Overview of Sentinel Analytic Tool Capabilities and IPW Analyses

13th Annual Sentinel Public Training

April 29th, 2022

Sentinel Operations Center | Harvard Pilgrim Health Care Institute

Agenda

01 **Introduction to Sentinel System and Overview of Analytic Capabilities**
Jennifer Lyons, PhD, MPH

02 **Inverse Probability Weighting: a Gentle Introduction**
Xiaojuan Li, PhD, MSPH

03 **Inverse Probability of Treatment Weighting (IPTW) in Sentinel**
John Connolly, ScD

Pre-Training Survey

Introduction to the Sentinel System

Jennifer Lyons, PhD, MPH

The Sentinel Initiative and Real World Data

The FDA has two big jobs. One—are the medical products we use SAFE? Two—are the medical products we use EFFECTIVE? In other words, are medical products doing the job they are supposed to do?

FDA is looking into how real world data like that in Sentinel might help FDA answer these important questions. Much of this real world data comes from health insurance companies and patients themselves.

How does Sentinel Work?

- Sentinel gets information from insurance claims, electronic health records, and patient reports.
- Sentinel uses computer programs to see how groups of patients are doing.
- This real world evidence can show if patients are getting bad side effects and maybe also if products are working.

What kinds of questions?

- What medicines are patients taking and why?
- Are medicines helping or hurting some patients more than others?
- Do side effects interfere with patients' lives?
- Are patients taking medicines the way their doctors prescribed?

What about privacy?

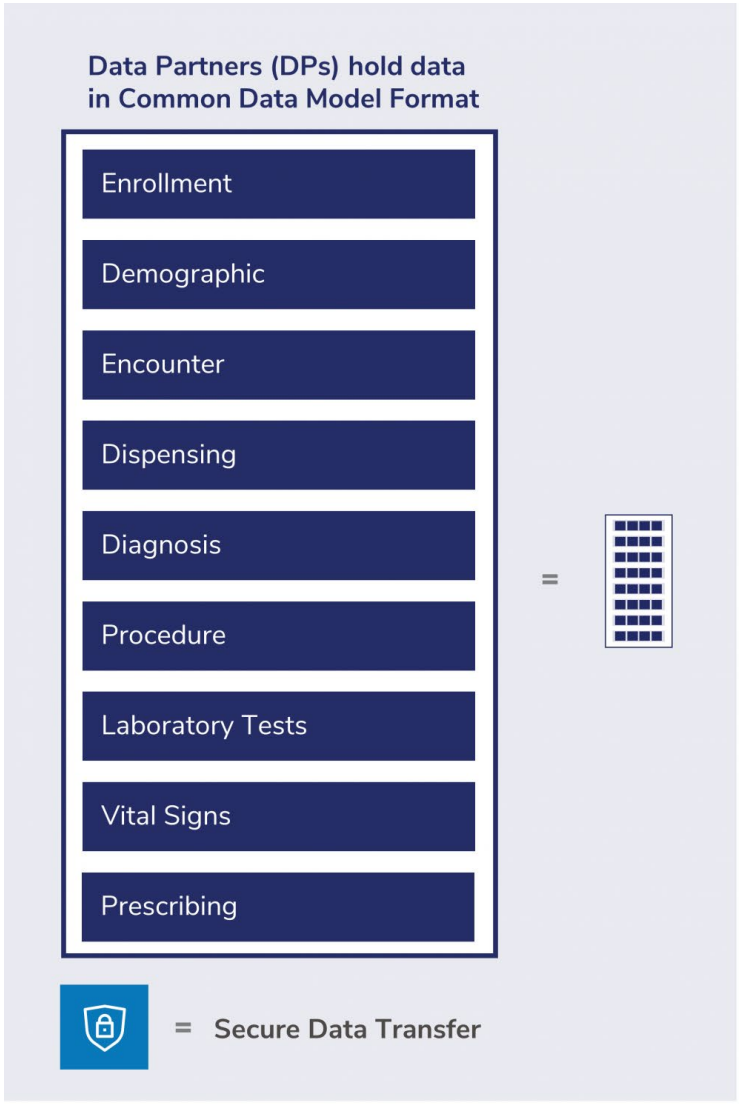
- No one looks at patients' names, addresses, phone numbers, or other identifying information.
- For more information please visit: https://www.sentinelinitiative.org/about/how-sentinel-protects-privacy-security

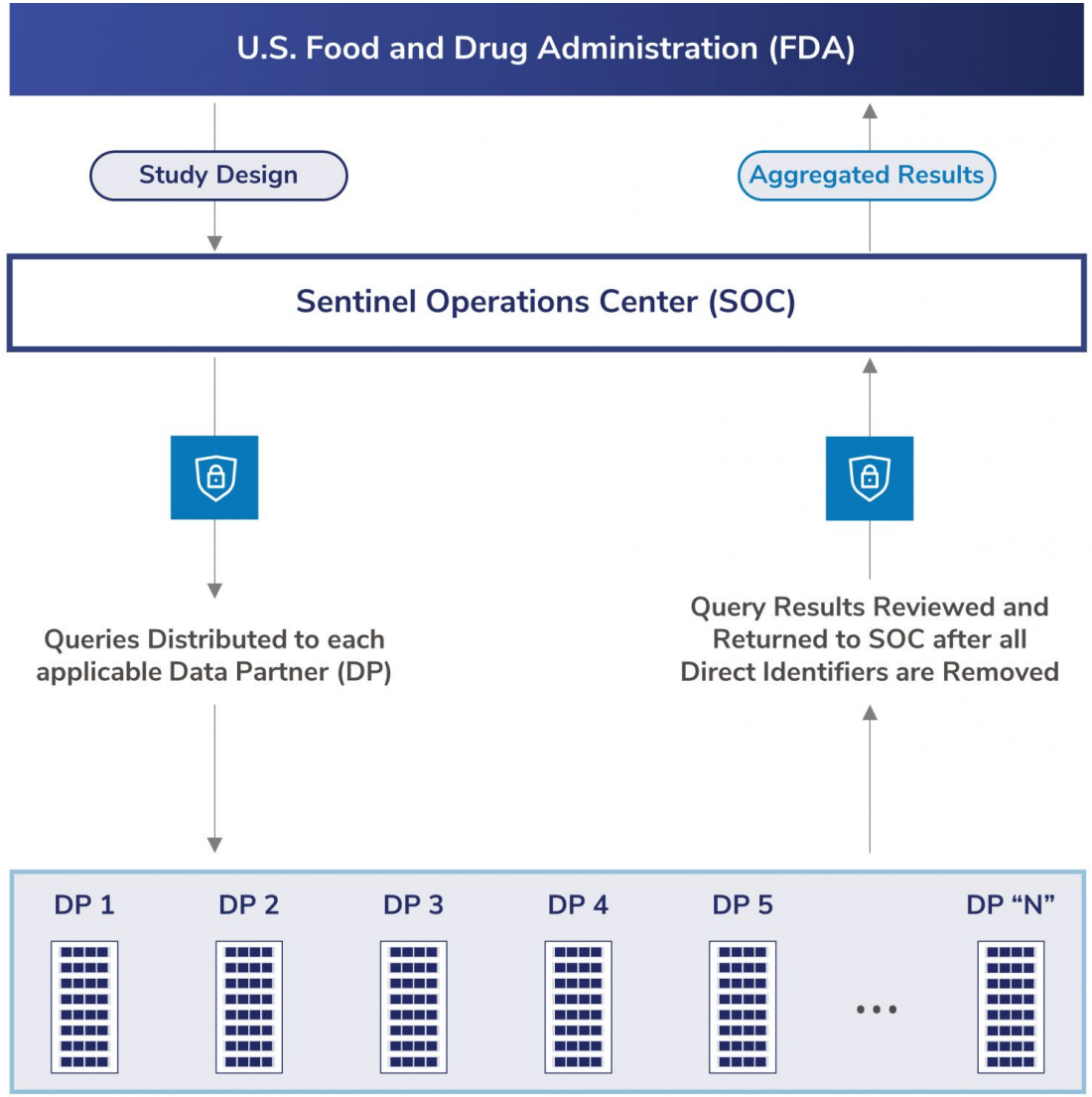
What happens next?

- FDA may use information from Sentinel to help determine whether medical products are safe and working.
- FDA warns patients and their doctors about bad side effects.
- If a patient has concerns about their medical products, they should contact their doctor.

https://www.sentinelinitiative.org/about/engaging-sentinels-stakeholders

Sentinel is a Distributed Data Network





https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

Collaborating Organizations

Lead: Harvard Pilgrim Health Care Institute

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

Point32Health

Data & Scientific Partners

HealthCore
Humana
OPTUM
TennCare
RTI International
veradigm
Penn Medicine
CVSHealth
aetna
GDIT
OPTUMLabs
pcornet
ADVANCE Collaborative
Massachusetts
Brigham Health
BWH Brigham and Women's Hospital
Kaiser Permanente
Colorado
Hawaii
Mid-Atlantic
Northern California
Northwest
Washington
CAPriCORN
GPC Greater Plains Collaborative
Booz | Allen | Hamilton
Marshfield Clinic Research Institute
Harvard T.H. Chan School of Public Health
CMS Centers for Medicare & Medicaid Services
NYC-CDRN New York City Clinical Data Research Network
UF College of Pharmacy University of Florida
Rutgers
REACHnet
IBM Watson Health
Vanderbilt University Medical Center
The Meyers Primary Care Institute
Kaiser Permanente Washington Health Research Institute
OneFlorida Clinical Research Consortium
PaTH Network patient empowered research
PEDSnet A Pediatric Learning Health System
HealthPartners Institute
School of Public Health University of Washington
UAB
HCA Healthcare
UNC Gillings School of Global Public Health
STAR Stakeholders, Technology, and Research CRN
Duke Clinical Research Institute
The University of Iowa College of Public Health
TriNetX
Sentinel Initiative

Sentinel Data Philosophy

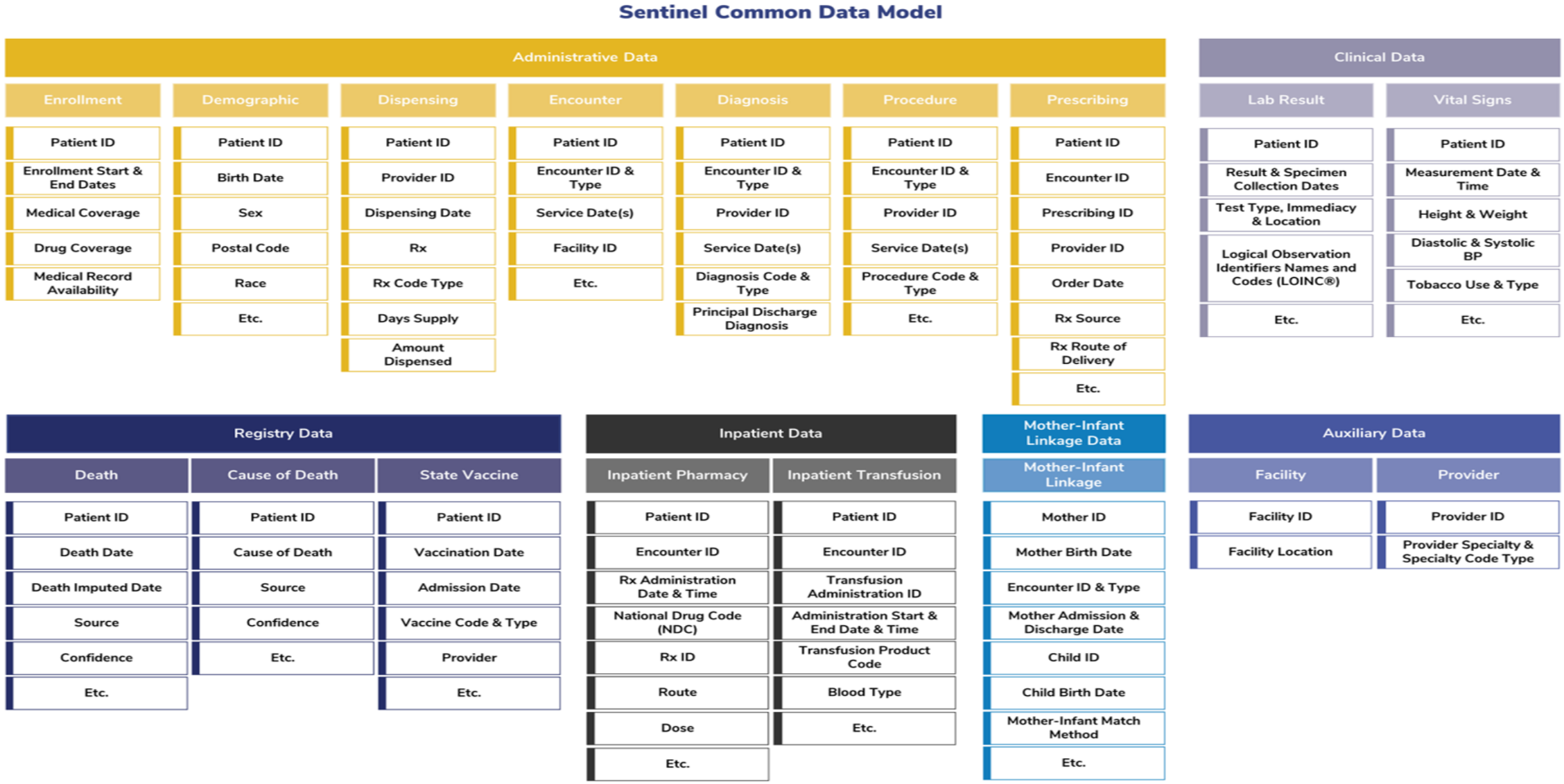
- Predominantly includes claims and a subset of electronic health record (EHR) and registry data and flexible enough to accommodate new data domains (e.g., free text)
  - Typically, we do not include empty tables – we expand as needed when fit for purpose

- Data are stored at most granular/raw level possible with minimal mapping
  - Distinct data types should be kept separate (e.g., prescriptions, dispensings)
  - Construction of medical concepts (e.g., outcome algorithms) from these elemental data is a project-specific design choice
  - Sentinel stores these algorithms in a library for future use

- Appropriate use and interpretation of local data requires the Data Partners' local knowledge and data expertise
  - Not all tables are populated by all Data Partners ➔ site-specificity is allowed

- Designed to meet FDA needs for analytic flexibility, transparency, and control

Available Data Elements



https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Single Patient Example Data in Common Data Model

DEMOGRAPHIC

PATID	BIRTH_DATE	SEX	HISPANIC	RACE	zip
PatID1	2/2/1984	F	N	5	32818

ENROLLMENT

PATID	ENR_START	ENR_END	MEDCOV	DRUGCOV
PatID1	7/1/2004	12/31/2006	Y	Y
PatID1	9/1/2007	6/30/2009	Y	Y

DISPENSING

PATID	RXDATE	NDC	RXSUP	RXAMT
PatID1	10/14/2005	00006074031	30	30
PatID1	10/14/2005	00185094098	30	30
PatID1	10/17/2005	00378015210	30	45
PatID1	10/17/2005	54092039101	30	30
PatID1	10/21/2005	00173073001	30	30
PatID1	10/21/2005	49884074311	30	30
PatID1	10/21/2005	58177026408	30	60
PatID1	10/22/2005	00093720656	30	30

ENCOUNTER

PATID	ENCOUNTERID	ADATE	DDATE	ENCTYPE
PatID1	EncID1	10/18/2005	10/20/2005	IP

DIAGNOSIS

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	DX	DX_CODETYPE	PDX
PatID1	EncID1	10/18/2005	Provider1	IP	296.2	9	P
PatID1	EncID1	10/18/2005	Provider1	IP	300.02	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	311	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	401.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	493.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	715.9	9	S

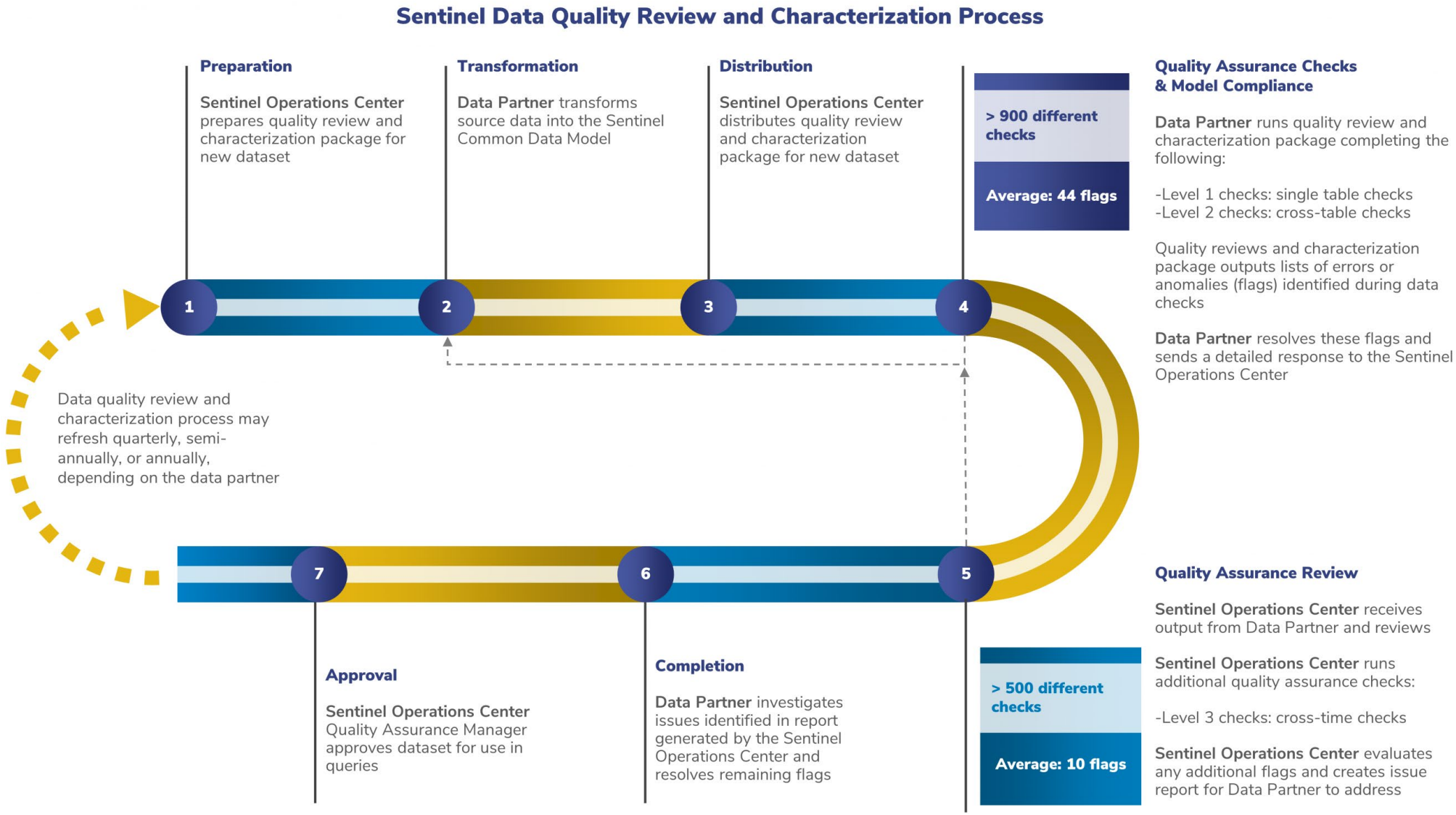
PROCEDURE

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4

MOTHER-INFANT LINKAGE

MPATID	ADATE	DDATE	CPATID	CBIRTH_DATE	CSEX	CENR_START	BIRTH_TYPE	MATCHMETHOD
PatID1	5/3/2006	5/5/2006	PatID2	5/2/2006	M	6/1/2006	1	SI

Data Quality Review and Characterization Process



https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

Data Quality Checks and Examples

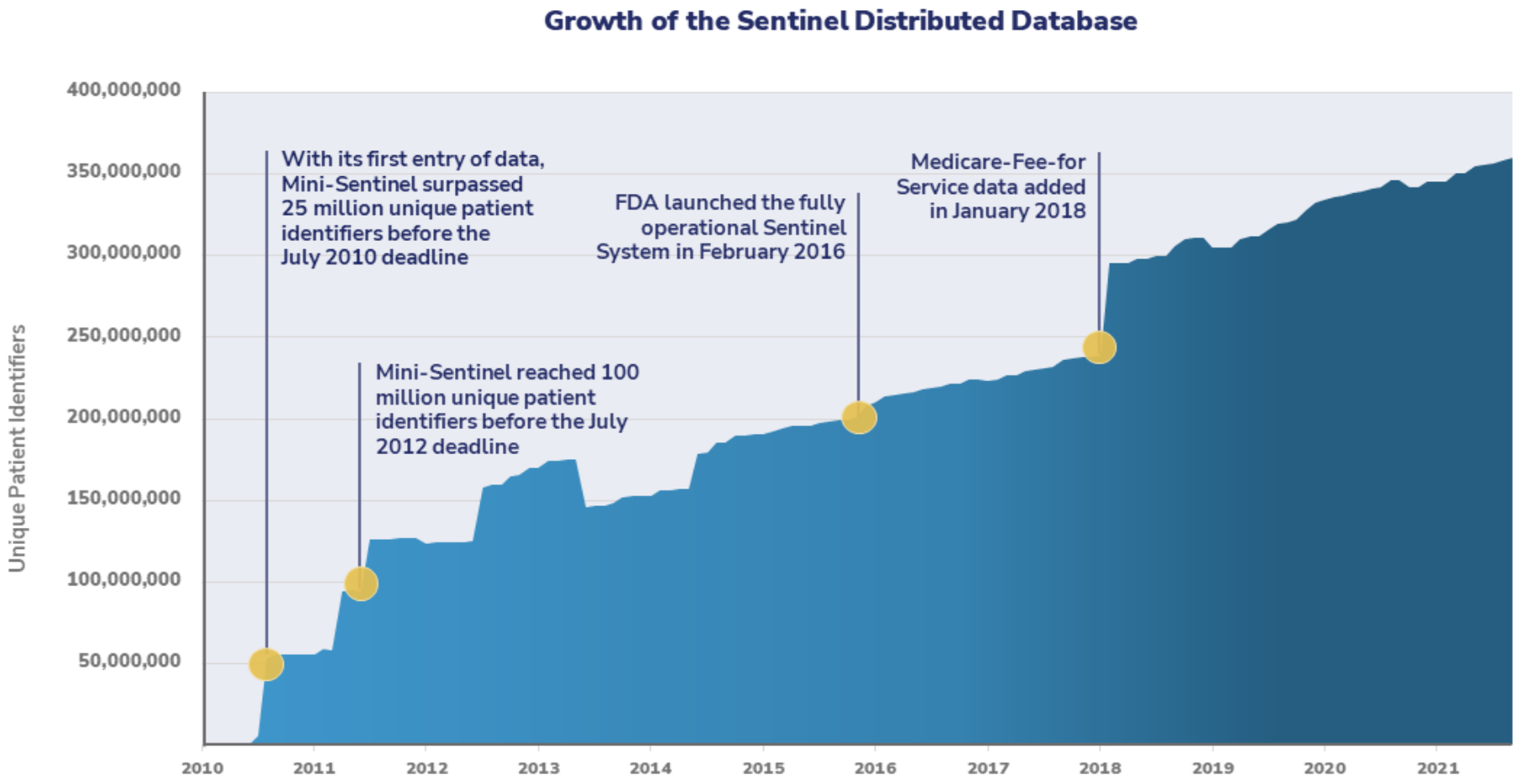
Types of Data Quality Checks and Examples

Level 1 Checks: Single table checks	✓ **Completeness** Admission date is not missing value ✓ **Validity** Admission date is in date format
Level 2 Checks: Cross-table checks	✓ **Accuracy** Admission date occurs before the patient's discharge ✓ **Integrity** Admission date occurs within the patient's active enrollment period
Level 3 Checks: Cross-time checks	✓ **Consistency of Trends** There is no sizable percent change in admission date record counts by month-year

https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

Growth of the Sentinel Distributed Database

A total of 360.2 million unique patient identifiers and 64.3 million members currently accruing new data (as of 6/2021)



https://www.sentinelinitiative.org/about/key-database-statistics

Overview of Sentinel Analytic Tool Capabilities

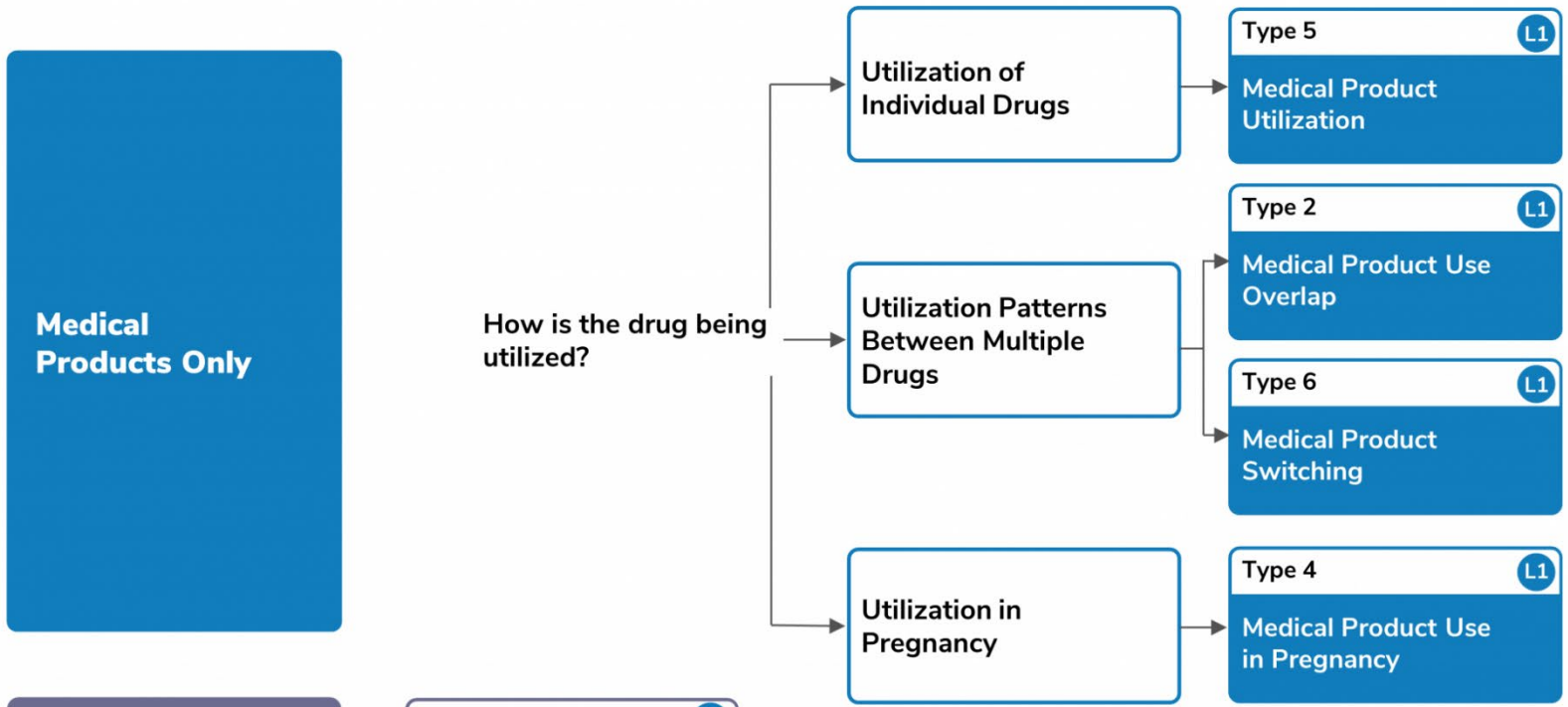
Active Risk Identification and Analysis (ARIA)

- Template computer programs with standardized questions
- Parameterized at program execution
- Pre-tested and quality-checked
- Standard output

https://www.sentinelinitiative.org/studies/drugs

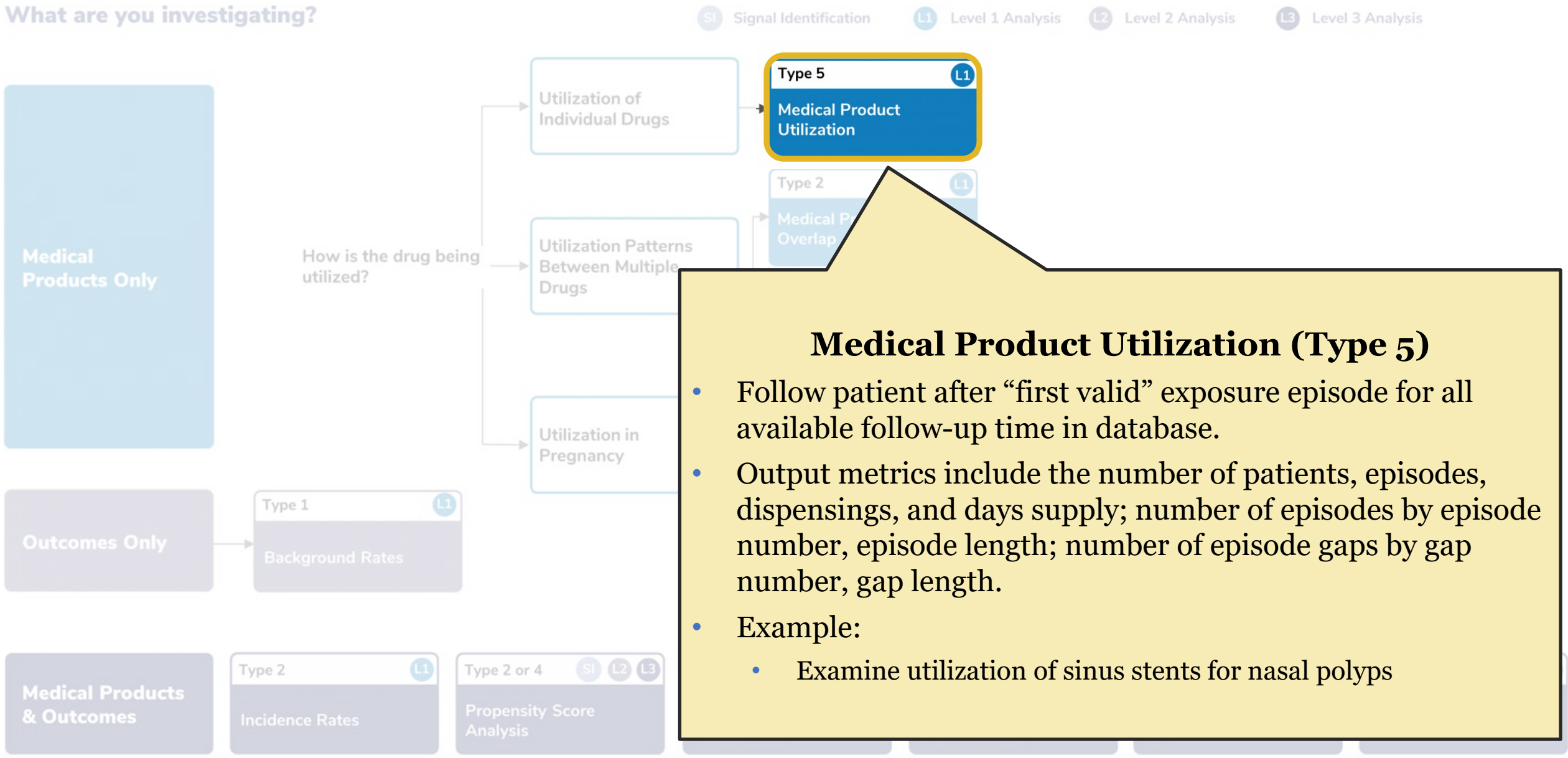
What are you investigating?

SI Signal Identification L1 Level 1 Analysis L2 Level 2 Analysis L3 Level 3 Analysis



Medical Products & Outcomes						
Type 2 L1 Incidence Rates	Type 2 or 4 SI L2 L3 Propensity Score Analysis	Type 2 or 4 L2 L3 Covariate Stratification	Type 3 SI L2 L3 Self-Controlled Risk Interval Design	Type 2 L2 Interrupted Time Series	Type 2 L1 Multiple Events Tool

https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools



Medical Product Utilization (Type 5)

- Follow patient after "first valid" exposure episode for all available follow-up time in database.
- Output metrics include the number of patients, episodes, dispensings, and days supply; number of episodes by episode number, episode length; number of episode gaps by gap number, gap length.
- Example:
  - Examine utilization of sinus stents for nasal polyps

https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools

What are you investigating?

L3 Level 3 Analysis

Medical Products Only

Outcomes Only

Medical Products & Outcomes

Type 2

Incidence Rates

Type 2 L2

Interrupted Time Series

Type 2 L1

Multiple Events Tool

Mometasone Furoate (MF) Sinus Implant Use in Patients with Nasal Polyps: A Descriptive Analysis

Details | **Additional Information**

Date Posted: Thursday, March 3, 2022

Status: COMPLETE

Medical Product: mometasone sinus implant

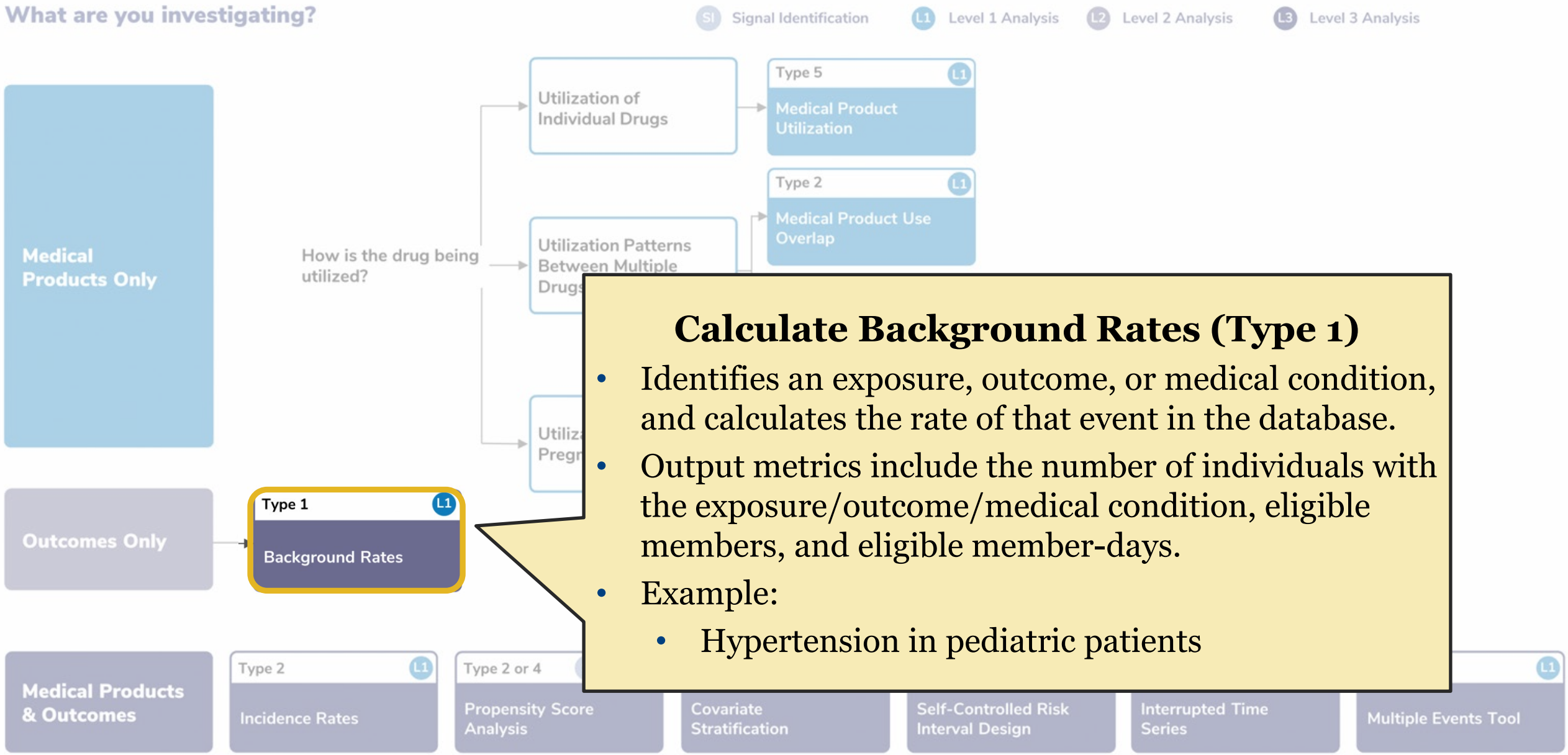
Table 2a. Descriptive Statistics of Cumulative Mometasone Furoate (MF) Sinus Stent Exposure Episode Duration in the Sentinel Distributed Database (SDD) between January 1, 2016 and April 30, 2021, in Days, Overall

Exposures	Total Patients	Mean	Standard Deviation	Minimum	Q1	Median	Q3	Maximum
Propel MF Sinus Stent Single Use Cohort	21,869	1.59	3.49	1	1	1	1	252
Sinuva MF Repeat Use Cohort	406	21.85	29.78	1	1	4	30	210
Sinuva MF Single Use Cohort	366	21.22	28.92	1	1	2	30	210
Sinuva MF Single Use and No Cataracts Cohort	270	22.77	28.51	1	1	30	30	180
Sinuva MF Single Use and No Glaucoma Cohort	349	21.37	29.27	1	1	2	30	210
Sinuva MF Single Use Incident on Self Cohort	403	21.71	29.67	1	1	2	30	210
Sinuva MF Single Use Incident on Self and No Cataracts Cohort	297	23.28	29.01	1	1	30	30	180
Sinuva MF Single Use Incident on Self and No Glaucoma Cohort	384	21.90	30.07	1	1	4	30	210

Deliverables (1)

Sentinel Modular Program Report: Mometasone Furoate (MF) Sinus Implant Use in Patients with Nasal Polyps: A Descriptive Analysis

https://www.sentinelinitiative.org/studies/drugs/individual-drug-queries/mometasone-furoate-mf-sinus-implant-use-patients-nasal-polyps



Calculate Background Rates (Type 1)

- Identifies an exposure, outcome, or medical condition, and calculates the rate of that event in the database.
- Output metrics include the number of individuals with the exposure/outcome/medical condition, eligible members, and eligible member-days.
- Example:
  - Hypertension in pediatric patients

https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools

Hypertension in Pediatric Patients: A Descriptive Analysis

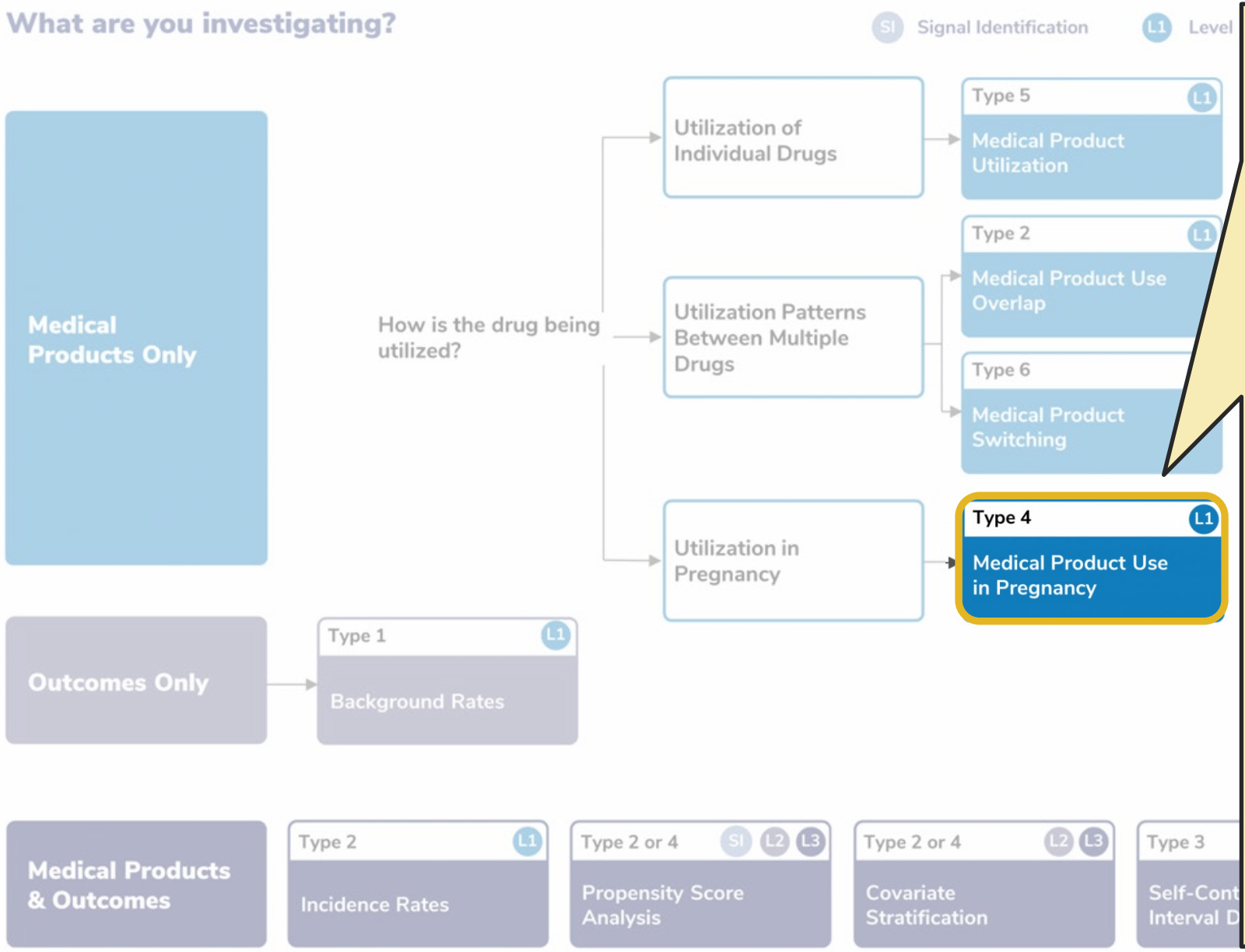
Project Title	**Hypertension in Pediatric Patients: A Descriptive Analysis**
Date Posted	Thursday, July 23, 2020
Project ID	cder_mpl1r_wp149
Population/ Cohort	Individuals 17 years of age and younger
Time Period	January 1, 2008 - April 30, 2019
Assessment Type	Exploratory Analyses
Study Type	Modular Program
Data Sources	Sentinel Distributed Database (SDD)
FDA Center	CDER

Table 2a. Summary of Members with Pediatric Hypertension in the Sentinel Distributed Database (SDD) between January 1, 2008 and April 30, 2019, by Hypertension Definition[1]

	Members with Diagnosis	Number of Diagnoses	Eligible Members[2]	Eligible Member-Years[2]	Members with Diagnosis per 10,000 Eligible Members
Hypertension Definition 1	62,363	272,204	26,493,696	67,740,191.5	23.54
Hypertension Definition 2	141,860	427,526	26,493,696	67,740,191.5	53.54

[1]Hypertension Definition 1: 2 outpatient claims within 183 days OR 1 inpatient claim
Hypertension Definition 2: Any hypertension claim
[2]Eligible members and member-years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period

https://www.sentinelinitiative.org/studies/drugs/individual-drug-queries/hypertension-pediatric-patients-descriptive-analysis



Construct Pregnancy Episodes and Identify Medical Product Use (Type 4)

- Identifies live births to create pregnancy episodes and assesses medical product use during pregnancy episodes and in a comparator group of women.
- Output metrics include number of pregnancy episodes, medication use stratified by trimester.
- Example:
  - Evaluate use of multiple sclerosis drugs among pregnant patients with live-birth deliveries

https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools

What are you investigating?

L2 Level 2 Analysis L3 Level 3 Analysis

Medical Products

Outcomes

Use of Multiple Sclerosis Drugs Among Pregnant Women with Live-Birth Deliveries: A Descriptive Analysis

Details Additional Information

Date Posted: Wednesday, October 20, 2021

Table 4. Medical Product of Interest Use During Any Trimester and Matched Non-Pregnant Episodes in the Sentinel Distributed Database (SDD) Among the Pregnant Cohort and Matched Comparator Cohort, by Calendar Year, from January 1, 2001 to December 31, 2020

	2017		2018		2019		2020	
	Number	Percent	Number	Percent	Number	Percent	Percent	Percent
Pregnant Cohort								
Medical Product of Interest								
All MS Drugs	153	0.1	130	0.1	116	0.1	28	0.1
Dalfampridine	3	0.0	2	0.0	2	0.0	1	0.0
Dimethyl fumarate	28	0.0	33	0.0	18	0.0	6	0.0
Fingolimod	14	0.0	11	0.0	9	0.0	3	0.0
Glatiramer Acetate	77	0.0	60	0.0	61	0.0	11	0.0
Interferon beta-1a	16	0.0	14	0.0	8	0.0	3	0.0
Interferon beta-1b	4	0.0	0	0.0	0	0.0	0	0.0
Peginterferon beta-1a	2	0.0	1	0.0	1	0.0	0	0.0
Teriflunomide	0	0.0	3	0.0	3	0.0	1	0.0
Alemtuzumab	1	0.0	0	0.0	1	0.0	0	0.0
Natalizumab	13	0.0	9	0.0	13	0.0	8	0.0
Ocrelizumab	0	0.0	0	0.0	4	0.0	1	0.0
Cladribine	0	0.0	0	0.0	0	0.0	0	0.0
Siponimod	0	0.0	0	0.0	0	0.0	0	0.0
Diroximel fumarate	0	0.0	0	0.0	0	0.0	0	0.0
Mitoxantrone	0	0.0	0	0.0	0	0.0	0	0.0

Deliverables (1)

Sentinel Modular Program Report: Use of Multiple Sclerosis Drugs Among Pregnant Women with Live-Birth Deliveries: A Descriptive Analysis

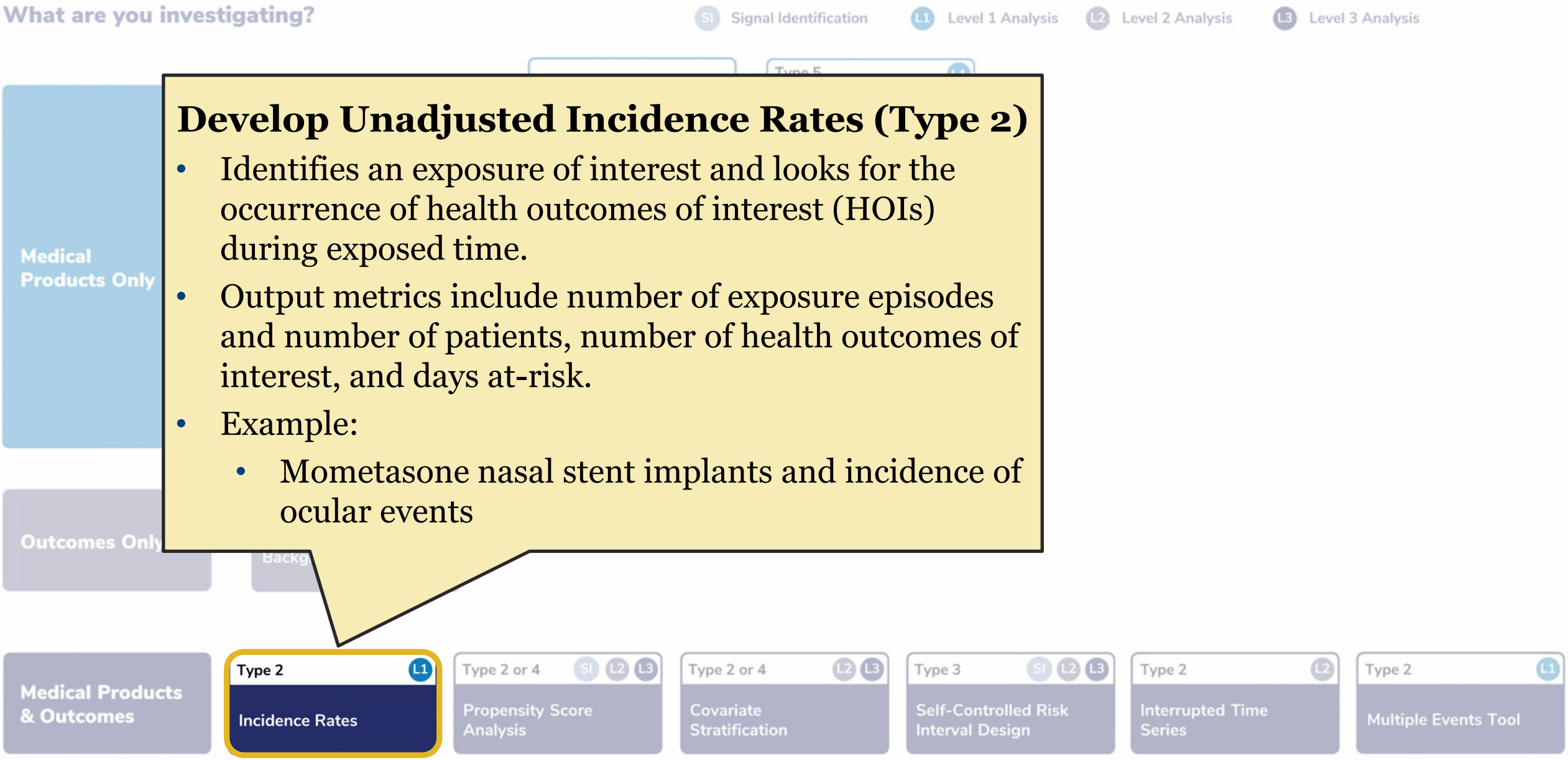
Medical Products & Outcomes

Type 2 — Incidence Rates

Type 2 L2 — terrupted Time eries

Type 2 L1 — Multiple Events Tool

https://www.sentinelinitiative.org/studies/drugs/individual-drug-queries/use-multiple-sclerosis-drugs-among-pregnant-women-live-birth



Develop Unadjusted Incidence Rates (Type 2)

- Identifies an exposure of interest and looks for the occurrence of health outcomes of interest (HOIs) during exposed time.
- Output metrics include number of exposure episodes and number of patients, number of health outcomes of interest, and days at-risk.
- Example:
  - Mometasone nasal stent implants and incidence of ocular events

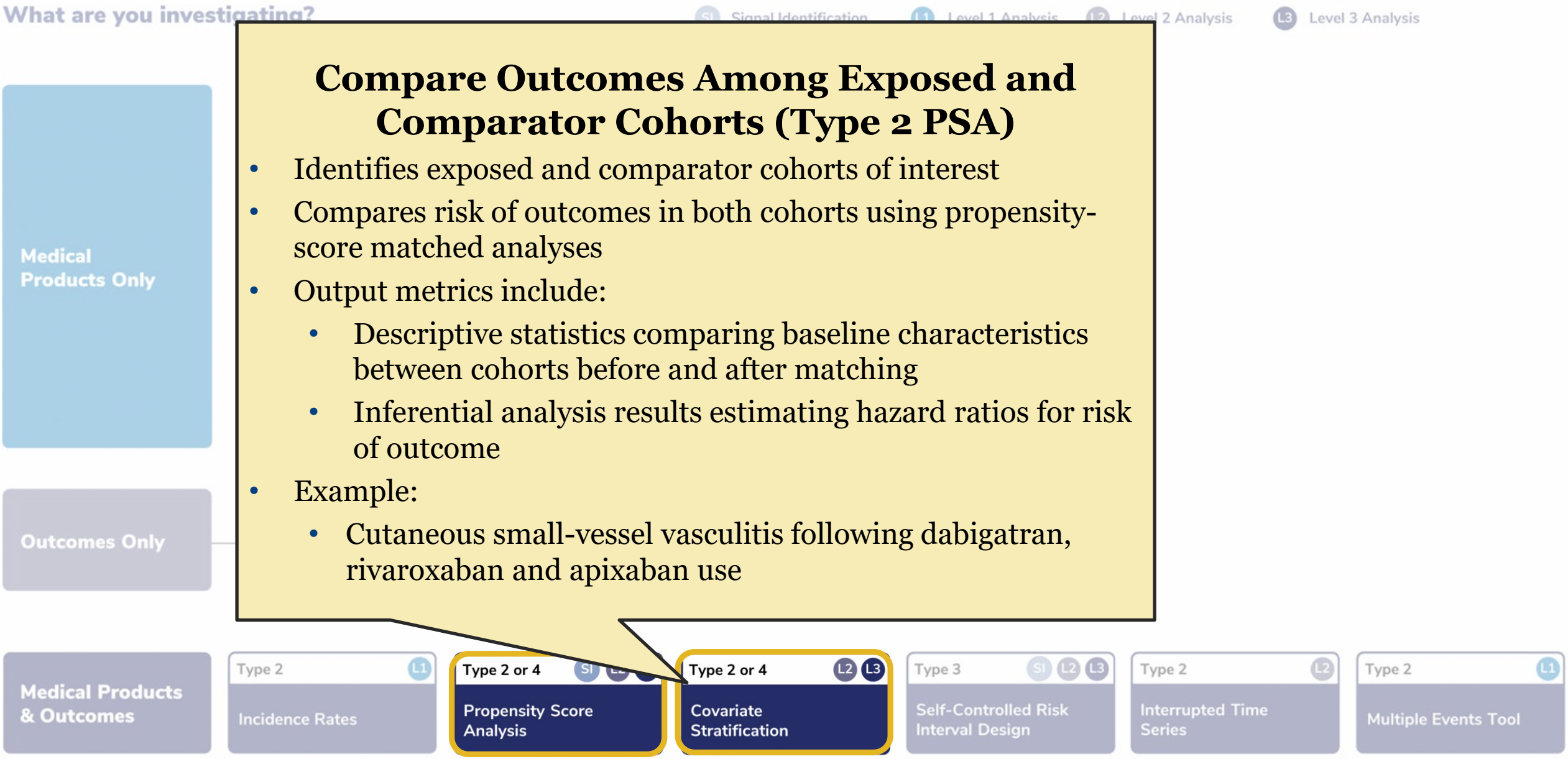
https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools

Glaucoma, Cataracts, Diminished Visual Acuity, and Nasal Septal Perforation following Mometasone Sinus Implant Use in Patients with Nasal Polyposis: A

Table 2. Summary of Glaucoma and Cataract Events in Single and Repeat Mometasone Stent Implant Users in the Sentinel Distributed Database (SDD) between January 1, 2016 and September 30, 2019, Overall

	Number of Users	Eligible Members[1]	Number of Exposed Patients per 1,000 Eligible Members	Years at Risk	Average Years at Risk	All Events	Number of Users with an Event	Number of Exposed Members with an Outcome per 1,000 Years at Risk
Glaucoma								
Single Propel Stent (One-year follow-up)	3,340	308,788	10.82	2,471.8	0.74	189	104	42.07
Single Sinuva Stent (One-year follow-up)	111	308,788	0.36	*****	*****	*****	*****	48.39
Single Sinuva Stent (One-year follow-up, incident with respect to self)	118	310,221	0.38	*****	*****	*****	*****	46.15
Repeat Propel Stent (One-year follow-up)	36	310,229	0.12	*****	*****	*****	*****	35.59
Repeat Sinuva Stent (One-year follow-up)	18	310,229	0.06	9.0	0.50	0	0	0.00
Single Propel Stent (Two-year follow-up)	3,321	308,788	10.75	3,666.2	1.10	329	140	
Single Sinuva Stent (Two-year follow-up)	111	308,788	0.36	*****	*****	*****	*****	44.98
Single Sinuva Stent (Two-year follow-up, incident with respect to self)	118	310,221	0.38	*****	*****	*****	*****	42.74
Repeat Propel Stent (Two-year follow-up)	36	310,229	0.12	*****	*****	*****	*****	23.87
Repeat Sinuva Stent (Two-year follow-up)	18	310,229	0.06	9.9	0.55	0	0	0.00

https://www.sentinelinitiative.org/studies/drugs/individual-drug-queries/glaucoma-cataracts-diminished-visual-acuity-and-nasal-septal



Compare Outcomes Among Exposed and Comparator Cohorts (Type 2 PSA)

- Identifies exposed and comparator cohorts of interest
- Compares risk of outcomes in both cohorts using propensity-score matched analyses
- Output metrics include:
  - Descriptive statistics comparing baseline characteristics between cohorts before and after matching
  - Inferential analysis results estimating hazard ratios for risk of outcome
- Example:
  - Cutaneous small-vessel vasculitis following dabigatran, rivaroxaban and apixaban use

https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools

What are you investigating?

L2 Level 2 Analysis L3 Level 3 Analysis

Cutaneous Small-Vessel Vasculitis following Dabigatran, Rivaroxaban, and Apixaban Use in Patients with Atrial Fibrillation: A Propensity Score Matched Analysis

Details | Additional Information

Date Posted: Wednesday, February 3, 2021

Status: COMPLETE

Table 2. Effect Estimates for Risk of Cutaneous Small-Vessel Vasculitis (CSVV) among New Initiators of Rivaroxaban and Warfarin in the Sentinel Distributed Database (SDD) between October 19, 2010 and February 29, 2020, by Analysis Type[1]

Medical Product	Number of New Users	Person Years at Risk	Average Person Days at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1,000 Person Years	Risk per 1,000 New Users	Incidence Rate Difference per 1,000 Person Years	Difference in Risk per 1,000 New Users	Hazard Ratio (95% Confidence Interval)	Wald P-Value
Site-Adjusted Analysis											
Rivaroxaban	328,249	131,787.96	146.64	0.40	55	0.42	0.17	-0.02	0.01	0.94 (0.67, 1.31)	0.710
Warfarin	618,915	218,317.79	128.84	0.35	96	0.44	0.16				
Fixed Ratio 1:1 Propensity Score Matched Conditional Analysis; Caliper= 0.05[2]											
Rivaroxaban	320,363	53,844.35	61.39	0.17	25	0.46	0.08	0.07	0.01	1.19 (0.67, 2.13)	0.556
Warfarin	320,363	53,844.35	61.39	0.17	21	0.39	0.07				
Fixed Ratio 1:1 Propensity Score Matched Unconditional Analysis; Caliper= 0.05											
Rivaroxaban	320,363	129,368.40	147.49	0.40	53	0.41	0.17	-0.04	0.01	0.94 (0.64, 1.39)	0.765
Warfarin	320,363	114,241.24	130.25	0.36	51	0.45	0.16				

[1]A total of 14 participating Data Partners converged to this propensity score analysis (PSA).

[2]Conditional analysis accounts for informative events and person-time.

Sentinel Analytic Package: Cutaneous Small-Vessel Vasculitis following Dabigatran, Rivaroxaban, and Apixaban Use in Patients with Atrial Fibrillation: A Propensity Score Matched Analysis

Sentinel Modular Program Report: Cutaneous Small-Vessel Vasculitis following Dabigatran, Rivaroxaban, and Apixaban Use in Patients with Atrial Fibrillation: A Propensity Score Matched Analysis

Medical Products & Outcomes

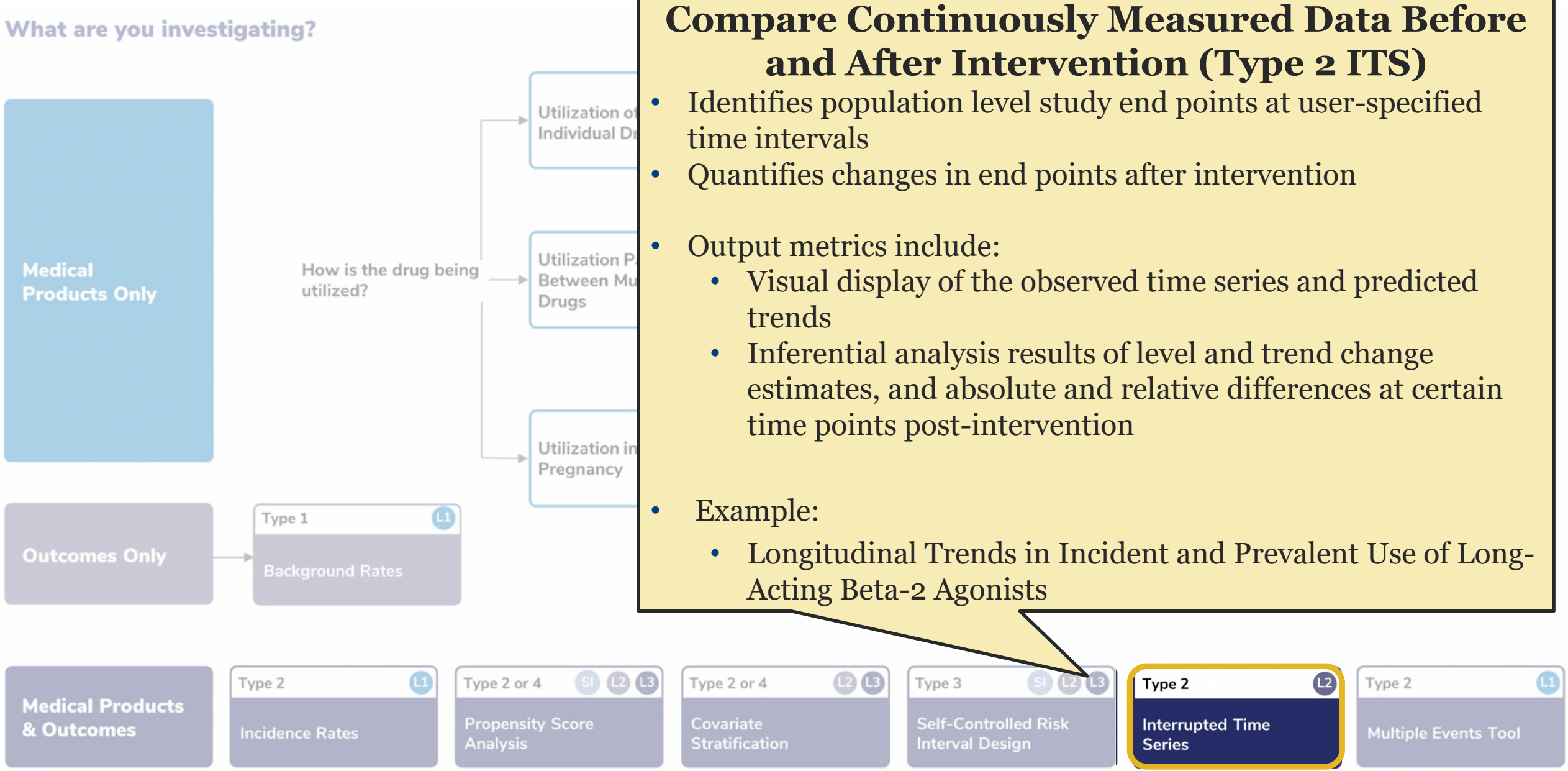
Type 2 L1 Incidence Rates

L2 L3

Type 2 L2 Interrupted Time Series

Type 2 L1 Multiple Events Tool

https://www.sentinelinitiative.org/studies/drugs/individual-drug-queries/cutaneous-small-vessel-vasculitis-following-dabigatran



Compare Continuously Measured Data Before and After Intervention (Type 2 ITS)

- Identifies population level study end points at user-specified time intervals
- Quantifies changes in end points after intervention

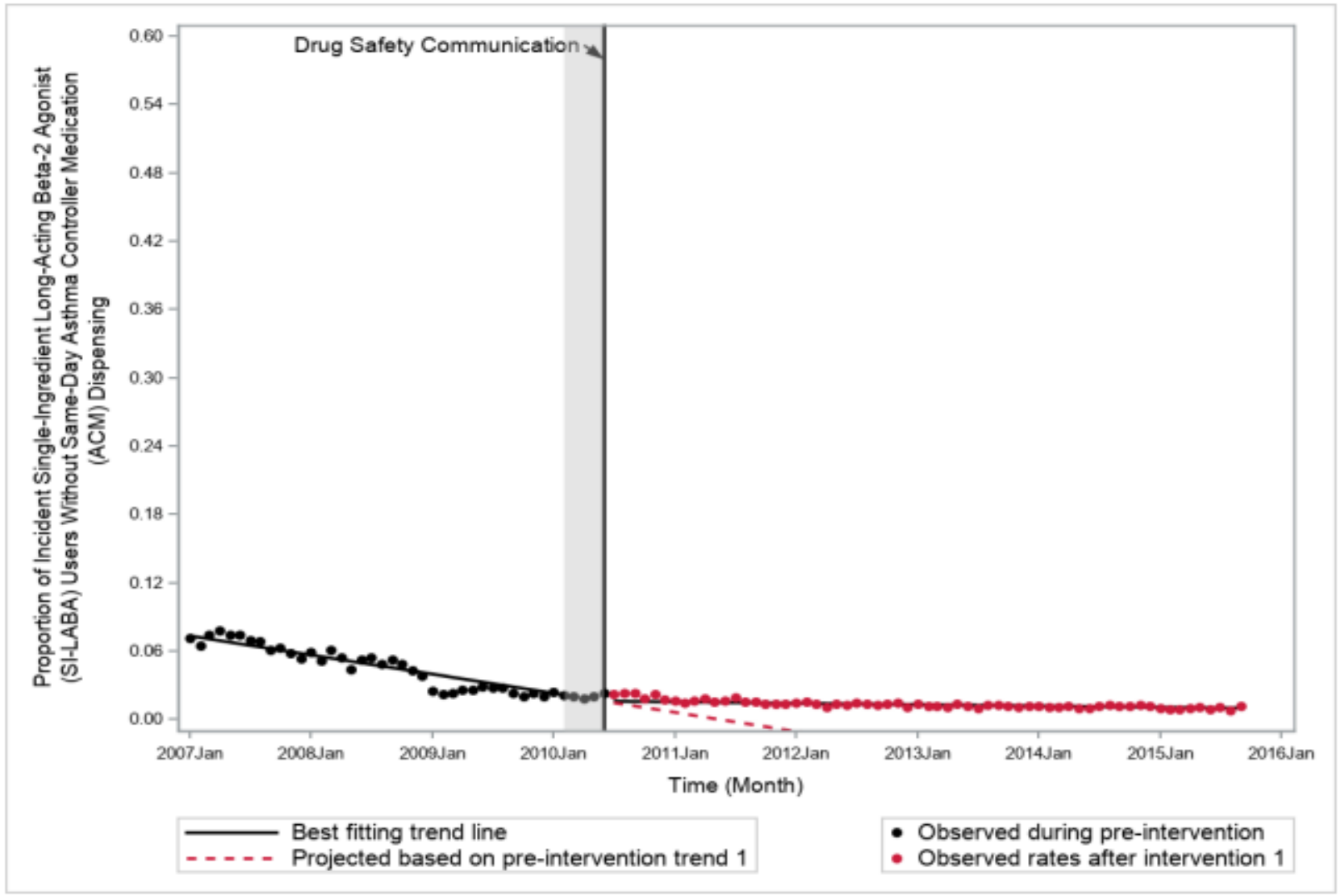
- Output metrics include:
  - Visual display of the observed time series and predicted trends
  - Inferential analysis results of level and trend change estimates, and absolute and relative differences at certain time points post-intervention

- Example:
  - Longitudinal Trends in Incident and Prevalent Use of Long-Acting Beta-2 Agonists

https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools

Longitudinal Trends in Incident and Prevalent use of Long-Acting Beta-2 Agonists:
An Interrupted Time Series Analysis

Figure 1. Proportion of Incident Single-Ingredient Long-Acting Beta-2 Agonist (SI-LABA) Users Without Same-Day Asth
Controller Medication (ACM) Dispensing Among Incident LABA Users Before and After June 2, 2010[1,2]



What are you investiga

Level 3 Analysis

Medical Products Only

Outcomes Only

Medical Products & Outcomes

Type 2

Multiple Events Tool

presence of ACM or FDC-LABA dispensings among LABA-naive patients with poorly-controlled

Sentinel's Public Documentation and SAS Program Depot (Public GIT) dev.sentinelsystem.org

Data Quality Review and Characterization Programs

Overview

This document describes the program package used to perform quality assurance (QA) review and characterization of data in the Sentinel Common Data Model (SCDM) format. This program package helps to ensure the data meets the necessary standards for data transformation consistency and quality.

Analytic programs that are executed against data that is not in SCDM format will likely yield errors. Successful execution of the QA package indicates that the source data adheres to SCDM rules. Note that data must be in the form of SAS® datasets in order to use these analytic programs.

The specifications for the QA Package can be found in the QA Documentation repository.

Folder Structure

- **docs**: Contains the QA Data Dictionaries: These are appendices to the specifications which describe datasets output by the QA Package into the `dplocal` and `msoc` folders
- **dplocal**: is where datasets with patient identifiers are saved. For more information about Sentinel's privacy standards, please refer to **The Sentinel System Principles and Policies**
- **inputfiles**: is the subfolder containing all input files and lookup tables needed to execute a request. Input files contain information on what tables should be output and the type of analyses conducted on the variables in each table
- **msoc**: is where aggregated program results are saved
- **sasprograms**: contains the file(s) to be executed

Requirements

- UNIX/Linux or Windows environment
- SAS version 9.4 or higher (as of OY 2021)
- SCDM formatted data (Medicare Claims Synthetic Public Use Files are available in the Sentinel Common Data Model Format **here**)

https://dev.sentinelsystem.org/projects/QA/repos/qa_package/browse

Cohort Identification and Descriptive Analysis (CIDA)

Sentinel Routine Querying System Overview

The purpose of this repository is to document version 11.2.4 of the Sentinel Routine Querying System, also known as the Query Request Package (QRP). This system is comprised of cohort identification and Analytic Modules. This version of the QRP contains version 1.2.4 of the QRP Reporting Tool.

This documentation describes QRP capabilities and provides the information required to build query packages (i.e., input and output specifications) to address questions of interest.

For details on modifications between release versions, view the Modification History table **here**.

Cohort Identification And Descriptive Analysis (CIDA) Module

QRP's Cohort Identification and Descriptive Analysis Module (CIDA) identifies and extracts cohorts of interest from the Sentinel Distributed Database based on user-defined options (e.g., exposures, outcomes, continuous enrollment requirements, incidence criteria, inclusion/exclusion criteria, relevant age groups, demographics).

CIDA calculates descriptive statistics for the cohort(s) of interest and outputs datasets needed for additional analyses.

CIDA Cohort Identification Strategies

- Type 1: **Extract information to calculate background rates**
- Type 2: **Extract information on exposures and follow-up time**
- Type 3: **Extract information for a self-controlled risk interval design**
- Type 4: **Extract information for medical product use during pregnancy**
- Type 5: **Extract information for medical product utilization**
- Type 6: **Extract information on manufacturer-level product utilization and switching patterns**

https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse

Downloading Sentinel Analytic Packages

Sentinel

Sentinel Analytic Packages

Overview

A Sentinel analytic package is a standard folder structure containing detailed user-defined specifications, input files, SAS® macros, and SAS programs used to conduct Sentinel's routine querying analyses. A package allows the user to select the cohort(s) of interest in order to examine their health profile and outcomes.

Sentinel's analytic request packages are intended to run on data formatted in accordance with the Sentinel Common Data Model (SCDM). Note that data must be in SAS datasets to use these analytic programs.

Analytic Request Packages Available for Download

Request ID	Summary
cder_mpl2p_wp028	Thromboembolic Stroke, Major Extracranial Bleeding, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Direct Oral Anticoagulant Use: An Inverse Probability of Treatment Weighting Analysis
cder_mpl2p_wp020	Intentional Self-Harm and Hospitalized Depression Following Sertraline Use: A Propensity Score Matched Analysis (an update to cder_mpl2p_wp012)
cder_mpl2p_wp012	Intentional Self-Harm and Hospitalized Depression Following Sertraline Use: A Propensity Score Matched Analysis
cder_mpl2r_wp012	Longitudinal Trends in Incident and Prevalent use of Long-Acting Beta-2 Agonists: An Interrupted Time Series Analysis
cder_mpl2r_wp012	Longitudinal Trends in Incident and Prevalent use of Long-Acting Beta-2 Agonists: An Interrupted Time Series Analysis
cder_mpl2p_wp021	Angioedema following Sacubitril/Valsartan Use in Patients with Heart Failure: A Propensity Score Analysis, Part 2
cder_mpl2r_wp016	Angioedema following Sacubitril/Valsartan Use in Patients with Heart Failure: A Propensity Score Analysis, Part 1
cder_mpl2r_wp014	Cutaneous Small-Vessel Vasculitis following Dabigatran, Rivaroxaban, and Apixaban Use in Patients with Atrial Fibrillation: A Propensity Score Matched Analysis
cder_mpl2p_wp025	Thromboembolic Stroke, Intracranial Hemorrhage, Gastrointestinal Bleeding, and Major Extracranial Bleeding following Dabigatran, Rivaroxaban, and Apixaban Use in Patients with Atrial Fibrillation: A Propensity Score Matched Analysis
cder_mpl2r_wp015	A New Propensity Score Matched Analysis Tool for Pregnancy: Replicating A Study of Oral Clefts following Topiramate Use during the First Trimester of Pregnancy
cder_mpl2p_wp015	Factors Related to the Assignment of Sodium Glucose Cotransporter-2 Inhibitors (SGLT-2i) versus Dipeptidyl Peptidase-4 Inhibitors (DPP-4i)
cder_mpl2p_wp017	Stroke, Intracranial Hemorrhage, and Bleeding following Dabigatran, Rivaroxaban, and Apixaban Use in Patients Aged 65 or Older: A Propensity Score Matched Analysis

https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse

Downloading Sentinel Analytic Packages

Sentinel

Thromboembolic Stroke, Major Extracranial Bleeding, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Direct Oral Anticoagulant Use: An Inverse Probability of Treatment Weighting Analysis

This analysis (cder_mpl2p_wp028) investigates the risk of stroke, intracranial hemorrhage, and bleeding outcomes associated with dabigatran, rivaroxaban, and apixaban in those aged 65 years or older in the Sentinel Distributed Database. We identified individuals with incident use of dabigatran, rivaroxaban, or apixaban and conducted a Propensity Score Analysis (PSA) comparing these non-vitamin K antagonist oral anticoagulants comparisons (1:1 propensity score matching). This analysis used inverse probability of treatment weighting (IPTW) to adjust for potential confounding, in contrast to a previous request which used propensity score matching.

For details on cohort identification for propensity score analyses, please visit the documentation. Please note that custom programming was also used to perform this analysis that is not included in Sentinel's Routine Querying System.

For instructions on how to run this query on Sentinel Common Data Model formatted data, please refer to the master branch. Refer to the Sentinel website for accompanying materials.

###Additional information

For details on using the Cohort Identification and Descriptive Analysis tool, visit the Sentinel Routine Querying Tool Documentation repository.

https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_mpl2p_wp028

Part 1 Questions

Inverse Probability Weighting for Observational Research: a Gentle Introduction

Xiaojuan Li, PhD, MSPH

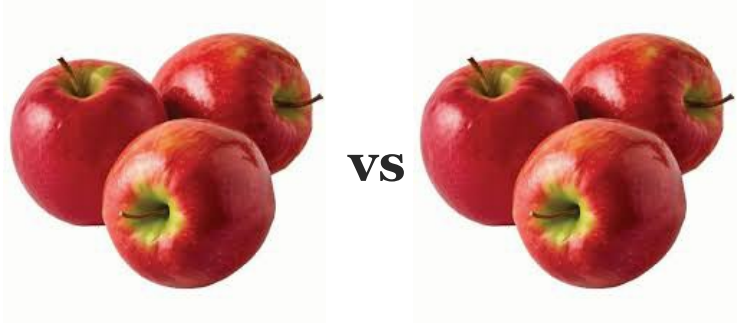
Contents

Sentinel

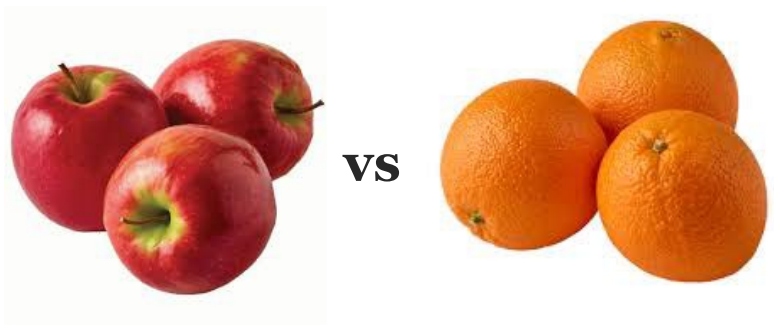
- Sentinel System was created in response to a legislative mandate (FDAAA 2007) to establish a system for monitoring risks associated with drug and biologic products using electronic healthcare data from disparate sources

- Observational (i.e., non-randomized) studies can inform drug safety monitoring

- A limitation of observational studies is potential bias due to **confounding**: are the exposure groups **comparable** in terms of their baseline risk for the outcome?



OR

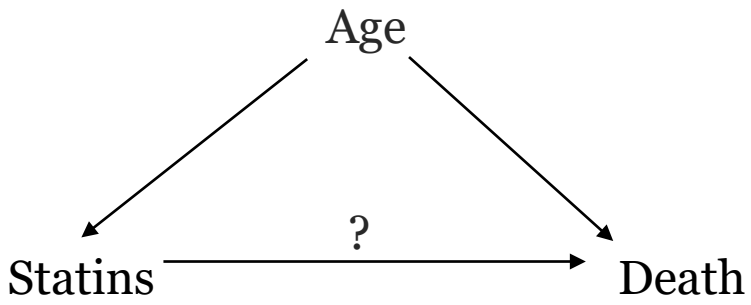


?

FDAAA = Food and Drug Administration Amendments Act

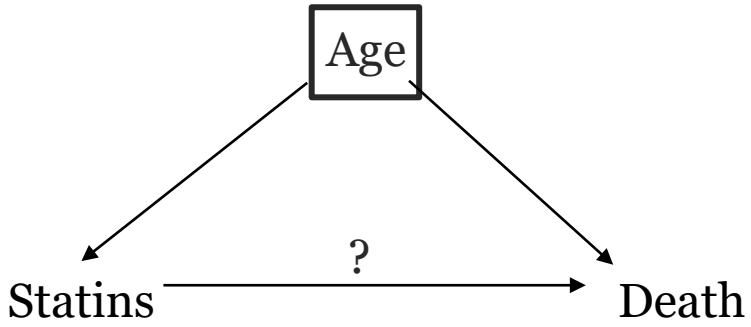
What is Confounding?

- Confounding arises when a factor is associated with both the exposure/treatment and outcome of interest



Addressing Confounding in Observational Studies

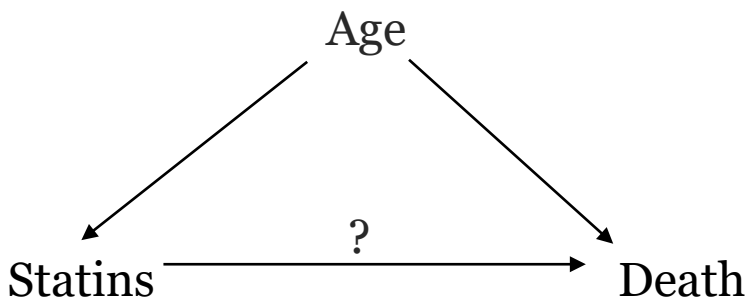
- In the **design** phase: ~~randomization~~, restriction, and matching
- In the **analysis** phase: standardization, stratification, or multivariable regression adjustment
- All methods require that we adequately measure the relevant **confounders**



Addressing Confounding via Inverse Probability Weighting

- Inverse probability weighting is another approach for confounding control

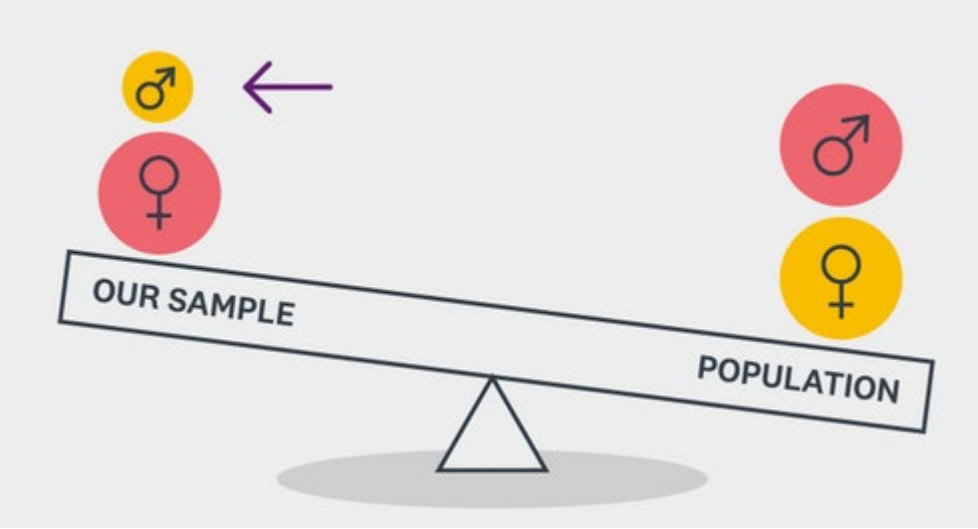
- By creating pseudo-population in which the association between exposure/treatment and measured confounders is removed



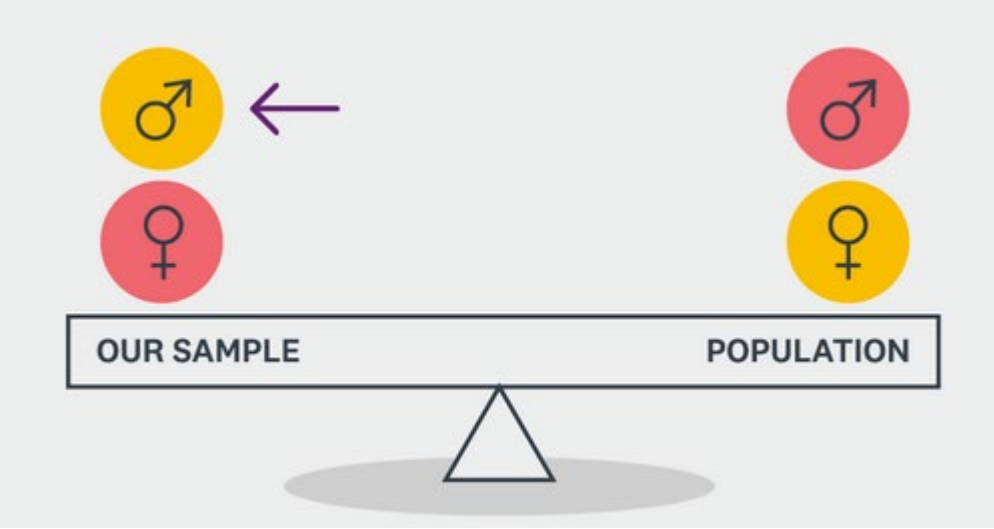
What is Inverse Probability Weighting?

- First developed for **survey sampling**

- A weighted estimation can eliminate this "**selection bias**" – makes a sample surveyed look more like the population



Before weighting



After weighting

Horvitz & Thompson. *J Am Stat Assoc* 1952; 47: 663-685
Source: https://www.surveymonkey.com/mp/survey-methodology/

Inverse Probability Weighting = standardization

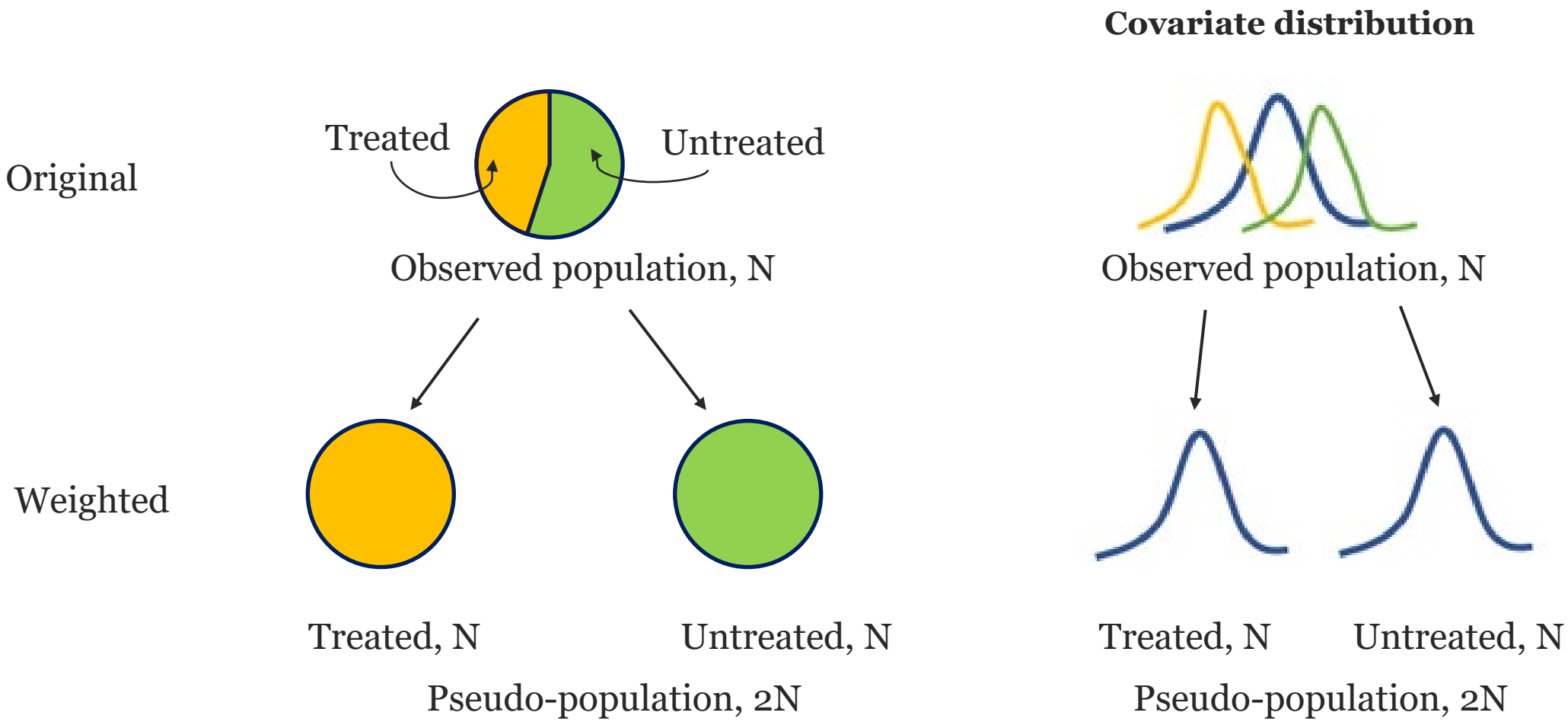
- Weighting in **survey sampling**: makes a **sample** surveyed look more like the population

- Weighting in **inverse probability of treatment weighting**: re-weights each **exposure/ treatment group** to look like the entire observed population sharing the same covariate distribution

- A non-parametric or semi-parametric equivalent to **standardization**

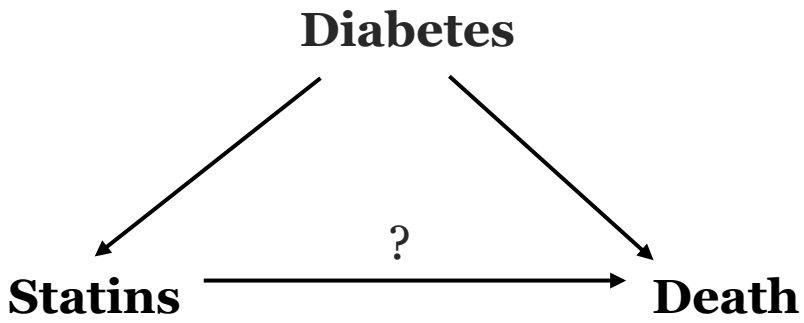
Horvitz & Thompson. *J Am Stat Assoc* 1952; 47: 663-85
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-6

Inverse Probability Weighting = standardization, a visualization

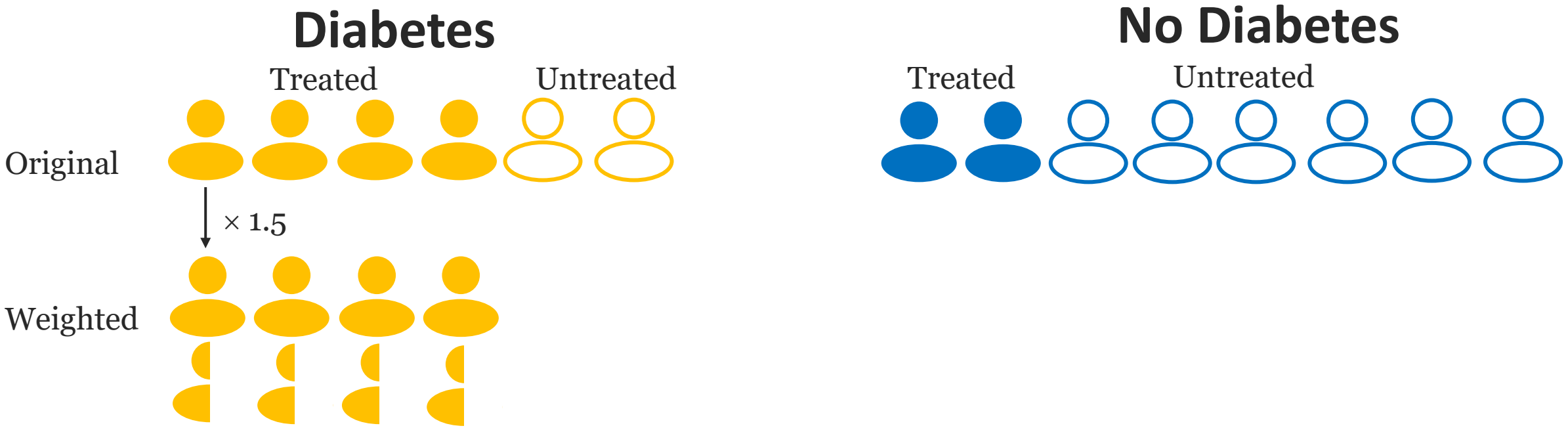


Adapted from http://www.baileydebarmore.com/epicode/calculating-ipw-and-smr-in-sas

How does Inverse Probability Weighting work, on a high-level?



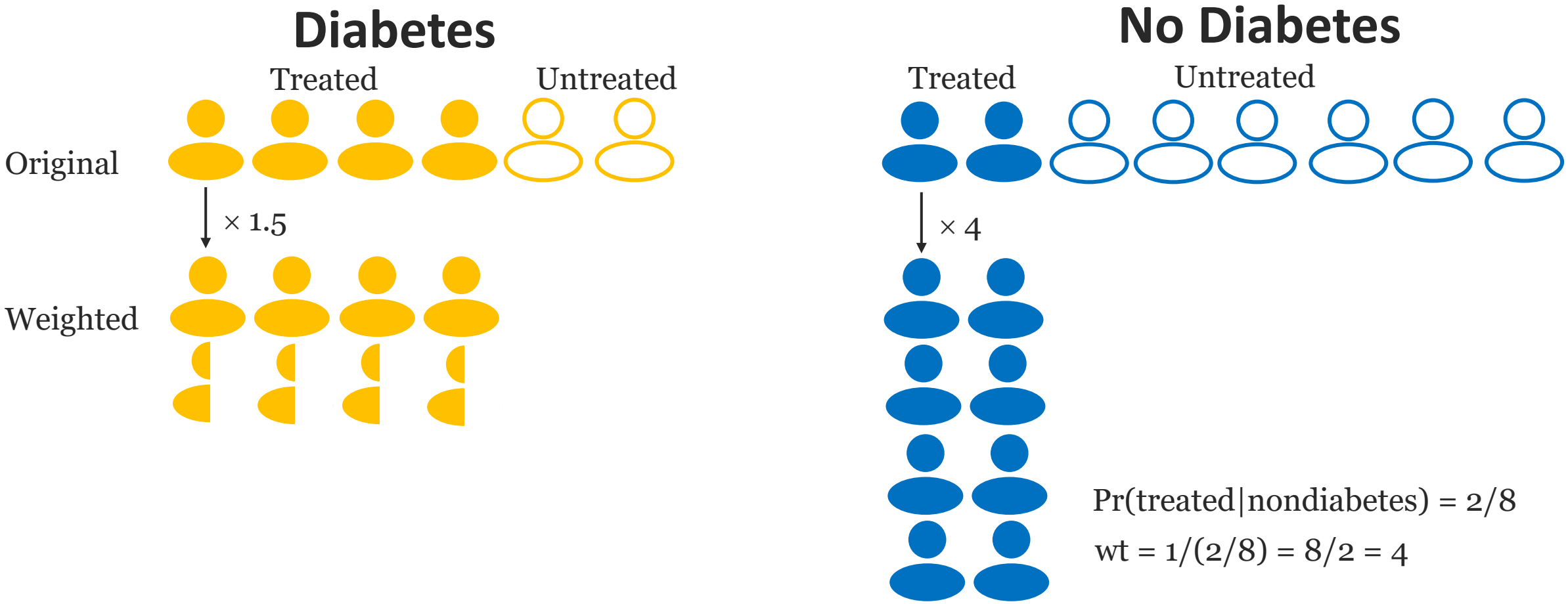
	Pr(diabetes)	Pr(diabetes|treated)	Pr(diabetes|untreated)	Balance?
Original	6/14 = 43%	4/6 = 67%	2/8 = 25%	Imbalanced



Pr(treated|diabetes) = 4/6

wt = 1/(4/6) = 6/4 = 1.5

	Pr(diabetes)	Pr(diabetes|treated)	Pr(diabetes|untreated)	Balance?
Original	6/14 = 43%	4/6 = 67%	2/8 = 25%	Imbalanced



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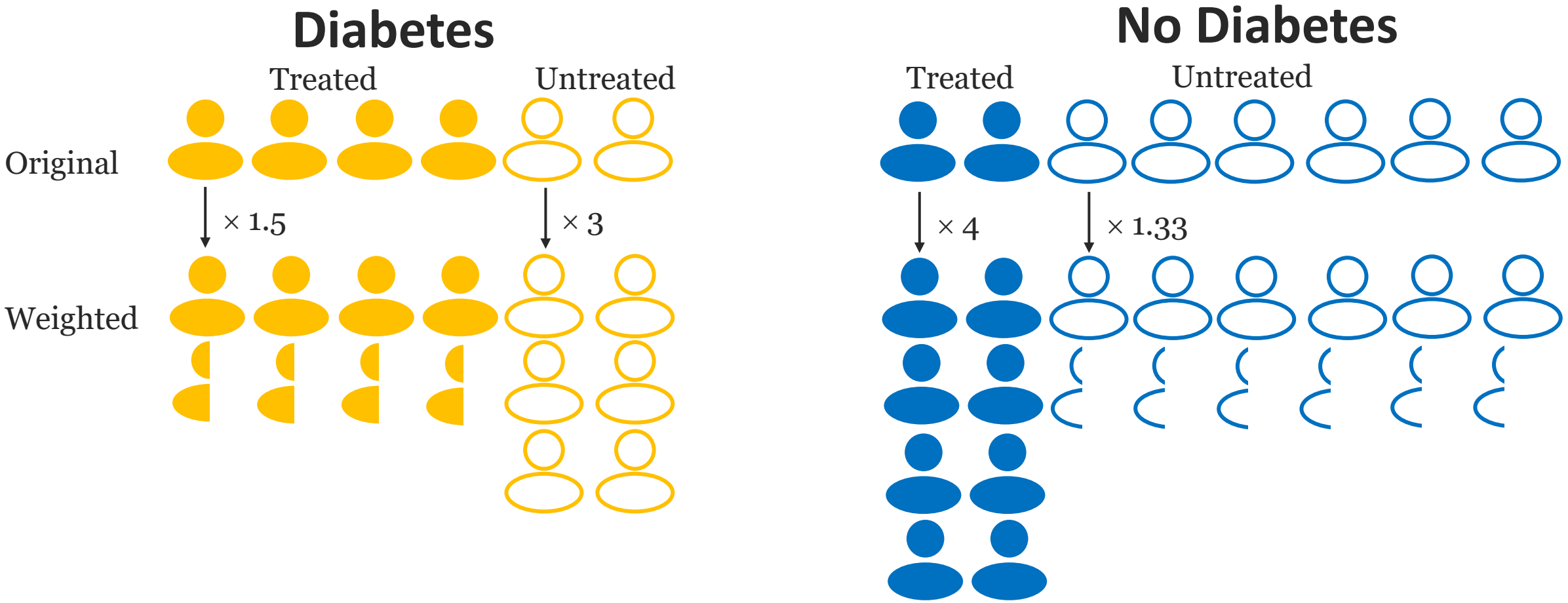

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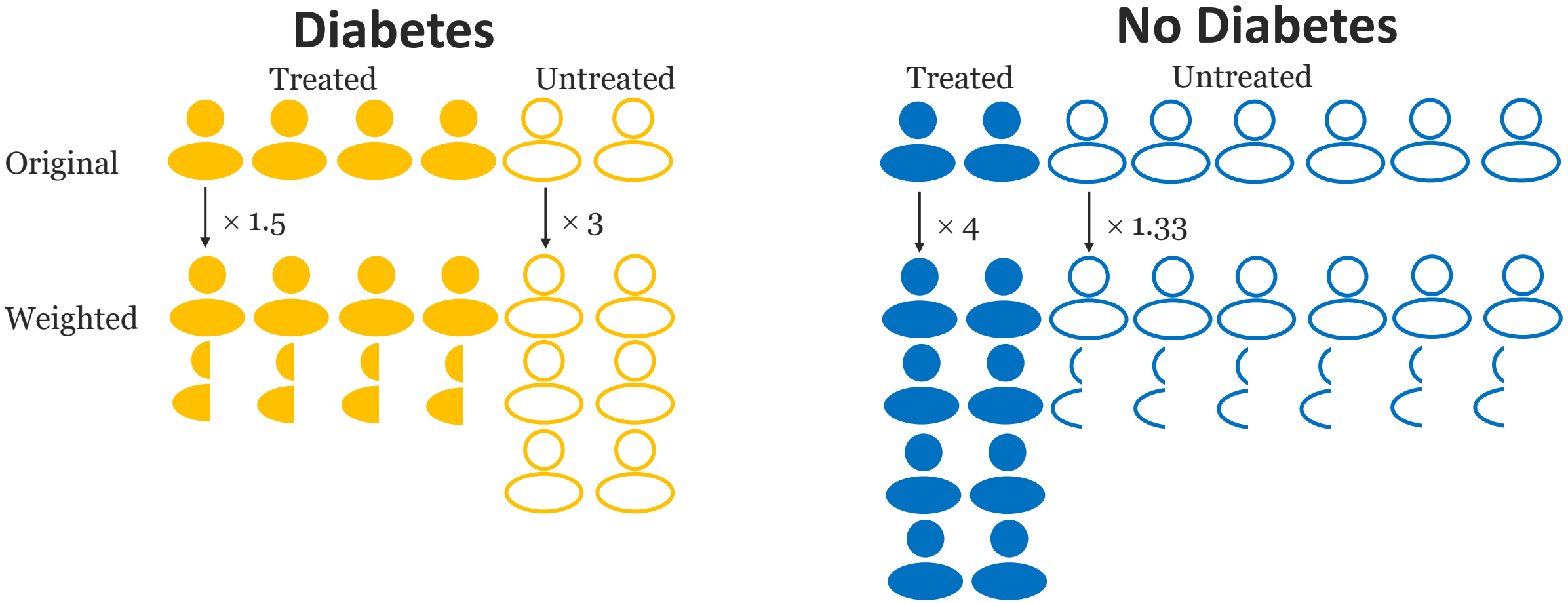
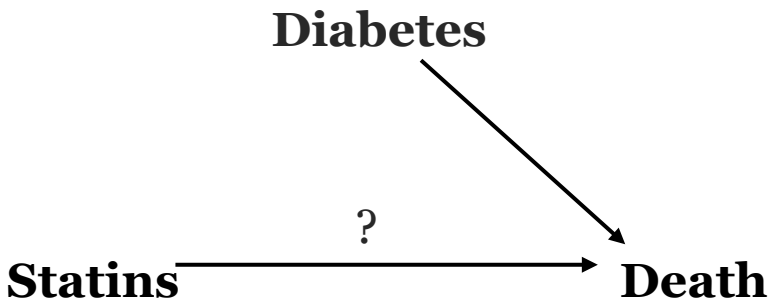


	Pr(diabetes)	Pr(diabetes|treated)	Pr(diabetes|untreated)	Balance?
Original	6/14 = 43%	4/6 = 67%	2/8 = 25%	Imbalanced
Weighted	12/28 = 6/14	4×1.5/(4×1.5+2×4)=6/14	2×3/(2×3+6×1.33)= 6/14	Balanced

Estimate Treatment Effect in the Weighted Sample

Use 2x2 table to get the disease incidence or means to do the analysis in the pseudo-population (weighted sample)



	Outcome	No event	Risk	Risk ratio	Risk difference
statins = 1	D_1	$14-D_1$	$D_1/14$	D_1/D_1	$(D_1-D_2)/14$
statins = 0	D_2	$14-D_2$	$D_2/14$	reference	reference

Implementation of Inverse Probability Weighted Estimation in Observational Studies

Step 1. Model exposure as function of confounders/covariates

Step 2. Assign each individual weight, $W = 1/(f(A|L))$

Step 3. Obtain measure of disease incidence/association of interest in the weighted sample; use robust variance estimator (or bootstrap) for variance/confidence intervals

Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686.

Exposure/Treatment Model

Step 1. Model exposure as function of confounders/covariates

- Binary exposure → logistic model
- Categorical exposure → generalized logit/polytomous logistic model
- Continuous exposure → polytomous logistic regression on quantiles (deciles) of exposure

Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686.

Assigning Weight

Step 1. Model exposure as function of confounders/covariates

Step 2. Assign each individual weight, $W = 1/(f(A|L))$

- Treated: $W = \frac{1}{P(A_i=1|L_i)}$
- Untreated: $W = \frac{1}{P(A_i=0|L_i)}$

Propensity Score (PS): conditional probability of being exposed given patient attributes,

$$f(A = 1|L)$$

Patients with similar PSs have similar distributions of the confounders used to estimate the PS (in expectation)

Rosenbaum & Rubin. *Biometriika* 1983a; 70: 41-55
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686

Assigning Weight

Step 1. Model exposure as function of confounders/covariates

Step 2. Assign each individual weight, $W = 1/(f(A|L))$

- Treated: $\mathrm{W} = \frac{1}{P(A_i=1|L_i)} = \frac{1}{PS}$

- Untreated: $\mathrm{W} = \frac{1}{P(A_i=0|L_i)} = \frac{1}{1-PS}$

Rosenbaum & Rubin. *Biometriika* 1983a; 70: 41-55
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686

Using Stabilized Weights to Improve Efficiency

- Common issue: large weights → unstable weighted estimator
  - treated individuals with low propensity score, or untreated individuals with high propensity score
- Solution 1: **stabilized weights**, $SW = \frac{f(A)}{f(A|L)}$ vs $W = \frac{1}{f(A|L)}$
  - marginal probability of treatment in the numerator
  - preserve sample size, while unstabilized weights double sample size
  - good check – mean=2 for IPTW; 1=sIPTW
- Solution 2: re-assess propensity score model
  - trim non-overlapping propensity score region
  - weight truncation

Xu et al. *Value Health* 2010; 13(2): 273-277
Lee et al. *PLOS One* 2011; 6(3): e18174

IPTW = inverse probability of treatment weight
sIPTW = stabilized inverse probability of treatment weight

Common Inverse Probability of Treatment Weighting Approaches

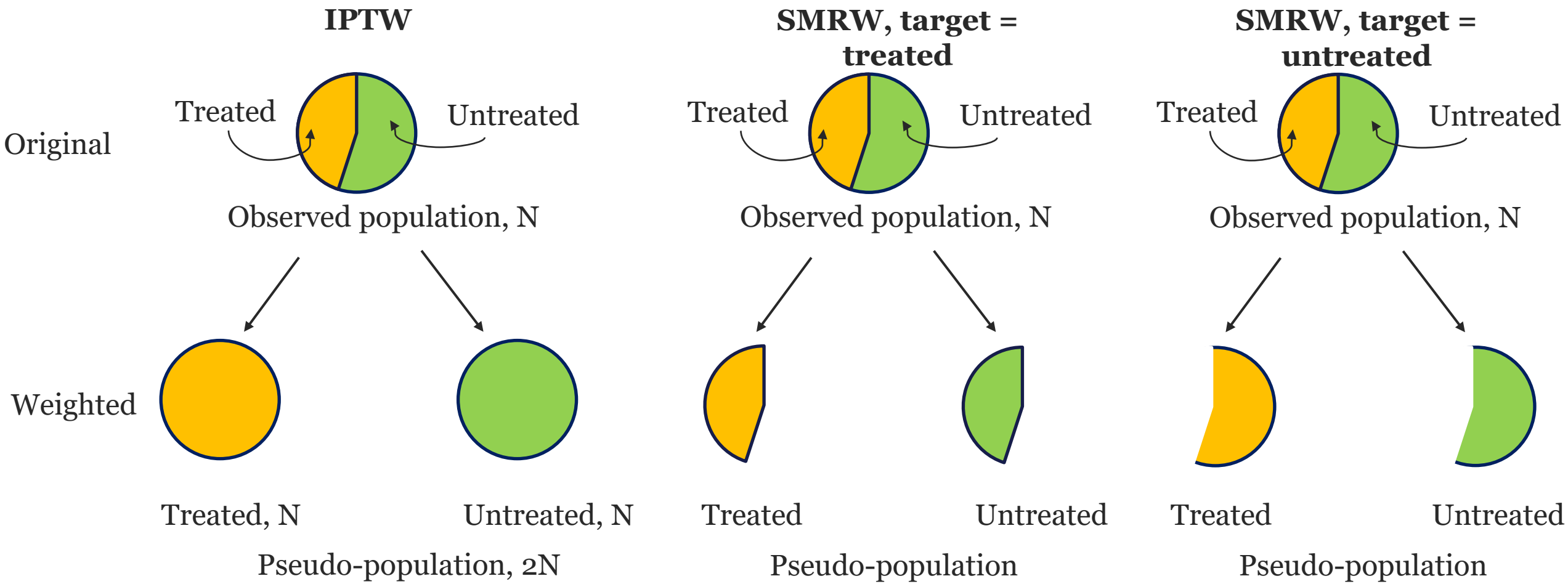
- Inverse probability of treatment weighting (IPTW):
  - standard population = observed population/study sample
  - treatment effect: average treatment effect (ATE)

- Standardized mortality ratio weighting (SMRW):
  - standard population = observed **treated** population
  - treatment effect: average treatment effect in the treated (ATT)
  - standard population = observed **untreated** population
  - treatment effect: average treatment effect in the untreated (ATU)

Horvitz & Thompson. *J Am Stat Assoc* 1952; 47: 663-685
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686

IPTW = inverse probability of treatment weighting
SMRW = standardized mortality ratio weighting

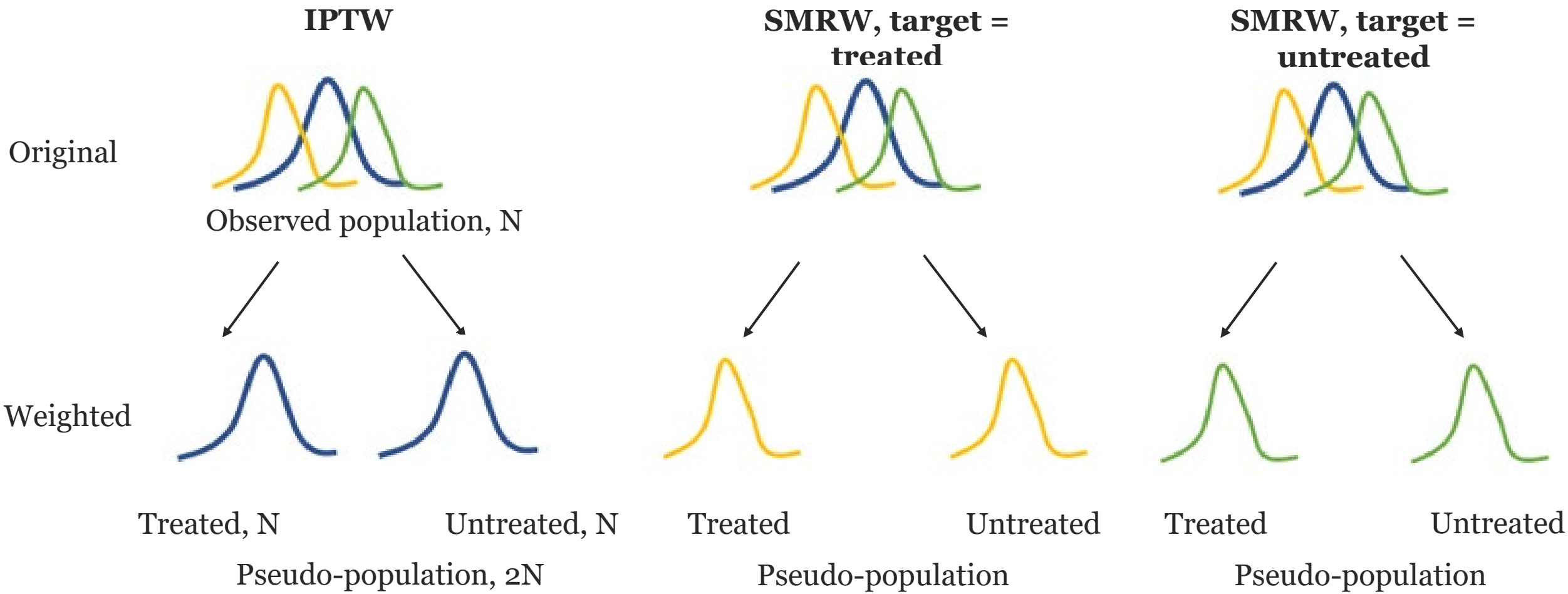
SMRW vs IPTW



Adapted from http://www.baileydebarmore.com/epicode/calculating-ipw-and-smr-in-sas

IPTW = inverse probability of treatment weighting
SMRW = standardized mortality ratio weighting

SMRW vs IPTW, Covariate Distribution



Adapted from http://www.baileydebarmore.com/epicode/calculating-ipw-and-smr-in-sas

IPTW = inverse probability of treatment weighting
SMRW = standardized mortality ratio weighting

Effect Estimation

Step 3. Obtain measure of disease incidence/association of interest in the weighted sample; robust variance estimator (or bootstrap) for variance/confidence intervals

- Option 1: 2x2 table
- Option 2: **fit a model** – inverse probability weighted estimation of marginal structural models
    - Using a weighted model to estimate the parameters of a marginal structural model
        - e.g., weighted logistic (Cox) model to estimate a marginal structural logistic (Cox) model
        - Adjusting for all confounding through weights
    - Model has no covariates → estimating a marginal effect; avoid potential bias through adjusting in time-varying setting

Robins. 1997 *Proceedings of the Section on Bayesian Statistical Inference* 1998:1-10
Robins et al. *Epidemiology* 2000; 11: 550-560
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686

IPTW vs Other Confounding Adjustment Methods

- Covariate-adjusted regression – include exposure & confounders in an outcome regression model
  - works well when the number of outcomes is large – ~10:1 "rule of thumb"
  - Conditional effect
- Covariate matching/stratification – matching/stratify exposed and unexposed individuals based on confounder values
  - works well when the number of confounders is small – "curse of dimensionality"

- Observational studies of drug safety typically have **rare outcomes** and involve **many confounders**
- Sometimes we know more about treatment assignment/selection process than disease process, and weighting is less prone to model misspecification

Peduzzi et al. *J Clin Epidemiol* 1996; 49(12): 1373-1379

IPTW vs Other PS-Based Methods: PS Matching & PS Stratification

- IPTW offers **strong confounding control,** comparable to 1:1 PS matching

- IPTW estimates a **different causal effect** than PS stratification: marginal vs. conditional

- Weighting-based adjustment methods are flexible and can estimate different causal effect of interest:
  - average treatment effect
  - average treatment effect among the treated
  - average treatment effect among the untreated
  - effect of “treat everyone” vs current practice
  - effect of treatment in an external population

Cole & Hernán. *Comput Methods Programs Biomed* 2004; 75: 45-49.
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686.
Edwards et al. *Am J Epidemiol* 2016; 184(4): 336-344.
Cole & Stuart. *Am J Epidemiol* 2010; 172(1): 107-115.

Limitations of IPTW

- Only achieve balance on measured variables
- Number of balancing variables may be limited by sample size
- Prone to positivity violation and unstable weights
- Tends to produce wider confidence intervals when having more extreme weights

For more information

Inverse probability weighting

- Hernán MA, Robins JM (2020). Chapter 12. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC

Marginal structural models

- Robins, et al. Epidemiology 2000; 11:550-70

Time-varying treatment

- Robins JM, Hernán MA. Estimation of the causal effects of time-varying exposure. 2008. p. 553-99

Dynamic treatment strategies

- Hernán et al, Basic Clin Pharmacol Toxicol 2006;98(3):237–42

Causal Inference Methods for Patient Centered Outcomes Using Observational Data

- http://cimpod.org/

Take home

- Inverse probability weighting is a flexible approach for confounding control
- Inverse probability weighting is non/semi-parametric equivalent to standardization
- Weighting cannot solve unmeasured confounding
- Assumptions are still needed to interpret results causally

Part 2 Questions

Break

20 minutes

Inverse Probability of Treatment Weighting (IPTW) in Sentinel

John Connolly, ScD

Agenda

01 How does IPTW work?

02 IPTW in Sentinel

03 Applied Example

04 Conclusions

Inverse Probability of Treatment Weighting (IPTW)

- The goal of IPTW is to remove the association between **measured confounders and exposure**

- Propensity score (PS) matching and stratification achieve this goal by putting patients into groups based on their PS

- In contrast, IPTW achieves this goal by **assigning patients a weight** based on their PS

Case example

- First, we will discuss a hypothetical application of IPTW
- The hypothetical case example will follow a previously published manuscript
- Our comparison of interest is **rivaroxaban vs. dabigatran**
- Our outcome of interest is **stroke**

Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, Hu M, Illoh O, Wei Y, Goulding MR, Chillarige Y, Southworth MR, MaCurdy TE, Kelman JA. Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. *The American Journal of Medicine* 2019 132(5):596-604.e11

How does IPTW work?

Imagine a hypothetical study population of 20 patients

Michelle
Julie
India
Theresa
Kimberly
Darcie
Ruby
Lowri
Devorah
Leeanna
Claire
Catina
Arline
Cami
Evelynn
Caron
Brandee
Merissa
Palma
Alita

How does IPTW work?

We want to estimate the causal risk ratio of rivaroxaban vs. dabigatran on stroke

	Exposure	Stroke
Michelle	Dabigatran	No
Julie	Dabigatran	Yes
India	Dabigatran	No
Theresa	Dabigatran	No
Kimberly	Rivaroxaban	No
Darcie	Rivaroxaban	No
Ruby	Rivaroxaban	No
Lowri	Rivaroxaban	Yes
Devorah	Dabigatran	Yes
Leeanna	Dabigatran	Yes
Claire	Dabigatran	No
Catina	Rivaroxaban	Yes
Arline	Rivaroxaban	Yes
Cami	Rivaroxaban	Yes
Evelynn	Rivaroxaban	Yes
Caron	Rivaroxaban	Yes
Brandee	Rivaroxaban	Yes
Merissa	Rivaroxaban	No
Palma	Rivaroxaban	No
Alita	Rivaroxaban	No

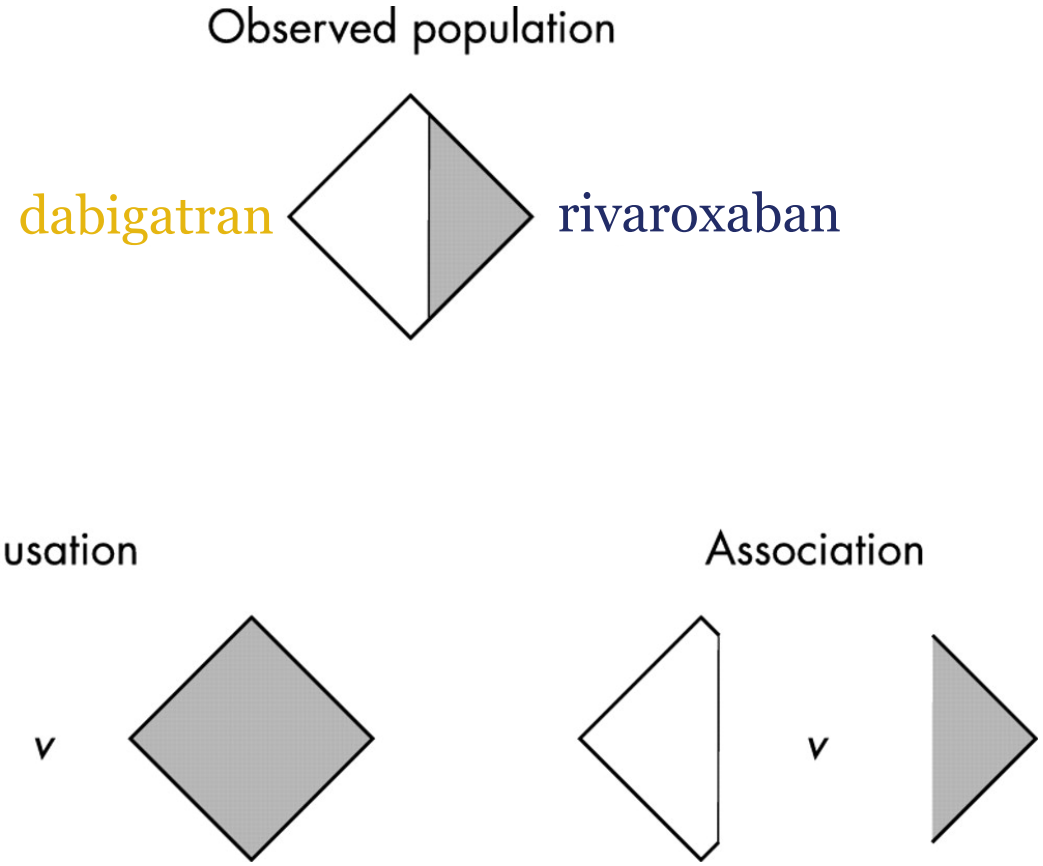
How does IPTW work?

In order to do this, we must adjust for cardiovascular disease (CVD)

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

How does IPTW work?

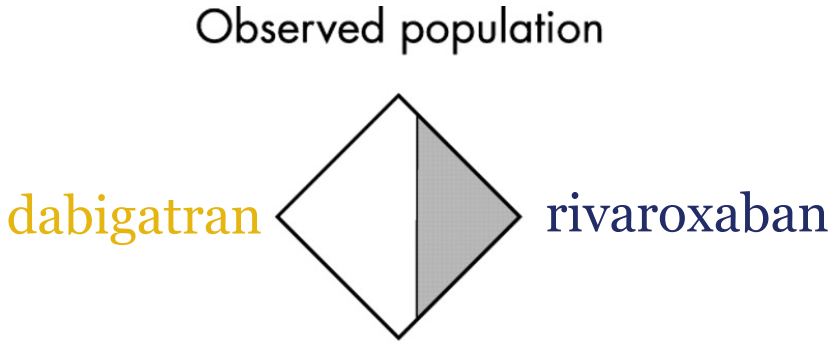
Our goal is to estimate the causal risk ratio of rivaroxaban on stroke relative to dabigatran



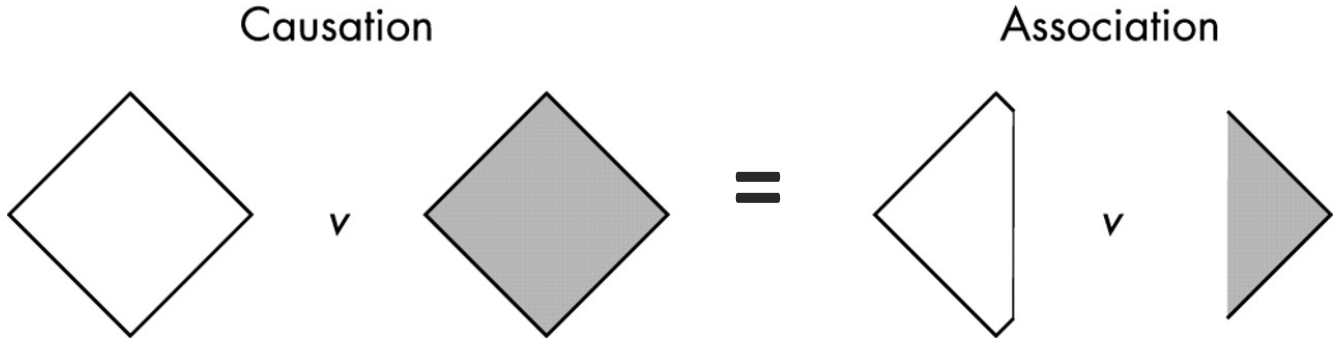
Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.
Available at: https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

How does IPTW work?

If we can **assume we have adjusted for confounding**, we can use the observed associational risk ratio to estimate the desired causal risk ratio



Causal Risk Ratio =
(Risk had everyone been given rivaroxaban) /
(Risk had everyone been given dabigatran)



Associational Risk Ratio =
(Observed risk in patients given rivaroxaban) /
(Observed risk in patients given dabigatran)

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.
Available at: https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

How does IPTW work?

In this simple situation, we can visualize IPTW

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

How does IPTW work?

First, we calculate the probability of our **confounder**, CVD

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

How does IPTW work?

Next, we calculate the probability of each **exposure** within CVD groups

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

How does IPTW work?

Next, we calculate the probability of each **exposure** within CVD groups

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

How does IPTW work?

Finally, we calculate the probability of **stroke** within each exposure and CVD group

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

How does IPTW work?

Finally, we calculate the probability of **stroke** within each exposure and CVD group

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	**No**
Julie	Dabigatran	**Yes**	**No**
India	Dabigatran	No	**No**
Theresa	Dabigatran	No	**No**
Kimberly	Rivaroxaban	No	**No**
Darcie	Rivaroxaban	No	**No**
Ruby	Rivaroxaban	No	**No**
Lowri	Rivaroxaban	**Yes**	**No**
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

How does IPTW work?

Finally, we calculate the probability of **stroke** within each exposure and CVD group

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	**Yes**	**Yes**
Leeanna	Dabigatran	**Yes**	**Yes**
Claire	Dabigatran	No	**Yes**
Catina	Rivaroxaban	**Yes**	**Yes**
Arline	Rivaroxaban	**Yes**	**Yes**
Cami	Rivaroxaban	**Yes**	**Yes**
Evelynn	Rivaroxaban	**Yes**	**Yes**
Caron	Rivaroxaban	**Yes**	**Yes**
Brandee	Rivaroxaban	**Yes**	**Yes**
Merissa	Rivaroxaban	No	**Yes**
Palma	Rivaroxaban	No	**Yes**
Alita	Rivaroxaban	No	**Yes**

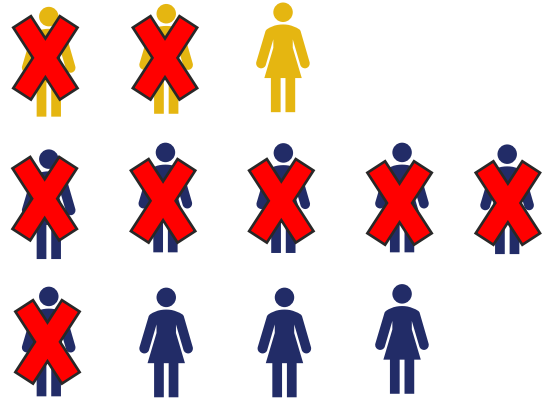
CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25

CVD = YES



Pr(CVD=YES) = 12/20 = 0.6

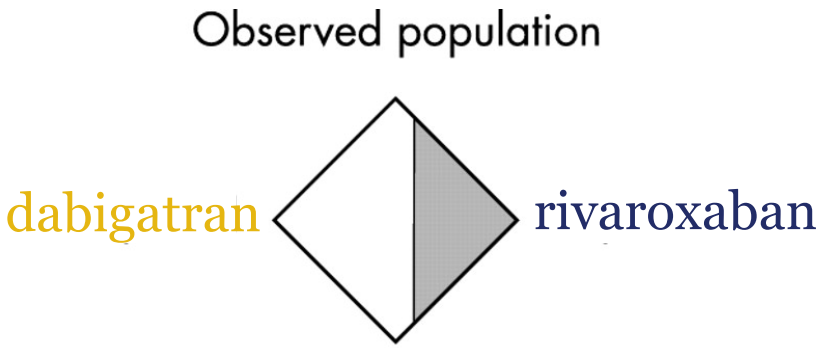
Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

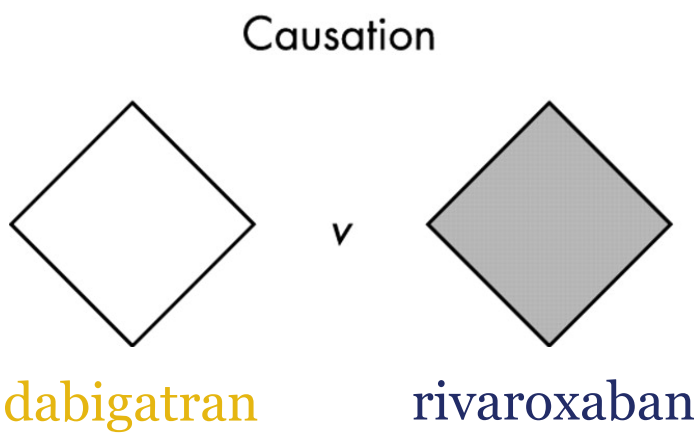
Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66
Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

How does IPTW work?

Recall the desired causal risk ratio:

$$\frac{\text{Risk had everyone been treated with rivaroxaban}}{\text{Risk had everyone been treated with dabigatran}}$$





How does IPTW work?

Recall the desired causal risk ratio:

$$\frac{\textbf{Risk had everyone been treated with rivaroxaban}}{\text{Risk had everyone been treated with dabigatran}}$$

Under the assumption that CVD status is sufficient to control for confounding, we can use the observed risk in the people who were actually exposed to rivaroxaban to estimate what would have happened if the entire population was exposed to rivaroxaban.

Association = causation

Recall our observed study population:

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

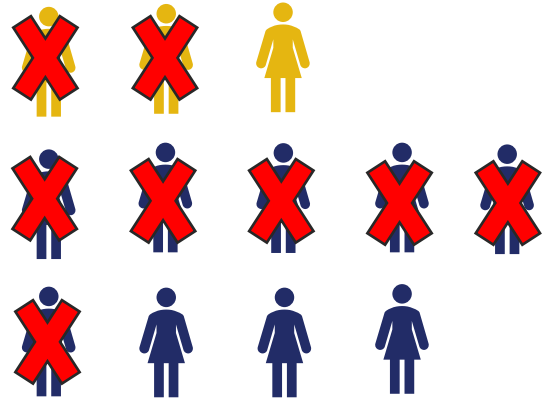
CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25

CVD = YES



Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

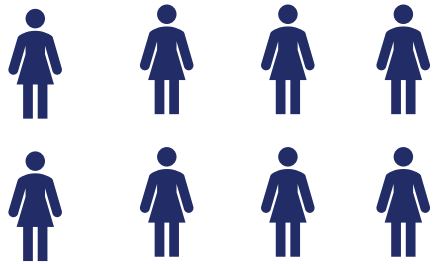
Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66
Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

What if everyone had been exposed to rivaroxaban?

What is the risk of stroke in the CVD=NO group?

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	?	No
Julie	Rivaroxaban	?	No
India	Rivaroxaban	?	No
Theresa	Rivaroxaban	?	No
Kimberly	Rivaroxaban	?	No
Darcie	Rivaroxaban	?	No
Ruby	Rivaroxaban	?	No
Lowri	Rivaroxaban	?	No
Devorah	Rivaroxaban	?	Yes
Leeanna	Rivaroxaban	?	Yes
Claire	Rivaroxaban	?	Yes
Catina	Rivaroxaban	?	Yes
Arline	Rivaroxaban	?	Yes
Cami	Rivaroxaban	?	Yes
Evelynn	Rivaroxaban	?	Yes
Caron	Rivaroxaban	?	Yes
Brandee	Rivaroxaban	?	Yes
Merissa	Rivaroxaban	?	Yes
Palma	Rivaroxaban	?	Yes
Alita	Rivaroxaban	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = ?

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) =?

What if everyone had been exposed to rivaroxaban?

We **observed** that 25% of patients who got rivaroxaban and had CVD=NO had stroke

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	?	No
Julie	Rivaroxaban	?	No
India	Rivaroxaban	?	No
Theresa	Rivaroxaban	?	No
Kimberly	Rivaroxaban	?	No
Darcie	Rivaroxaban	?	No
Ruby	Rivaroxaban	?	No
Lowri	Rivaroxaban	?	No
Devorah	Rivaroxaban	?	Yes
Leeanna	Rivaroxaban	?	Yes
Claire	Rivaroxaban	?	Yes
Catina	Rivaroxaban	?	Yes
Arline	Rivaroxaban	?	Yes
Cami	Rivaroxaban	?	Yes
Evelynn	Rivaroxaban	?	Yes
Caron	Rivaroxaban	?	Yes
Brandee	Rivaroxaban	?	Yes
Merissa	Rivaroxaban	?	Yes
Palma	Rivaroxaban	?	Yes
Alita	Rivaroxaban	?	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = ?

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

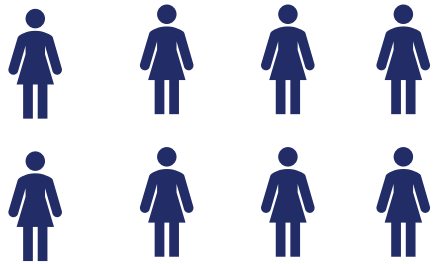
Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) =?

What if everyone had been exposed to rivaroxaban?

Therefore, we **assume** that the risk is the same in our counterfactual scenario

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	?	No
Julie	Rivaroxaban	?	No
India	Rivaroxaban	?	No
Theresa	Rivaroxaban	?	No
Kimberly	Rivaroxaban	?	No
Darcie	Rivaroxaban	?	No
Ruby	Rivaroxaban	?	No
Lowri	Rivaroxaban	?	No
Devorah	Rivaroxaban	?	Yes
Leeanna	Rivaroxaban	?	Yes
Claire	Rivaroxaban	?	Yes
Catina	Rivaroxaban	?	Yes
Arline	Rivaroxaban	?	Yes
Cami	Rivaroxaban	?	Yes
Evelynn	Rivaroxaban	?	Yes
Caron	Rivaroxaban	?	Yes
Brandee	Rivaroxaban	?	Yes
Merissa	Rivaroxaban	?	Yes
Palma	Rivaroxaban	?	Yes
Alita	Rivaroxaban	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = ?

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

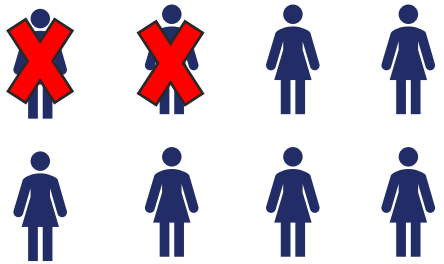
Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) =?

What if everyone had been exposed to rivaroxaban?

Therefore, we **assume** that the risk is the same in our counterfactual scenario

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	Yes	No
Julie	Rivaroxaban	Yes	No
India	Rivaroxaban	No	No
Theresa	Rivaroxaban	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	No	No
Devorah	Rivaroxaban	?	Yes
Leeanna	Rivaroxaban	?	Yes
Claire	Rivaroxaban	?	Yes
Catina	Rivaroxaban	?	Yes
Arline	Rivaroxaban	?	Yes
Cami	Rivaroxaban	?	Yes
Evelynn	Rivaroxaban	?	Yes
Caron	Rivaroxaban	?	Yes
Brandee	Rivaroxaban	?	Yes
Merissa	Rivaroxaban	?	Yes
Palma	Rivaroxaban	?	Yes
Alita	Rivaroxaban	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = 2/8 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

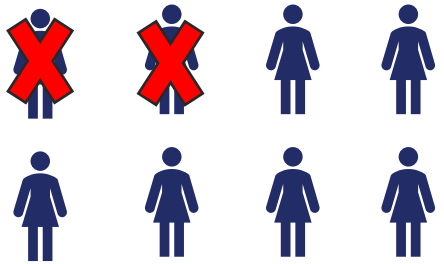
Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) =?

What if everyone had been exposed to rivaroxaban?

We can repeat the same process for CVD=YES

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	Yes	No
Julie	Rivaroxaban	Yes	No
India	Rivaroxaban	No	No
Theresa	Rivaroxaban	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	No	No
Devorah	Rivaroxaban	?	Yes
Leeanna	Rivaroxaban	?	Yes
Claire	Rivaroxaban	?	Yes
Catina	Rivaroxaban	?	Yes
Arline	Rivaroxaban	?	Yes
Cami	Rivaroxaban	?	Yes
Evelynn	Rivaroxaban	?	Yes
Caron	Rivaroxaban	?	Yes
Brandee	Rivaroxaban	?	Yes
Merissa	Rivaroxaban	?	Yes
Palma	Rivaroxaban	?	Yes
Alita	Rivaroxaban	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = 2/8 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

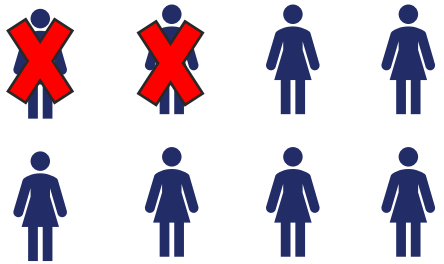
Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) =?

What if everyone had been exposed to rivaroxaban?

We **observed** that 66% of patients who got rivaroxaban and had CVD=YES had a stroke

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	Yes	No
Julie	Rivaroxaban	Yes	No
India	Rivaroxaban	No	No
Theresa	Rivaroxaban	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	No	No
Devorah	Rivaroxaban	?	Yes
Leeanna	Rivaroxaban	?	Yes
Claire	Rivaroxaban	?	Yes
Catina	Rivaroxaban	?	Yes
Arline	Rivaroxaban	?	Yes
Cami	Rivaroxaban	?	Yes
Evelynn	Rivaroxaban	?	Yes
Caron	Rivaroxaban	?	Yes
Brandee	Rivaroxaban	?	Yes
Merissa	Rivaroxaban	?	Yes
Palma	Rivaroxaban	?	Yes
Alita	Rivaroxaban	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = 2/8 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

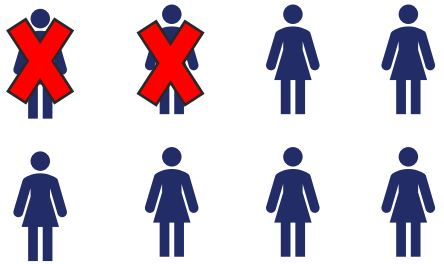
Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) =?

What if everyone had been exposed to rivaroxaban?

Therefore, we **assume** that the risk is the same in our counterfactual scenario

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	Yes	No
Julie	Rivaroxaban	Yes	No
India	Rivaroxaban	No	No
Theresa	Rivaroxaban	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	No	No
Devorah	Rivaroxaban	?	Yes
Leeanna	Rivaroxaban	?	Yes
Claire	Rivaroxaban	?	Yes
Catina	Rivaroxaban	?	Yes
Arline	Rivaroxaban	?	Yes
Cami	Rivaroxaban	?	Yes
Evelynn	Rivaroxaban	?	Yes
Caron	Rivaroxaban	?	Yes
Brandee	Rivaroxaban	?	Yes
Merissa	Rivaroxaban	?	Yes
Palma	Rivaroxaban	?	Yes
Alita	Rivaroxaban	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = 2/8 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

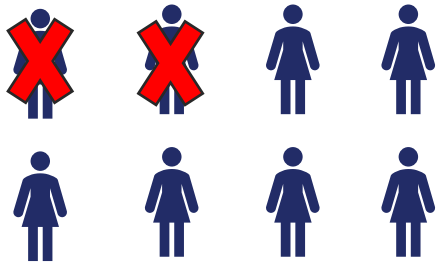
Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) =?

What if everyone had been exposed to rivaroxaban?

Therefore, we **assume** that the risk is the same in our counterfactual scenario

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	Yes	No
Julie	Rivaroxaban	Yes	No
India	Rivaroxaban	No	No
Theresa	Rivaroxaban	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	No	No
Devorah	Rivaroxaban	Yes	Yes
Leeanna	Rivaroxaban	Yes	Yes
Claire	Rivaroxaban	Yes	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	No	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

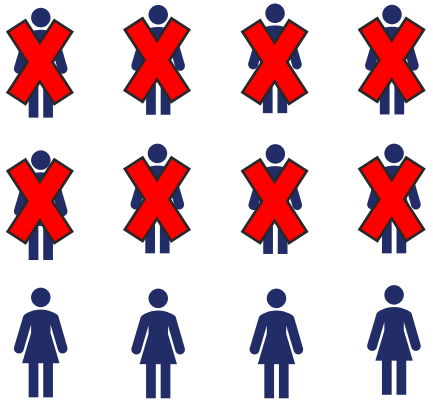


Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = 2/8 = 0.25

CVD = YES



Pr(CVD=YES) = 12/20 = 0.6

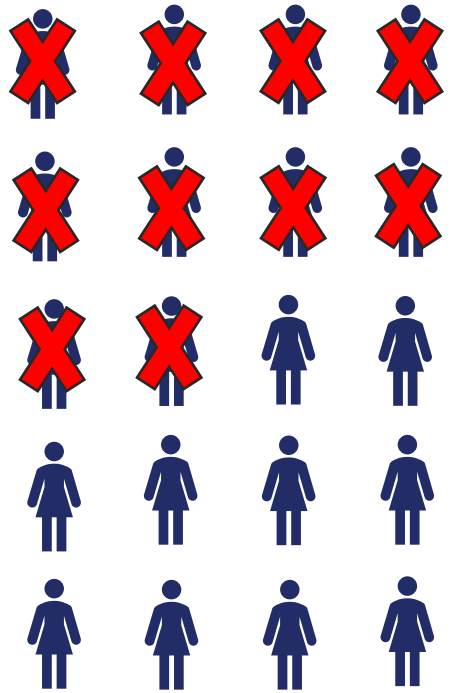
Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) = 8/12 = 0.66

What if everyone had been exposed to rivaroxaban?

We can now answer our question: the risk of stroke if everyone got rivaroxaban is 10/20 = 0.5

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	Yes	No
Julie	Rivaroxaban	Yes	No
India	Rivaroxaban	No	No
Theresa	Rivaroxaban	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	No	No
Devorah	Rivaroxaban	Yes	Yes
Leeanna	Rivaroxaban	Yes	Yes
Claire	Rivaroxaban	Yes	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	No	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

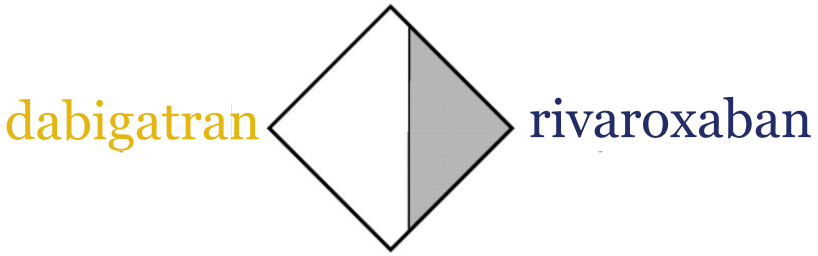


How does IPTW work?

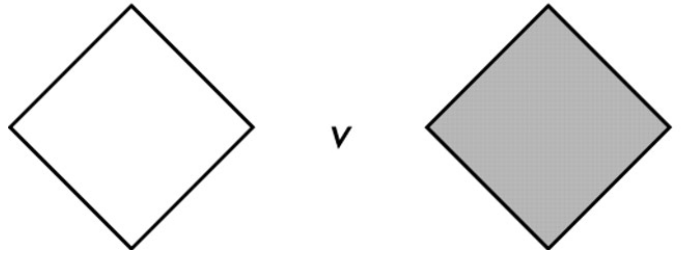
Recall the desired causal risk ratio:

$$\frac{\text{Risk had everyone been treated with rivaroxaban}}{\text{Risk had everyone been treated with dabigatran}}$$

Observed population



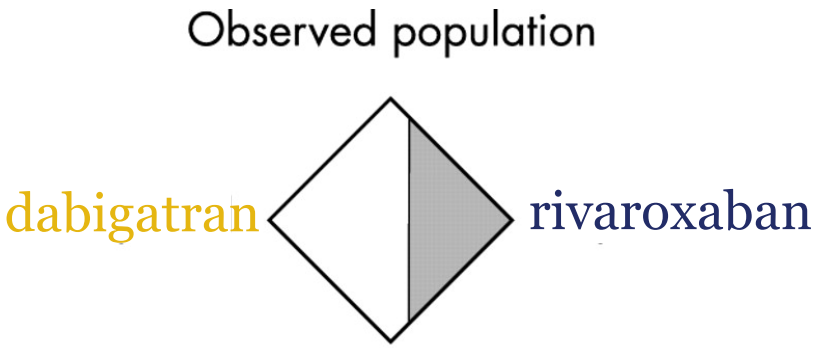
Causation

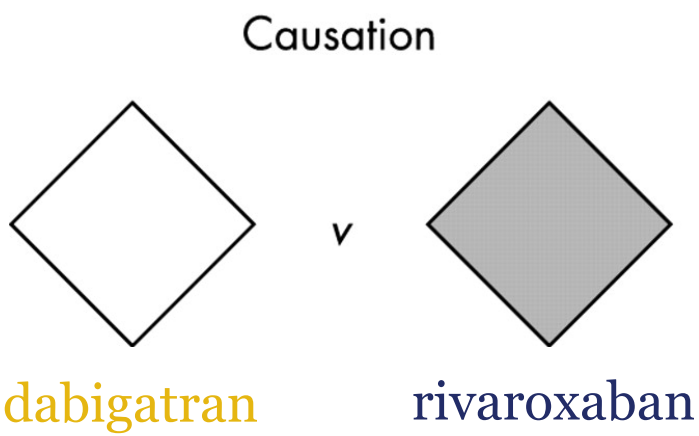


How does IPTW work?

Recall the desired causal risk ratio:

$$\frac{0.5}{\text{Risk had everyone been treated with dabigatran}}$$





How does IPTW work?

Recall the desired causal risk ratio:

$$\frac{0.5}{\textbf{Risk had everyone been treated with dabigatran}}$$

Under the assumption that CVD status is sufficient to control for confounding, we can use the observed risk in the people who were actually exposed to dabigatran to estimate what would have happened if the entire population was exposed to dabigatran.

Association = causation

Recall our observed study population

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

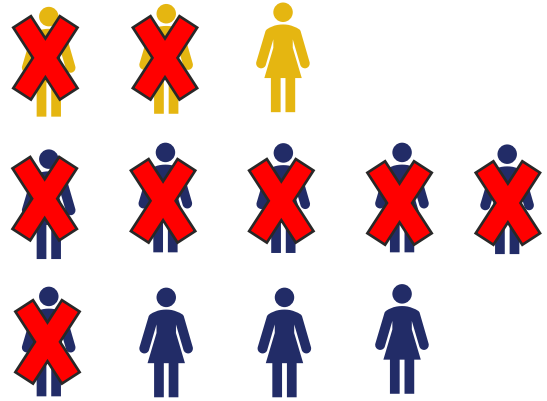
CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25

CVD = YES



Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66
Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

What if everyone had been exposed to dabigatran?

We can use the same process we used with the rivaroxaban group

	Exposure	Stroke	CVD
Michelle	Dabigatran	?	No
Julie	Dabigatran	?	No
India	Dabigatran	?	No
Theresa	Dabigatran	?	No
Kimberly	Dabigatran	?	No
Darcie	Dabigatran	?	No
Ruby	Dabigatran	?	No
Lowri	Dabigatran	?	No
Devorah	Dabigatran	?	Yes
Leeanna	Dabigatran	?	Yes
Claire	Dabigatran	?	Yes
Catina	Dabigatran	?	Yes
Arline	Dabigatran	?	Yes
Cami	Dabigatran	?	Yes
Evelynn	Dabigatran	?	Yes
Caron	Dabigatran	?	Yes
Brandee	Dabigatran	?	Yes
Merissa	Dabigatran	?	Yes
Palma	Dabigatran	?	Yes
Alita	Dabigatran	?	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 1
Pr(rivaroxaban | CVD=NO) = 0

Pr(Stroke | dabigatran, CVD=NO) = ?
Pr(Stroke | rivaroxaban, CVD=NO) = 0

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 1
Pr(rivaroxaban | CVD=YES) = 0

Pr(Stroke | dabigatran, CVD=YES) = ?
Pr(Stroke | rivaroxaban, CVD=YES) = 0

What if everyone had been exposed to dabigatran?

We **observed** that 25% of the CVD=NO dabigatran patients had stroke

	Exposure	Stroke	CVD
Michelle	Dabigatran	?	No
Julie	Dabigatran	?	No
India	Dabigatran	?	No
Theresa	Dabigatran	?	No
Kimberly	Dabigatran	?	No
Darcie	Dabigatran	?	No
Ruby	Dabigatran	?	No
Lowri	Dabigatran	?	No
Devorah	Dabigatran	?	Yes
Leeanna	Dabigatran	?	Yes
Claire	Dabigatran	?	Yes
Catina	Dabigatran	?	Yes
Arline	Dabigatran	?	Yes
Cami	Dabigatran	?	Yes
Evelynn	Dabigatran	?	Yes
Caron	Dabigatran	?	Yes
Brandee	Dabigatran	?	Yes
Merissa	Dabigatran	?	Yes
Palma	Dabigatran	?	Yes
Alita	Dabigatran	?	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 1
Pr(rivaroxaban | CVD=NO) = 0

Pr(Stroke | dabigatran, CVD=NO) = ?
Pr(Stroke | rivaroxaban, CVD=NO) = 0

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 1
Pr(rivaroxaban | CVD=YES) = 0

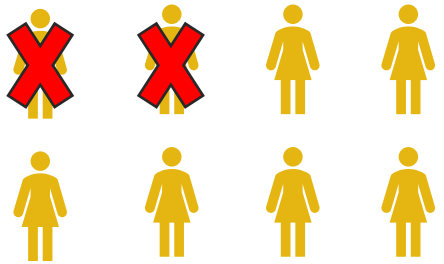
Pr(Stroke | dabigatran, CVD=YES) = ?
Pr(Stroke | rivaroxaban, CVD=YES) = 0

What if everyone had been exposed to dabigatran?

Therefore, we'll **assume** that same risk in our counterfactual scenario

	Exposure	Stroke	CVD
Michelle	Dabigatran	Yes	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Dabigatran	No	No
Darcie	Dabigatran	No	No
Ruby	Dabigatran	No	No
Lowri	Dabigatran	No	No
Devorah	Dabigatran	?	Yes
Leeanna	Dabigatran	?	Yes
Claire	Dabigatran	?	Yes
Catina	Dabigatran	?	Yes
Arline	Dabigatran	?	Yes
Cami	Dabigatran	?	Yes
Evelynn	Dabigatran	?	Yes
Caron	Dabigatran	?	Yes
Brandee	Dabigatran	?	Yes
Merissa	Dabigatran	?	Yes
Palma	Dabigatran	?	Yes
Alita	Dabigatran	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 1
Pr(rivaroxaban | CVD=NO) = 0

Pr(Stroke | dabigatran, CVD=NO) = 2/8 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 0

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 1
Pr(rivaroxaban | CVD=YES) = 0

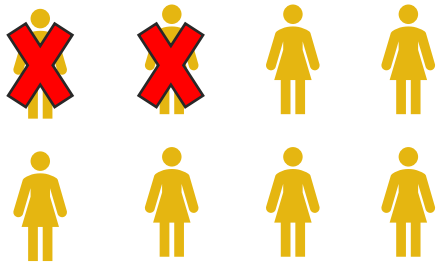
Pr(Stroke | dabigatran, CVD=YES) = ?
Pr(Stroke | rivaroxaban, CVD=YES) = 0

What if everyone had been exposed to dabigatran?

We **observed** that 66% of dabigatran patients with CVD=YES had stroke

	Exposure	Stroke	CVD
Michelle	Dabigatran	Yes	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Dabigatran	No	No
Darcie	Dabigatran	No	No
Ruby	Dabigatran	No	No
Lowri	Dabigatran	No	No
Devorah	Dabigatran	?	Yes
Leeanna	Dabigatran	?	Yes
Claire	Dabigatran	?	Yes
Catina	Dabigatran	?	Yes
Arline	Dabigatran	?	Yes
Cami	Dabigatran	?	Yes
Evelynn	Dabigatran	?	Yes
Caron	Dabigatran	?	Yes
Brandee	Dabigatran	?	Yes
Merissa	Dabigatran	?	Yes
Palma	Dabigatran	?	Yes
Alita	Dabigatran	?	Yes

CVD = NO



Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 1
Pr(rivaroxaban | CVD=NO) = 0

Pr(Stroke | dabigatran, CVD=NO) = 2/8 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 0

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 1
Pr(rivaroxaban | CVD=YES) = 0

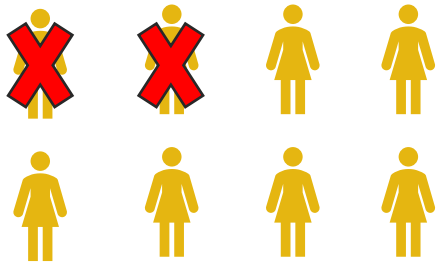
Pr(Stroke | dabigatran, CVD=YES) = ?
Pr(Stroke | rivaroxaban, CVD=YES) = 0

What if everyone had been exposed to dabigatran?

Therefore, we'll **assume** that same risk in our counterfactual scenario

	Exposure	Stroke	CVD
Michelle	Dabigatran	Yes	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Dabigatran	No	No
Darcie	Dabigatran	No	No
Ruby	Dabigatran	No	No
Lowri	Dabigatran	No	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	Yes	Yes
Catina	Dabigatran	Yes	Yes
Arline	Dabigatran	Yes	Yes
Cami	Dabigatran	Yes	Yes
Evelynn	Dabigatran	Yes	Yes
Caron	Dabigatran	Yes	Yes
Brandee	Dabigatran	No	Yes
Merissa	Dabigatran	No	Yes
Palma	Dabigatran	No	Yes
Alita	Dabigatran	No	Yes

CVD = NO

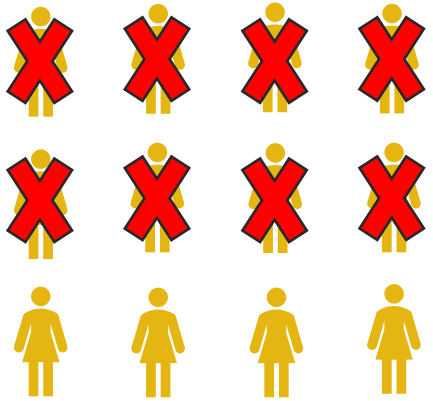


Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 1
Pr(rivaroxaban | CVD=NO) = 0

Pr(Stroke | dabigatran, CVD=NO) = 2/8 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 0

CVD = YES



Pr(CVD=YES) = 12/20 = 0.6

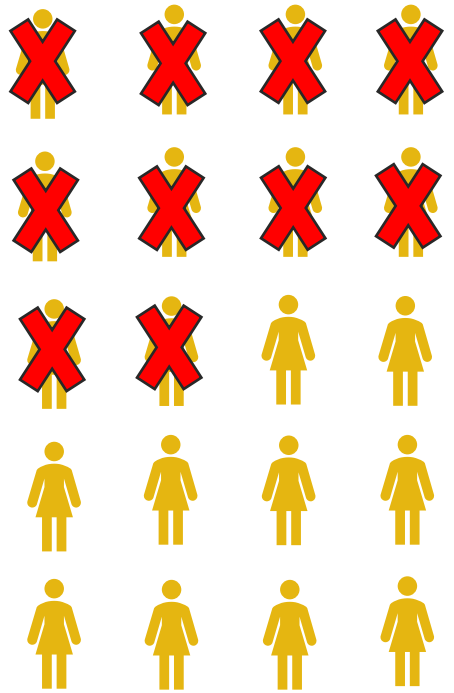
Pr(dabigatran | CVD=YES) = 1
Pr(rivaroxaban | CVD=YES) = 0

Pr(Stroke | dabigatran, CVD=YES) = 8/12 = 0.66
Pr(Stroke | rivaroxaban, CVD=YES) = 0

What if everyone had been exposed to dabigatran?

We can now answer our question: the risk of stroke if everyone got dabigatran is 10/20 = 0.5

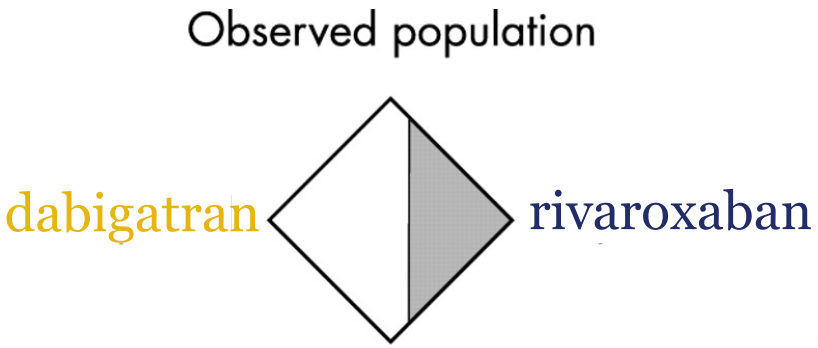
	Exposure	Stroke	CVD
Michelle	Dabigatran	Yes	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Dabigatran	No	No
Darcie	Dabigatran	No	No
Ruby	Dabigatran	No	No
Lowri	Dabigatran	No	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	Yes	Yes
Catina	Dabigatran	Yes	Yes
Arline	Dabigatran	Yes	Yes
Cami	Dabigatran	Yes	Yes
Evelynn	Dabigatran	Yes	Yes
Caron	Dabigatran	Yes	Yes
Brandee	Dabigatran	No	Yes
Merissa	Dabigatran	No	Yes
Palma	Dabigatran	No	Yes
Alita	Dabigatran	No	Yes

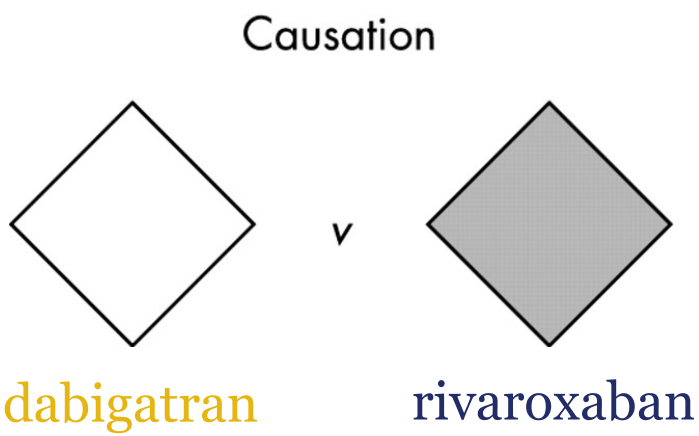


Inverse Probability of Treatment Weighting (IPTW)

Recall the desired causal risk ratio:

$$\frac{0.5}{\textbf{Risk had everyone been treated with dabigatran}}$$





Inverse Probability of Treatment Weighting (IPTW)

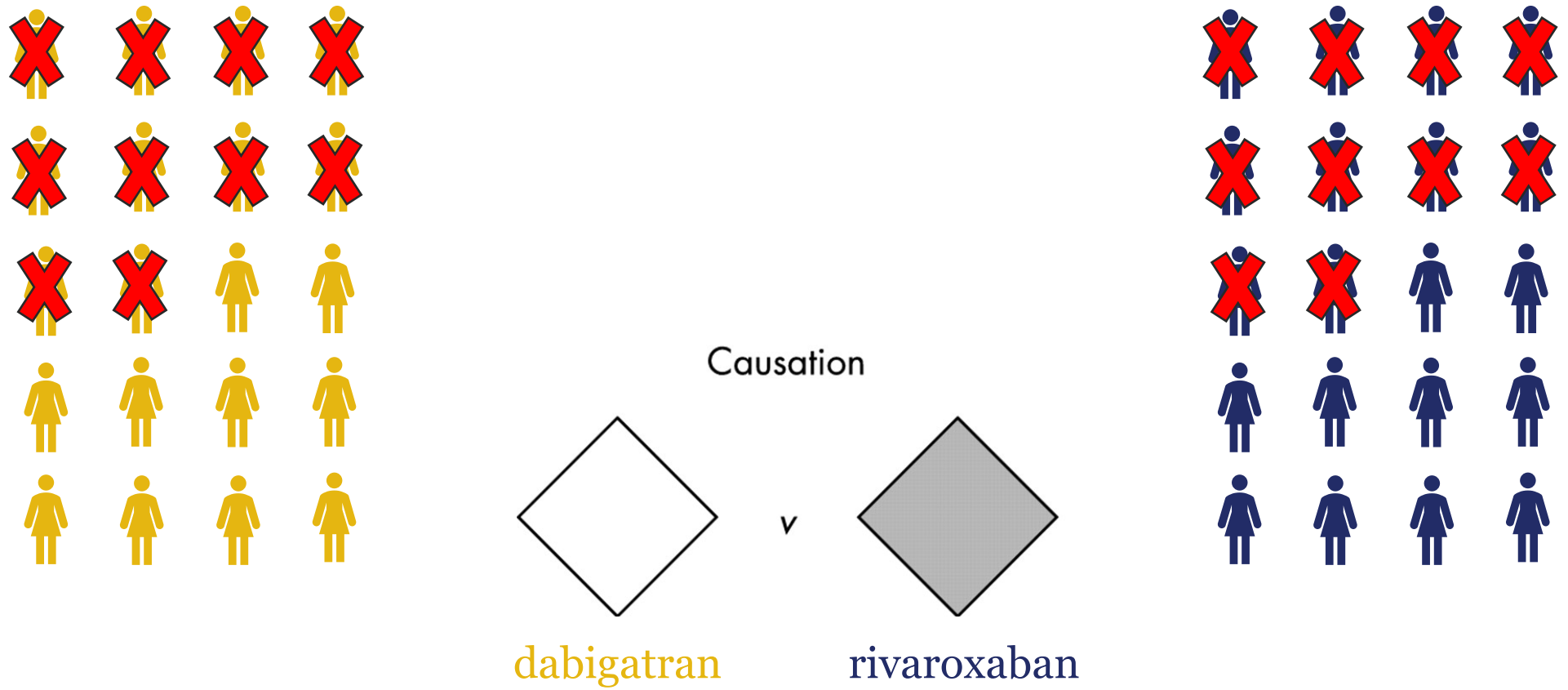
Recall the desired causal risk ratio:

$$\frac{0.5}{0.5} = 1$$

For reference, the unadjusted risk ratio was 1.26

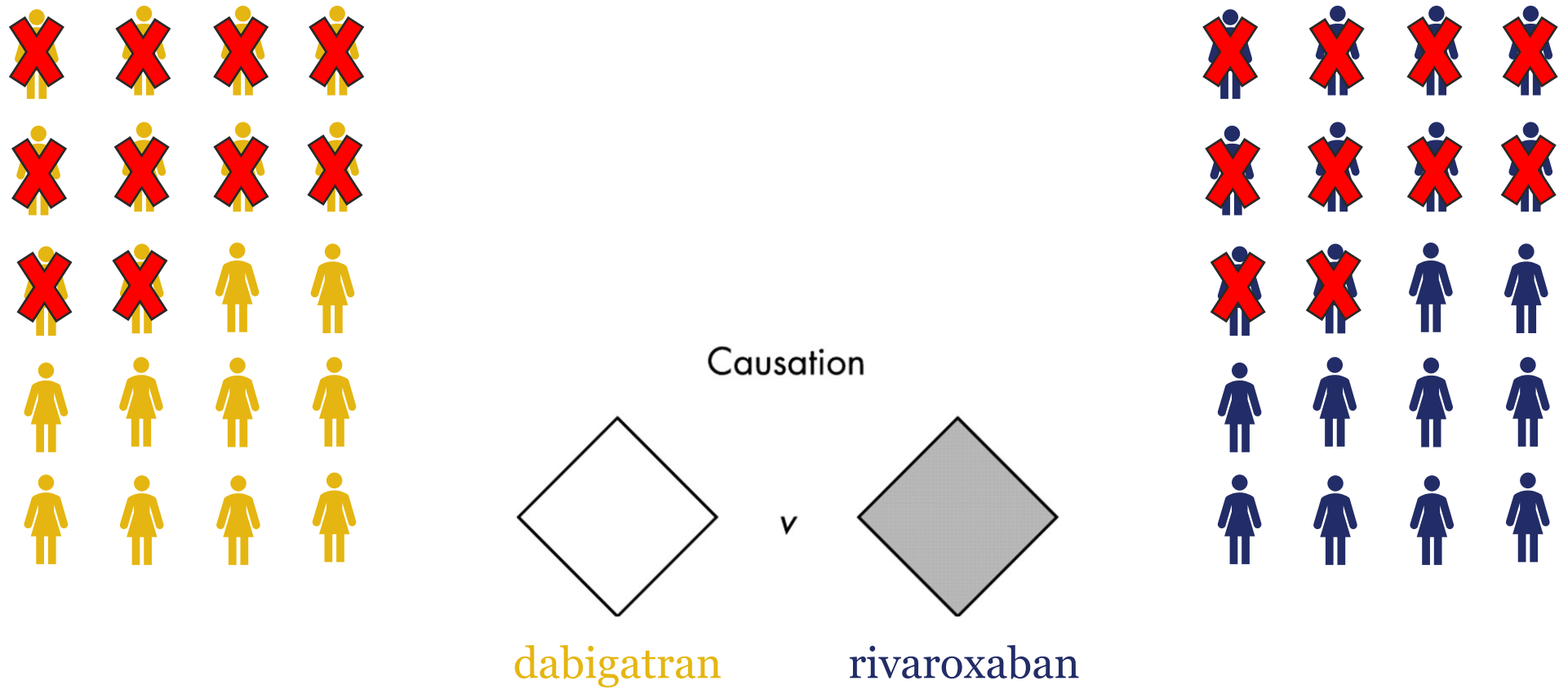
Inverse Probability of Treatment Weighting (IPTW)

Let's consider both counterfactual scenarios at the same time



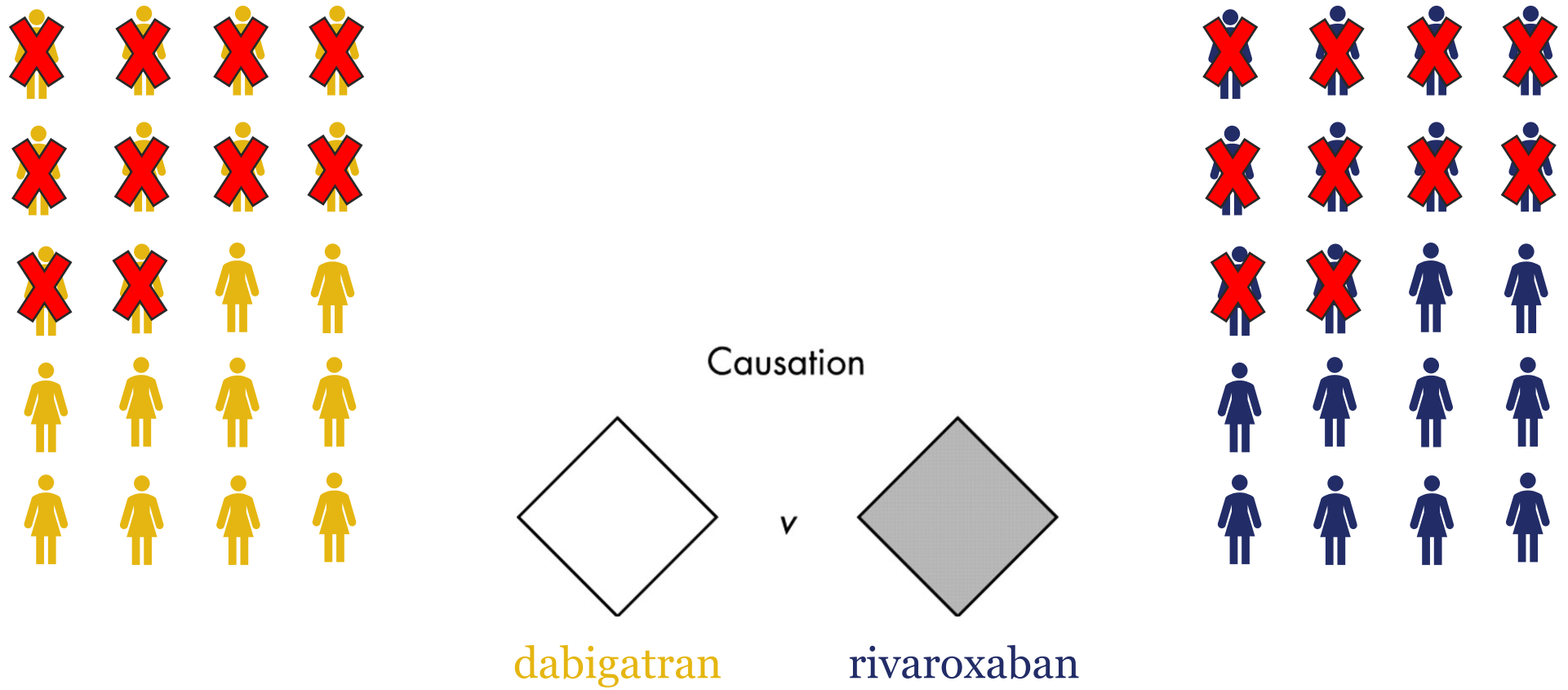
Inverse Probability of Treatment Weighting (IPTW)

Our counterfactual ("pseudo") population twice as large as the original (40 patients vs. 20 patients)



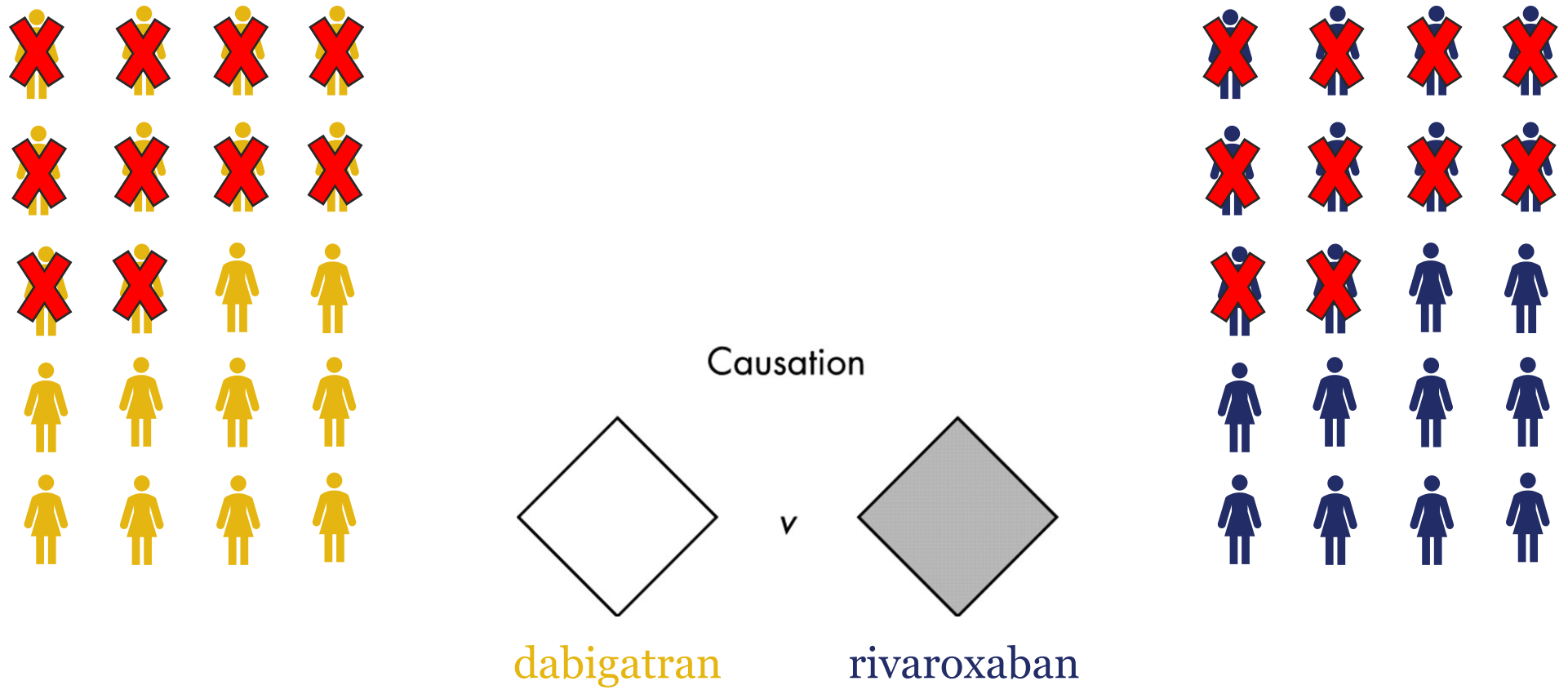
Inverse Probability of Treatment Weighting (IPTW)

Why? We essentially “copied” each patient twice: once into each exposure group



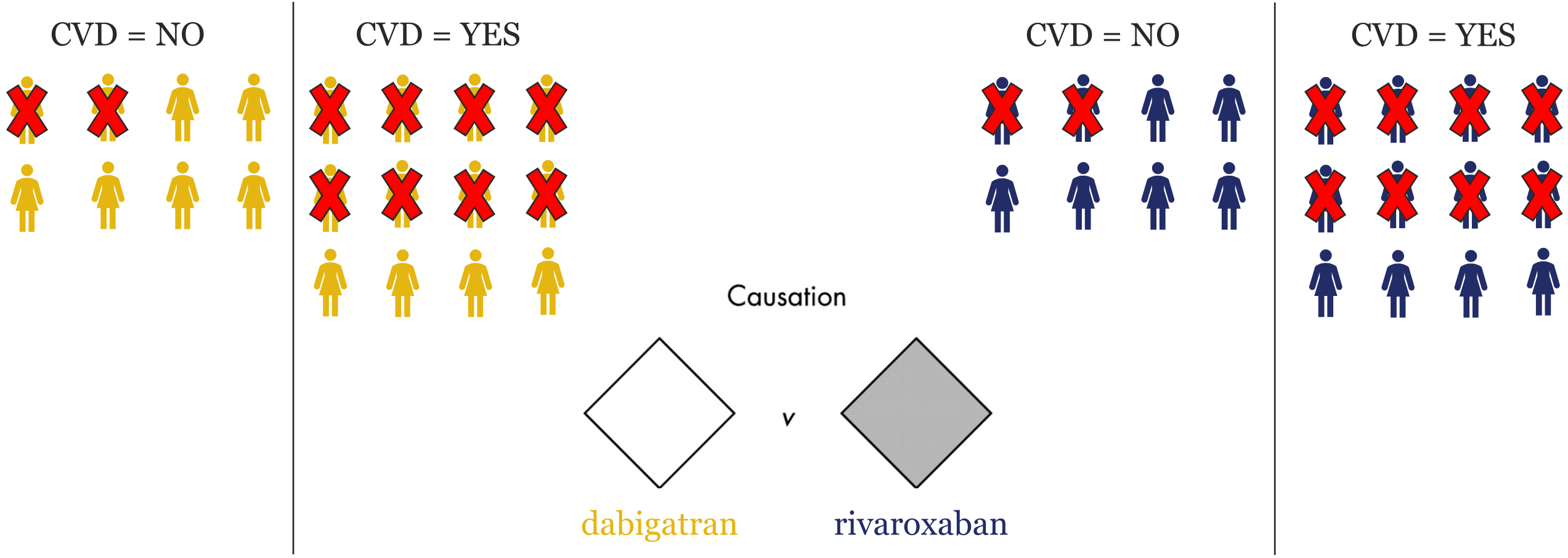
Inverse Probability of Treatment Weighting (IPTW)

Within our pseudo-population, there is **no confounding** because CVD is unassociated with exposure



Inverse Probability of Treatment Weighting (IPTW)

Within our pseudo-population, there is **no confounding** because CVD is unassociated with exposure



How does IPTW work?

We implicitly calculated IPT weights in our previous example

How does IPTW work?

In our observed population there were 4 CVD=NO patients treated with rivaroxaban

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66
Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

Creating IPTW Weights

In our counterfactual scenario, there were 8 CVD=NO patients treated with rivaroxaban

	Exposure	Stroke	CVD
Michelle	Rivaroxaban	Yes	No
Julie	Rivaroxaban	Yes	No
India	Rivaroxaban	No	No
Theresa	Rivaroxaban	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	No	No
Devorah	Rivaroxaban	Yes	Yes
Leeanna	Rivaroxaban	Yes	Yes
Claire	Rivaroxaban	Yes	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	No	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 0
Pr(rivaroxaban | CVD=NO) = 1

Pr(Stroke | dabigatran, CVD=NO) = 0
Pr(Stroke | rivaroxaban, CVD=NO) = 2/8 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 0
Pr(rivaroxaban | CVD=YES) = 1

Pr(Stroke | dabigatran, CVD=YES) = 0
Pr(Stroke | rivaroxaban, CVD=YES) = 8/12 = 0.66

Creating IPTW Weights

We implicitly weighted each observed CVD=NO rivaroxaban patient by 2

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO

Pr(CVD=NO) = 8/20 = 0.4

Pr(dabigatran | CVD=NO) = 4/8 = 0.5
Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5

Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25
Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25

CVD = YES

Pr(CVD=YES) = 12/20 = 0.6

Pr(dabigatran | CVD=YES) = 3/12 = 0.25
Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75

Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66
Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

Creating IPTW Weights

Our counterfactual question is equivalent to weighting by 1 / Pr(Observed Exposure | CVD)

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO	CVD = YES
	
Pr(CVD=NO) = 8/20 = 0.4	Pr(CVD=YES) = 12/20 = 0.6
Pr(dabigatran | CVD=NO) = 4/8 = 0.5 Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5	Pr(dabigatran | CVD=YES) = 3/12 = 0.25 Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75
Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25 Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25	Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66 Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

Creating IPTW Weights

We arrived at a weight of 2 because 1 / Pr(Rivaroxaban | CVD=NO) = 1 / 0.5 = 2

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO	CVD = YES
	
Pr(CVD=NO) = 8/20 = 0.4	Pr(CVD=YES) = 12/20 = 0.6
Pr(dabigatran | CVD=NO) = 4/8 = 0.5 **Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5**	Pr(dabigatran | CVD=YES) = 3/12 = 0.25 Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75
Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25 Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25	Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66 Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

Creating IPTW Weights

The weights for the other 3 CVD/exposure combinations can be similarly calculated

	Exposure	Stroke	CVD
Michelle	Dabigatran	No	No
Julie	Dabigatran	Yes	No
India	Dabigatran	No	No
Theresa	Dabigatran	No	No
Kimberly	Rivaroxaban	No	No
Darcie	Rivaroxaban	No	No
Ruby	Rivaroxaban	No	No
Lowri	Rivaroxaban	Yes	No
Devorah	Dabigatran	Yes	Yes
Leeanna	Dabigatran	Yes	Yes
Claire	Dabigatran	No	Yes
Catina	Rivaroxaban	Yes	Yes
Arline	Rivaroxaban	Yes	Yes
Cami	Rivaroxaban	Yes	Yes
Evelynn	Rivaroxaban	Yes	Yes
Caron	Rivaroxaban	Yes	Yes
Brandee	Rivaroxaban	Yes	Yes
Merissa	Rivaroxaban	No	Yes
Palma	Rivaroxaban	No	Yes
Alita	Rivaroxaban	No	Yes

CVD = NO	CVD = YES
	
Pr(CVD=NO) = 8/20 = 0.4	Pr(CVD=YES) = 12/20 = 0.6
Pr(dabigatran | CVD=NO) = 4/8 = 0.5 **Pr(rivaroxaban | CVD=NO) = 4/8 = 0.5**	Pr(dabigatran | CVD=YES) = 3/12 = 0.25 Pr(rivaroxaban | CVD=YES) = 9/12 = 0.75
Pr(Stroke | dabigatran, CVD=NO) = 1/4 = 0.25 Pr(Stroke | rivaroxaban, CVD=NO) = 1/4 = 0.25	Pr(Stroke | dabigatran, CVD=YES) = 2/3 = 0.66 Pr(Stroke | rivaroxaban, CVD=YES) = 6/9= 0.66

How does IPTW work?

- To calculate an IPT weight, one needs the **probability of the observed exposure given the confounders**
- In simple situations, we can calculate this probability by hand; in most studies, we need models
- For **exposed** patients, the probability of the observed exposure given confounders is their propensity score (PS)
- For **reference** patients, it's 1 minus their PS

IPTW in Sentinel Tools

- After calculating a PS at each Data Partner, the tool enforces **mandatory** trimming of non-overlap
- Trimming non-overlap helps avoid assigning patients extremely large weights
- Next, investigators must choose the exact type of IPT weight

Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ* 2019; 367:15657

Types of IPT Weights

- The exact form of the weight depends on the treatment effect of interest and whether the weight is "stabilized"

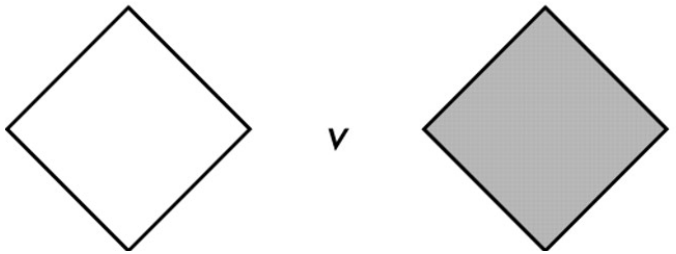
Treatment Effect	Exposure of Interest Weight (Unstabilized)	Reference Weight (Unstabilized)	Exposure of Interest Weight (Stabilized)	Reference Weight (Stabilized)
Average Treatment Effect (ATE)	$\frac{1}{PS}$	$\frac{1}{1-PS}$	$\frac{\Pr(Exp.\,in\,trimmed\,pop.)}{PS}$	$\frac{1-\Pr(Exp.\,in\,trimmed\,pop.)}{1-PS}$
Average Treatment Effect in the Treated (ATT)	N/A	N/A	1	$\frac{PS}{1-PS}$

Average Treatment Effect (ATE) Weights

- ATE weights use the **full population** (exposed + reference combined) as the reference standard

- Therefore, the weighted patient characteristics will reflect the distribution in the **full population**

- ATE contrasts if the full study population had been exposed vs. had the full study population been exposed to the reference



Average Treatment Effect (ATE) Weights

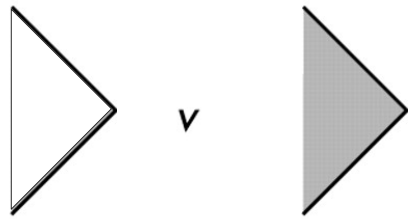
- ATE weights can be either unstabilized or stabilized; our example used unstabilized weights

Treatment Effect	Exposure of Interest Weight (Unstabilized)	Reference Weight (Unstabilized)	Exposure of Interest Weight (Stabilized)	Reference Weight (Stabilized)
Average Treatment Effect (ATE)	$\frac{1}{PS}$	$\frac{1}{1-PS}$	$\frac{\Pr(Exp.\,in\,trimmed\,pop.)}{PS}$	$\frac{1-\Pr(Exp.\,in\,trimmed\,pop.)}{1-PS}$

- Both forms return **similar point estimates and 95% confidence intervals** in Sentinel queries

Average Treatment Effect in the Treated (ATT) weights

- ATT weights use the **treated population only** as the reference standard
- Therefore, the weighted patient characteristics will reflect the distribution in the **treated patients**
- ATT contrasts if the treated population had been exposed vs. had the treated population been exposed to the reference
- ATT is essentially an ATE within a subgroup: the treated patients



Average Treatment Effect in the Treated (ATT) weights

- ATT weights are 1 for the exposed group and the PS odds for the reference group

Treatment Effect	Exposure of Interest Weight (Unstabilized)	Reference Weight (Unstabilized)	Exposure of Interest Weight (Stabilized)	Reference Weight (Stabilized)
Average Treatment Effect in the Treated (ATT)	N/A	N/A	1	$\frac{PS}{1-PS}$

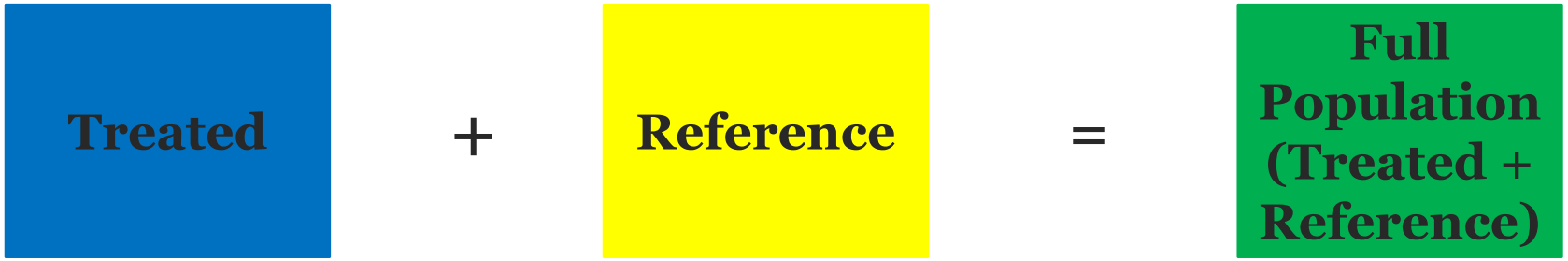
ATE or ATT?

- ATE and ATT effects are expected to be **the same in a randomized trial**
- That's because there are **no systematic differences** between treated and untreated patients
- In observational studies, the two effects may differ when there are systematic differences
- Specifically, systematic differences in characteristics that **modify the treatment effect**

ATE or ATT?

- Which effect to prefer depends on the research question

- To which type of population do you want to generalize the results?



IPTW in Sentinel

- After the investigator selects the type of weight the tool estimates a hazard ratio and robust 95% confidence interval according to Shu et al.
- Recent manuscript outlining how to perform IPTW with **risk-set (summary) level data**
- To maximally protect patient privacy, Sentinel Data Partners (DPs) typically do not share one row per patient "individual level" datasets with the Sentinel Operations Center
- Instead, DPs return summary level information about the risk sets formed at each site
- Risk-set data requires appropriate statistical techniques

Shu D, Yoshida K, Fireman BH, Toh S. Inverse probability weighted Cox model in multi-site studies without sharing individual-level data. *Statistical Methods in Medical Research* 2020; 29(6): 1668-1681

Considerations for IPTW in Sentinel

- Subgroup analyses require re-estimation of the PS within that subgroup
- Consequences of PS misspecification within subgroup are more severe for IPTW than for PS matching or PS stratification
- This is because IPTW uses the PS value directly to do adjustment; matching/stratification do not

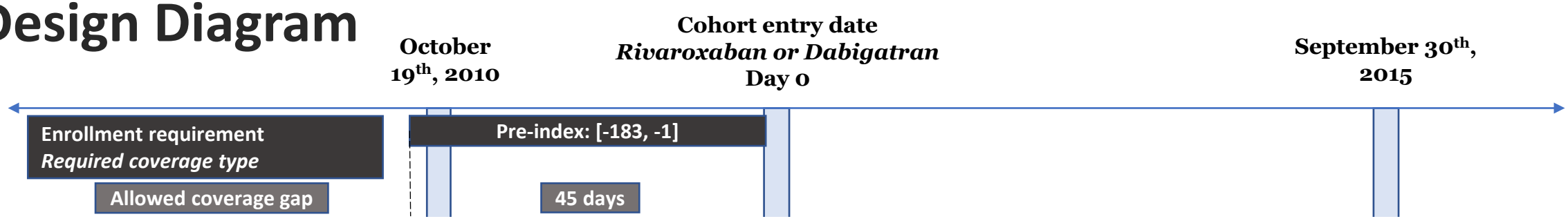
Izem R, Liao J, Hu M, Wei Y, Akhtar S, Wernecke M, MaCurdy TE, Kelman J, Graham DJ.
Comparison of propensity score methods for pre-specified subgroup analysis with survival data.
J Biopharmaceutical Stat 2020, DOI: 10.1080/10543406.2020.1730868

Applied example

- We replicated a previously published manuscript and previous PS-matched Sentinel analysis comparing direct oral anticoagulant (DOAC) users aged 65+ in Medicare
- For this workshop, we focus on one DOAC comparison: **rivaroxaban vs. dabigatran**
- We also focus on one outcome of interest: **thromboembolic stroke**

Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, Hu M, Illoh O, Wei Y, Goulding MR, Chillarige Y, Southworth MR, MaCurdy TE, Kelman JA. Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. *The American Journal of Medicine* 2019 132(5):596-604.e11

Design Diagram



***Exclusion Criteria**

Window 1: *Use of other DOAC, dialysis, kidney transplant, pulmonary embolism, joint replacement, mitral stenosis, valve repair/replacement*
Window 2: *Institutional stay (IS) encounter*

****Inclusion Criteria**

Atrial fibrillation

*****Covariates:**

Window I: *Age, race, sex*
Window II: *HAS-BLED, CHA_2DS_s VaSc, cardiovascular risk factors, prescription drug use, health services utilization*

Applied example

- Estimated PS model based on demographics, health characteristics, medical product use, and healthcare utilization variables
- Performed subgroup analysis by Male/Female sex
- Estimated separate PS models overall and within each sex subgroup

Applied example

- We adjusted for confounding using IPTW with stabilized ATE weights

- After selecting the type of IPT weight, investigators must decide whether to truncate the weights

Weight Truncation in Sentinel

- Patients whose **PS conflicts with their exposure group** will have very large weights
- Very large weights raise questions about how well the PS model is specified
- Large IPTW weights can **reduce statistical precision** and widen 95% confidence intervals

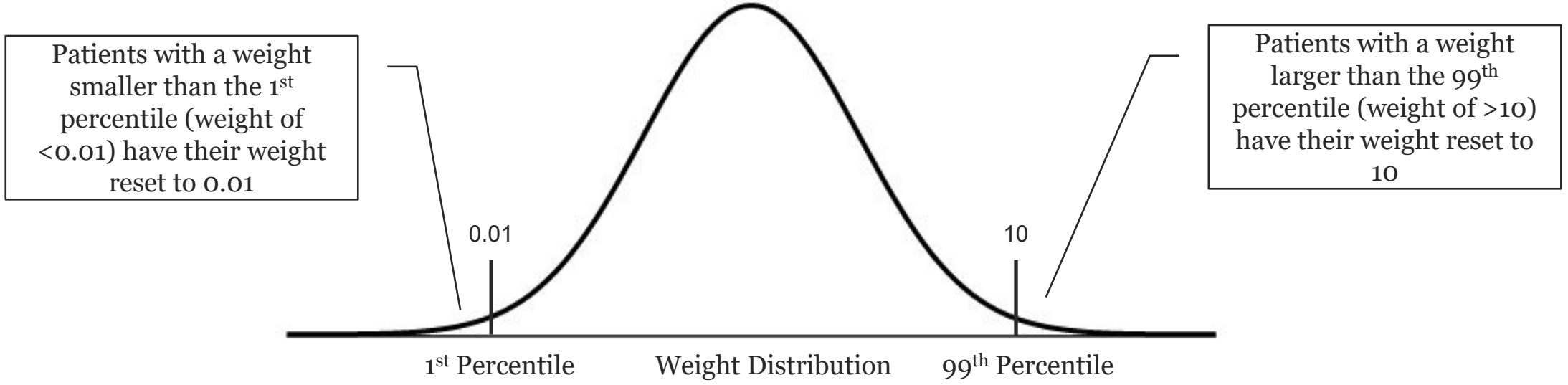
Weight Truncation in Sentinel

- Mandatory trimming of non-overlapping PS regions reduces the likelihood of very large weights
- Weight truncation can reduce the influence of patients with very large weights, if they exist
- The Sentinel tools requires **pre-specification** of weight truncation thresholds
- Users may select multiple truncation thresholds
- Truncated weights at 3 pre-specified levels:
  1. No truncation
  2. Truncation at $1^{st}/99^{th}$ percentile – "1% truncation"
  3. Truncation at $2.5^{th}/97.5^{th}$ percentile – "2.5% truncation"

Weight Truncation in Sentinel

- Weight truncation resets weights over the specified threshold to the value of the threshold

- Operationalized symmetrically; i.e. truncate weights at 1st and 99th percentile of weight distribution



Weight Truncation in Sentinel

- **If the PS model is correct**, weight truncation represents a **bias-variance tradeoff**

- **If the PS model is incorrect**, weight truncation can reduce both bias AND variance; however, the optimal amount of truncation is situation-specific and unknowable

- Recommend **multiple truncation levels** with **pre-specified rule** that the estimate using the most "well-behaved" weights is the primary analysis

Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. *PLOS One* 2011; 6(3): e18174

What does it mean for weights to be “well-behaved”?

- The **observed mean weight is close to the expected mean weight**
- If two truncation levels have the same mean weight, the one with **a smaller standard deviation is preferred**
- For unstabilized ATE weights, the expected mean weight is 2; for stabilized ATE weights, the expected mean weight is 1
- For ATT weights, the expected mean weight is 2 times the prevalence of exposure

What does it mean for weights to be “well-behaved”?

- Deviations from the expected mean weight indicate:
  - A mis-specified propensity score model
  - Combinations of covariates for which patients either always or never receive the exposure

- In Sentinel queries, we review weight distributions and select a threshold with FDA **before** calculating effect estimates

Weight Distribution (Stabilized ATE)

No truncation

Data Partner (Masked)	Number of Patients	Minimum	Maximum	Mean	Standard Deviation
DP01	194583	0.575	3.621	1.000	0.136
Aggregated	194583	0.575	3.621	1.000	0.136

Truncated at 1st and 99th percentiles

Data Partner (Masked)	Number of Patients	Minimum	Maximum	Mean	Standard Deviation
DP01	194583	0.733	1.424	0.999	0.131
Aggregated	194583	0.733	1.424	0.999	0.131

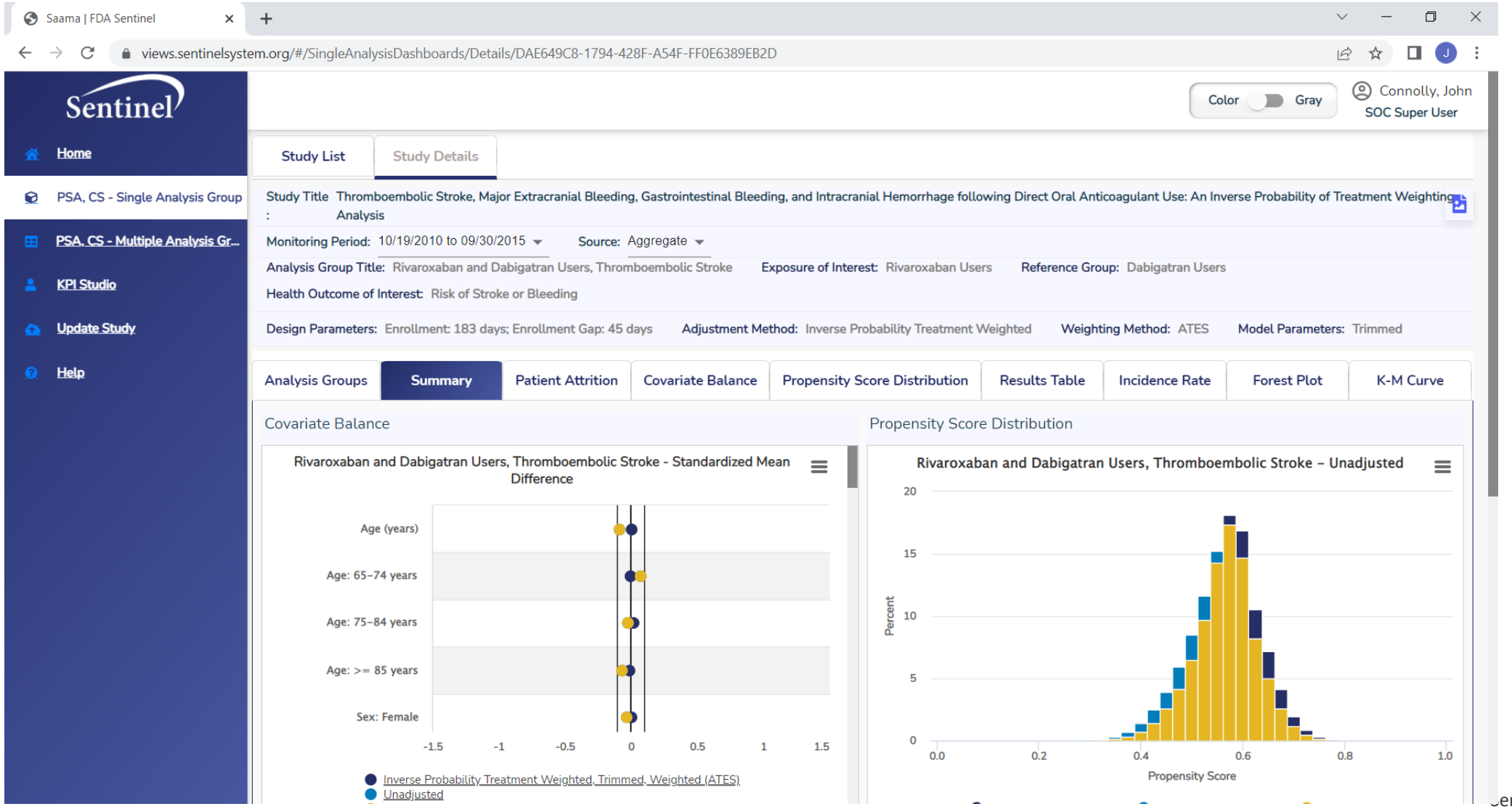
Truncated at 2.5th and 97.5th percentiles

Data Partner (Masked)	Number of Patients	Minimum	Maximum	Mean	Standard Deviation
DP01	194583	0.773	1.322	0.998	0.125
Aggregated	194583	0.773	1.322	0.998	0.125

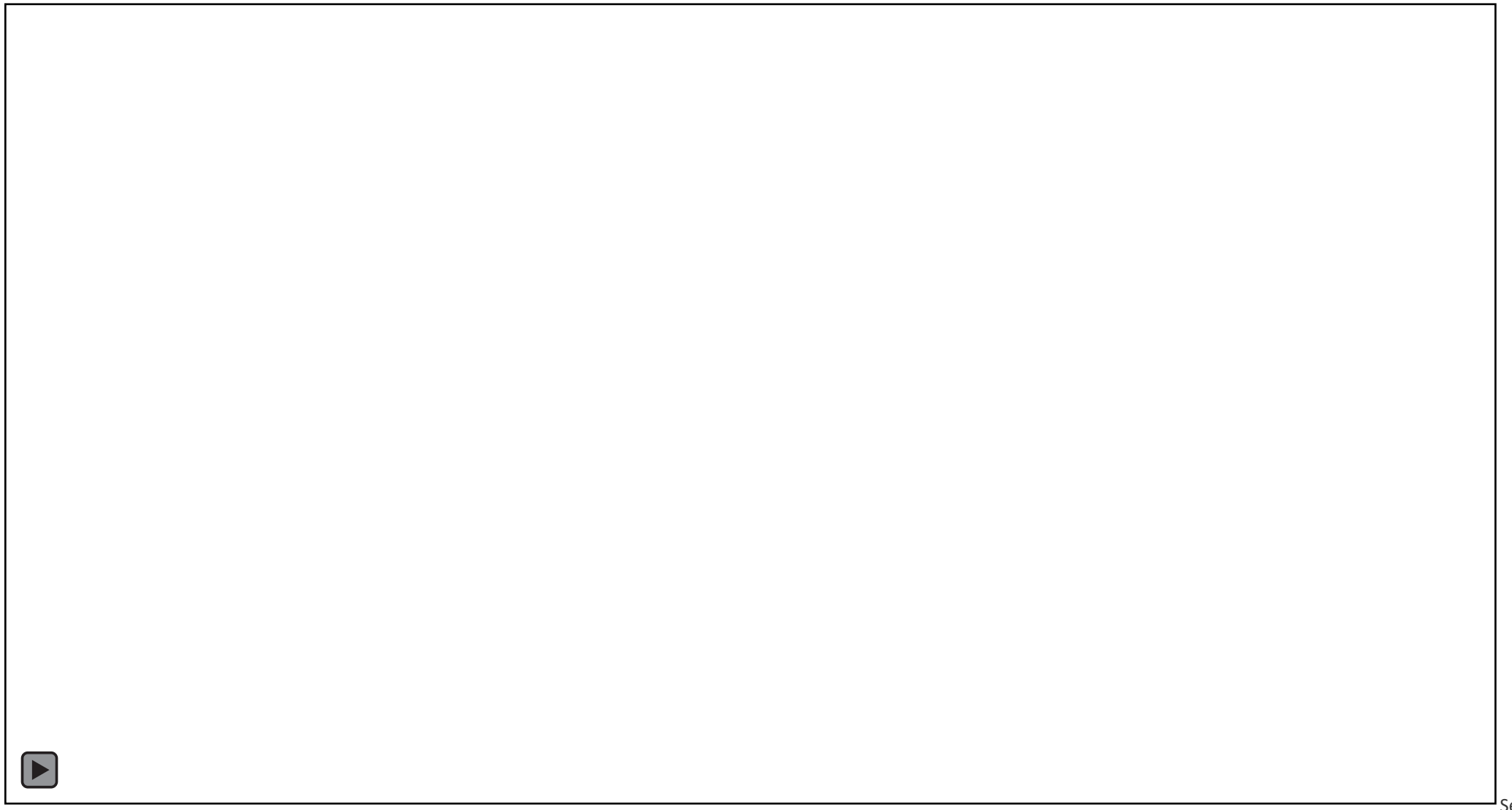
Sentinel Views

- Results for this applied example were generated using Sentinel Views
- Views is a web-based data visualization application
- Provides interactive, customizable dashboards to display results

Sentinel Views



Sentinel Views



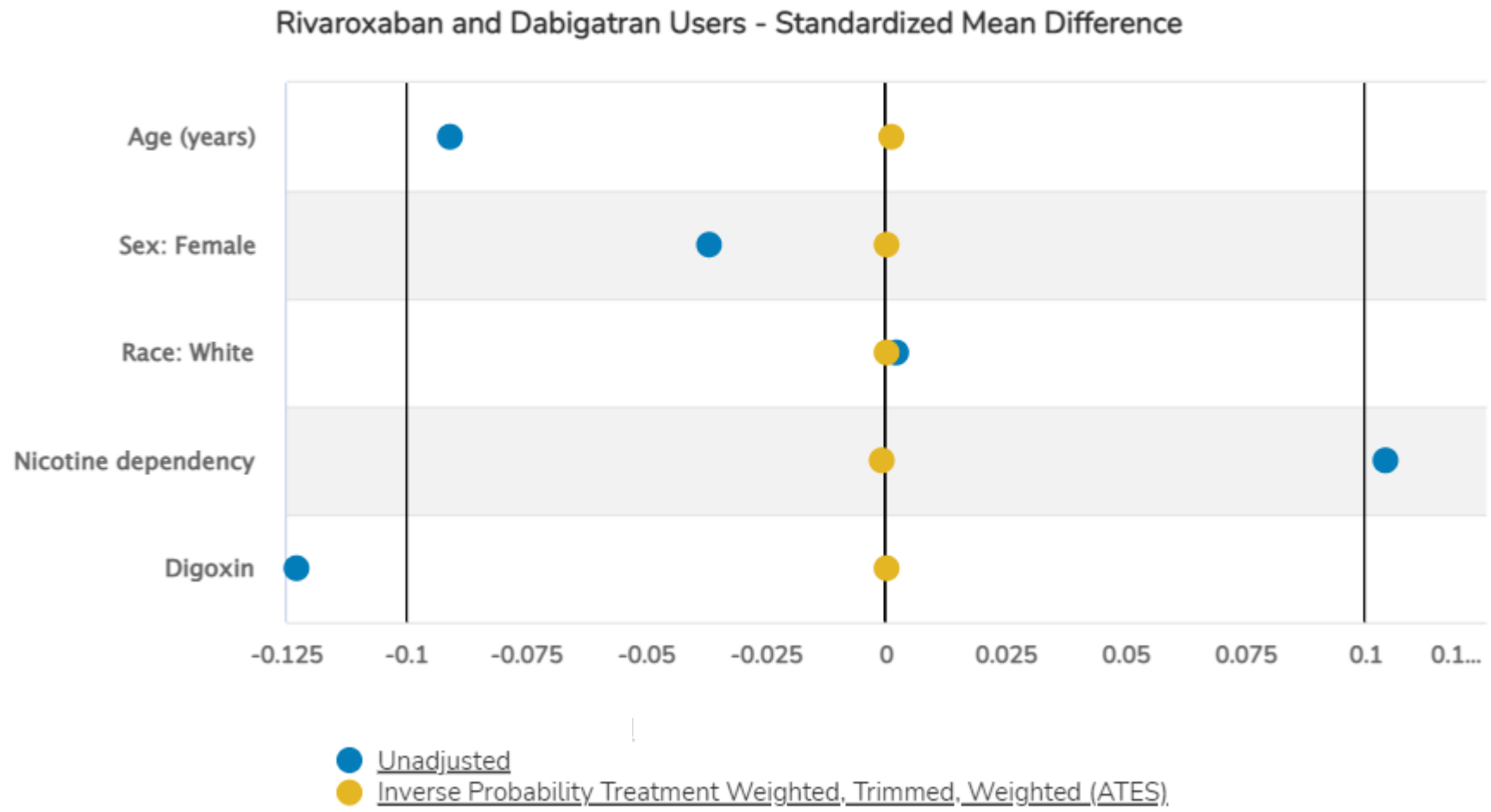
Sentinel Views

- A subset of approved queries will be made available to the public on Views

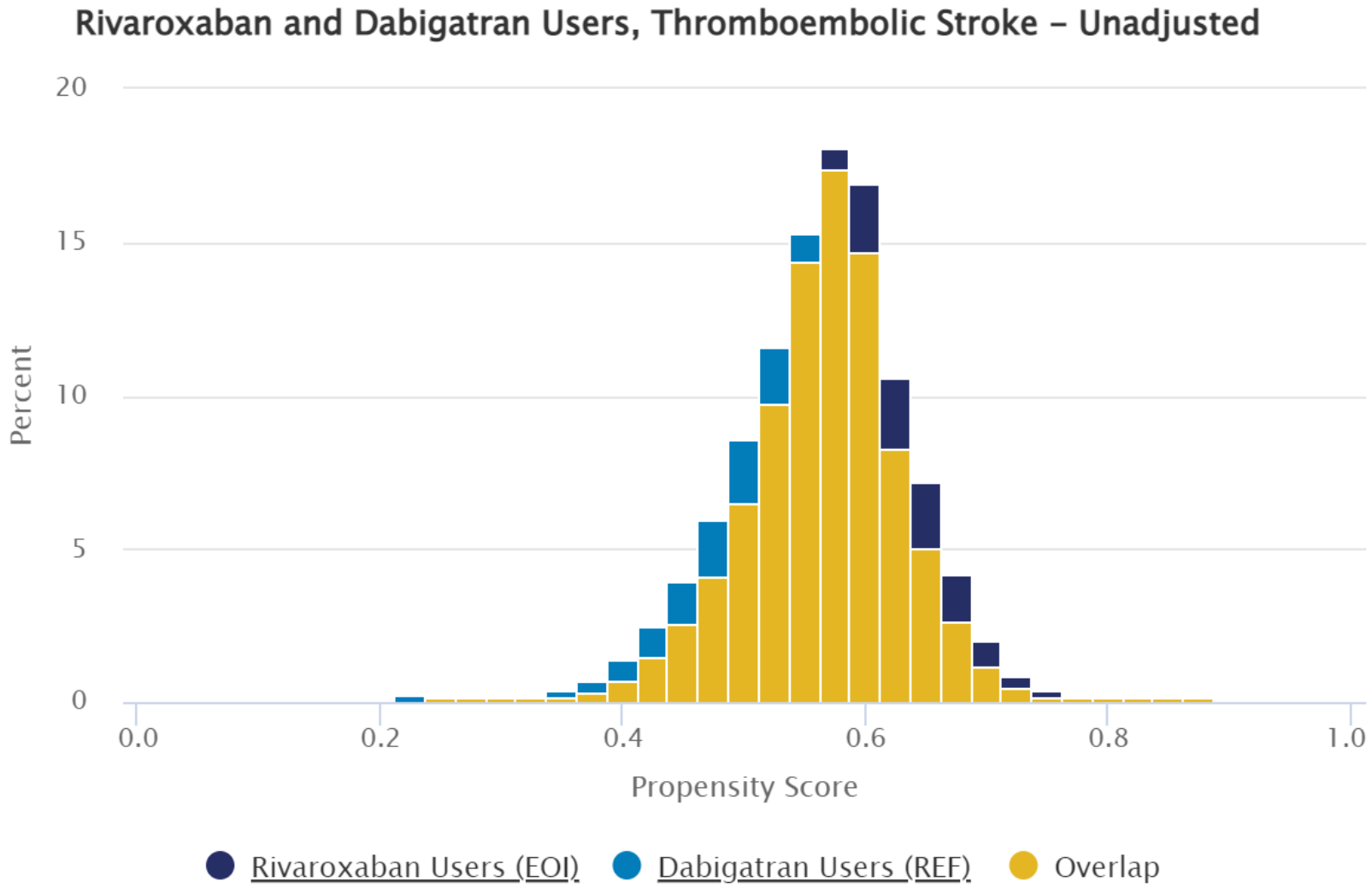
- Goals for public use are:
  1. Increased awareness of Sentinel System as a resource for public health
  2. Increased access to Sentinel System's tools through an interactive resource

- Views can be publicly accessed at views.sentinelsystem.org

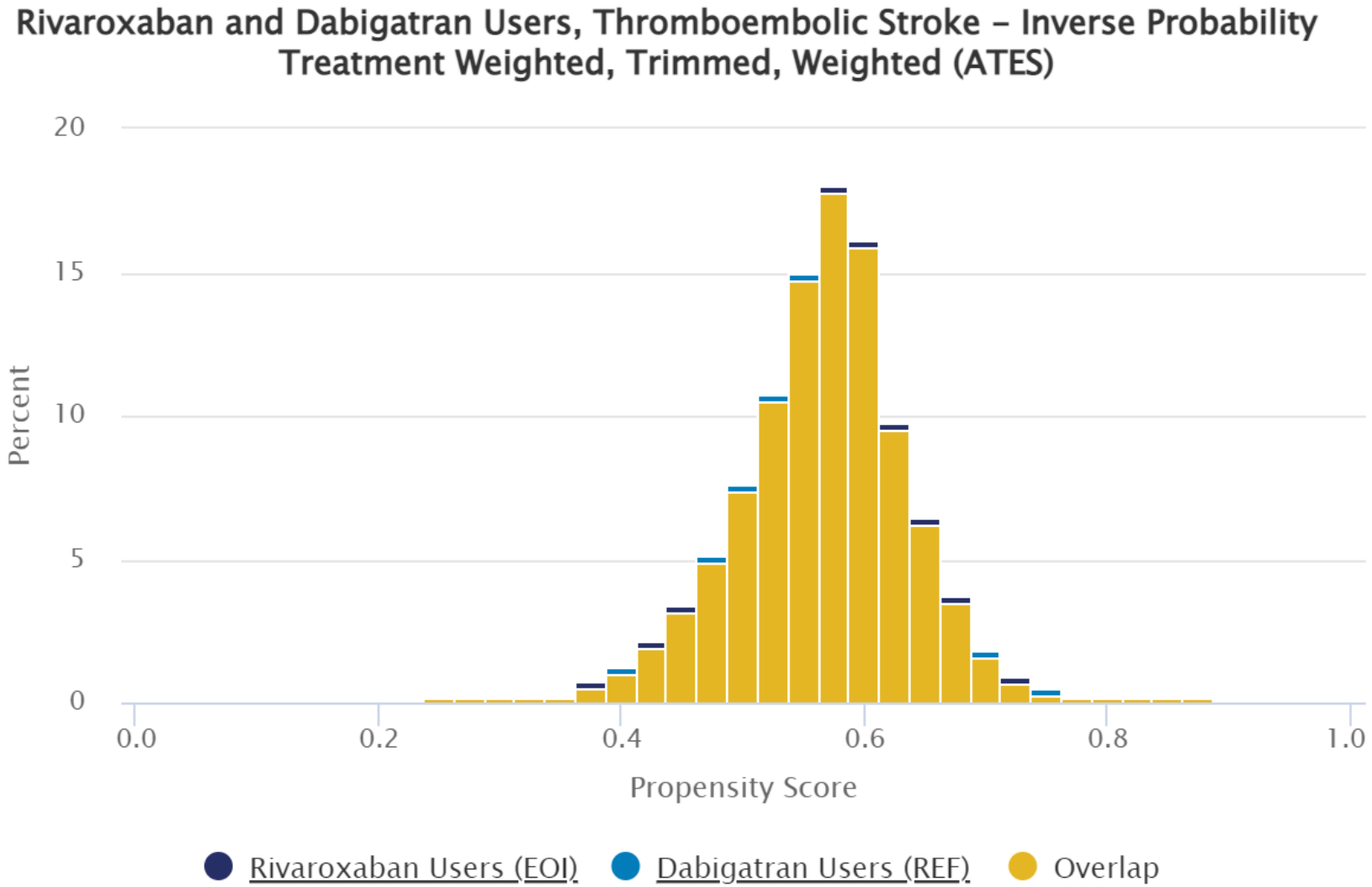
Selected Patient Characteristics – Rivaroxaban vs. Dabigatran



Unadjusted Propensity Score Distribution



ATE Weighted Propensity Score Distribution

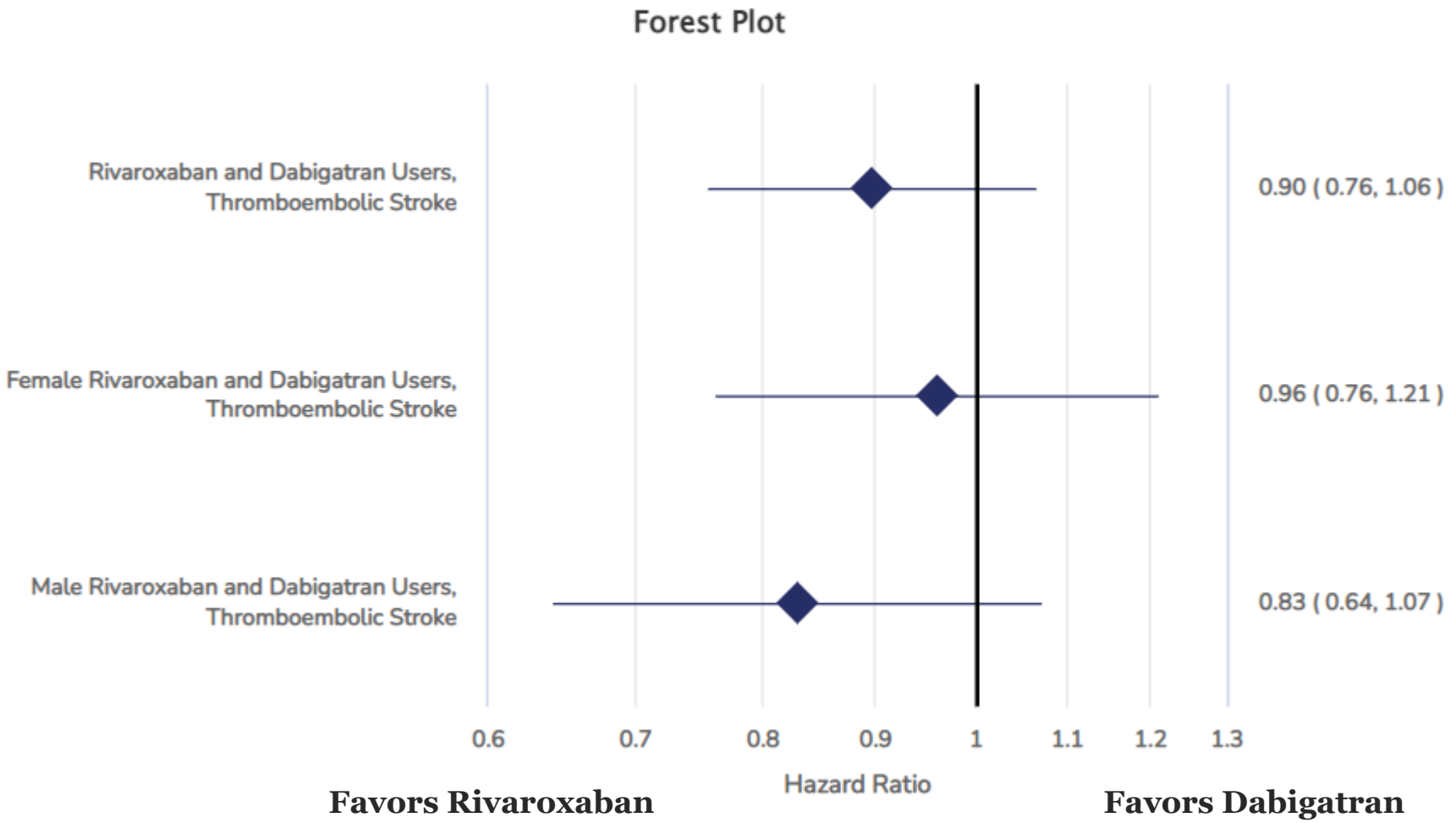


Effect Estimates

Effect Estimates for Rivaroxaban and Dabigatran Users, Thromboembolic Stroke by Analysis Type											
Medical Product	**Number of New Users**	**Person Years at Risk**	**Average Person Days at Risk**	**Average Person Years at Risk**	**Number of Events**	**Incidence Rate per 1,000 Person Years**	**Risk per 1,000 New Users**	**Incidence Rate Difference per 1,000 Person Years**	**Difference in Risk per 1,000 New Users**	**Hazard Ratio (95% CI)**	**Wald P-Value**
Site-Adjusted Analysis, Unweighted											
Rivaroxaban Users	110,113	37,140.10	123.20	0.34	292	7.86	2.65	-1.29	-0.25	0.87 (0.74, 1.03)	0.116
Dabigatran Users	84,473	26,783.01	115.81	0.32	245	9.15	2.90				
Inverse Probability of Treatment Weighted Analysis; Unweighted; Trimmed											
Rivaroxaban Users	110,112	37,140.01	123.20	0.34	292	7.86	2.65	-1.29	-0.25		
Dabigatran Users	84,471	26,782.83	115.81	0.32	245	9.15	2.90				
Inverse Probability of Treatment Weighted Analysis; Weight = ATES[1, 2]											
Rivaroxaban Users	110,111	37,119.03	123.13	0.34	295	7.95	2.68	-1.06	-0.18	0.90 (0.76, 1.06)	-
Dabigatran Users	84,481	26,791.17	115.83	0.32	241	9.01	2.86				

[1]All values in this section are weighted
[2]ATES = Average Treatment Effect, Stabilized

Subgroup Analysis by Sex



Propensity Score Methods in Sentinel

Method	Strengths	Limitations
PS matching	• 1:1 matching offers strong confounding control • Intuitive analysis • Can estimate marginal ATT or conditional effect • Adjusted Kaplan-Meier curves	• Reduced sample size may lead to statistical imprecision, especially after 1:1 matching
PS stratification	• Retains sample size over PS matching • Retains sample size over IPTW if no trimming	• Potentially reduced confounding control compared to matching and IPTW • No adjusted Kaplan-Meier curves • Estimates conditional effect only
IPTW	• Strong confounding control comparable to 1:1 matching • Can estimate either marginal ATT or ATE • Retains sample size over PS matching • Adjusted Kaplan-Meier curves	• Estimates marginal effects only • Must re-estimate PS model within subgroups • Must deal with potentially large weights

Conclusions

- The addition of IPTW to Sentinel tools met FDA's need for increased **analytic flexibility**
- IPTW offers strong confounding control **without sample size loss** inherent to 1:1 matching
- Sentinel Operations Center developed a method to perform IPTW using **risk-set data**
- Proven to produce equivalent effect estimate to traditional patient-level analysis

Conclusions

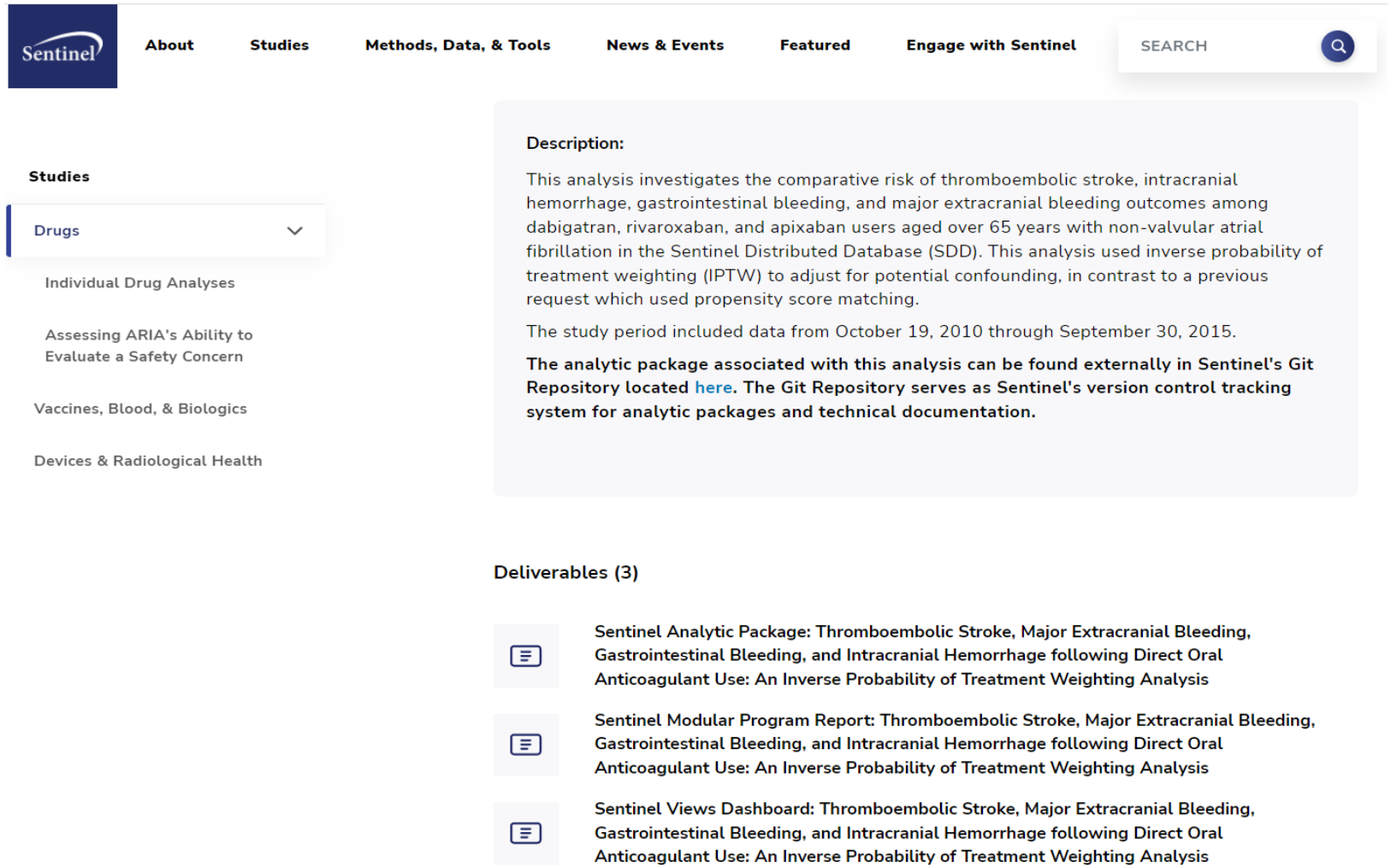
- Query Request Package (QRP) is sent to DPs and produces appropriate analytic dataset to perform IPTW

- A local reporting tool (QRPL) is run on the analytic dataset created by QRP to generate final output including effect estimates
  - Run **after** selecting weight truncation threshold

- QRP and QRPL can be run on any dataset stored in the Sentinel Common Data Model (SCDM)

Conclusions

- QRP and QRPL for the applied example, along with the Views dashboard, can be found here:



Conclusions

- Sentinel's newly implemented IPTW capability was successfully applied in a query comparing risk of stroke and bleeding outcomes among DOAC users

- Effect estimates were similar to a previous version of the same query using PS matching

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Part 3 Questions

Post-Training Survey

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Thank You