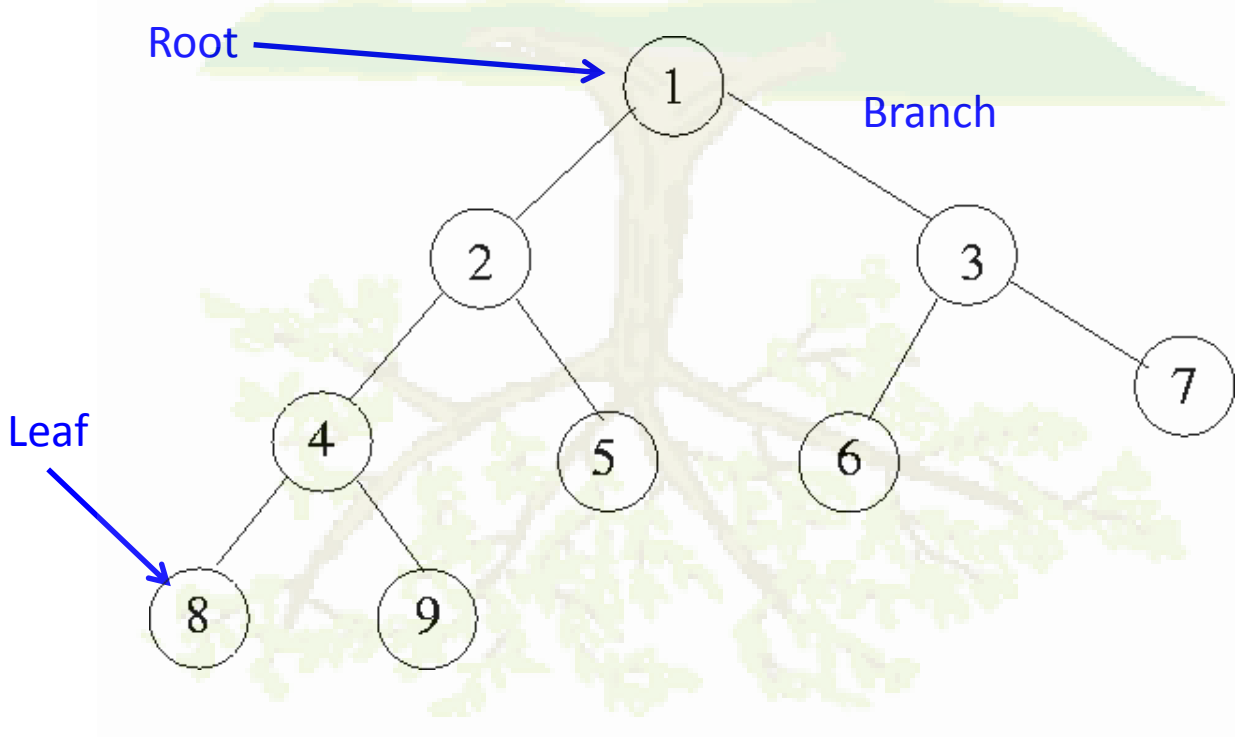
What is a Hierarchical Tree Structure?



System Organ Class
Gastrointestinal disorders

High Level Group Term
Gastrointestinal signs and symptoms

High Level Term
Nausea and vomiting symptoms

Preferred Term
Nausea

Lowest Level Term
Feeling queasy

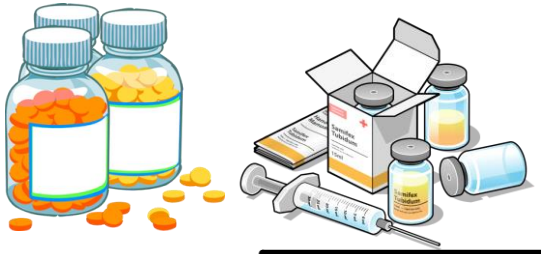
Examples:

MedDRA reporting terms

Multi-level Clinical Classification System

Medi-Span Therapeutic Classification System

What is an Exposure-Oriented Scan?



Diseases of the Nerve and Sense Organs

- Central Nervous System Infection
- Hereditary and degenerative nervous system condition
- Paralysis
- Epilepsy; convulsions
  - Epilepsy
  - Convulsions
    - Convulsions
      - Convulsions ICD-9-CM 780.3
      - Febrile convulsions NO ICD-9-CM 780.31
      - Complex febrile convulsions ICD-9-CM 780.32
      - Post traumatic seizures ICD-9-CM 780.33
      - Other convulsions ICD-9-CM 780.39

TreeScan and FAERS: Similarities and Differences

How are TreeScan and FAERS alike?

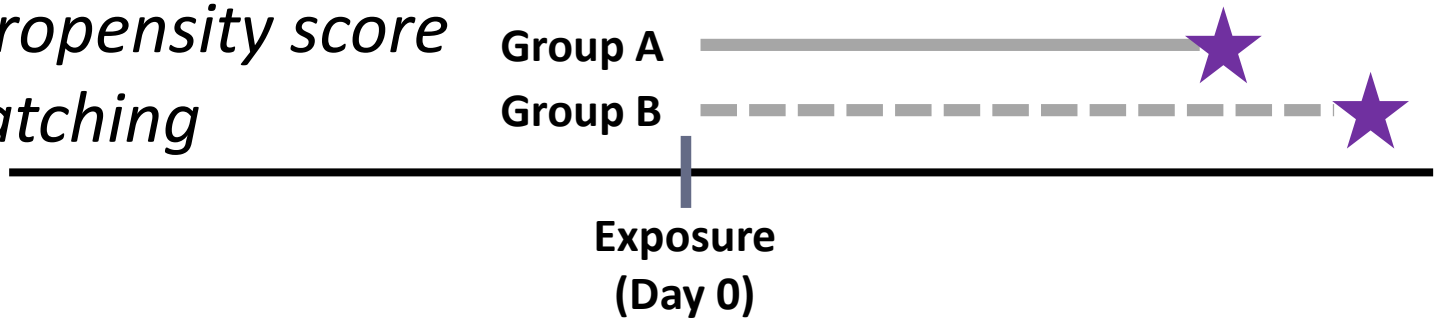
- General Safety Net: No need to specify exposure-outcome pair of interest
- Hypothesis Generation: Both produce hypotheses that necessitate further investigation
- Tree Structure: Both use data structured in hierarchical trees

How are TreeScan and FAERS different?

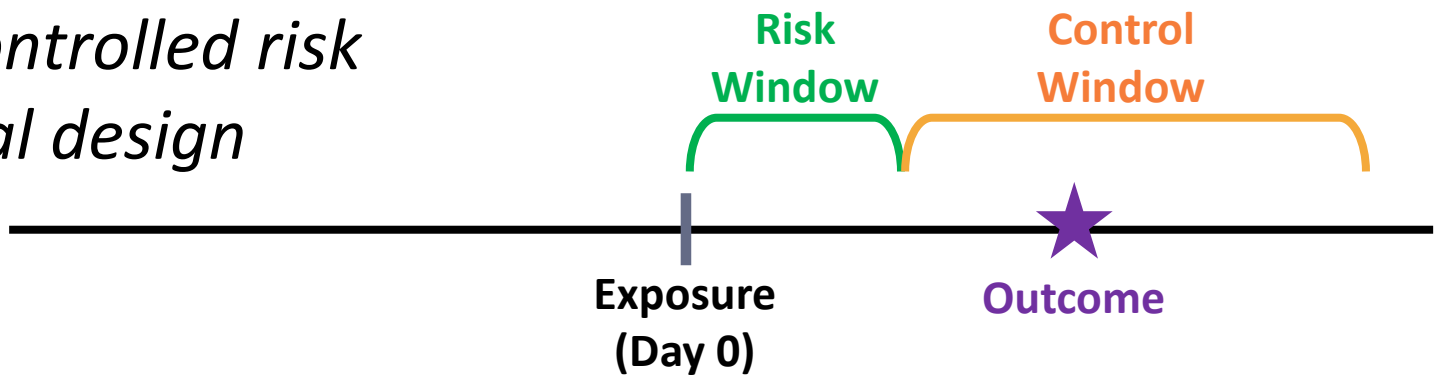
- Different Data Sources: TreeScan utilizes longitudinal data and familiar epidemiological designs
- Different Analytic Datasets: TreeScan uses aggregated data and requires additional programs for patient-level returns

TreeScan: Adding Multiple Outcomes to Designs for Exposure-Outcome Pairs

New user cohort design with propensity score 1:1 matching



Self-controlled risk interval design



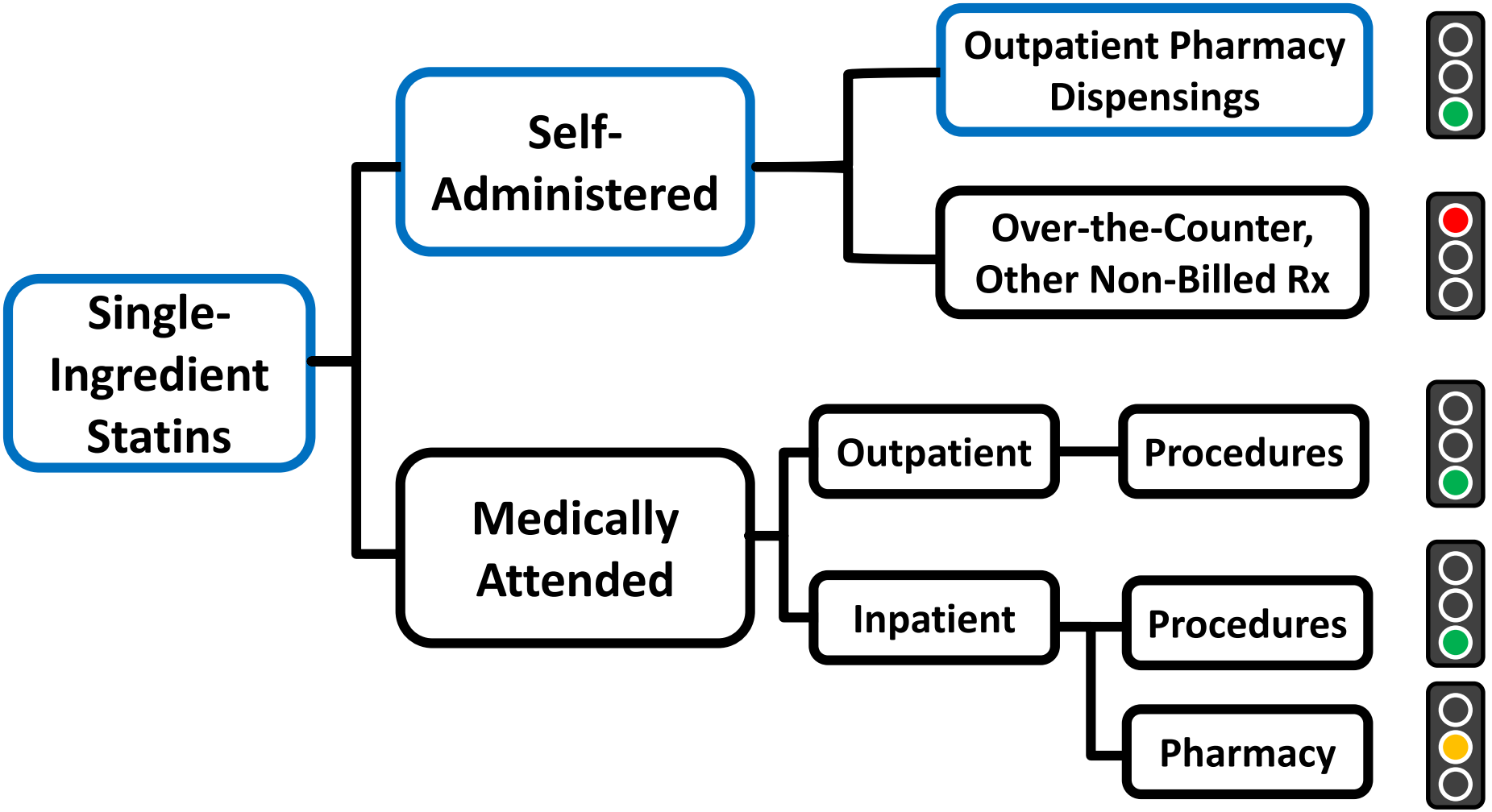
Self-Controlled Risk Interval Design

- Main Advantages
  - Controls for time-invariant confounding
  - Easy to implement

- Main Disadvantages
  - Vulnerable to time-varying confounding (requires stable clinical status)
  - Can miss a prolonged elevation of adverse event occurrence

Training Example: Monitoring Single-Ingredient Statins for 8000+ Outcomes using a Self-Controlled Risk Interval Design

Statins are outpatient pharmacy dispensings

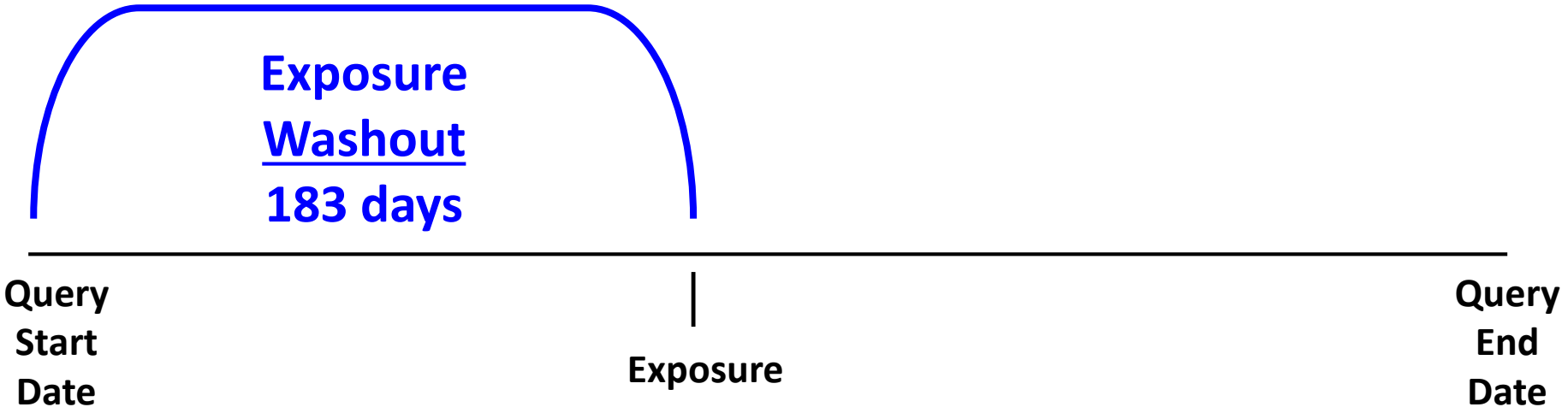


Why Single-Ingredient Statins?

- Simvastatin
- Atorvastatin (High Intensity)
- Pravastatin
- Rosuvastatin (High Intensity)
- Lovastatin
- Pitavastatin
- Fluvastatin

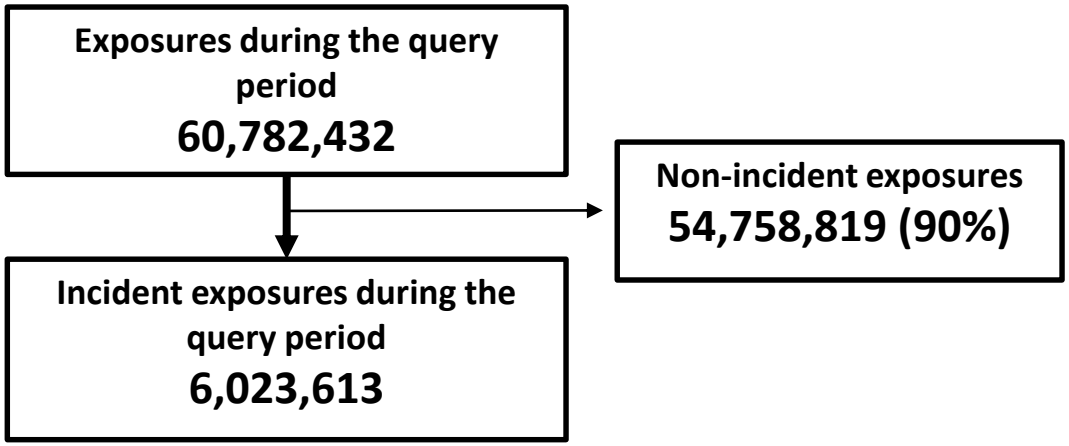
Statins have a large sample size and an established safety record.

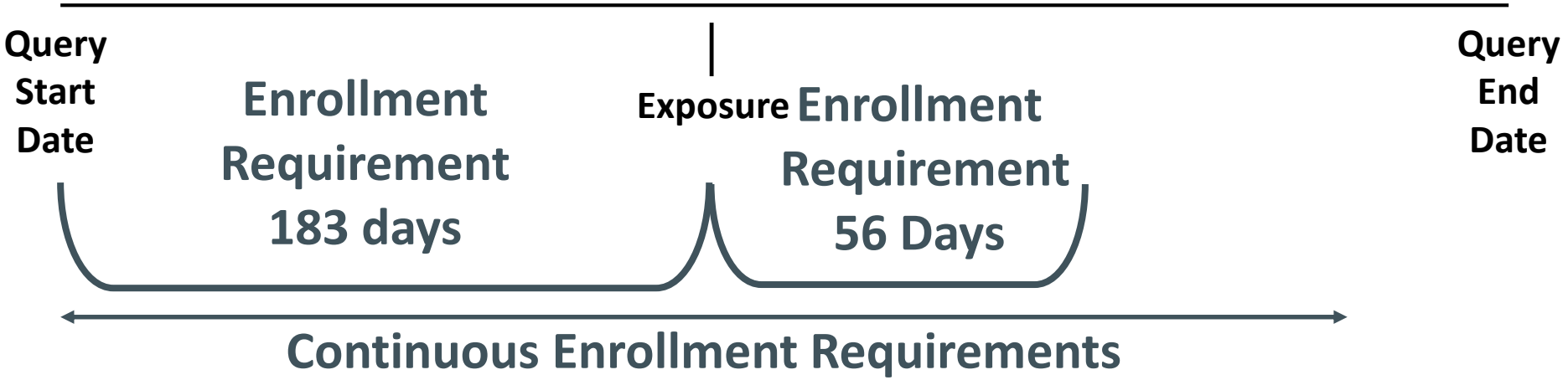
TreeScan: Building a Cohort with a Self-Controlled Risk Interval Design



Find single-ingredient statin and check for incidence (no use in prior 183 days).

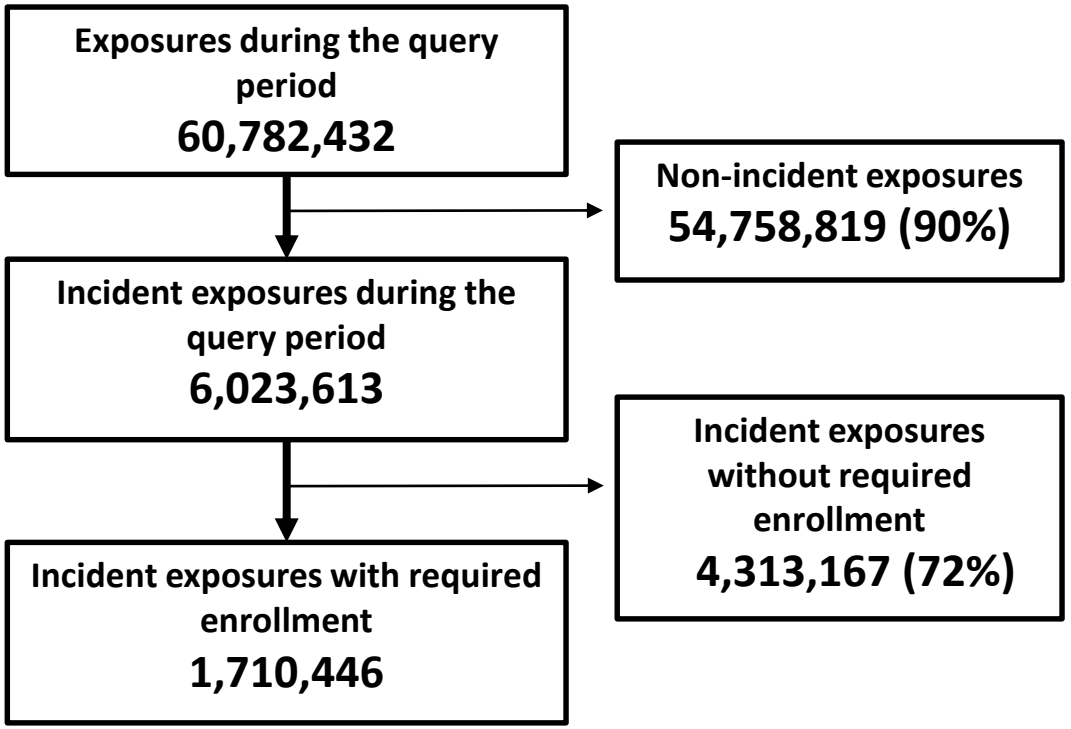
Simvastatin Cohort Attrition in 35% of Sentinel Distributed Database





Check for required enrollment (183 + 1 + 56 = 240 days with medical and pharmacy)

Simvastatin Cohort Attrition in 35% of Sentinel Distributed Database

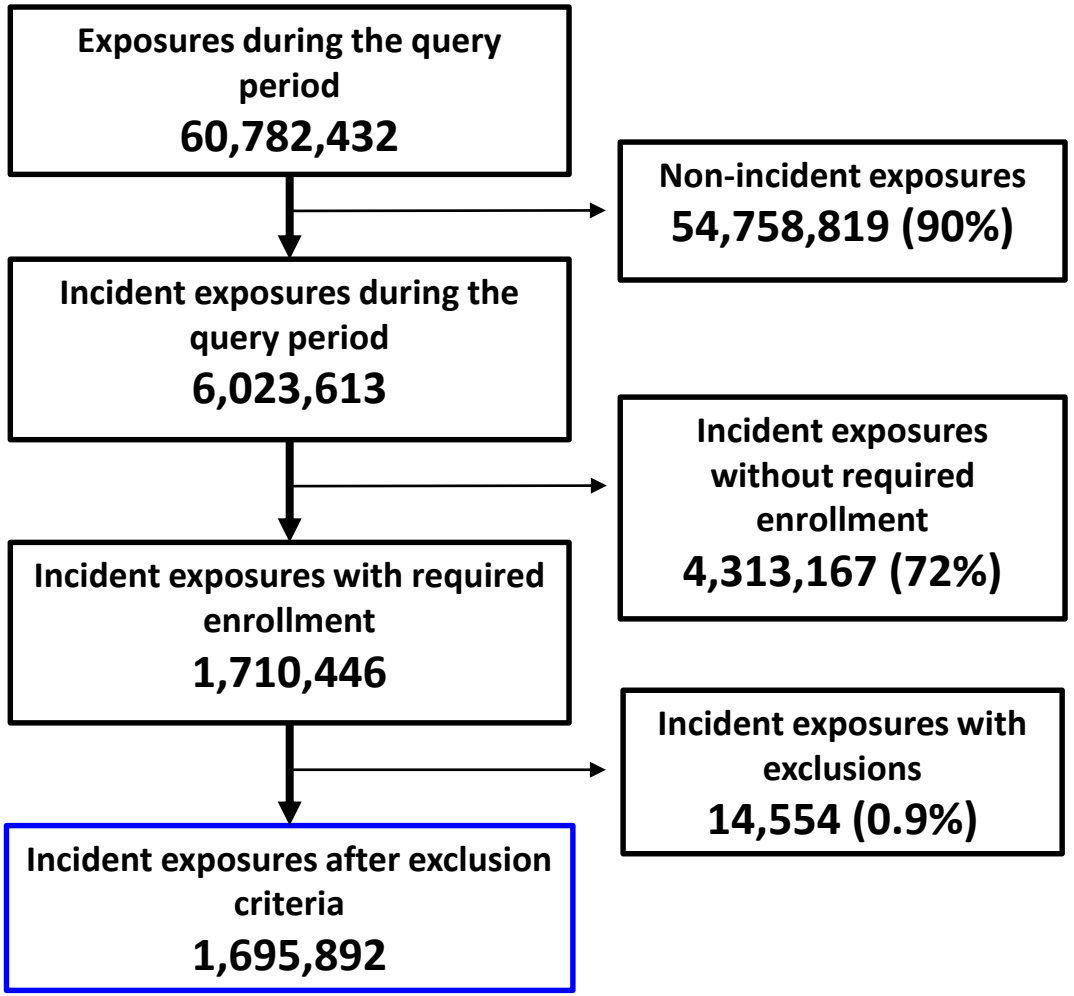


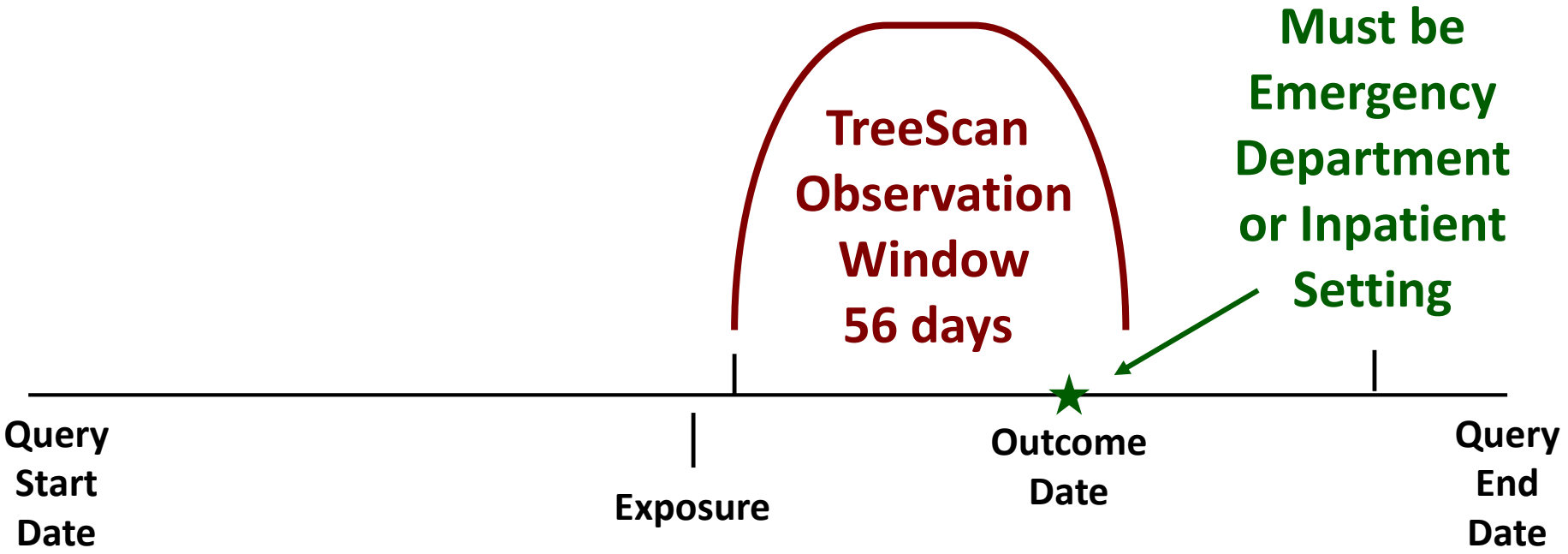
- Must be 18 years old on index date
- No recent history of Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG), Coronary Thrombolysis

Check for inclusions (age) and exclusions (evidence of recent procedures).

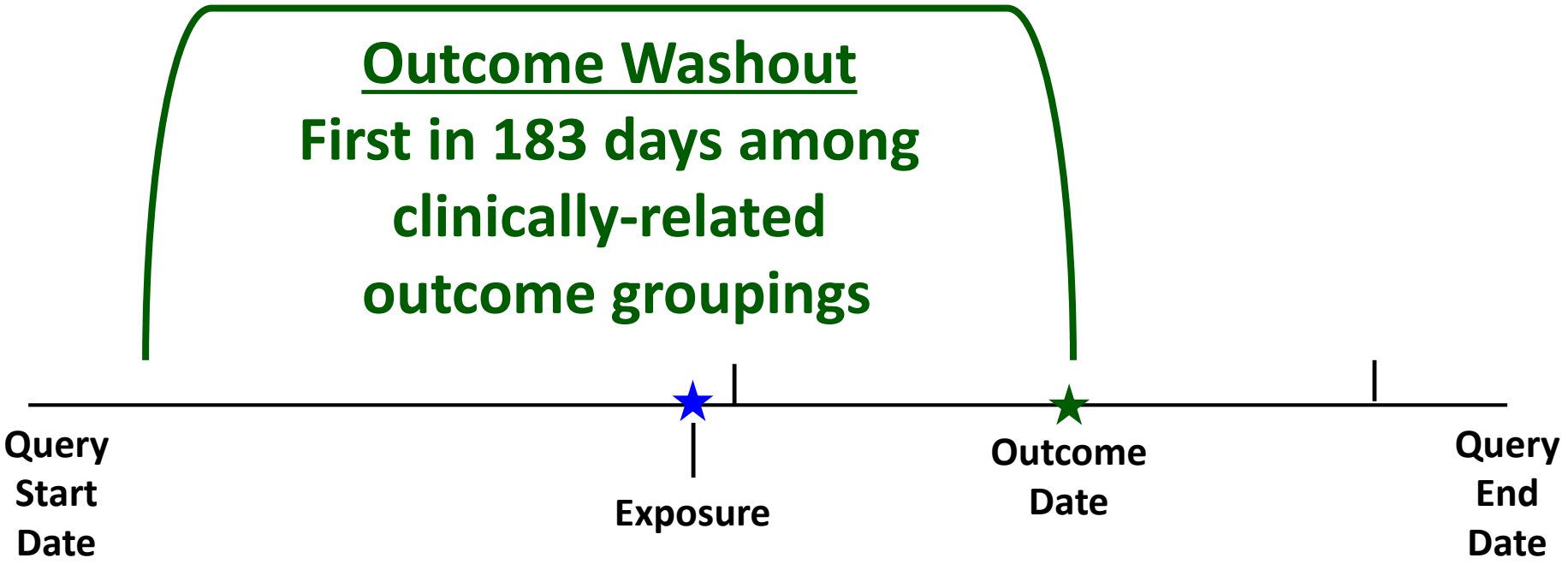
Simvastatin Cohort Attrition in 35% of Sentinel Distributed Database

Exposed Cohort



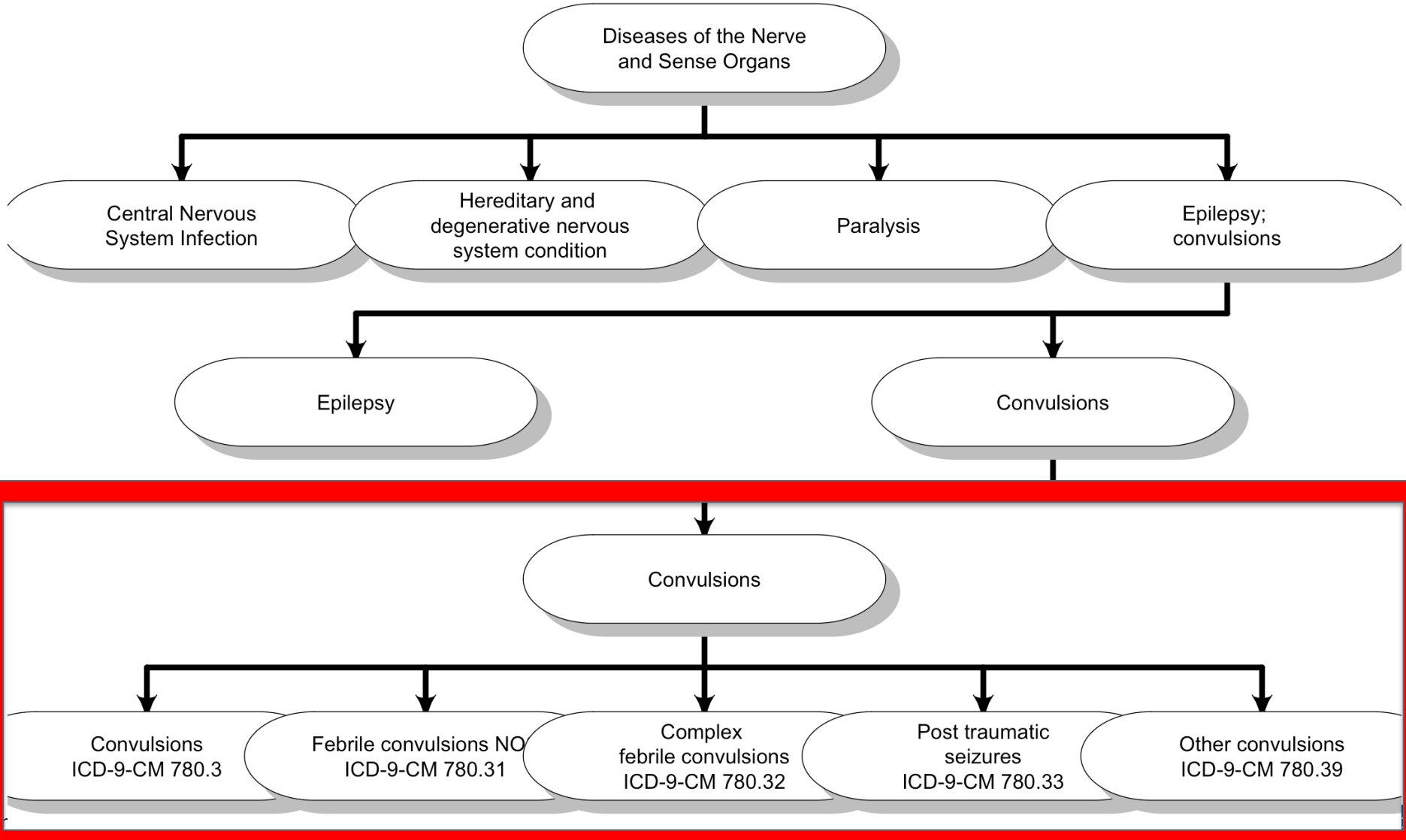


Find all potential outcomes in TreeScan Observation Window (1-56 days).



Check that outcome is incident with respect to the hierarchical tree.

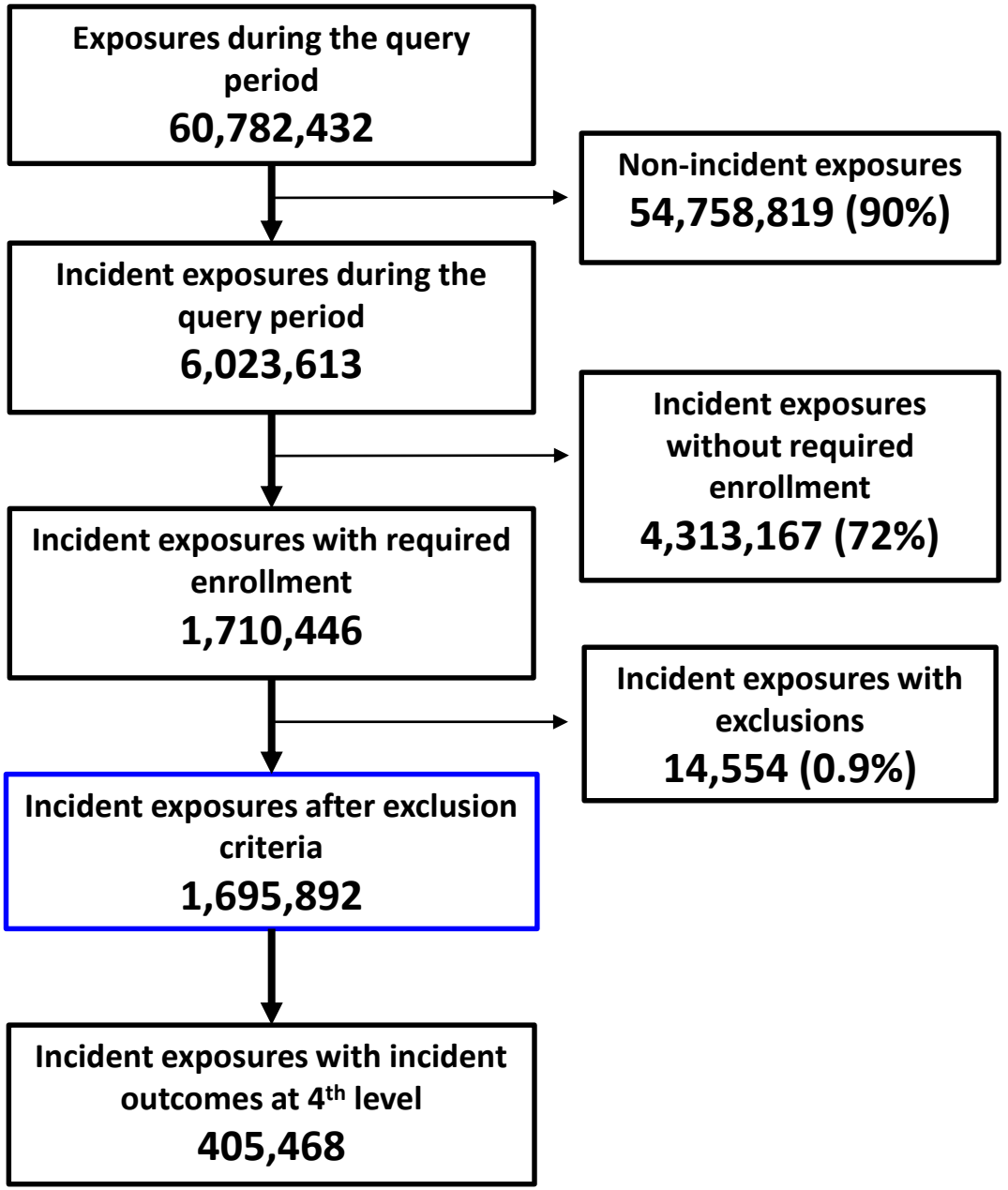
What is a Clinically-Related Grouping?



Simvastatin Cohort Attrition in 35% of Sentinel Distributed Database

Exposed Cohort

Analytic Cohort

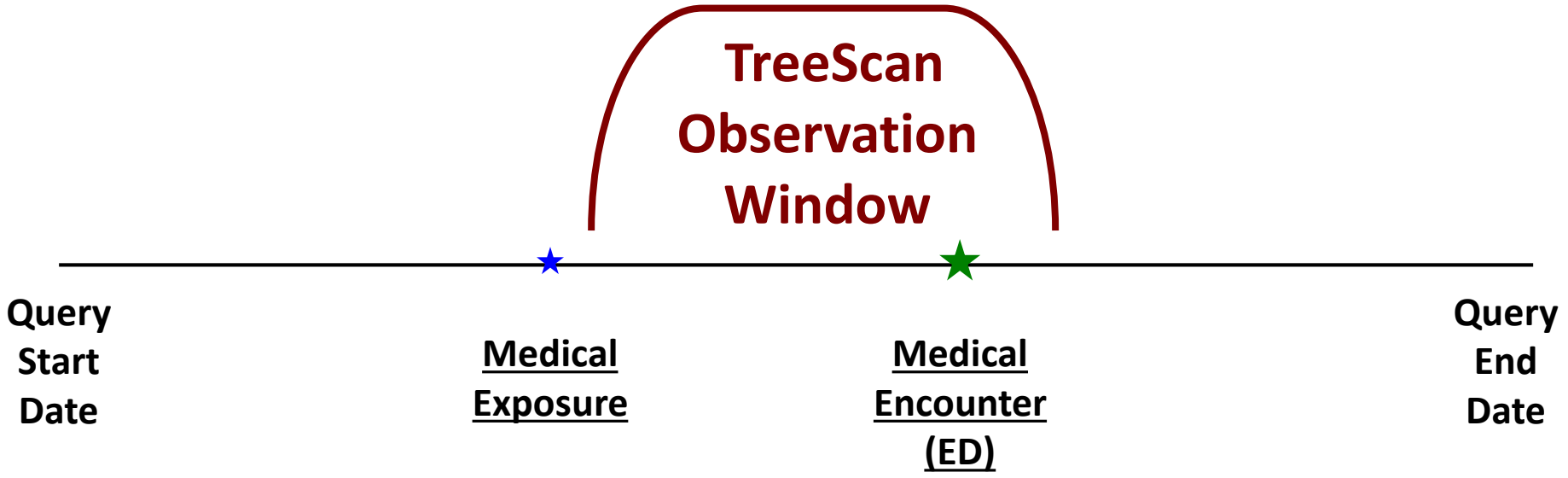


But, You Haven't Selected the Risk Window!

- Simulations show you should not unless you clearly understand what it is

  https://www.sentinelinitiative.org/sites/default/files/PRISM/TreeScanPower_FinalReport.pdf

- With 8000+ outcomes, it's not possible to select a universal risk window



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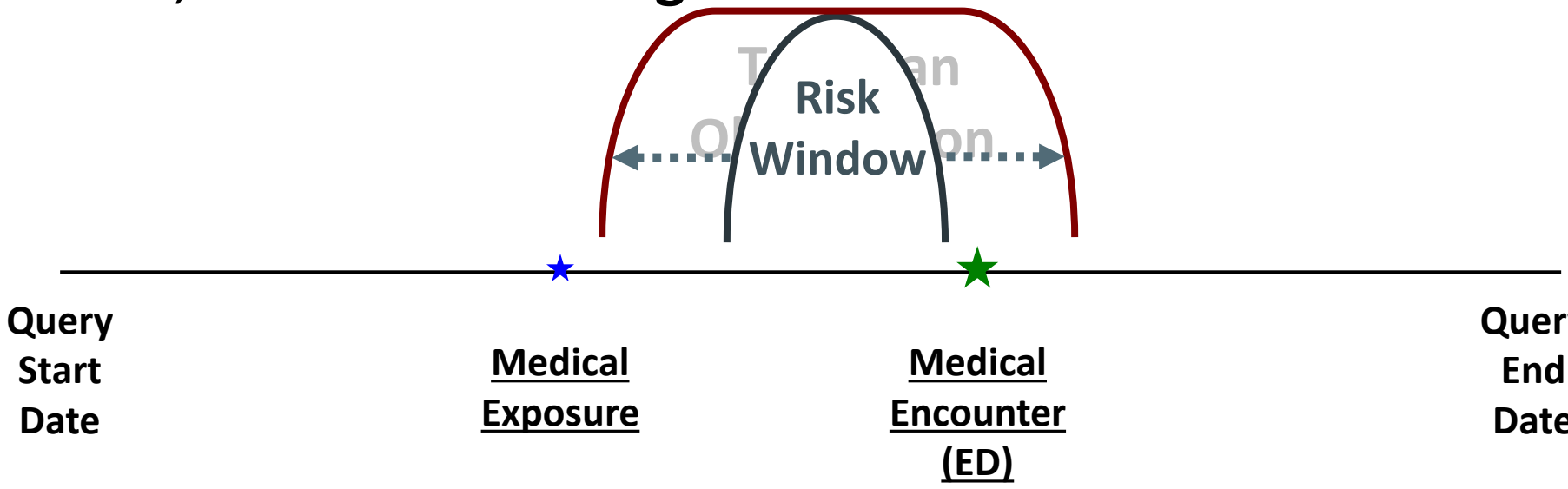
- With 8000+ outcomes, it's not possible to select a universal risk window
- So, we use a **scanning** risk window:



But, That's Thousands of Hypothesis Tests!

- Yes, it's 8000+ outcomes and outcome-related groupings multiplied by hundreds of risk windows
  - But they are highly-overlapping
- We account for all the multiple hypothesis testing using a Monte Carlo based method and a maximum likelihood test statistic.
  - NULL: There is no outcome or grouping of outcomes occurring during a particular risk window.
  - When we reject the null, we call that an "alert"

What is a TreeScan "Alert"?

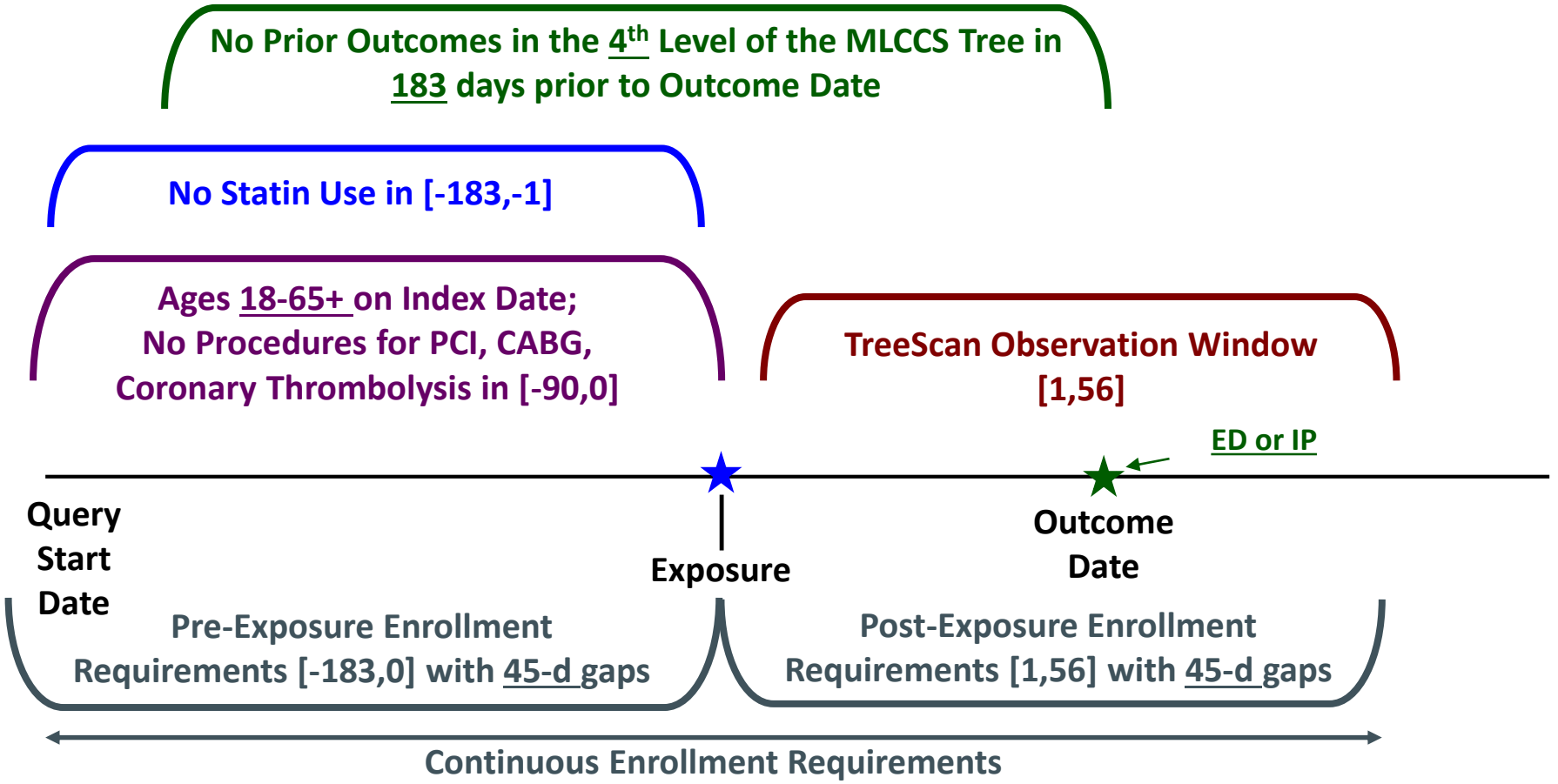
- A statistically significant finding of greater than expected occurrence of an exposure-outcome pair while controlling for multiple hypothesis testing
- An "Alert" is not a "Signal"
  - Use of the term "signal" has regulatory implications and is an FDA decision
  - May not contain "new safety information"
- An Alert requires further triage

How are Alerts Triaged?

- Known Adverse Reaction or already in the label
  - Example: Various Vaccinations and Cellulitis / Rash
- Rule out possible Adverse Reactions due to time-varying confounding
  - Example: Pneumococcal Polysaccharide Vaccine and Spleen Surgery
- Narrow to list of possible Adverse Reactions that merit follow-up
  - Consider using alternative study mechanisms or tools

Statins Design Diagram

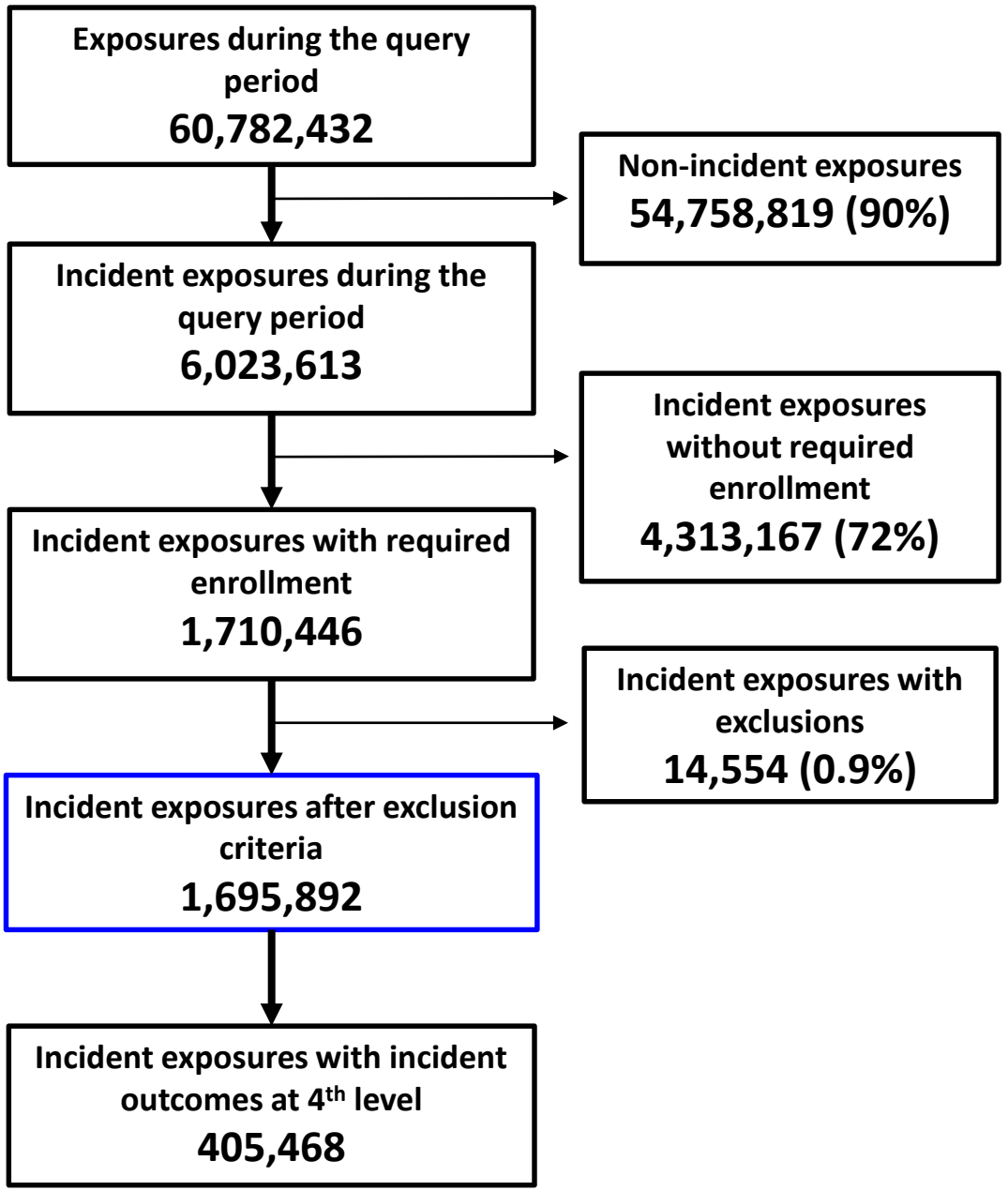
Single Ingredient Statins Only



*Not drawn to scale

Results

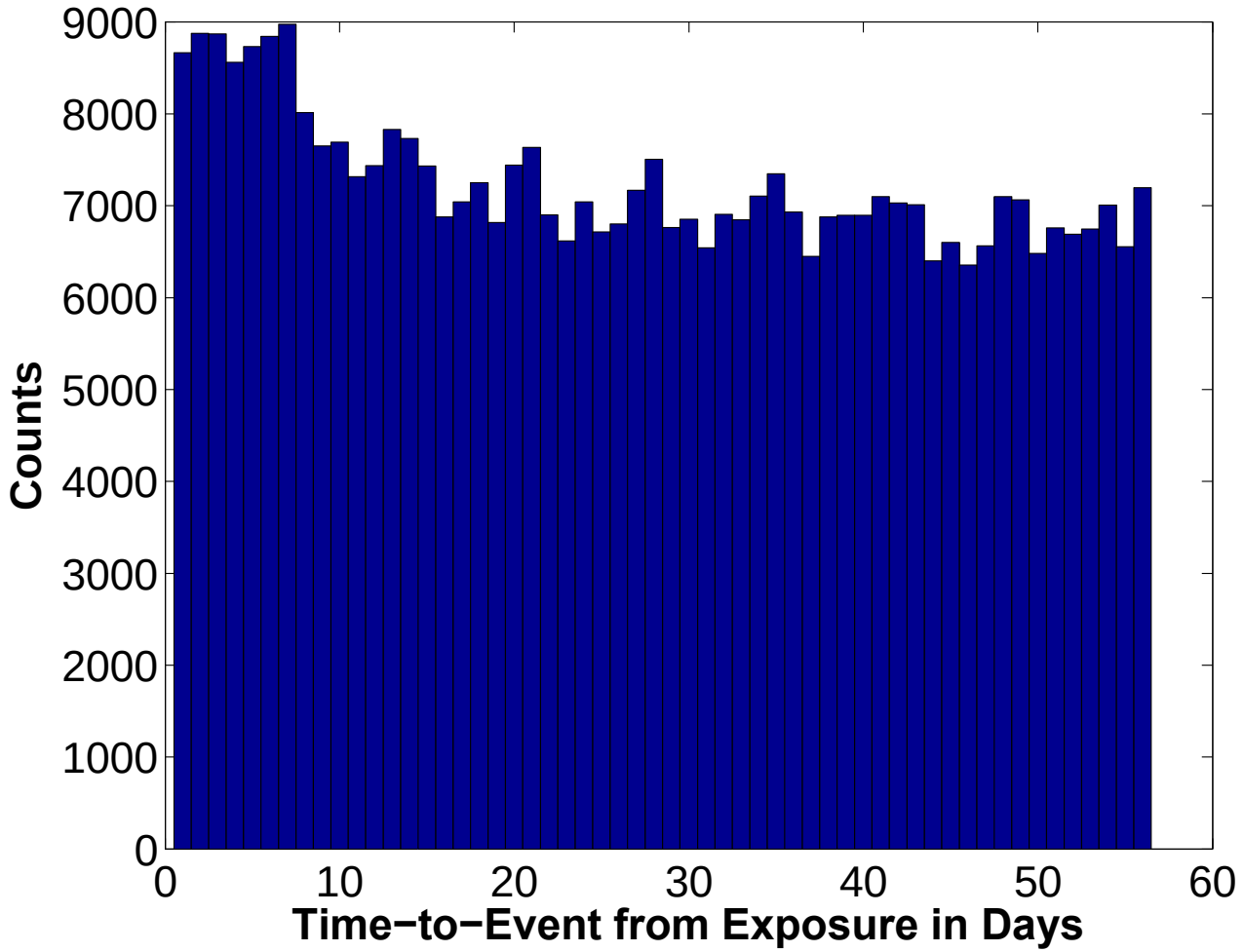
Simvastatin Cohort Attrition



Exposed Cohort

Analytic Cohort

405,468 Incident Outcomes following New Simvastatin Use



Simvastatin Primary Results (11 alerts)

Node Name	Node ID	Node Outcomes	Node Outcomes in RW	Relative Risk	RW Start	RW End	Test Statistic	P Value
Unstable angina (intermediate coronary syndrome)	07020402	2269	523	1.68	1	7	40.02701	0.0001
…Intermediate Coronary Syndrome	4111	2269	523	1.68	1	7	40.02701	0.0001
Angina Pectoris	07020401	1408	377	1.77	1	8	32.471868	0.0001
….Angina Pectoris NEC & NOS	4139	1353	360	1.76	1	8	30.19576	0.0001
Cardiac arrest and ventricular fibrillation	07021000	459	160	1.95	44	56	15.776195	0.0006
…Cardiac Arrest	4275	307	106	2.61	47	56	21.913557	0.0001
Disorders of lipid metabolism	03060000	7449	2269	1.22	1	13	21.133046	0.0001
Other forms of chronic heart disease	07020405	5447	1676	1.24	1	13	17.869037	0.0001
Hemorrhage or hematoma complicating a procedure	16100205	990	227	1.67	1	7	16.958573	0.0002
…Hematoma Complicating a Procedure	99812	451	113	2.25	1	6	19.953413	0.0001
Conditions associated with dizziness or vertigo	06080200	4633	628	1.3	1	5	15.334017	0.0011
…Dizziness & Giddiness	7804	4210	578	1.32	1	5	15.663721	0.0006
Respiratory failure	08060100	3063	804	1.29	42	54	14.00441	0.0031
Surgical Complication-Peripheral Vascular	9972	121	40	3.32	1	6	13.141528	0.0099
Coronary atherosclerosis	07020404	6247	1243	1.2	1	8	13.138919	0.01
Lower extremity aneurysm	4423	82	28	4.29	1	5	13.127157	0.01

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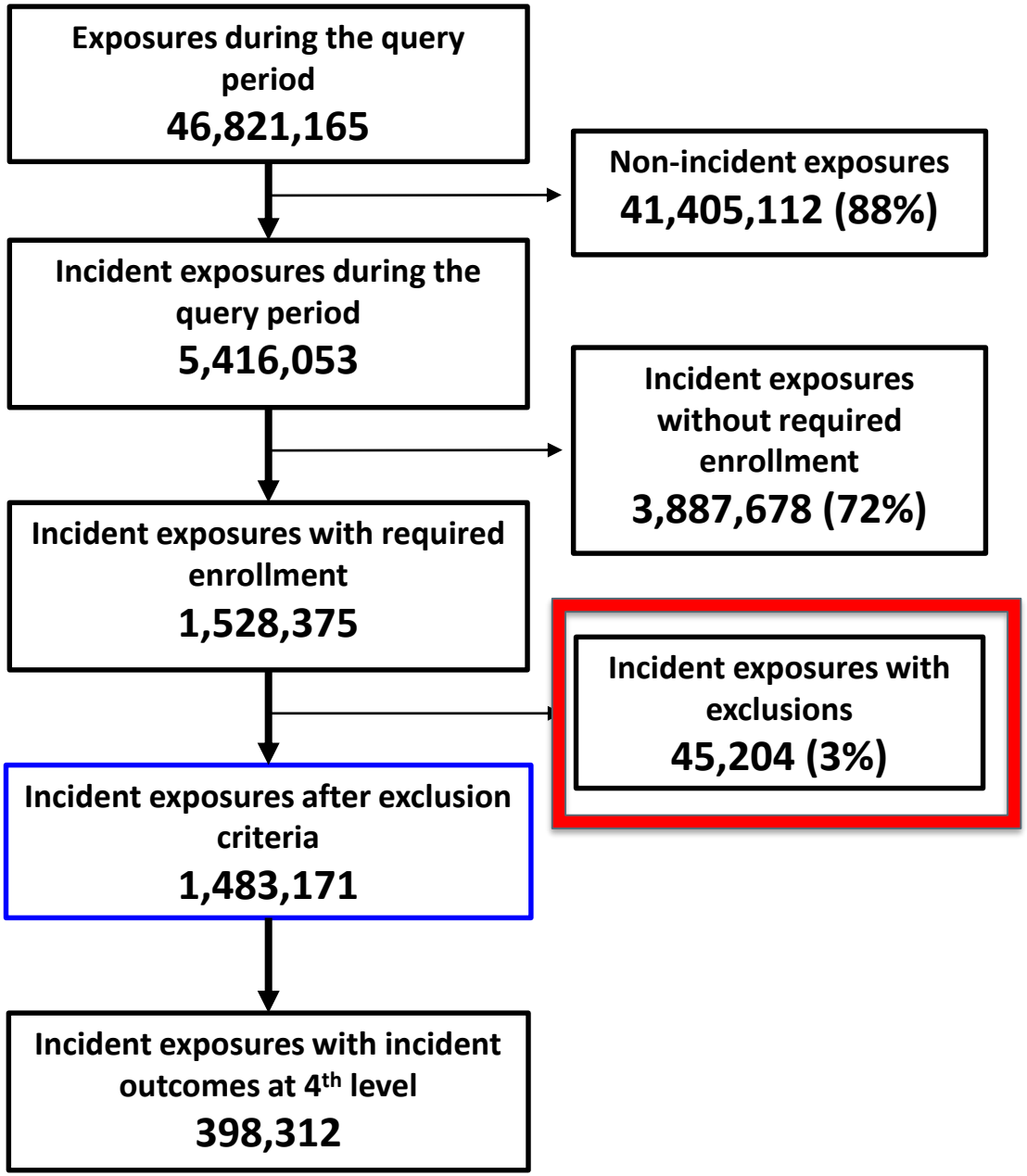
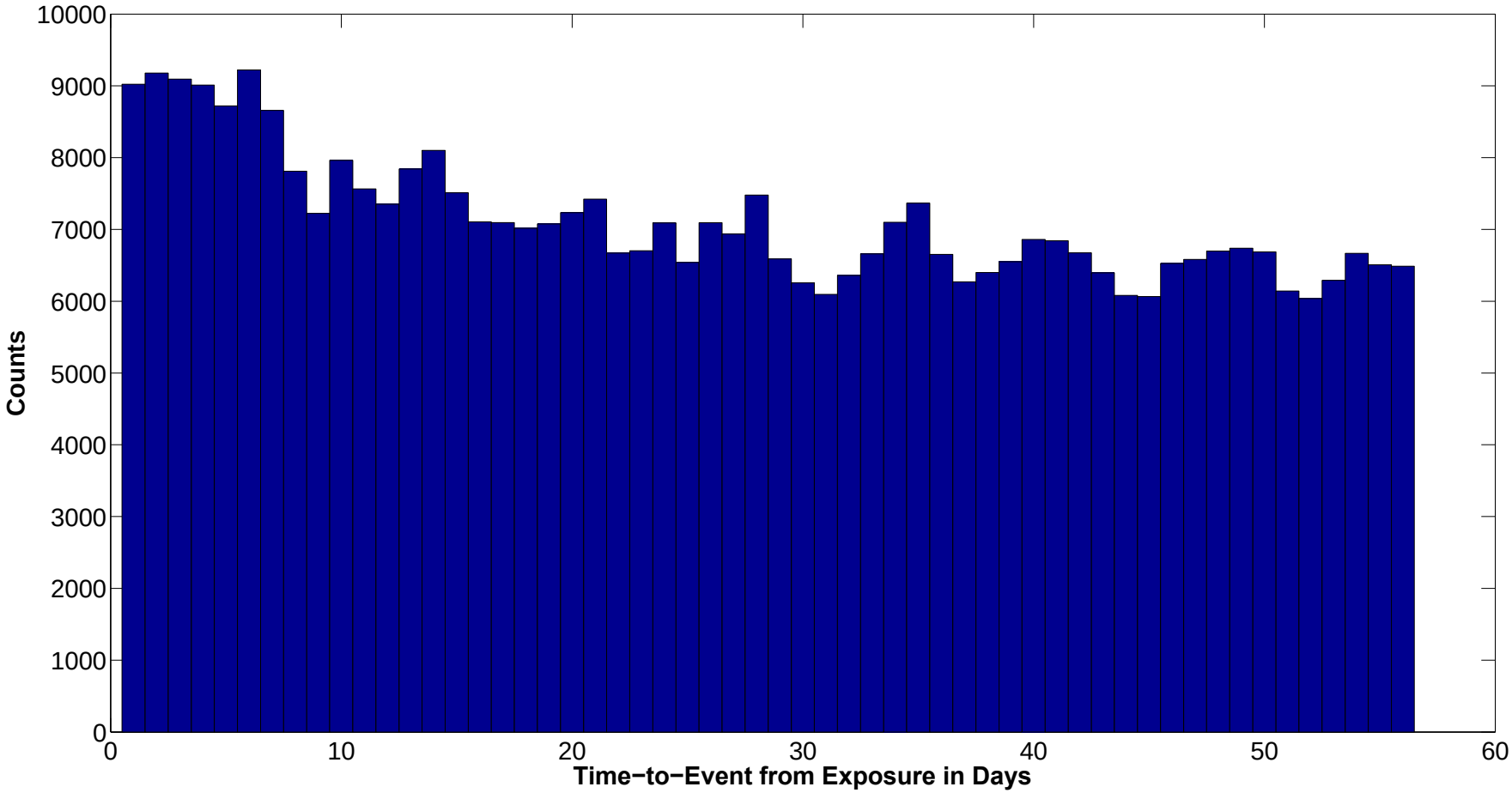
Atorvastatin Cohort Attrition



Exposed Cohort

Analytic Cohort

398,312 Incident Outcomes following New Atorvastatin Use



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Coronary atherosclerosis	07020404	5522	1794	1.29	1	13	25.951448	0.0001
….Coronary atherosclerosis- Native Vessel	41401	2946	851	1.33	1	11	17.198595	0.0003
Lower extremity aneurysm	4423	100	45	5.19	1	6	22.402413	0.0001
Angina pectoris	07020401	1387	352	1.58	1	8	20.024826	0.0001
…Angina Pectoris NEC & NOS	4139	1334	337	1.57	1	8	18.708754	0.0002
Hematoma complicating a procedure	99812	457	171	1.95	1	11	16.032192	0.0008
Cardiac arrest	4275	383	169	2.07	38	54	15.839396	0.0008
Respiratory failure	08060100	3594	1033	1.26	42	56	14.164177	0.0036

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“Alerts” are nearly all related to cardiovascular complications and all present in the simvastatin results.

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RW = Risk Window

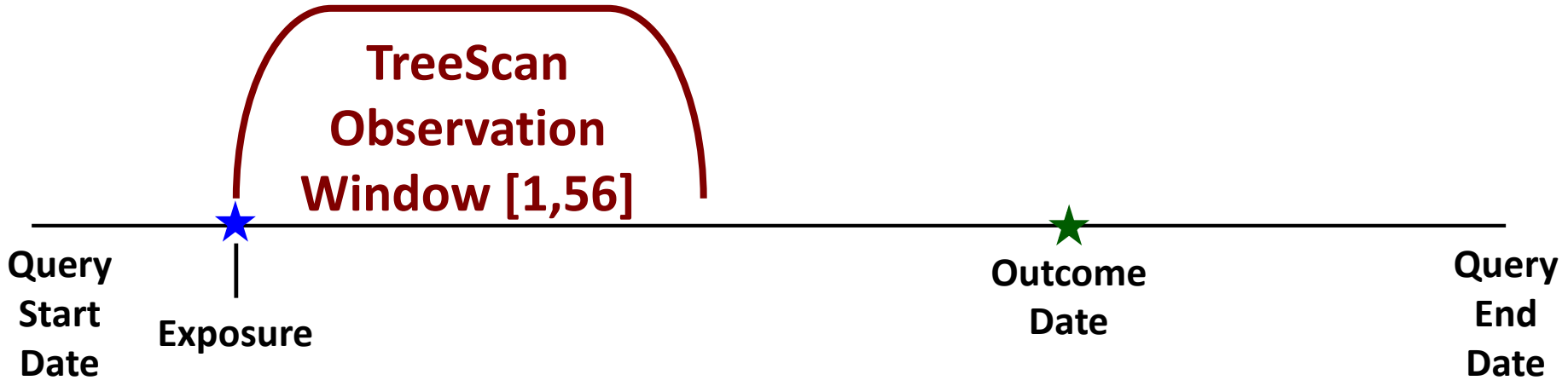
Other Statin Results

Name	Exposure Cohort	Analytic Dataset	Alerts
PRAVASTATIN	739,483 episodes	182,559 events	Unstable angina
ROSUVASTATIN	614,382 episodes	130,611 events	None
LOVASTATIN	266,578 episodes	55,165 events	None
PITAVASTATIN	22,051 episodes	3,692 events	None
FLUVASTATIN	15,351 episodes	3,095 events	None

- Sensitivity Analysis: No new alerts at the 3rd level (ie, more aggregated level) not driven by lower level results

Why not Rhabdomyolysis?

- Graham et al found a mean time of onset that exceed the observation period for this study (21-1050 days, mean: 348 days)



1. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of Hospitalized Rhabdomyolysis in Patients Treated With Lipid-Lowering Drugs. *JAMA.* 2004;292(21):2585–2590. doi:10.1001/jama.292.21.258

Statins Takeaways

- No new, unexpected alerts identified
  - Alerts were clinically explainable given drug's indication and patient population
  - Suggest method has ability to filter out noise even in large samples (discriminate)
- Despite exclusions, there is still some lingering pre-existing disease
  - May be masking (drowning out) the temporal patterns of other potential alerts.

Limitations

- Self-Controlled Design:
  - Depends on onset times in the data model
  - Cannot distinguish sustained elevated risk of outcome
  - Is vulnerable to time-varying confounding
- Current TreeScan Software Limitations:
  - Acute outcome events only with fixed follow-up
  - New version with varying follow-up available in 2018
    - Removes potential selection bias
    - Increase size of cohort and time available for study

Summary

- TreeScan supports multiple common study designs
  - Right design for right product
- Self-controlled TreeScan methods perform…
  - Best when applied to stable patients (e.g., contraceptives, vaccines)
  - Moderate performance for statins; Better performance when excluding recently hospitalized / unstable patients
  - Poor performance for acutely ill, unstable patients

SURVEILLANCE TOOLS

- Active Risk Identification and Analysis (ARIA)
- Routine Querying Tools (Modular Programs)
- Software Toolkits
- Health Outcome of Interest Validations and Literature Reviews

Software Toolkits

Sentinel has a library of standalone programming tools written to standardize routine programming procedures such as selecting a cohort of members exposed to specific medical products, creating continuous treatment episodes, or identifying continuous enrollment periods in the Common Data Model. Each tool is a self-contained SAS® macro. They can be used in combination to facilitate development of Sentinel routine querying tools.

A description of each macro along with the macro code are available at the links below. Any visitor to this website with access to data in the Common Data Model format can use these software toolkits.

SURVEILLANCE TOOLS

- Active Risk Identification and Analysis (ARIA)
- Routine Querying Tools (Modular Programs)
- Software Toolkits
- Health Outcome of Interest Validations and Literature Reviews

Software Toolkits

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Submit Comment

TreeExtraction Documentation

Project Title	**TreeExtraction Documentation**
Date Posted	*Wednesday, February 7, 2018*
Status	In progress
Deliverables	Sentinel Reusable Programs: TREE Extraction Program v1.2 SAS Package Toolkit: TreeExtraction v1.2 Macros and Input Files
Related Links	TreeScan for Drugs

COMMUNICATIONS

- FDA Safety Communications
- Publications and Presentations
- Sentinel Initiative Events
- Report Finder

Submit Comment

2017 ICPE Workshop: TreeScan™: A Novel Data-Mining Tool for Medical Product Safety Surveillance

Project Title	**2017 ICPE Workshop: TreeScan™: A Novel Data-Mining Tool for Medical Product Safety Surveillance**
Date	*Saturday, August 26, 2017*
Location	**Presentation** TreeScan™: A Novel Data-Mining Tool for Medical Product Safety Surveillance **Workshop Materials** 2011DxTree.txt Bernoulli.txt

Questions?

Knowledge Check

Website: www.zeetings.com/sentinel

Access code: Sentinel

Thank you!