Sentinel Public Training: Morning Session

Review of Sentinel Capabilities

Judith C. Maro, PhD[2]

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

Sentinel Program Overview

What is the Sentinel System?

One of the FDA's biggest jobs is to make sure drugs, vaccines, and medical devices are safe. FDA wants to know if patients get bad side effects from these products. To make it faster and easier to learn about problems, FDA created a special program called the Sentinel System.

How the Sentinel System Works

Sentinel System's 3 important parts

- **Information: The system looks at billing claims and patient records.**
- **Expert Team: Sentinel works with scientists, doctors and computer experts.**
- **Computer Programs: They study large groups of patients who take the same medicine, or use the same device.**

Personal privacy

- **No one at FDA or the Sentinel Operations Center has access to your name, address, or any other information that identifies you.**
- **For more information, visit sentinelinitiative.org.**

Sentinel asks questions like:

- **How many patients take the same drug?**
- **How many patients are getting bad side effects (swelling, bleeding, etc.)?**
- **Are side effects more common after taking one drug than after another drug that treats the same problem?**

How does FDA use the information?

- **FDA can choose to collect more information.**
- **FDA can provide updated safety information for patients and providers.**
- **If you have concerns about your own medical products, please contact your doctor.**

https://www.sentinelinitiative.org/sentinel-system-story

Collaborating Organizations

Sentinel

Lead – HPHC Institute

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

Data & Scientific Partners

Blue Cross Blue Shield Massachusetts
HealthCore Anthem
HCA Healthcare
health care systems research network
Department of Population Health Sciences, Duke University School of Medicine
Vanderbilt School of Medicine
OPTUM
HUMANA
Kaiser Permanente
aetna

Scientific Partners

Penn Medicine
IQVIA
Weill Cornell Medicine
Cincinnati Children's change the outcome
IBM
UNC Gillings School of Global Public Health
Harvard T.H. Chan School of Public Health
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School
AHIP America's Health Insurance Plans
UF College of Pharmacy, University of Florida
UAB
UIC
The University of Iowa College of Public Health
Rutgers

https://www.sentinelinitiative.org/collaborators

Sentinel Infrastructure: Available Data Elements

Sentinel Data Philosophy

- Includes claims, 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

Administrative Data

Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID
Enrollment Start & End Dates	Birth date	Dispensing Date	Service Date(s)	Service date(s)	Service Date(s)
Drug Coverage	Sex	National Drug Code (NDC)	Encounter ID	Encounter ID	Encounter ID
Medical Coverage	Zip code	Days Supply	Encounter Type and Provider	Encounter Type and Provider	Encounter Type and Provider
Medical Record Availability	Etc.	Amount Dispensed	Facility	Diagnosis Code & Type	Procedure Code & Type
			Etc.	Principle Discharge Diagnosis	Etc.

Clinical Data

Lab Result	Vital Signs
Patient ID	Patient ID
Result & Specimen Collection Dates	Measurement Date & Time
Test Type, Immediacy & Location	Height & Weight
Logical Observation Identifiers Names and Codes (LOINC®)	Diastolic & Systolic BP
Etc.	Tobacco Use & Type
	Etc.

Registry Data

Death	Cause of Death	State Vaccine
Patient ID	Patient ID	Patient ID
Death Date	Cause of Death	Vaccination Date
Source	Source	Admission Date
Confidence	Confidence	Vaccine Code & Type
Etc.	Etc.	Provider
		Etc.

Inpatient Data

Inpatient Pharmacy	Inpatient Transfusion
Patient ID	Patient ID
Administration Date & Time	Administration Start & End Date & Time
Encounter ID	Encounter ID
National Drug Code (NDC)	Transfusion Administration ID
Route	Transfusion Product Code
Dose	Blood Type
Etc.	Etc.

Mother-Infant Linkage Data

Mother-Infant Linkage
Mother ID
Mother Birth Date
Encounter ID & Type
Admission & Discharge Date
Child ID
Child Birth Date
Mother-Infant Match Method
Etc.

https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model

Single Patient Example Data in Model

DEMOGRAPHIC

PATID	BIRTH_DATE	SEX	HISPANIC	RACE	zip
PatID1	2/2/1964	F	N	5	32818

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
PatID1	10/23/2005	00310027510	30	15

ENROLLMENT

PATID	ENR_START	ENR_END	MEDCOV	DRUGCOV
PatID1	7/1/2004	12/31/2004	Y	N
PatID1	1/1/2005	12/31/2005	Y	Y

DEATH

PATID	DEATHDT	DTIMPUTE	SOURCE	CONFIDENCE
PatID1	12/27/2005	N	S	E

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	305.6	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	311	9	P
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

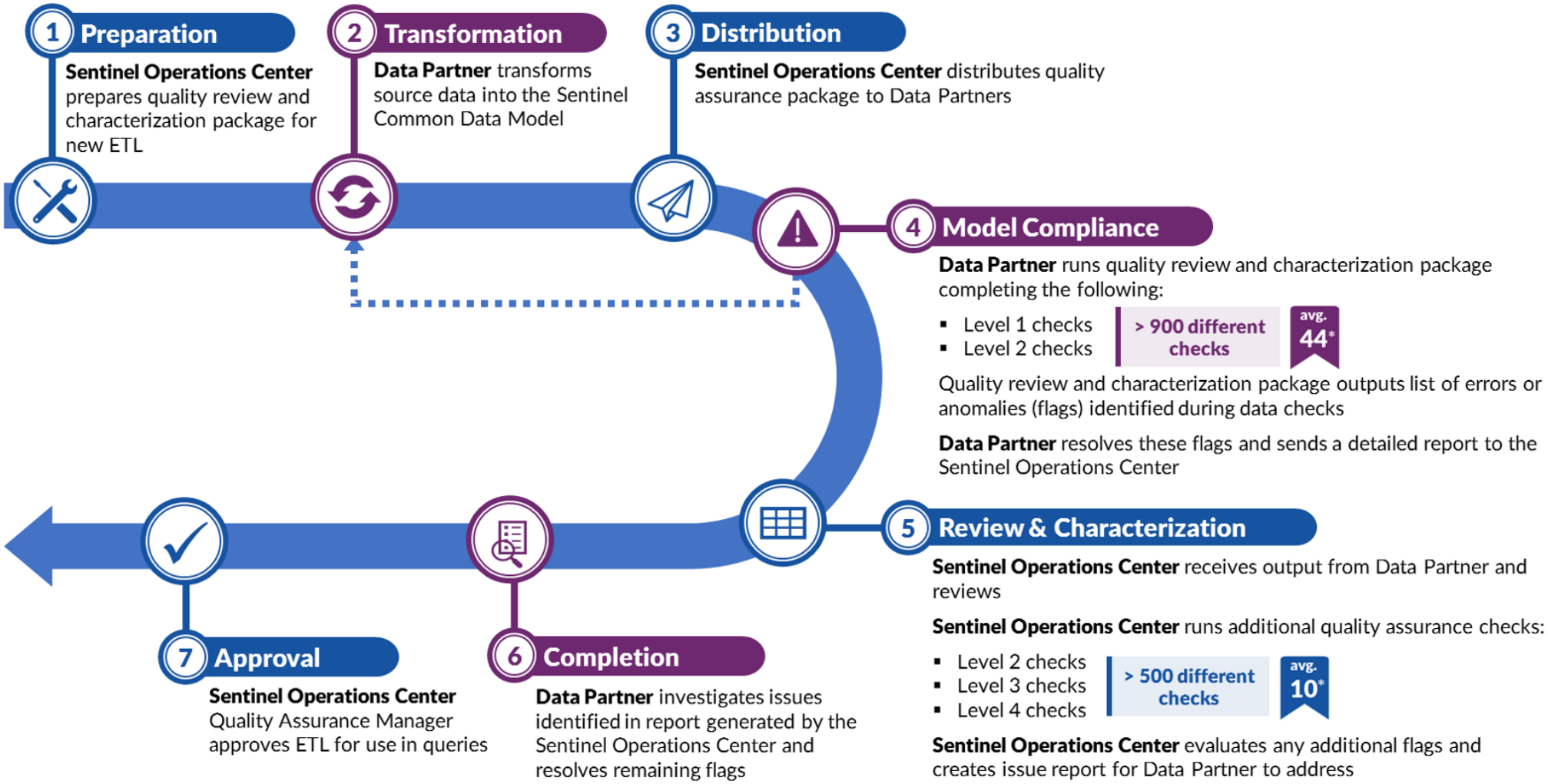
PROCEDURE

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99222	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99238	C4
PatID1	EncID1	10/18/2005	Provider2	IP	27445	C4

CAUSE OF DEATH

PATID	COD	CODETYPE	CAUSETYPE	SOURCE	CONFIDENCE
PatID1	J18.0	10	U	S	E

Data Quality Review and Characterization Process



* On average, there are 44 flags identified by the program and 10 additional flags identified by the Sentinel Operations Center per ETL

https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization

Data Quality Checks and Examples

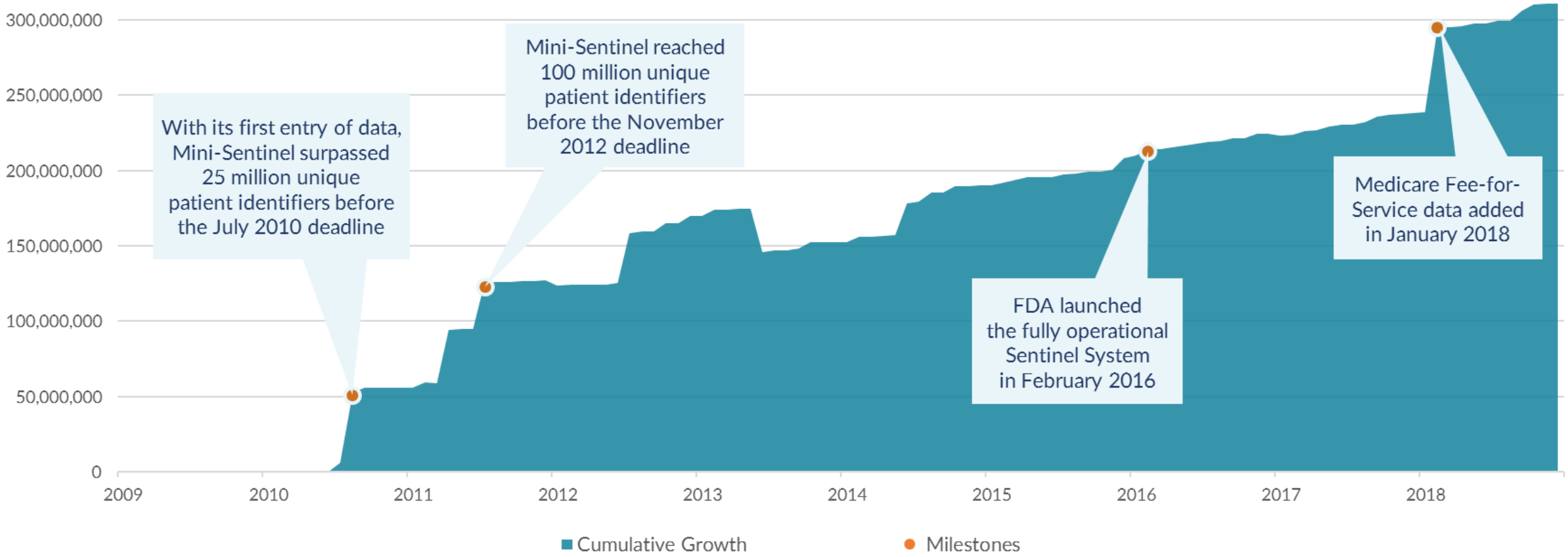
Level 1 Checks	**Completeness** ✓ Admission date is not missing value **Validity** ✓ Admission date is in date format	Sentinel Common Data Model Compliance
Level 2 Checks	**Accuracy** ✓ Admission date occurs before the patient's discharge date **Integrity** ✓ Admission date occurs within the patient's active enrollment period	Cross-Variable and Cross-Tabular
Level 3 Checks	**Consistency of Trends** ✓ There is no sizable percent change in admission date record counts by month-year	Cross-ETLs
Level 4 Checks	**Plausibility** ✓ There is no sizable percent change in the number of prostate cancer encounters by sex*	Cross-ETLs

**Under development*

https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization

Growth of the Sentinel Distributed Database

- 70 million members currently accruing new data



The area above depicts the cumulative number of unique patient identifiers in the Sentinel Distributed Database from 2010 to present. If patients move health plans, they may have more than one patient identifier.

http://www.sentinelinitiative.org/sentinel/data/snapshot-database-statistics

Mechanism to Transform Commercial Data

Submit Comment

SAS Code for Transforming the IBM MarketScan® Research Databases (MarketScan) into the Sentinel Common Data Model

Project Title	**SAS Code for Transforming the IBM MarketScan® Research Databases (MarketScan) into the Sentinel Common Data Model**
Date Posted	*Tuesday, January 29, 2019*
Status	Complete
Description	The Sentinel Operations Center and IBM Watson Health have partnered to make SAS® code available for transforming the IBM MarketScan® Commercial and Medicare Supplemental Databases into the Sentinel Common Data Model. If your organization currently licenses either of these databases and wishes to leverage the analytic infrastructure developed by Sentinel by transforming these data into the Sentinel Common Data Model, please click the 'Submit Comment' button on this page to request access. The Sentinel Operations Center will send you a MarketScan License Verification form. Contingent on license validation by IBM Watson Health, Sentinel will share the SAS code and documentation with your organization.

https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model/sas-code-transforming-ibm-marketscan-research

Sentinel Data Queries:
Routine Querying Tools

Sentinel Infrastructure Supports Multiple Aims

Sentinel Infrastructure

Sentinel System

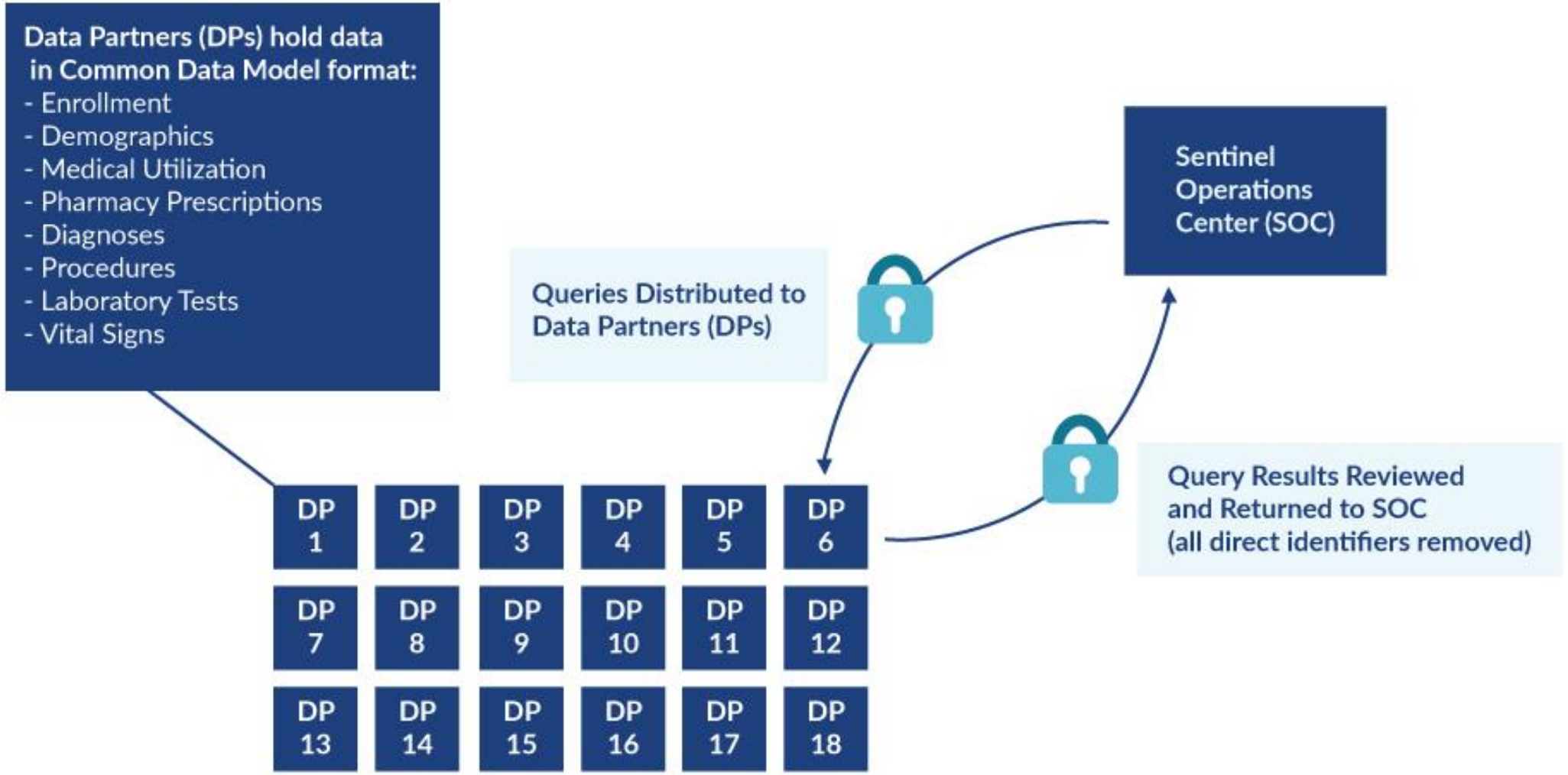
Routine queries and other activities that use pre-existing data

- PRISM
- BloodSCAN
- ARIA

FDA-Catalyst

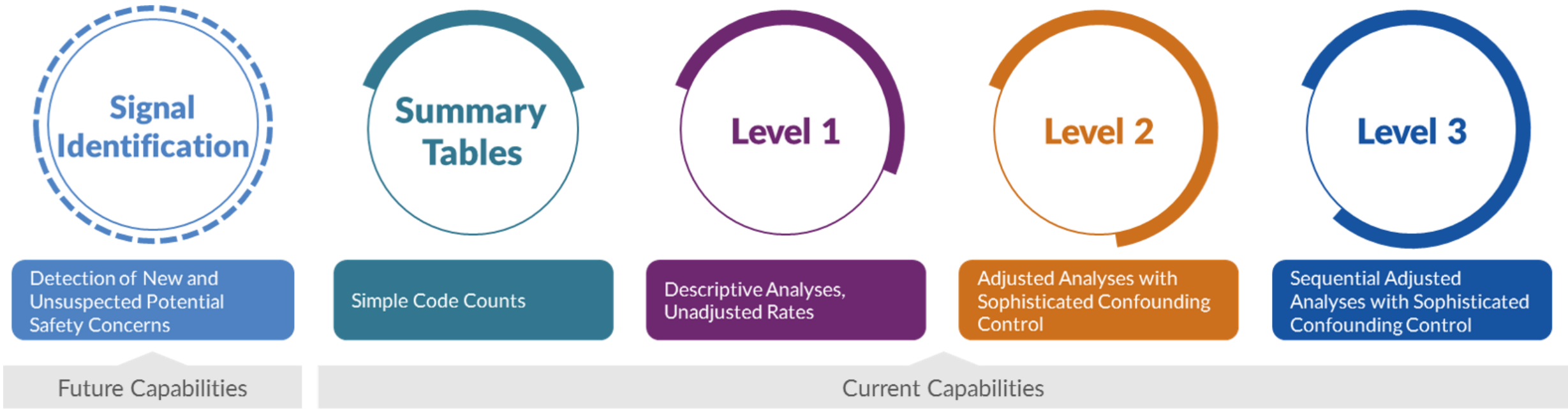
Routine queries + interventions and interactions with members and/or providers

Sentinel is a Distributed Data Network



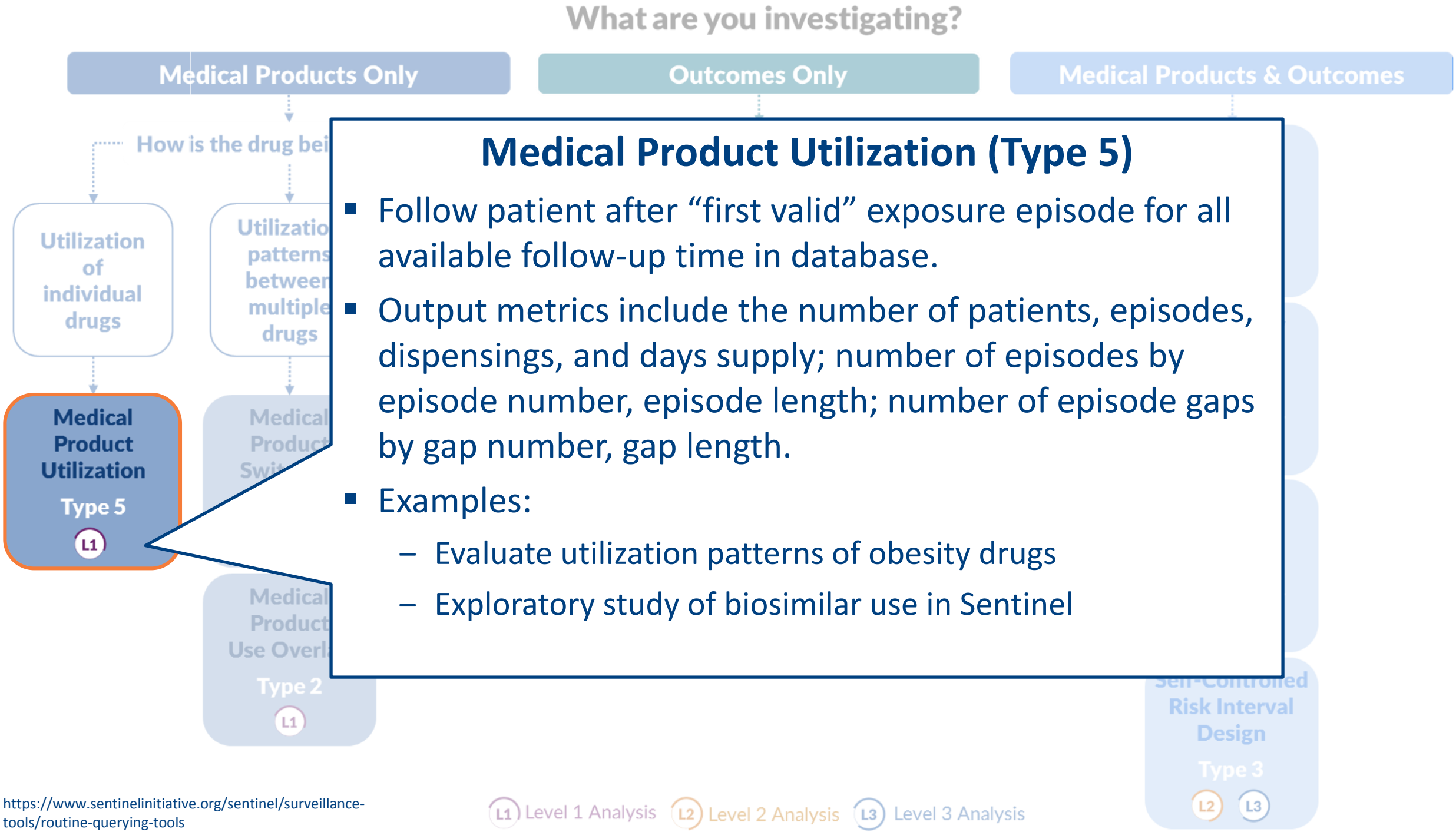
https://www.sentinelinitiative.org/sentinel/sentinels-distributed-database

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/active-risk-identification-and-analysis-aria

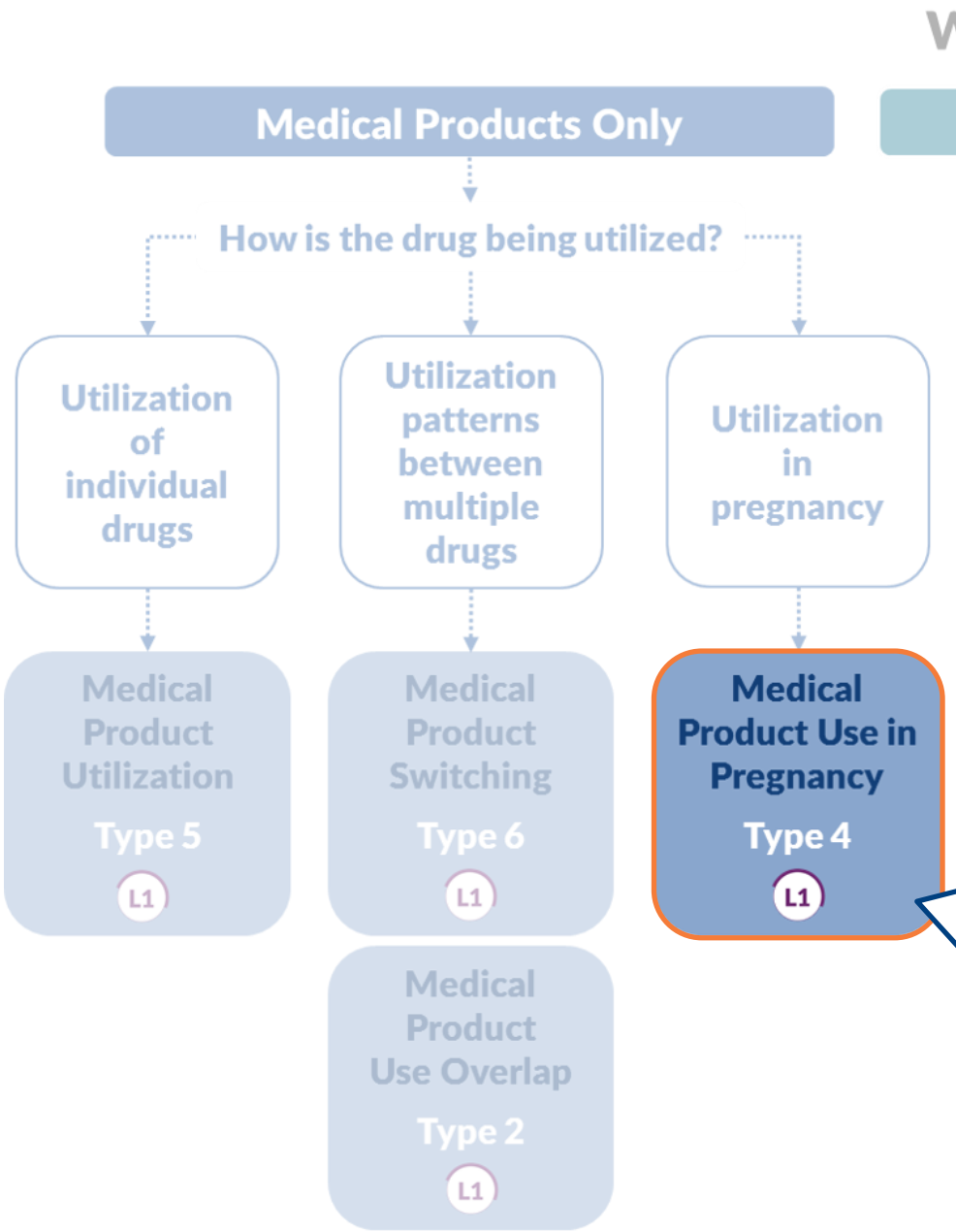


https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools

Submit Comment

Utilization Patterns of Obesity Drugs

Project Title	**Utilization Patterns of Obesity Drugs**
Date Posted	*Tuesday, March 19, 2019*
Project ID	cder_mpl1r_wp129
Status	Complete
Deliverables	Sentinel Modular Program Report: Utilization Patterns of Obesity Drugs, Report 1 Sentinel Modular Program Report: Utilization Patterns of Obesity Drugs, Report 2
Description	This request examines utilization patterns of nine obesity drugs in the Sentinel Distributed Database (SDD) between January 1, 2008 and December 31, 2017. This request was distributed to 17 Data Partners on December 21, 2018.
Medical Product	benzphetamine bupropion/naltrexone diethylpropion liraglutide lorcaserin HCL orlistat phendimetrazine phentermine HCL phentermine/topiramate



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 utilization patterns of phosphodiesterase 5 inhibitors in pregnant women

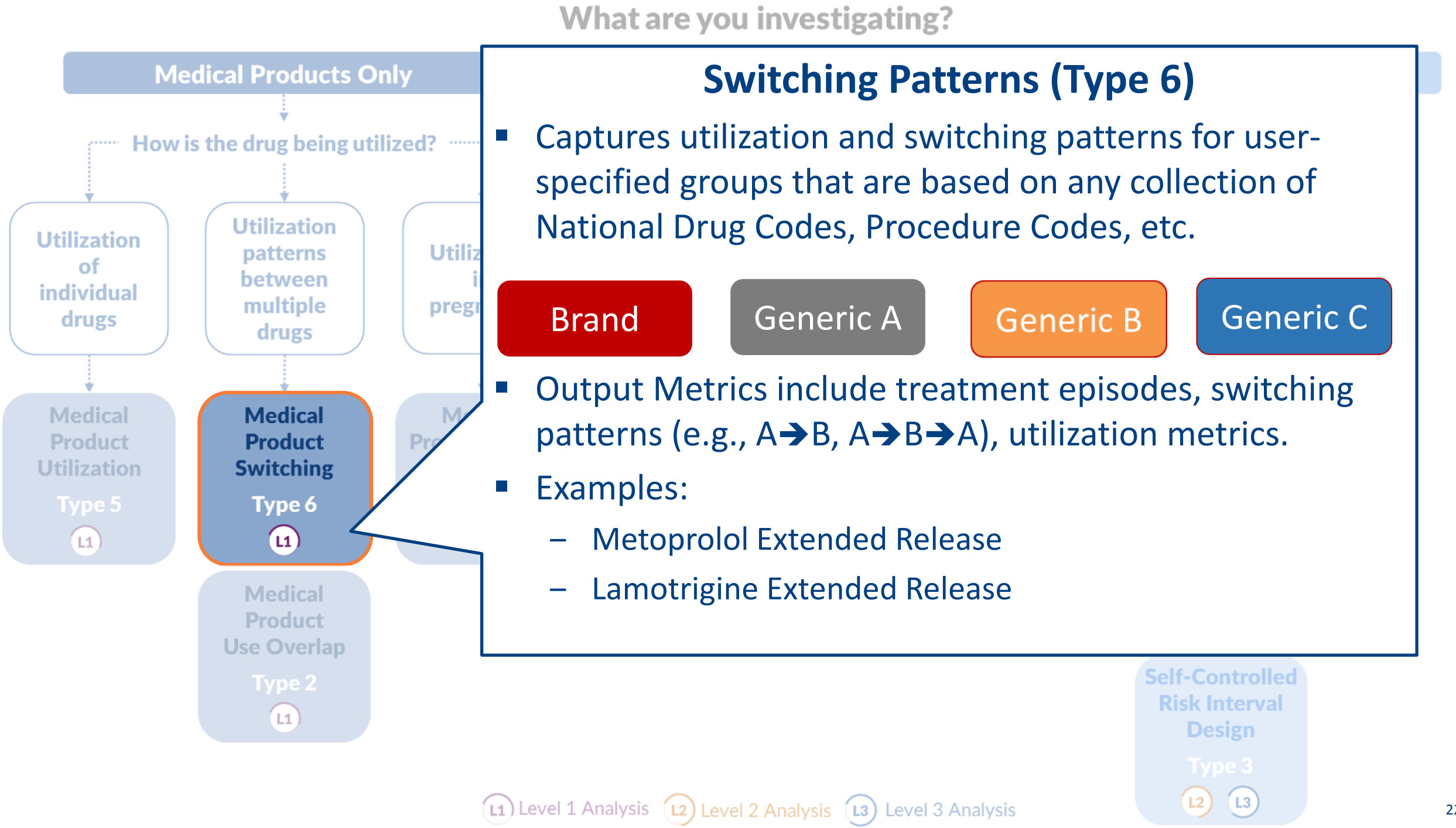
L1 Level 1 Analysis L2 Level 2 Analysis L3 Level 3 Analysis

Submit Comment

Phosphodiesterase Type 5 (PDE5) Inhibitor Utilization Among Women

Project Title	**Phosphodiesterase Type 5 (PDE5) Inhibitor Utilization Among Women**
Date Posted	*Friday, October 12, 2018*
Project ID	cder_mpl1r_wp111-112
Status	Complete
Deliverables	Sentinel Modular Program Report: Phosphodiesterase Type 5 (PDE5) Inhibitor Utilization Among Reproductive-Aged Women, Report 1 Sentinel Modular Program Report: Phosphodiesterase Type 5 (PDE5) Inhibitor Utilization Among Pregnant Women, Report 2
Description	The goal of this query was to estimate phosphodiesterase type 5 (PDE5) inhibitor utilization among women in the Sentinel Distributed Database (SDD). Report 1 contains estimates of phosphodiesterase type 5 (PDE5) inhibitor use among reproductive-aged women. Report 2 contains estimates of PDE5 inhibitor use that occurred during a pregnancy ending in a live-born delivery or within 90 days prior to pregnancy start, among women. Data from January 1, 2001 to March 31, 2018 from 16 Data Partners contributing to the SDD were included in this report. This request was distributed to Data Partners on August 27, 2018.
Medical Product	phosphodiesterase type 5 (PDE5) inhibitor

https://www.sentinelinitiative.org/drugs/assessments/phosphodiesterase-type-5-pde5-inhibitor-utilization-among-women

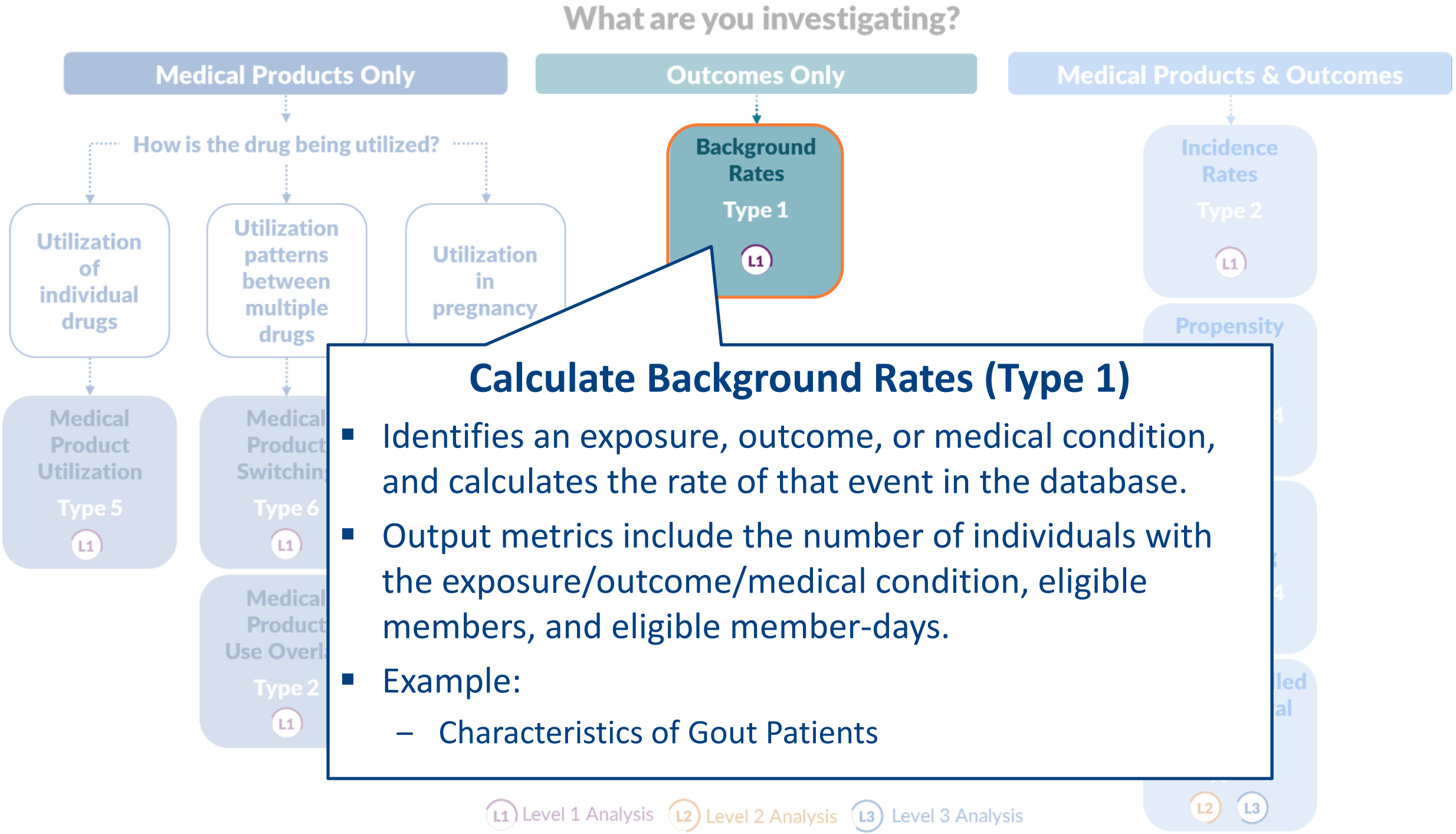

What are you investigating?
Medical Products Only
How is the drug being utilized?
Utilization of individual drugs
Utilization patterns between multiple drugs
Medical Product Utilization
Type 5
L1
Medical Product Switching
Type 6
L1
Medical Product Use Overlap
Type 2
L1
Switching Patterns (Type 6)
Captures utilization and switching patterns for user-specified groups that are based on any collection of National Drug Codes, Procedure Codes, etc.
Brand
Generic A
Generic B
Generic C
Output Metrics include treatment episodes, switching patterns (e.g., A➔B, A➔B➔A), utilization metrics.
Examples:
Metoprolol Extended Release
Lamotrigine Extended Release
Self-Controlled Risk Interval Design
Type 3
L2
L3
L1 Level 1 Analysis
L2 Level 2 Analysis
L3 Level 3 Analysis

Submit Comment

Evaluation of Switching Patterns in FDA's Sentinel System: A New Tool to Assess Generic Drugs

Project Title	**Evaluation of Switching Patterns in FDA's Sentinel System: A New Tool to Assess Generic Drugs**
Date	*Friday, August 17, 2018*
Location	Drug Saf. 2018 Aug 17. doi: 10.1007/s40264-018-0709-4
Description	The aim of this study was to develop and implement a tool for analyzing manufacturer-level drug utilization and switching patterns within the U.S. Food and Drug Administration's Sentinel System. A descriptive tool was designed to analyze data in the Sentinel Common Data Model and was tested with two case studies, metoprolol extended release (ER) and lamotrigine ER, using claims data from four Sentinel Data Partners. This developed tool was able to elucidate novel utilization and switching patterns in two case studies. Such information can be used to support surveillance of generic drugs and biosimilars.

https://www.sentinelinitiative.org/communications/publications/evaluation-switching-patterns-fdas-sentinel-system-new-tool-assess



Calculate Background Rates (Type 1)

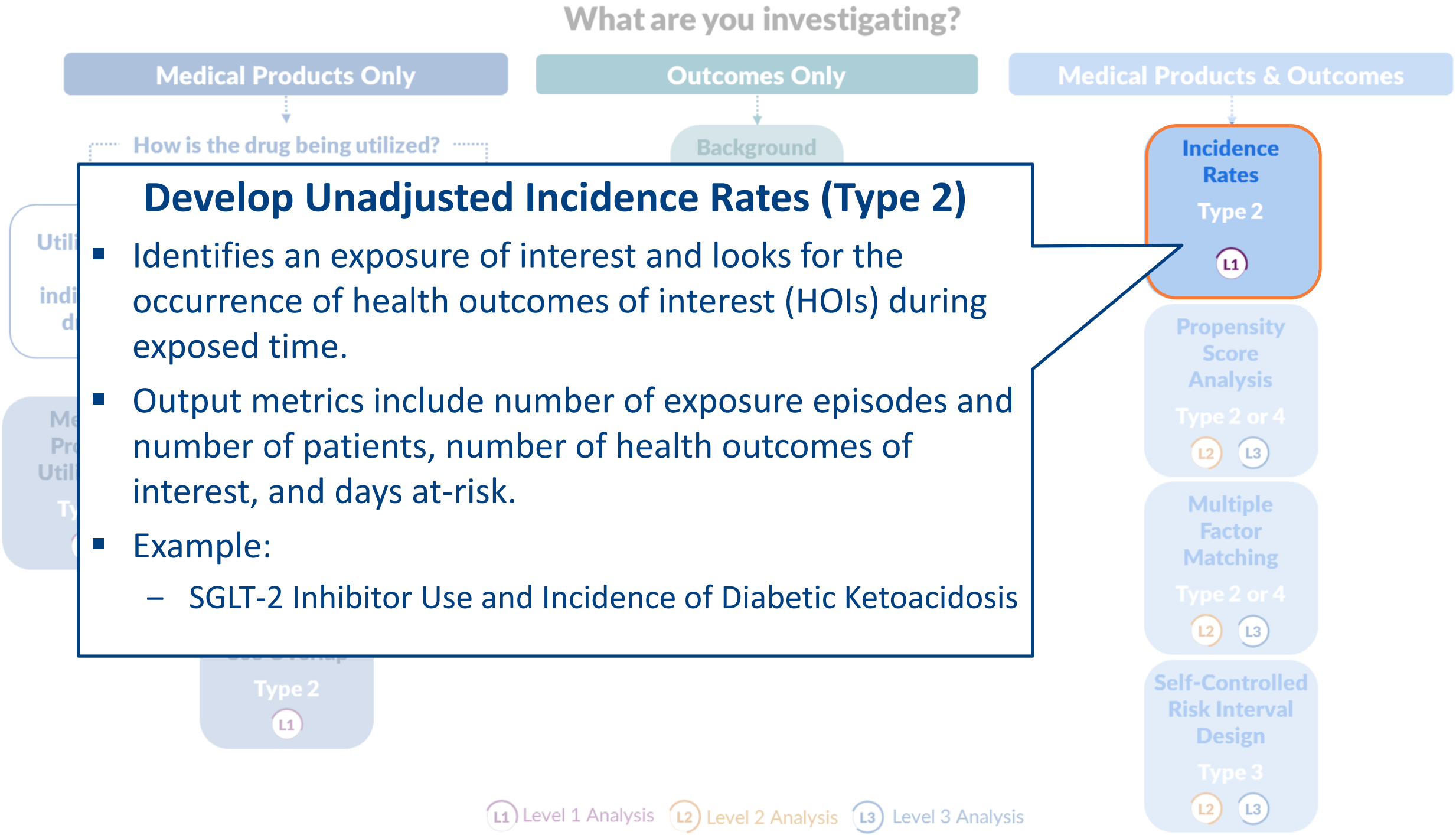
- Identifies an exposure, outcome, or medical condition, and calculates the rate of that event in the database.
- Output metrics include the number of individuals with the exposure/outcome/medical condition, eligible members, and eligible member-days.
- Example:
  - Characteristics of Gout Patients

Submit Comment

Characteristics of Gout Patients and Use of Urate-Lowering Therapies

Project Title	**Characteristics of Gout Patients and Use of Urate-Lowering Therapies**
Date Posted	*Friday, March 22, 2019*
Project ID	cder_mpl1r_wp123, cder_mpl1r_wp126
Status	Complete
Deliverables	Sentinel Modular Program Report: Characteristics of Gout Patients and Use of Urate-Lowering Therapies, Report 1 Sentinel Modular Program Report: Characteristics of Gout Patients and Use of Urate-Lowering Therapies, Report 2 Sentinel Modular Program Report: Characteristics of Gout Patients and Use of Urate-Lowering Therapies, Report 3
Description	The goal of this request was to assess characteristics of gout patients and use of urate lowering therapies (ULT) among individuals in the Sentinel Distributed Database (SDD). This request contains three reports: • Report 1 examines counts of individuals with gout diagnoses, and cardiovascular morbidities and gout severity among those individuals. • Report 2 contains counts of individuals using the ULTs febuxostat and allopurinol, and captures switching between ULT drug products and doses. • Report 3 contains cumulative exposure duration of febuxostat and allopurinol prior to dose or drug switching.

https://www.sentinelinitiative.org/drugs/assessments/characteristics-gout-patients-and-use-urate-lowering-therapies



Develop Unadjusted Incidence Rates (Type 2)

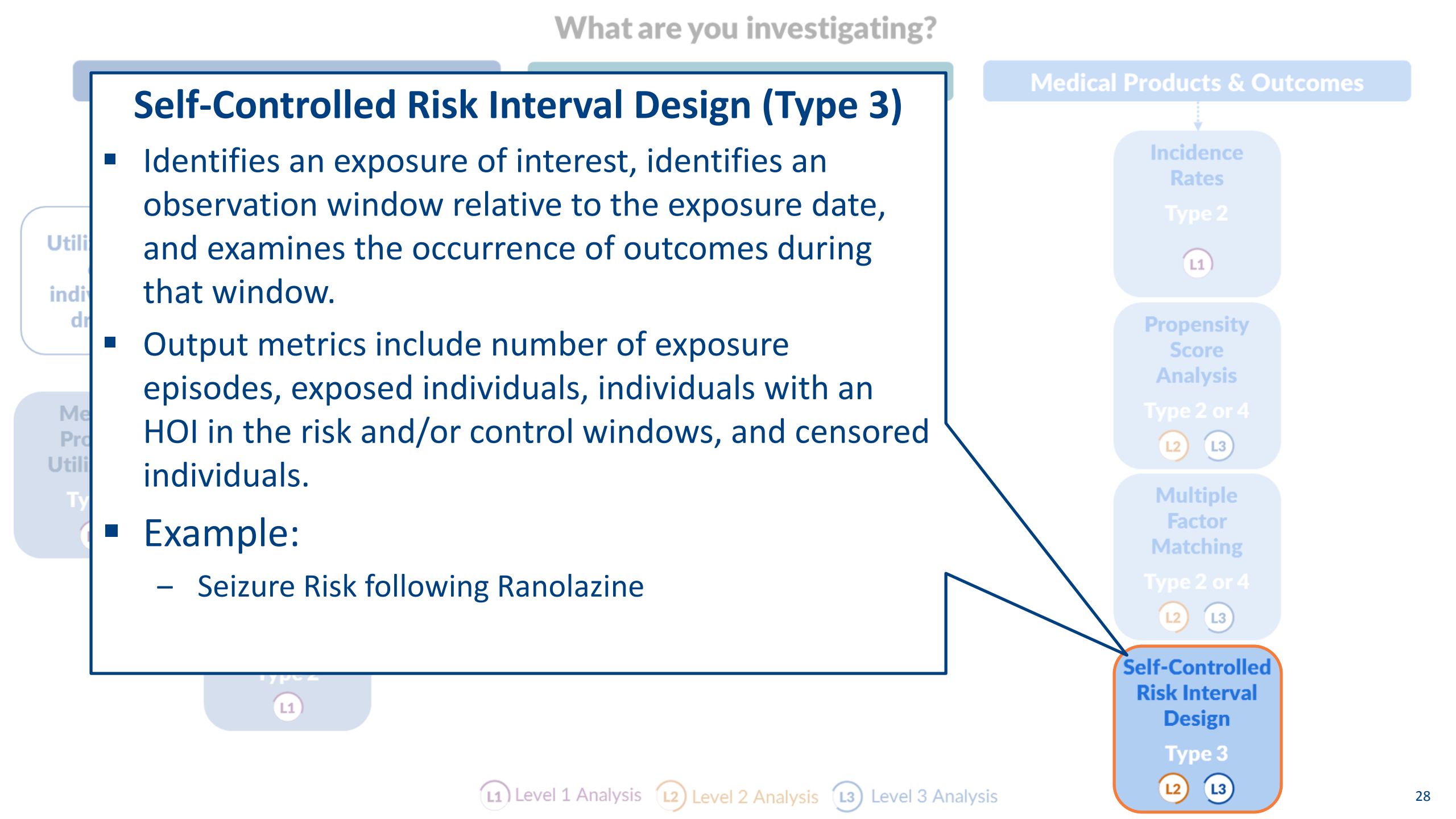
- Identifies an exposure of interest and looks for the occurrence of health outcomes of interest (HOIs) during exposed time.
- Output metrics include number of exposure episodes and number of patients, number of health outcomes of interest, and days at-risk.
- Example:
  - SGLT-2 Inhibitor Use and Incidence of Diabetic Ketoacidosis

Submit Comment

SGLT-2 Inhibitor Use and Incidence of Diabetic Ketoacidosis in Patients with Diabetes Mellitus

Project Title	**SGLT-2 Inhibitor Use and Incidence of Diabetic Ketoacidosis in Patients with Diabetes Mellitus**
Date Posted	*Tuesday, March 19, 2019*
Project ID	cder_mpl1p_wp026
Status	Complete
Deliverables	Sentinel Modular Program Report: SGLT-2 Inhibitor Use and Incidence of Diabetic Ketoacidosis in Patients with Diabetes Mellitus
Description	The goal of this request was to estimate rates of diabetic ketoacidosis (DKA) among new users of sodium-glucose cotransporter-2 (SGLT-2) inhibitors canagliflozin, dapagliflozin, empagliflozin, or sitagliptin in the Sentinel Distributed Database (SDD). Data from March 1, 2013 through June 30, 2018 from 17 Data Partners contributing to the SDD were included in this report. This request was distributed to Data Partners on November 28, 2018.
Medical Product	canagliflozin dapagliflozin empagliflozin sitagliptin sodium-glucose cotransporter-2 (SGLT-2) inhibitor
Health Outcome	diabetic ketoacidosis

https://www.sentinelinitiative.org/drugs/assessments/sglt-2-inhibitor-use-and-incidence-diabetic-ketoacidosis-patients-diabetes



Self-Controlled Risk Interval Design (Type 3)

- Identifies an exposure of interest, identifies an observation window relative to the exposure date, and examines the occurrence of outcomes during that window.
- Output metrics include number of exposure episodes, exposed individuals, individuals with an HOI in the risk and/or control windows, and censored individuals.
- Example:
  - Seizure Risk following Ranolazine

What are you investigating?

Submit Comment

Seizure following Ranolazine Use

Project Title	Seizure following Ranolazine Use
Date Posted	*Thursday, January 3, 2019*
Status	Complete
Deliverables	Sentinel Modular Program Report: Seizure following Ranolazine Use, Report 1 Sentinel Modular Program Report: Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis, Report 2 Sentinel Modular Program Report: Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis (an update to cder_mpl2p_wp002), Report 3 Sentinel Analytic Packages: Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis
Related Links	Prevalent and Incident Dispensings of Ranolazine 2017 ICPE Symposium: Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year Seizure Algorithm Defined in "Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis" Use of FDA's Sentinel System to Quantify Seizure Risk Immediately Following New Ranolazine Exposure

L1 Level 1 Analysis L2 Level 2 Analysis L3 Level 3 Analysis

http://www.sentinelinitiative.org/drugs/assessments/ranexa-ranolazine-and-seizures

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

Data Quality Review and Characterization Programs

Quality Assurance (QA) Package

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.

Folder Structure

- **docs:** is where specifications are saved; specifications provide details about the request parameters and functionality of the QA package
- **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 9.3 or higher
- 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)

OVERVIEW

The purpose of this repository is to document version 7.3.0 of the Sentinel Routine Querying System. Functional documentation sections describe the capabilities of the tools in the system. Technical documentation sections specify the tools' inputs and outputs and provide the information required to build analytic packages to address research questions of interest.

SENTINEL ROUTINE QUERYING SYSTEM TOOLS

Sentinel's Routine Querying System includes three tools:

The **COHORT IDENTIFICATION AND DESCRIPTIVE ANALYSIS (CIDA) TOOL** identifies and extracts cohorts of interest from the Sentinel Distributed Database based on requester-defined options (e.g., exposures, outcomes, continuous enrollment requirements, incidence criteria, inclusion/exclusion criteria, relevant age groups, demographics).

The CIDA tool calculates descriptive statistics for the cohort(s) of interest and outputs datasets that may be useful for additional analyses. The CIDA tool may be used alone or in conjunction with the Propensity Score Analysis Tool or the Multiple Factor Matching Tool.

There are six cohort identification strategies available:

- 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 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_wp009	Stroke, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Apixaban or Warfarin Use in Patients with Non-Valvular Atrial Fibrillation: a Propensity Score Matched Analysis
cder_mpl2p_wp006	Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis (an update to cder_mpl2p_wp002)
cder_mpl2p_wp005	Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a Propensity Score Matched Analysis
cder_mpl2p_wp001	Venous Thromboembolism following Continuous or Extended Cycle Contraceptive Use: a Propensity Score Matched Analysis
cder_mpl2p_wp004	Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis
cder_mpl2p_wp002	Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis

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

Questions?

info@sentinelsystem.org

Query Design:
Building Design Diagrams and Specifications

Dr. Judith C. Maro

Agenda for this Morning's Session

- Introducing Case Study Basics and Training Materials
- Using Sentinel Query Builder to Design a Medical Product Utilization Query
- Designing an Incidence Rates Query including a Propensity-Score Matched Analysis

Chosen Case Study is a Completed Analysis

- How ARIA Analyses Have Been Used by FDA

Drug Name	Outcome Assessed	ARIA Analysis	Regulatory Determination / Use	Date Posted
Antipsychotic agents (including haloperidol injection)	• Ischemic stroke • Hemorrhagic stroke	Level 1, Level 2	Sentinel data was used to support decisions around potential labeling changes for antipsychotics and stroke risk. FDA decided that no action is necessary at this time, based on available information. • Level 1 Results • Level 2 Results • Results among SSRI Users • 2017 ICPE Symposium	12/8/2017

- Dr. Jane Huang will present the completed analysis in Afternoon Session A.

http://www.sentinelinitiative.org/drugs/how-aria-analyses-have-been-used-fda

Stroke Risk Following New Use of Antipsychotics

Sentinel

- **Elderly populations (65+) with dementia** were most studied in randomized controlled trials.

Typical Antipsychotics
1. Prochlorperazine (Compazine)
2. Haloperidol (Haldol)
3. Loxapine (Loxitane)
4 Thioridazine (Mellaril)
5. Molindone (Moban)
6. Thiothizene (Navane)
7. Pimozide (Orap)
8. Fluphenazine (Prolixin)
9. Trifluoperazine (Stelazine)
10. Chlorpromazine (Thorazine)
11. Perphenazine (Trilafon)

Atypical Antipsychotics
1. Aripiprazole (Abilify)
2. Asenapine Maleate (Saphris)
3. Clozapine (Clozaril)
4. Iloperidone (Fanapt)
5. Lurasidone (Latuda)
6. Olanzapine (Zyprexa)
7. Olanzapine/Fluoxetine (Symbyax)
8. Paliperidone (Invega)
9. Quetiapine (Seroquel)
10. Risperidone (Risperdal)
11. Ziprasidone (Geodon)

Existing language in safety labels regarding cerebrovascular risk among elderly patients with dementia

Use of Sentinel for Evidence Generation

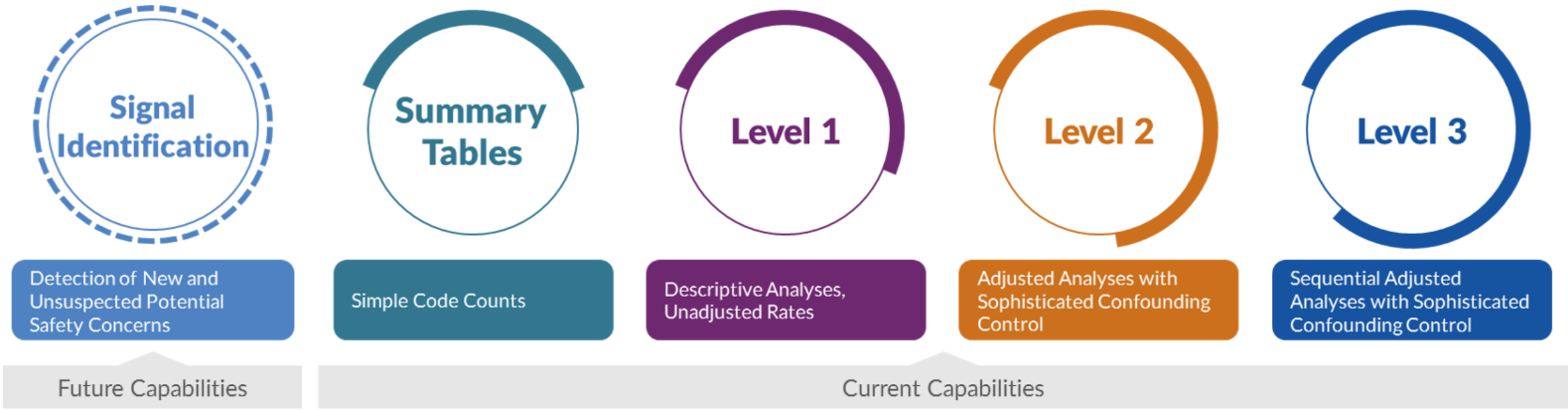
Regulatory Questions

- Does the increased risk of stroke observed in randomized controlled trials of atypical antipsychotics (in elderly dementia patients) also exist in the **non-elderly and non-demented**?
- Do **non-elderly/non-demented** users of **typical antipsychotics** have a higher risk of **stroke** compared to users of **atypical antipsychotics**?

Initial Feasibility

- Do we have enough **exposed persons** in this population?
- Do we have enough **events** in this population to have an adequately powered analysis?

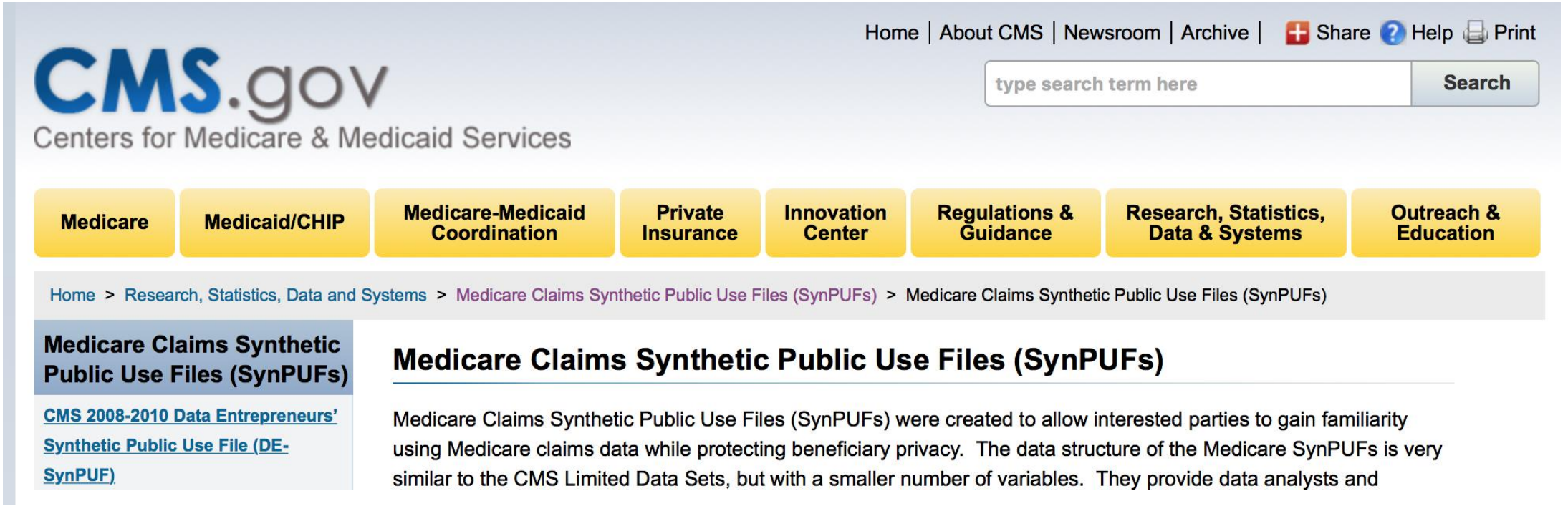
Active Risk Identification and Analysis (ARIA)



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

https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria

Data Entrepreneurs' Synthetic Public Use Files



https://www.cms.gov/Research-Statistics-Data-and-Systems/Downloadable-Public-Use-Files/SynPUFs/index.html

SynPUFs: Not Intended for Actual Inference

I. Number of Claims per Beneficiary by Service Type Over Three Years

Table 4. Comparison of Estimates from the *DE-SynPUF* and an Actual Medicare 5% Beneficiary Sample by Claim Types—Distribution of Number of Claims per Beneficiary over Three Years

Claim Type	Types	10%	20%	80%	90%
IP	***DE-SynPUF***	1	1	3	4
IP	Actual	1	1	4	5
OP	***DE-SynPUF***	2	3	16	21
OP	Actual	2	3	21	34
CAR	***DE-SynPUF***	4	12	99	104
CAR	Actual	5	15	103	147
PDE	***DE-SynPUF***	3	5	103	137
PDE	Actual	14	30	174	242

NOTE:
IP: Inpatient
OP: Outpatient
CAR: Carrier
PDE: Prescription Drug Events

https://www.cms.gov/Research-Statistics-Data-and-Systems/Downloadable-Public-Use-Files/SynPUFs/Downloads/SynPUF_DUG.pdf

Publicly Available Formatted Data

Sentinel

Submit Comment

Medicare Claims Synthetic Public Use Files in Sentinel Common Data Model Format

Project Title	Medicare Claims Synthetic Public Use Files in Sentinel Common Data Model Format
Date Posted	*Wednesday, March 27, 2019*
Status	Complete
Deliverables	Sentinel's SynPUFs Software Toolkit SynPUFs Example Sentinel Modular Program Report
Related Links	Centers for Medicare and Medicaid Services Synthetic Public Use Files (SynPUFs)
Description	Sentinel has made available the CMS 2008-2010 Data Entrepreneurs' Synthetic Public Use Files (SynPUFs) in the Sentinel Common Data Model (SCDM) format. This transformation of data allows for the running of Sentinel's Routine Querying System tools, including the Cohort Identification and Descriptive Analysis (CIDA) tool, on the SynPUFs data. The CMS SynPUFs are available in the form of 20 mutually exclusive datasets, which together make up a 5% sample of the entire CMS database from 2008-2010. Each of the 20 datasets contains about 110,000 members. The intended use of these data in SCDM format is to generate familiarity with the CIDA tool and its capabilities and to allow for methodological expansion.

- 2.2M synthetic beneficiaries
- 20 mutually exclusive data samples

http://www.sentinelinitiative.org/sentinel/surveillance-tools/software-toolkits/Medicare-SynPUFs-in-SCDM

Using Design Diagrams and Specification Documents

PDS Pharmacoepidemiology & Drug Safety

Official Journal of the International Society for Pharmacoepidemiology

ISPE

ORIGINAL REPORT | Open Access

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

Correction(s) for this article

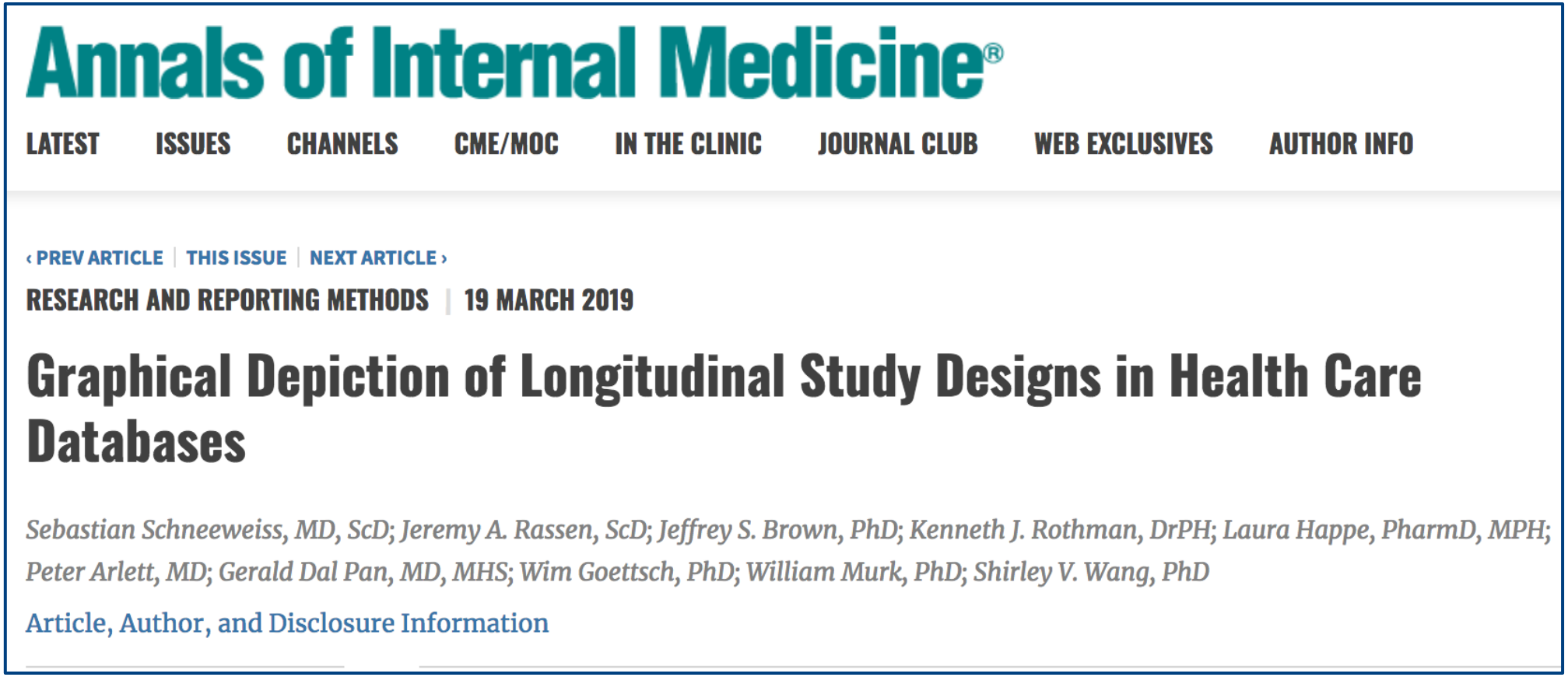
Shirley V. Wang, Sebastian Schneeweiss, Marc L. Berger, Jeffrey Brown, Frank de Vries, Ian Douglas, Joshua J. Gagne, Rosa Gini, Olaf Klungel, C. Daniel Mullins, Michael D. Nguyen ... See all authors

First published: 15 September 2017 | https://doi.org/10.1002/pds.4295 | Cited by: 14

This article is a joint publication by *Pharmacoepidemiology and Drug Safety* and *Value in Health*.

SECTIONS PDF TOOLS SHARE

Using Design Diagrams and Specification Documents



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RESEARCH AND REPORTING METHODS | 19 MARCH 2019

Graphical Depiction of Longitudinal Study Designs in Health Care Databases

Sebastian Schneeweiss, MD, ScD; Jeremy A. Rassen, ScD; Jeffrey S. Brown, PhD; Kenneth J. Rothman, DrPH; Laura Happe, PharmD, MPH; Peter Arlett, MD; Gerald Dal Pan, MD, MHS; Wim Goettsch, PhD; William Murk, PhD; Shirley V. Wang, PhD

Article, Author, and Disclosure Information

Downloading Sentinel Analytic Packages

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

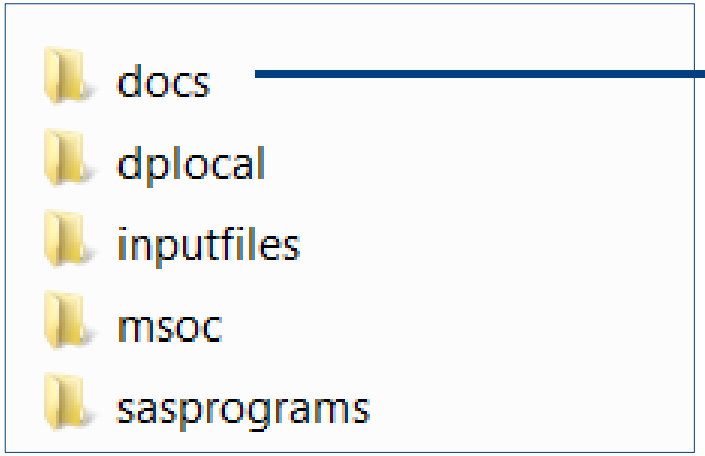
Request ID	Summary
cder_mpl2p_wp009	Stroke, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Apixaban or Warfarin Use in Patients with Non-Valvular Atrial Fibrillation: a Propensity Score Matched Analysis
cder_mpl2p_wp006	Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis (an update to cder_mpl2p_wp002)
cder_mpl2p_wp005	Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a Propensity Score Matched Analysis
cder_mpl2p_wp001	Venous Thromboembolism following Continuous or Extended Cycle Contraceptive Use: a Propensity Score Matched Analysis
cder_mpl2p_wp004	Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis
cder_mpl2p_wp002	Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis

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

Specifications in all Downloadable Analytic Packages

Sentinel

Downloaded folders:



Specifications for cder_mpl2p_wp004

This request utilized the Cohort Identification and Descriptive Analysis (CIDA) tool with Propensity Score Matching (PSM), version 3.3.2, to investigate the risk of ischemic and hemorrhagic stroke among new users of typical antipsychotics compared to new users of atypical antipsychotics with varying risk windows.

Query Period: January 1, 2001 - September 30, 2015
Coverage Requirement: Medical and Drug Coverage
Enrollment Requirement: 183 days
Enrollment Gap: 45 days
Age Group(s): 18-64 years

	Primary Analysis: Exposure/Comparator Pair 1		Sensitivity Analysis 1: Exposure/Comparator Pair 2	
Drug/Exposure				
Incident Exposure/Comparator	All typical antipsychotics	All atypical antipsychotics	All typical antipsychotics (risk window = 1-15 days)	All atypical antipsychotics (risk window = 1-15 days)
Incident w/ Respect to:	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics
Washout	183 days	183 days	183 days	183 days
Cohort Definition	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period
Episode Gap	30 days	30 days	30 days	30 days
Episode Extension Period	None	None	None	None
Minimum Episode Duration	1 day	1 day	1 day	1 days
Maximum Episode Duration	None	None	15 days	15 days
Minimum Days Supplied	1 day	1 day	1 day	1 day
Episode Truncation at Death	Yes	Yes	Yes	Yes
Episode Truncation for Exposure	All atypical antipsychotics	All typical antipsychotics	All atypical antipsychotics	All typical antipsychotics
Inclusion/Exclusion				
Pre-Existing Condition	Hemorrhagic and ischemic stroke	Hemorrhagic and ischemic stroke	Hemorrhagic and ischemic stroke	Hemorrhagic and ischemic stroke
Include/Exclude	Exclude	Exclude	Exclude	Exclude
Care Settings/PDX	Any	Any	Any	Any
Lookback Period	-183, 0	-183, 0	-183, 0	-183, 0
Pre-Existing Condition	Dementia	Dementia	Dementia	Dementia
Include/Exclude	Exclude	Exclude	Exclude	Exclude
Care Settings/PDX	Any	Any	Any	Any
Lookback Period	-183, -1	-183, -1	-183, -1	-183, -1

Specifications Also in Every Report

Submit Comment

Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis

Project Title	**Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis**
Date Posted	*Thursday, November 2, 2017*
Project ID	cder_mpl2p_wp004
Status	Complete
Deliverables	Sentinel Modular Program Report: Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis, Report 1 Sentinel Modular Program Report: Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis, Report 2 Sentinel Modular Program Report: Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis, Report 3 Sentinel Modular Program Report: Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis, Report 4 Sentinel Analytic Package: Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis

http://www.sentinelinitiative.org/drugs/assessments/antipsychotics-and-stroke-psm

Using Query Builder for Drug Utilization Analysis with a Case Study

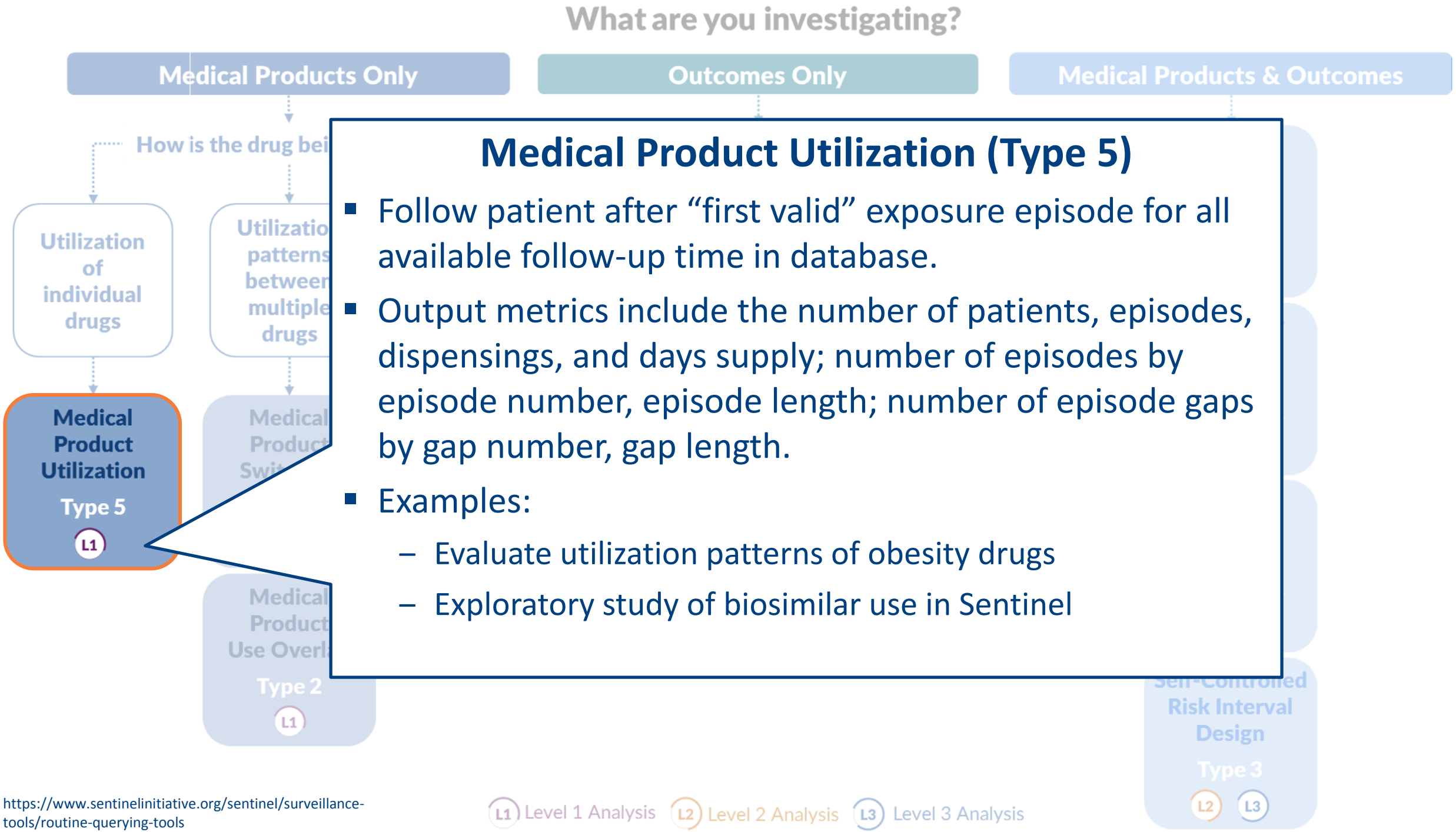
Use of Sentinel for Evidence Generation

Regulatory Questions

- Does the increased risk of stroke observed in randomized controlled trials of atypical antipsychotics (in elderly dementia patients) also exist in the **non-elderly and non-demented**?
- Do **non-elderly/non-demented** users of **typical antipsychotics** have a higher risk of **stroke** compared to users of **atypical antipsychotics**?

Initial Feasibility

- Do we have enough **exposed persons** in this population?
- Do we have enough **events** in this population to have an adequately powered analysis?



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

Sentinel Query Builder

What is it?

- An online platform that allows FDA to visualize, draft, and submit medical product utilization requests.

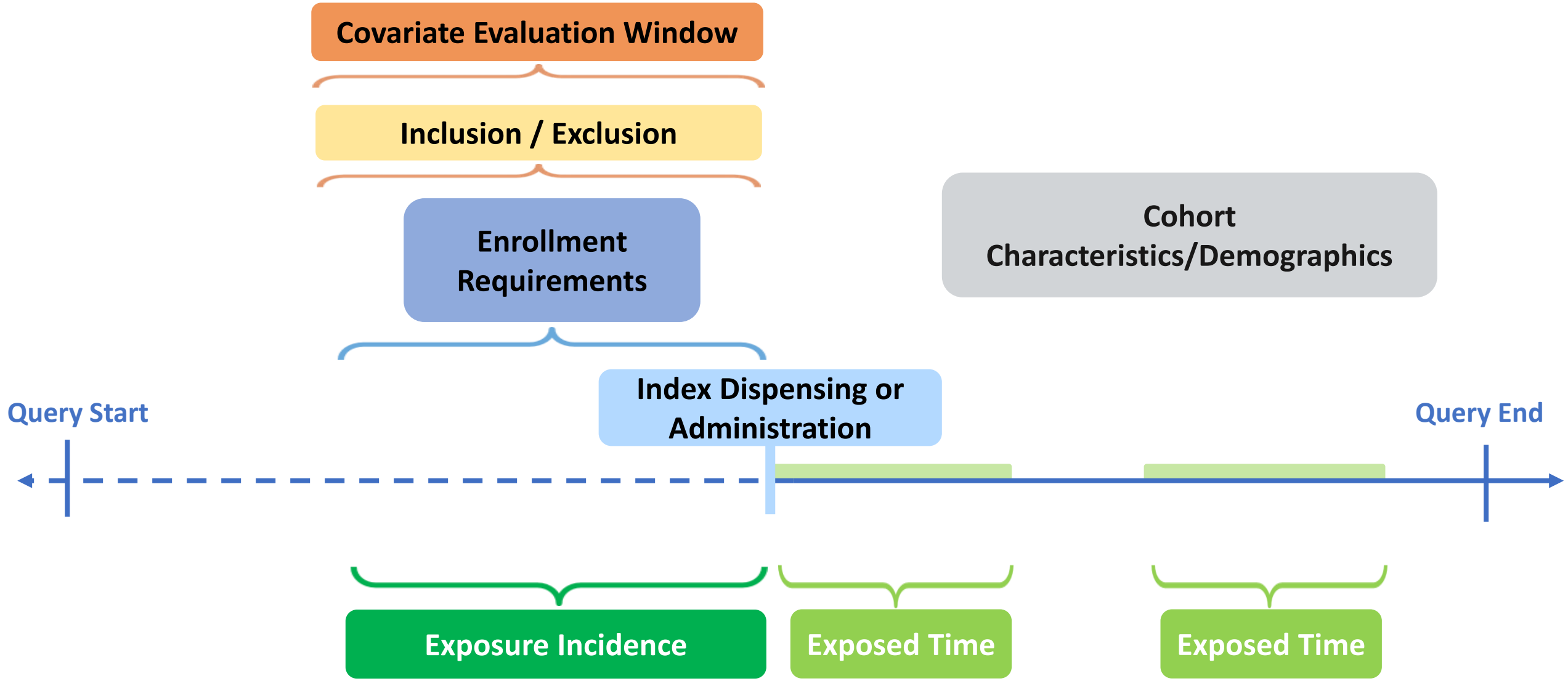
What does it do?

- It creates a Cohort Identification and Descriptive Analysis (CIDA) SAS Analytic Package (i.e., computer program) that can be executed against any data formatted into the Sentinel Common Data Model.

When can non-FDA users try it out?

- In several months time, after it has finished beta testing and been put into production, and with the approval of the FDA.

Medical Product Utilization Design Diagram



Identify Treatment Cohorts of Interest

- It is important to organize your cohorts according to relevant groupings.

Typical Antipsychotics
1. Prochlorperazine (Compazine)
2. Haloperidol (Haldol)
3. Loxapine (Loxitane)
4 Thioridazine (Mellaril)
5. Molindone (Moban)
6. Thiothizene (Navane)
7. Pimozide (Orap)
8. Fluphenazine (Prolixin)
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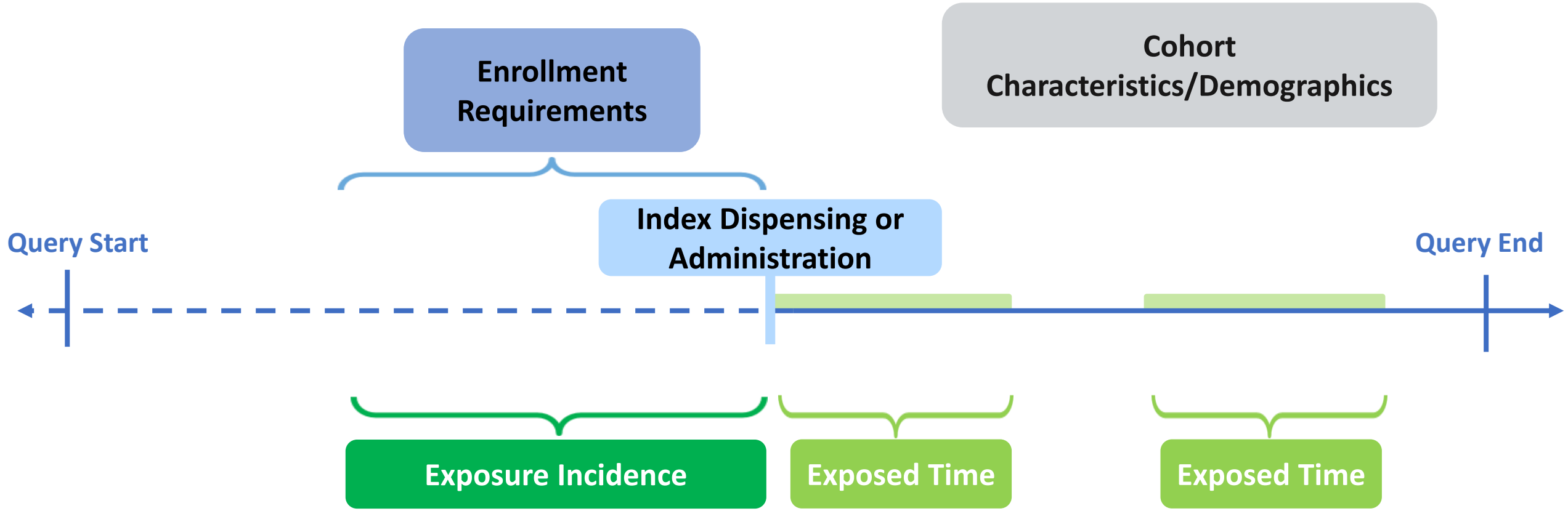
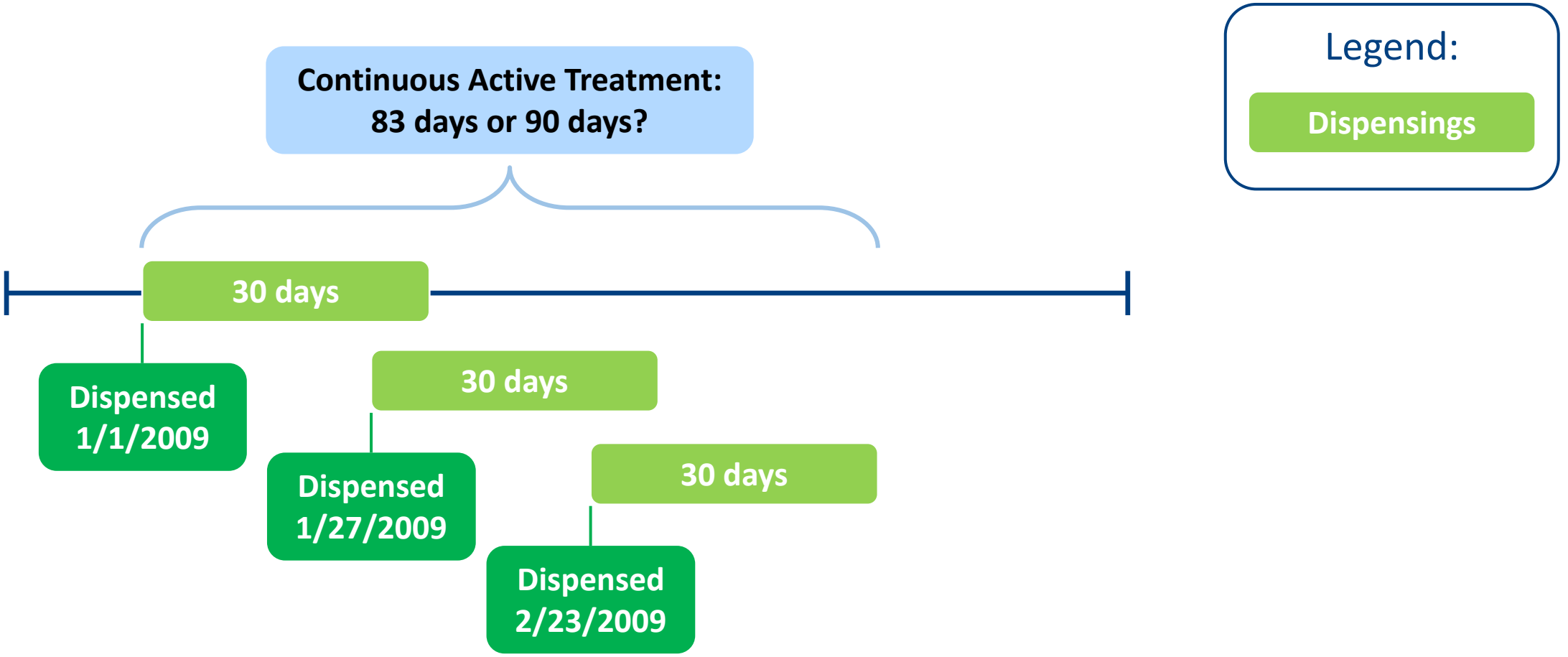
7. Olanzapine/Fluoxetine (Symbyax)
8. Paliperidone (Invega)
9. Quetiapine (Seroquel)
10. Risperidone (Risperdal)
11. Ziprasidone (Geodon)

Medical Product Utilization Design Diagram



Exposed Time: Concatenating Dispensings

1. **Stockpiling** is used to evaluate early refilling behavior, same day dispensings
   - Defaulted in Query Builder to keep any overlapping dispensings



Exposed Time: Concatenating Dispensings

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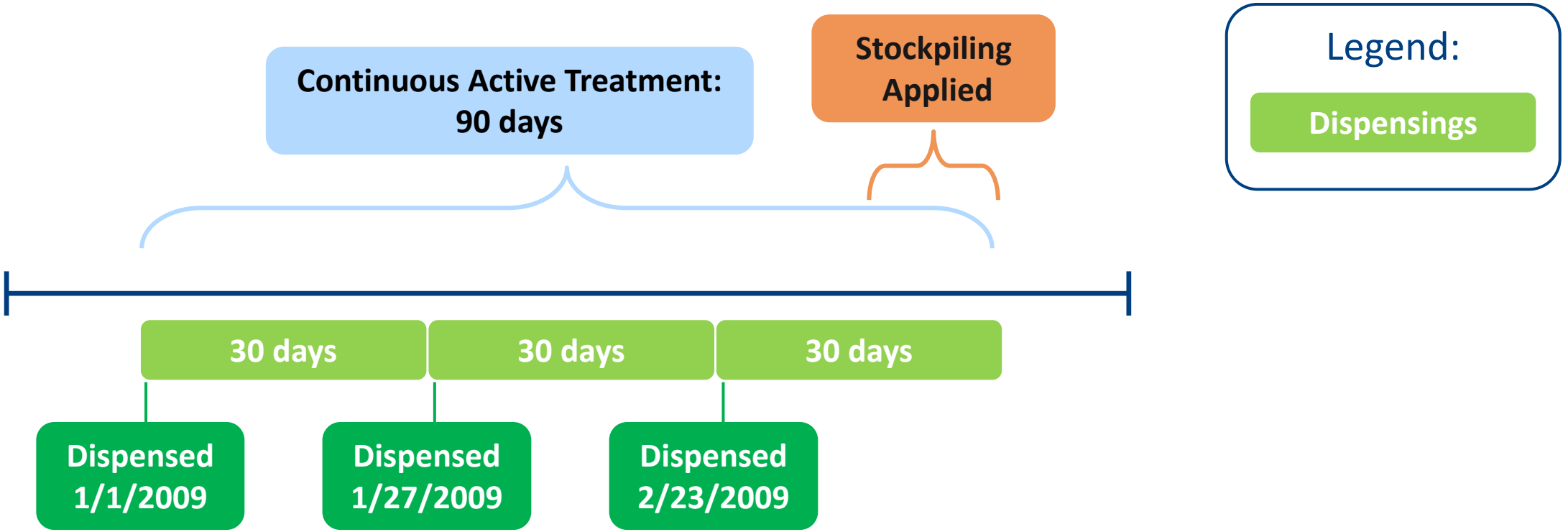
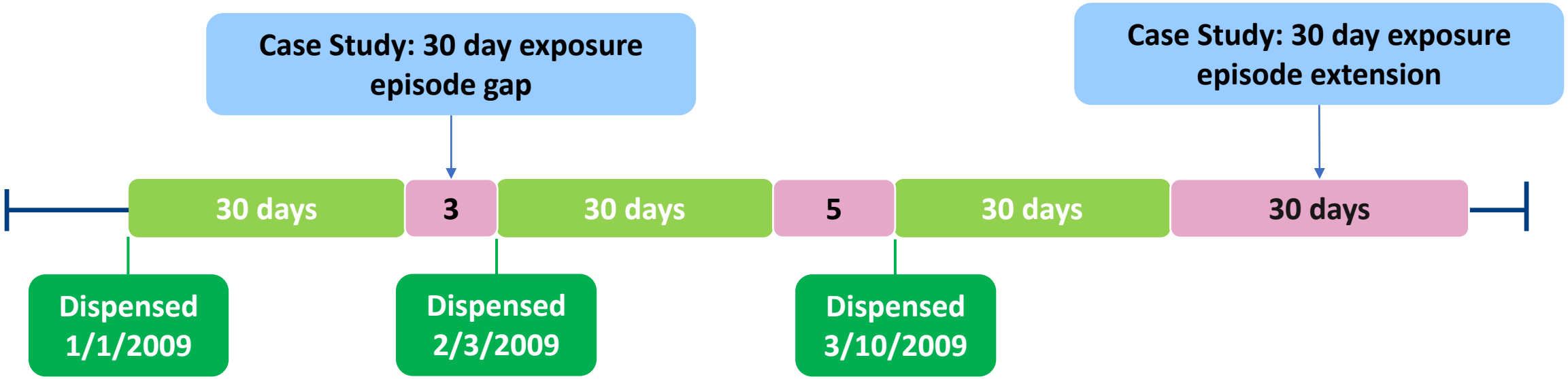


Exposed Time: Concatenating Dispensings

1. **Stockpiling** is used to evaluate early refilling behavior, same day dispensings
   - Defaulted in Query Builder to keep any overlapping dispensings
2. **Gaps** are bridged to deal with late refill behavior
3. **Extension** days are added after any episode gaps have been bridged



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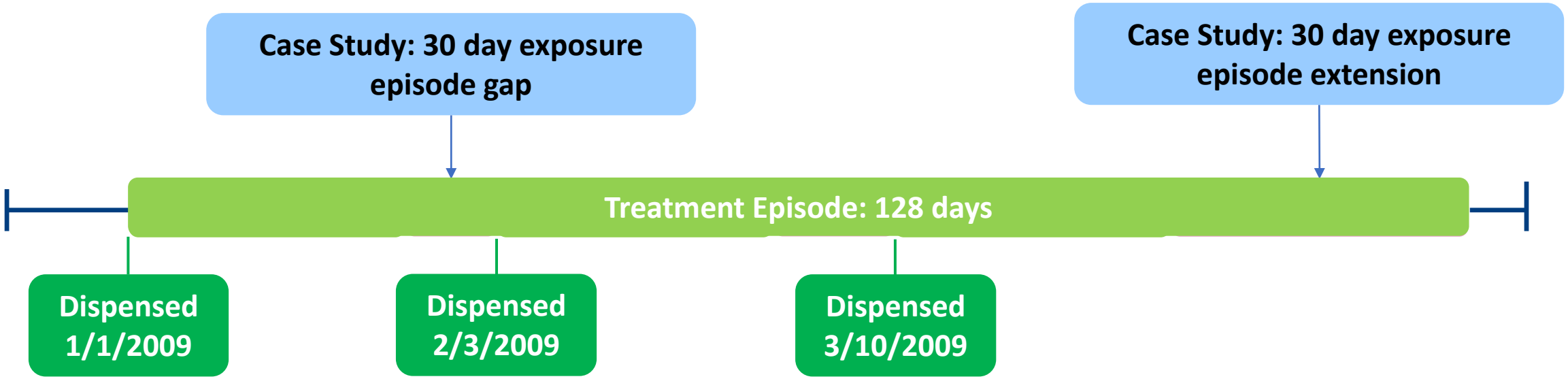
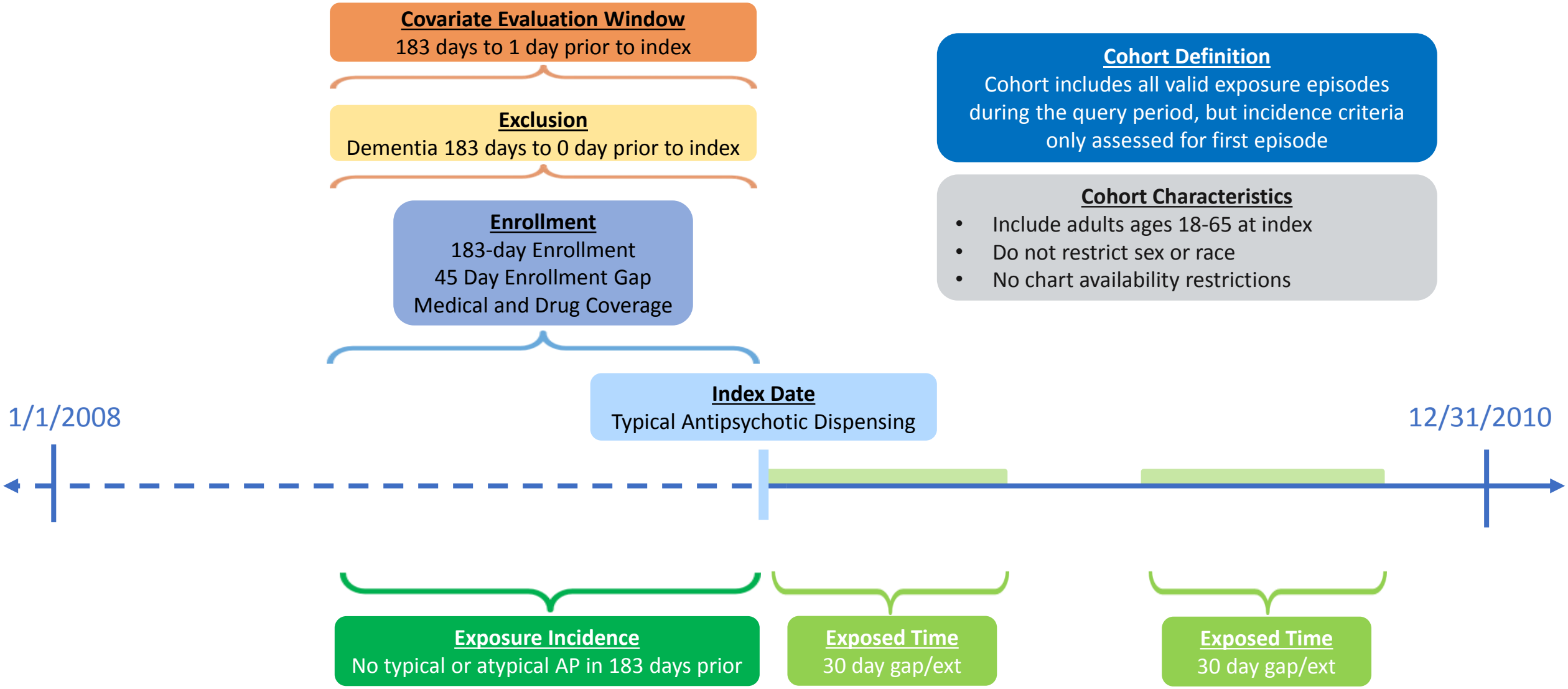


Medical Product Utilization Design Diagram

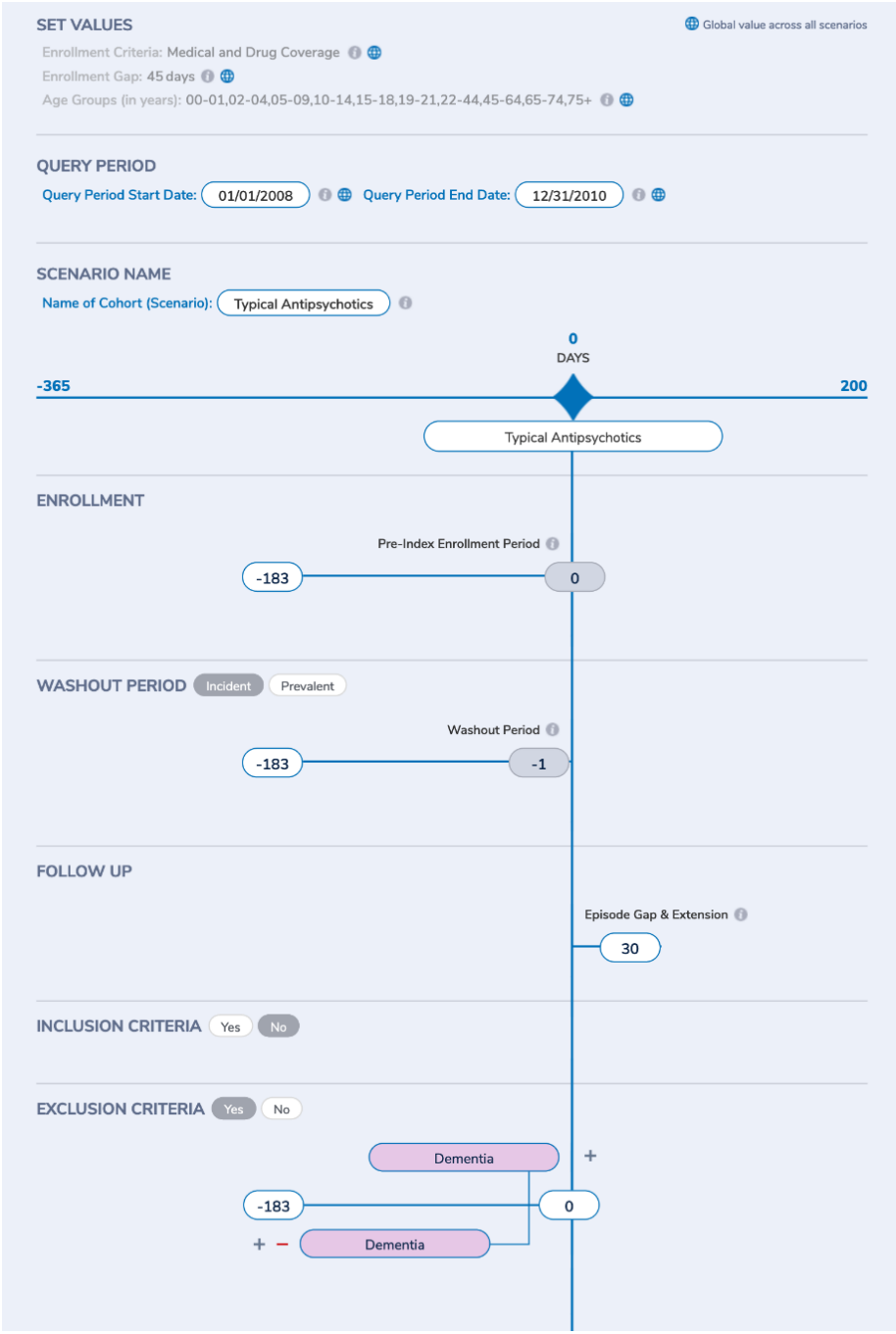


Medical Product Utilization Report Output using SynPUFs

Reminder: Synthetic Data

Exported Design Diagram

- One Diagram Per Scenario



Exported Specifications

Specifications for Type 5 Request: soc_querybuilder_wp002

The SOC has requested execution of the Query Builder to examine utilization of typical and atypical antipsychotics.

Enrollment criteria: Medical & Drug
Enrollment gap: 45 days
Age groups: 0-1, 2-4, 5-9, 10-14, 15-18, 19-21, 22-44, 45-64, 65-74, 75+
Query period: 1/1/2008-12/31/2010
Baseline covariate table: Yes
Covariate evaluation window: -183, -1

	Exposure						Inclusion/Exclusion Criteria				
Scenario	Index exposure	Code category	Cohort name	Pre-index enrollment period	Treatment episode gap and extension	Washout period	Criteria	Condition name	Sub condition	Evaluation period start	Evaluation period end
1	Typical Antipsychotics	Drugs	Typical Antipsychotics	-183 days	30 days	-183 days	Exclusion	Atypical Antipsychotics	Atypical Antipsychotics	-183	0
							Exclusion	Dementia	Stroke	-183	0
2	Atypical Antipsychotics	Drugs	Atypical Antipsychotics	-183 days	30 days	-183 days	Exclusion	Typical Antipsychotics	Typical Antipsychotics	-183	0
							Exclusion	Dementia	Stroke	-183	0

ICD-9, ICD-10, HCPCS, and CPT codes are provided by Optum360.
NDC codes are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

Baseline Table – Demographics

Sentinel

Table 1a: Baseline table (Typical Antipsychotics)		
Characteristic	**N/Mean**	**%/Std Dev[1]**
Number of unique patients	73,654	
Demographics		
Mean Age	71.4	14.8
Age: 22-44	4,923	6.7%
Age: 45-64	12,751	17.3%
Age: 65-74	23,480	31.9%
Age: 75+	32,500	44.1%
Gender (Female)	45,387	61.6%
Gender (Male)	28,267	38.4%
Race (Black or African American)	8,500	11.5%
Race (Unknown)	5,618	7.6%
Race (White)	59,536	80.8%
Hispanic Origin	2,402	3.3%
Year (2008)	18,558	25.2%
Year (2009)	33,976	46.1%
Year (2010)	21,120	28.7%

Table 1b: Baseline table (Atypical Antipsychotics)		
Characteristic	**N/Mean**	**%/Std Dev[1]**
Number of unique patients	64,445	
Demographics		
Mean Age	71.7	14.3
Age: 22-44	3,856	6.0%
Age: 45-64	10,426	16.2%
Age: 65-74	21,824	33.9%
Age: 75+	28,339	44.0%
Gender (Female)	39,615	61.5%
Gender (Male)	24,830	38.5%
Race (Black or African American)	7,350	11.4%
Race (Unknown)	5,037	7.8%
Race (White)	52,058	80.8%
Hispanic Origin	2,115	3.3%
Year (2008)	15,339	23.8%
Year (2009)	29,648	46.0%
Year (2010)	19,458	30.2%

- The two cohorts are very comparable at baseline without further adjustment.

Baseline Table – Covariates

Typical Antipsychotics

Recorded history of:		
Prior combined comorbidity score	3.0	3.2
Acquired Hypothyroidism	16,999	23.1%
Acute Myocardial Infarction	1,545	2.1%
Alzheimer's Disease	0	0.0%
Alzheimer's Disease, Related Disorders, or Senile	0	0.0%
Anemia	25,350	34.4%
Asthma	7,769	10.5%
Atrial Fibrillation	18,223	24.7%
Benign Prostatic Hyperplasia	6,172	8.4%
Breast Cancer	5,681	7.7%
Cataracts	11,794	16.0%
Chronic Kidney Disease	22,354	30.4%
Chronic Obstructive Pulmonary Disease	20,787	28.2%
Colorectal Cancer	3,051	4.1%
Depression	19,352	26.3%
Diabetes	39,758	54.0%
Endometrial Cancer	521	0.7%
Glaucoma	6,837	9.3%
Heart Failure	19,191	26.1%
Hip / Pelvic Fracture	3,468	4.7%
Hyperlipidemia	37,042	50.3%
Hypertension	47,582	64.6%
Ischemic Heart Disease	26,501	36.0%
Lung Cancer	3,693	5.0%
Osteoporosis	8,529	11.6%
Prostate Cancer	4,519	6.1%
Rheumatoid Arthritis / Osteoarthritis	25,520	34.6%
Stroke / Transient Ischemic Attack	8,621	11.7%

Atypical Antipsychotics

Recorded history of:		
Prior combined comorbidity score	2.7	3.2
Acquired Hypothyroidism	13,955	21.7%
Acute Myocardial Infarction	1,209	1.9%
Alzheimer's Disease	0	0.0%
Alzheimer's Disease, Related Disorders, or Senile	0	0.0%
Anemia	20,681	32.1%
Asthma	6,145	9.5%
Atrial Fibrillation	15,079	23.4%
Benign Prostatic Hyperplasia	5,186	8.0%
Breast Cancer	4,750	7.4%
Cataracts	10,440	16.2%
Chronic Kidney Disease	18,311	28.4%
Chronic Obstructive Pulmonary Disease	16,484	25.6%
Colorectal Cancer	2,509	3.9%
Depression	14,189	22.0%
Diabetes	32,724	50.8%
Endometrial Cancer	368	0.6%
Glaucoma	5,878	9.1%
Heart Failure	15,231	23.6%
Hip / Pelvic Fracture	2,578	4.0%
Hyperlipidemia	31,263	48.5%
Hypertension	39,458	61.2%
Ischemic Heart Disease	22,095	34.3%
Lung Cancer	3,180	4.9%
Osteoporosis	7,109	11.0%
Prostate Cancer	4,052	6.3%
Rheumatoid Arthritis / Osteoarthritis	21,583	33.5%
Stroke / Transient Ischemic Attack	6,946	10.8%

Descriptive Statistics on Treatment Episodes

Sentinel

Table 2a: Descriptive statistics of cumulative exposure duration, all episodes, in days								
Exposures	Total Patients	Mean	STD	Min	Q1	Median	Q3	Max
Typical Antipsychotics	73,654	73.17	35.24	1	60	60	60	424
Atypical Antipsychotics	64,445	67.92	28.32	1	60	60	60	390

Table 3a: Descriptive statistics of first exposure episode duration, in days								
Exposures	Total Episodes	Mean	STD	Min	Q1	Median	Q3	Max
Typical Antipsychotics	73,654	60.87	15.14	1	60	60	60	257
Atypical Antipsychotics	64,445	61.70	18.66	1	60	60	60	222

Table 4a: Descriptive statistics of all exposure episode durations, in days								
Exposures	Total Episodes	Mean	STD	Min	Q1	Median	Q3	Max
Typical Antipsychotics	88,532	60.87	15.36	1	60	60	60	257
Atypical Antipsychotics	71,029	61.62	18.55	1	60	60	60	222

Table 5a: Descriptive statistics of days supplied per dispensing								
Exposures	Total Dispensings	Mean	STD	Min	Q1	Median	Q3	Max
Typical Antipsychotics	92,650	30.29	11.59	1	30	30	30	90
Atypical Antipsychotics	72,544	31.82	16.56	1	30	30	30	90

Table 6a: Descriptive statistics of the length of all gaps between treatment episodes, in days								
Exposures	Total Gaps	Mean	STD	Min	Q1	Median	Q3	Max
Typical Antipsychotics	88,532	343.09	237.06	0	141	313	522	872
Atypical Antipsychotics	71,029	369.50	241.50	0	165	348	563	872

Censoring Data

Table 7: Counts of reason for censoring, all episodes and first episode								
	Total		Disenrollment		Evidence of death		Episode end	
	N	%	N	%	N	%	N	%
Exposures								
Typical Antipsychotics	88,532	100.0	3,437	3.9	220	0.2	85,166	96.2
Atypical Antipsychotics	71,029	100.0	2,980	4.2	186	0.3	68,109	95.9
Patients' First Episode								
Typical Antipsychotics	73,654	100.0	2,639	3.6	185	0.3	71,071	96.5
Atypical Antipsychotics	64,445	100.0	2,633	4.1	167	0.3	61,867	96.0

Attrition Data

- First losses are those without proper enrollment
- Second losses are demographic
- Third losses are lack of the index-defining exposure
- Remaining losses are query-dependent

Medical Product Utilization Query Takeaways

- This is Synthetic Data.
- BUT, if it were real, then …
  - I learned my cohorts were quite comparable at baseline.
  - I learned about the treatment pattern and the time-at-risk contributed during a first treatment episode.
  - I learned about the sample size I might expect in a subsequent inferential query.
    - Estimate losses due to 1:1 matching
    - Estimate losses due to removal of individuals with a history of stroke

Limitations of Query Builder (Simplified CIDA)

- Demographics, enrollment criteria, and baseline table concepts are fixed.
- Exposures selected based on generic names.
  - Some medical products have non-specific generic names (e.g., oral birth control).
  - Procedures use simple text searches.
- Inclusion and exclusion clinical concepts defined by codelists from CMS's Chronic Conditions Warehouse*
  - Later versions will allow code upload.
- Exposures cannot be truncated on user-defined code occurrence.
- BUT, specification process is simplified and may suffice.

*https://www.ccwdata.org/web/guest/home

Questions?

info@sentinelsystem.org

Case Study Part 2:
Designing an Incidence Rates Query Leading to a Propensity-Score Matched Analysis

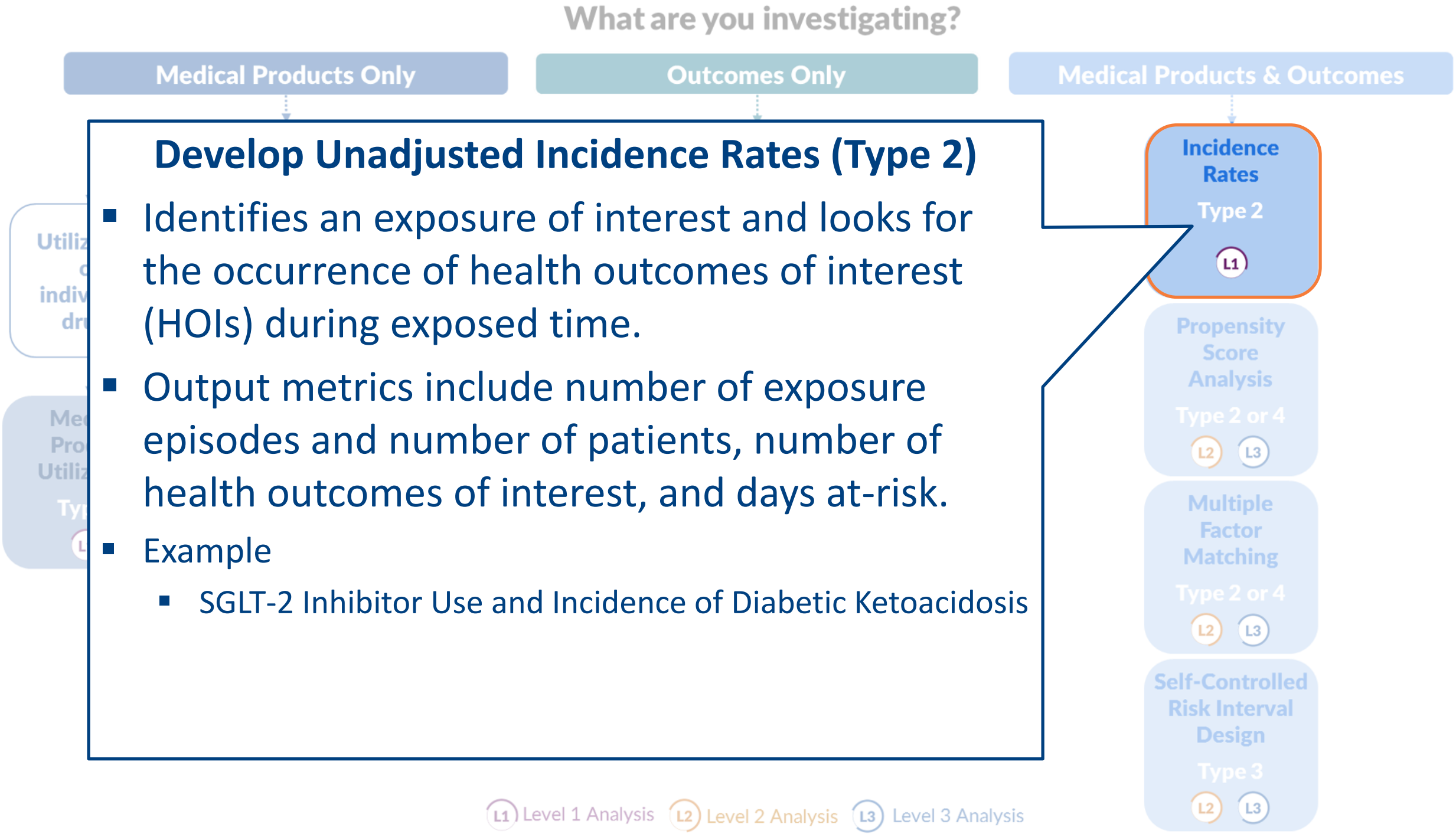
Use of Sentinel for Evidence Generation

Regulatory Questions

- Does the increased risk of stroke observed in randomized controlled trials of atypical antipsychotics (in elderly dementia patients) also exist in the **non-elderly and non-demented**?
- Do **non-elderly/non-demented** users of **typical antipsychotics** have a higher risk of **stroke** compared to users of **atypical antipsychotics**?

Initial Feasibility

- Do we have enough **exposed persons** in this population?
- Do we have enough **events** in this population to have an adequately powered analysis?

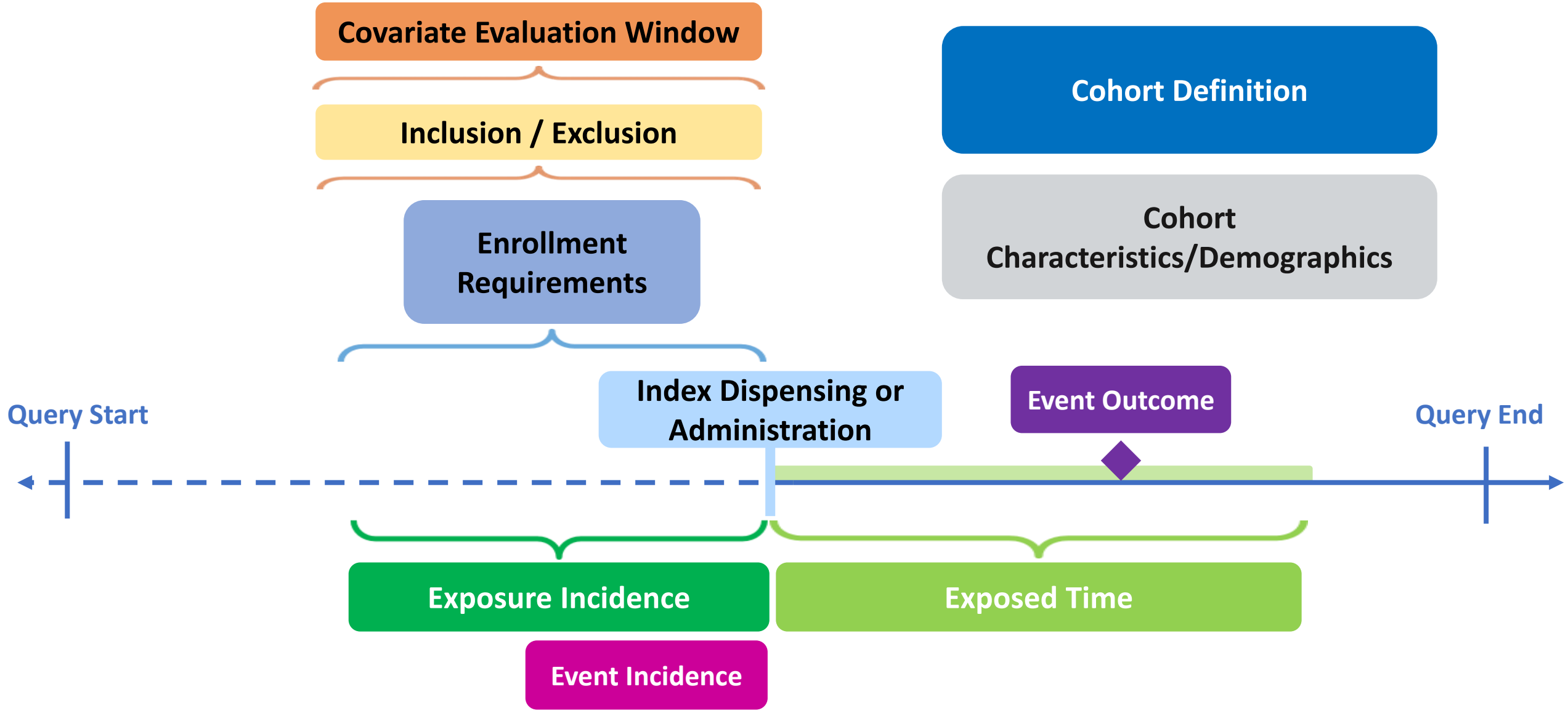

What are you investigating?
Medical Products Only
Outcomes Only
Medical Products & Outcomes
Develop Unadjusted Incidence Rates (Type 2)
Identifies an exposure of interest and looks for the occurrence of health outcomes of interest (HOIs) during exposed time.
Output metrics include number of exposure episodes and number of health outcomes of interest, and days at-risk.
Example
SGLT-2 Inhibitor Use and Incidence of Diabetic Ketoacidosis
Incidence Rates
Type 2
L1
Propensity Score Analysis
Type 2 or 4
L2
L3
Multiple Factor Matching
Type 2 or 4
L2
L3
Self-Controlled Risk Interval Design
Type 3
L2
L3
L1 Level 1 Analysis
L2 Level 2 Analysis
L3 Level 3 Analysis

Defining a Study Question

Sentinel

Design overview	Study Design	• Select type of analysis; identify cohorts of interest
	Study Population	• Select query period • Define demographic and enrollment requirements for contributing population • Define inclusion/exclusion criteria
	Exposures	• Identify and define cohort-defining events • Determine cohort re-entry requirements • Identify incidence criteria and associated washout periods
	Follow-up	• Assign parameters to create concept of 'exposed time'
	Censoring	• Identify events that will result in truncation of exposed time
	Outcomes	• Identify and define main outcomes of interest
Analysis	Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Incidence Rates Design Diagram



Translating Study Questions into CIDA Parameters

Specifications for Type 2 Request: public_mpl1r_wp001

The SOC has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) tool, version 7.3.0, to estimate users of typical and atypical antipsychotics who experience stroke or intracranial hemorrhage in the Sentinel Distributed Database (SDD). The Propensity Score Analysis tool will be used to estimate the association between typical antipsychotics compared to atypical antipsychotics and risk of ischemic stroke and intracranial hemorrhage.

Query period: 1/1/2008 - 12/31/2010
Coverage requirement: Medical and drug
Pre-index enrollment requirement: 183 days
Post-index enrollment requirement: 0
Enrollment gap: 45 days
Age groups: 18-39, 40-54, 55-65 years
Stratifications: Age group, sex, calendar year
Censor output categorization: 0-364, 365-729, 730-1094, 1095+ days
Envelope macro: Reclassify encounters during inpatient stay as inpatient
Propensity score analysis: 1:1 matching
Propensity score caliper: 0.05

		Exposure									
	Group	Index Exposure	Cohort definition	Incident exposure washout period	Incident w/ respect to:	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Minimum days supplied	Maximum exposure episode duration	Censor treatment episode at evidence of:
1	typ_IS	Typical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
2	typ_ICH	Typical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
3	atyp_IS	Atypical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
4	atyp_ICH	Atypical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics

NDC codes are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

Translating Study Questions into CIDA Parameters

		Inclusion/Exclusion Criteria							Event Outcome							Covariates
	Group	Inclusion/ exclusion group	Criteria	Care setting	Principal diagnosis position	Evaluation period start	Evaluation period end	Number of instances the criteria should be found in evaluation period	Event	Care setting	Principal diagnosis position	Event washout conditions	Event washout care setting	Event washout period	Blackout period	Covariates
1	typ_IS	Dementia	Exclude	Any care setting	Any position	-183	0	1	Ischemic stroke	Inpatient hospital stay	Principal	Stroke (ischemic stroke and intracranial hemorrhage)	Any care setting	60	1	See Covariate Tab
2	typ_ICH	Dementia	Exclude	Any care setting	Any position	-183	0	1	Intracranial hemorrhage	Inpatient hospital stay	Principal	Stroke (ischemic stroke and intracranial hemorrhage)	Any care setting	60	1	See Covariate Tab
3	atyp_IS	Dementia	Exclude	Any care setting	Any position	-183	0	1	Ischemic stroke	Inpatient hospital stay	Principal	Stroke (ischemic stroke and intracranial hemorrhage)	Any care setting	60	1	See Covariate Tab
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Defining a Study Question

Sentinel

Design overview

Study Design	• Select type of analysis; identify cohorts of interest
Study Population	• Select query period • Define demographic and enrollment requirements for contributing population • Define inclusion/exclusion criteria
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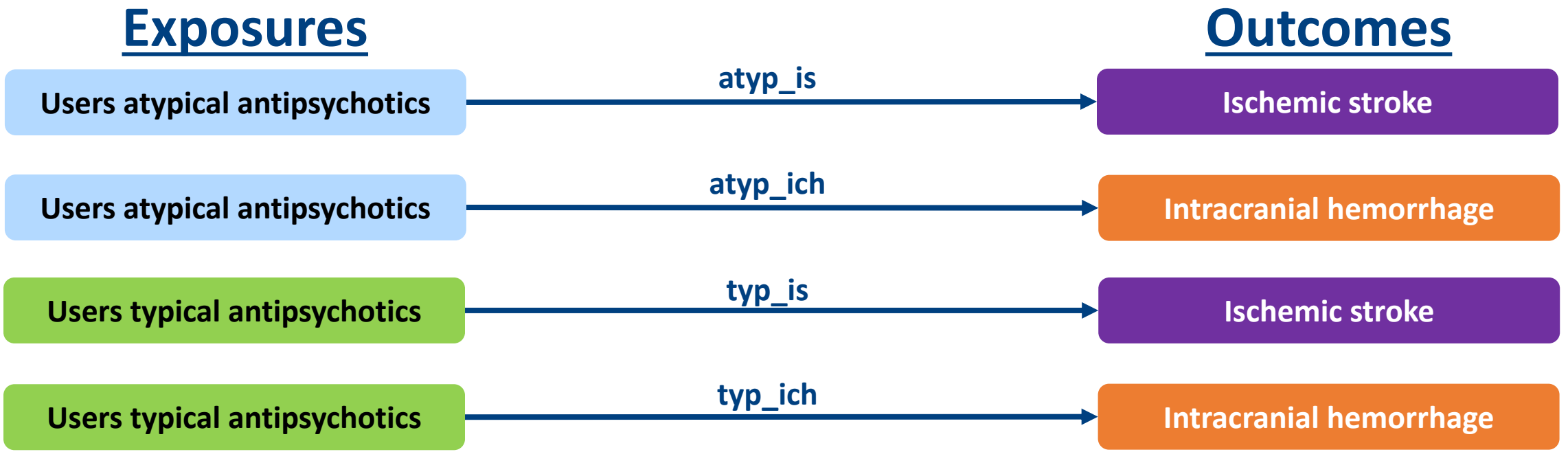
Analysis

Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

How Many Cohorts of Interest Are There?

- CIDA **requires** definition of the study population, exposure episodes, outcomes, and inclusions or exclusions
  - When parameters change that adjust cohort-defining criteria, a new scenario must be created
- Concept brief: 2 cohorts, 2 outcomes=4 scenarios



Specifying Scenarios

	Exposure									
Group	Index Exposure	Cohort definition	Incident exposure washout period	Incident w/ respect to:	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Minimum days supplied	Maximum exposure episode duration	Censor treatment episode at evidence of:
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Defining a Study Question

Sentinel

Design overview

Study Design	• Retrospective new-user cohort of 4 unique analysis groups
Study Population	• Select query period • Define demographic and enrollment requirements for contributing population • Define inclusion/exclusion criteria
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Defining a Study Population

Sentinel

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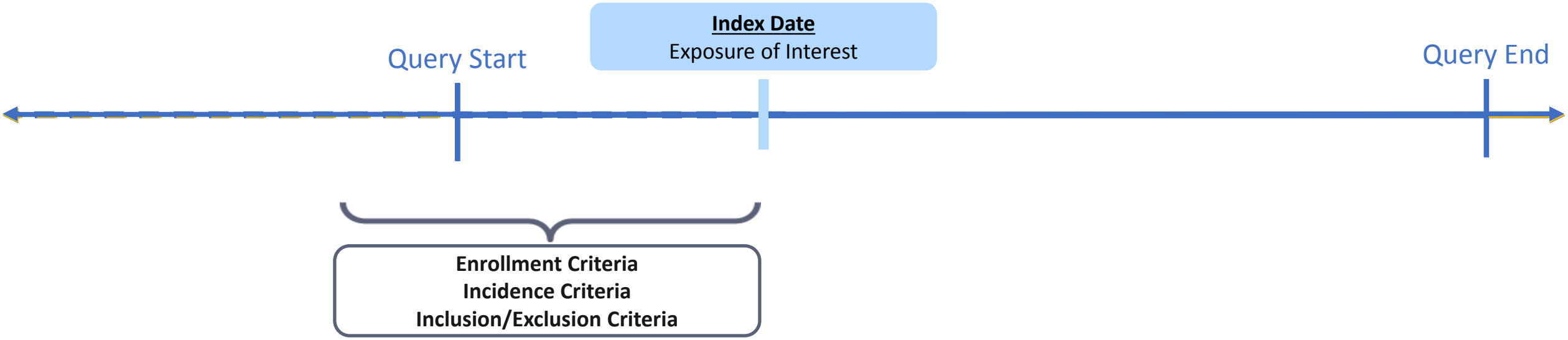
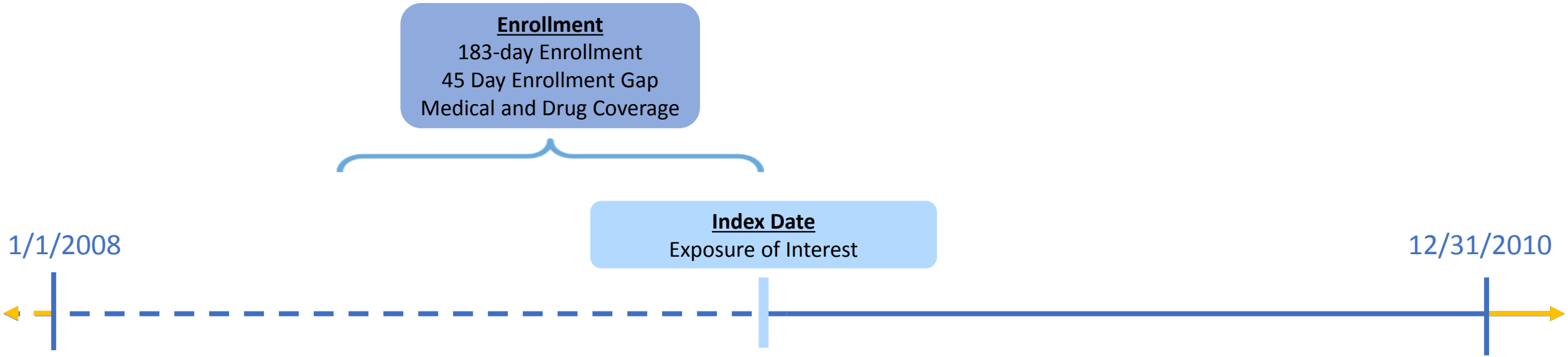
Query Period Binds the Index Date

- Enrollment Criteria, Inclusion and Exclusion Criteria, and Exposure Incidence may be assessed Prior to Index Date



Enrollment Characteristics

- User-Specified Coverage Type and Enrollment Gap may be specified.

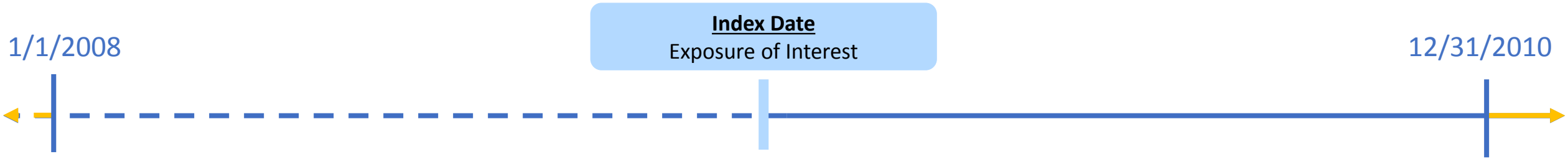


Demographic Characteristics

- Age group, race, and sex stratifications are customizable.

Cohort Characteristics

- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions



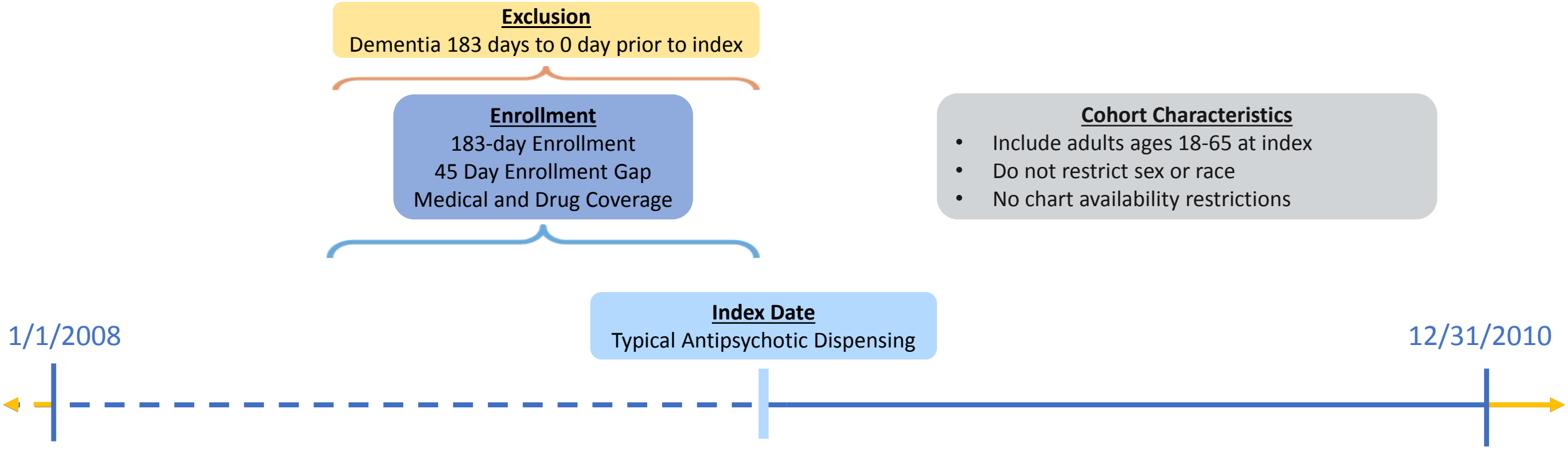
Specifications: Demographic and Enrollment Characteristics

* **Query period:**	1/1/2008 - 12/31/2010
Coverage requirement:	Medical and Drug
Pre-index enrollment requirement:	183 days
Post-index enrollment requirement:	0
Enrollment gap:	45 days
Age groups:	18-39, 40-54, 55-65 years
* **Stratifications:**	Age group, Sex, Calendar Year
Censor output categorization:	0-364, 365-729, 730-1094, 1095+ days
* **Envelope macro:**	Reclassify encounters during inpatient stay as inpatient
Propensity score analysis:	1:1 matching
Propensity score caliper:	0.05

* Global Parameters

Exclusion Criteria

- Clinical Concepts can be care setting-specific (e.g., Inpatient, Outpatient).



Specifications: Inclusion and Exclusion Criteria

		Inclusion/Exclusion Criteria						
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3	atyp_IS	Dementia	Exclude	Any care setting	Any position	-183	0	1
4	atyp_ICH	Dementia	Exclude	Any care setting	Any position	-183	0	1

Defining a Study Population

Sentinel

Design overview

Study Design	• Retrospective new-user cohort of 4 unique analysis groups
Study Population	• 2008-2010 • 18-65 years, 6-months prior continuous insurance eligibility • Exclude use of any AP in the previous 183 days, OR dementia in 183 days prior to AP initiation
Exposures	• Identify and define cohort-defining events • Determine cohort re-entry requirements • Identify incidence criteria and associated washout periods
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Censoring	• Identify events that will result in truncation of exposed time
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Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Defining Exposures

Sentinel

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Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Index Dispensing or Administration

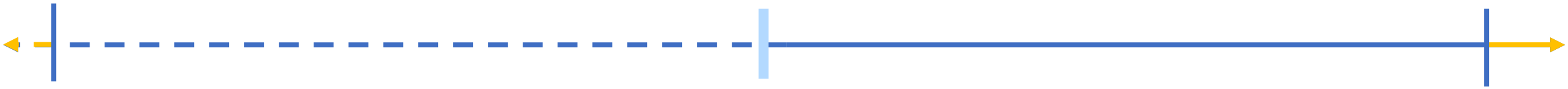
- Many parameters are defined relative to Index.

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Characteristics
- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions

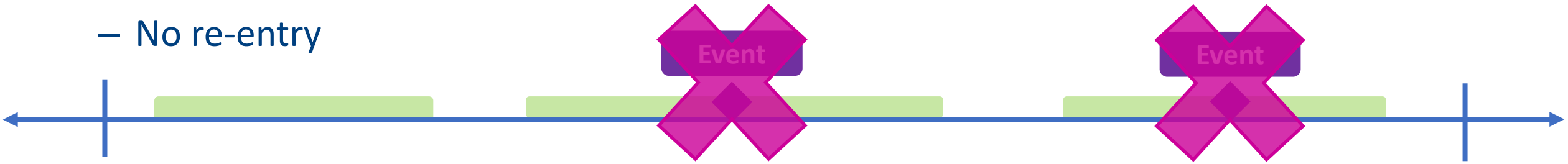
Index Date
Typical Antipsychotic Dispensing



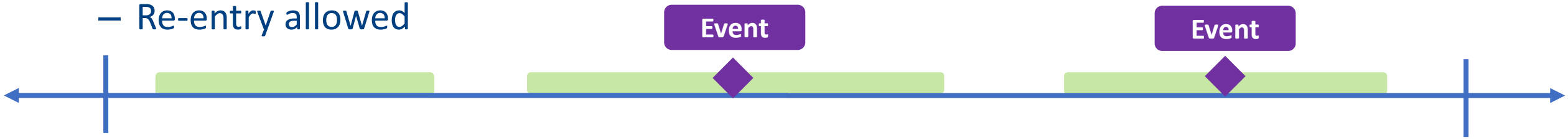
Scenario 1

How Many Valid Index Dates? Cohort Definition

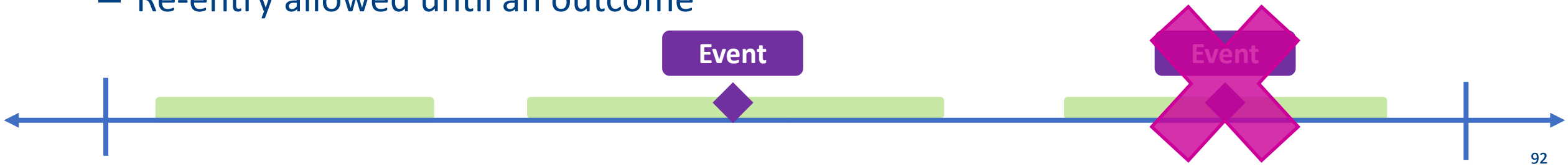
- Cohort Definition 01
  - No re-entry



- Cohort Definition 02:
  - Re-entry allowed



- Cohort Definition 03:
  - Re-entry allowed until an outcome



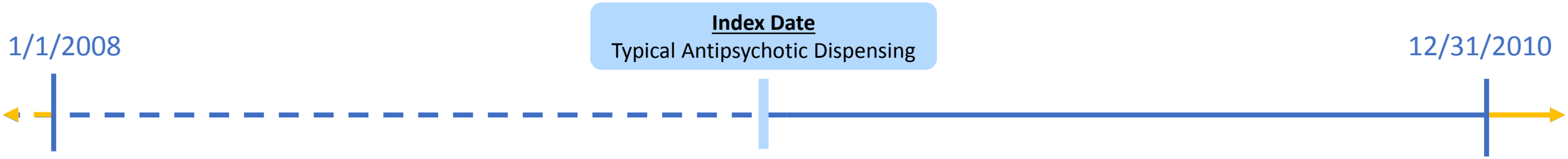
Cohort Definition

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions



Scenario 1

New User Definition

- Exposure Incidence ends at Day -1

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
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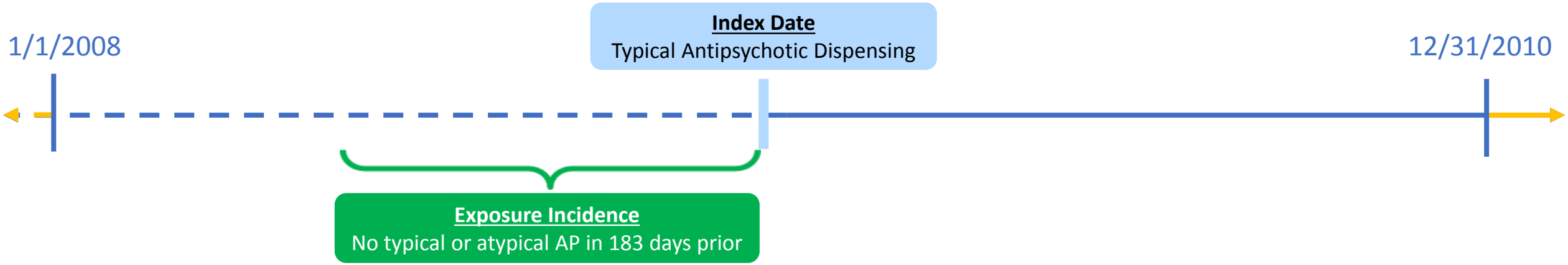

Scenario 1

Specifications: Index Exposure Parameters

	Exposure										
Group	Index Exposure	Cohort definition	Incident exposure washout period	Incident w/ respect to:	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Minimum days supplied	Maximum exposure episode duration	Censor treatment episode at evidence of:
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Defining Exposures

Sentinel

Design overview

Study Design	• Retrospective new-user cohort of 4 unique analysis groups
Study Population	• 2008-2010 • 18-65 years, 6-months prior continuous insurance eligibility • Exclude use of any AP in the previous 183 days, OR dementia in 183 days prior to AP initiation
Exposures	• New users of typical vs atypical AP • Do not allow for cohort re-entry • Incident with respect to all typical and atypical AP in prior 6mo
Follow-up	• Assign parameters to create concept of 'exposed time'
Censoring	• Identify events that will result in truncation of exposed time
Outcomes	• Identify and define main outcomes of interest

Analysis

Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Defining a Follow-up Period

Sentinel

Design overview

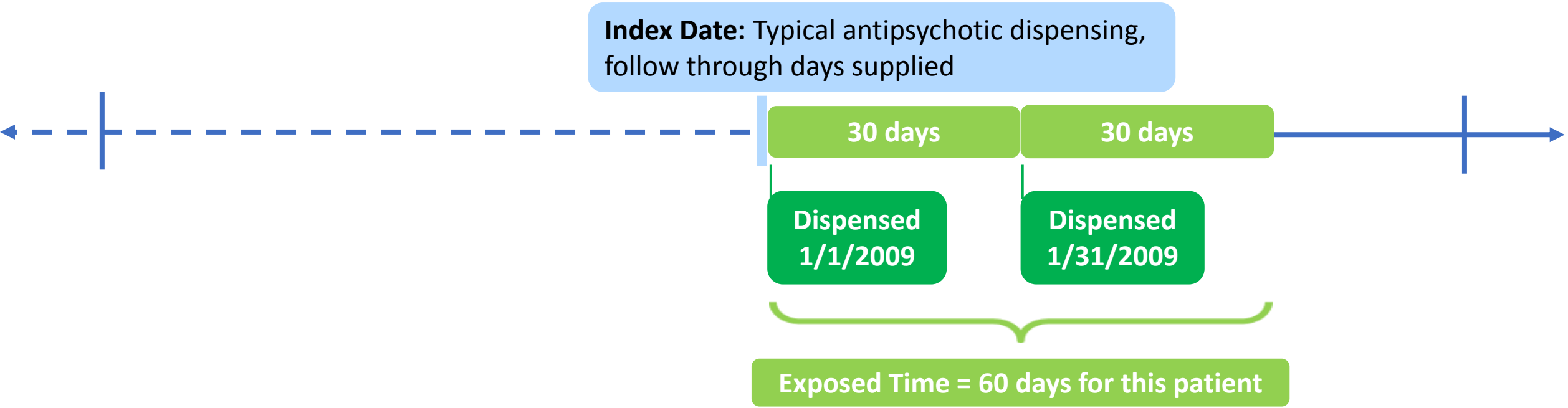
Study Design	• Retrospective new-user cohort of 4 unique analysis groups
Study Population	• 2008-2010 • 18-65 years, 6-months prior continuous insurance eligibility • Exclude use of any AP in the previous 183 days, OR dementia in 183 days prior to AP initiation
Exposures	• New users of typical vs atypical AP • Do not allow for cohort re-entry • Incident with respect to all typical and atypical AP in prior 6mo
Follow-up	• Assign parameters to create concept of 'exposed time'
Censoring	• Identify events that will result in truncation of exposed time
Outcomes	• Identify and define main outcomes of interest

Analysis

Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

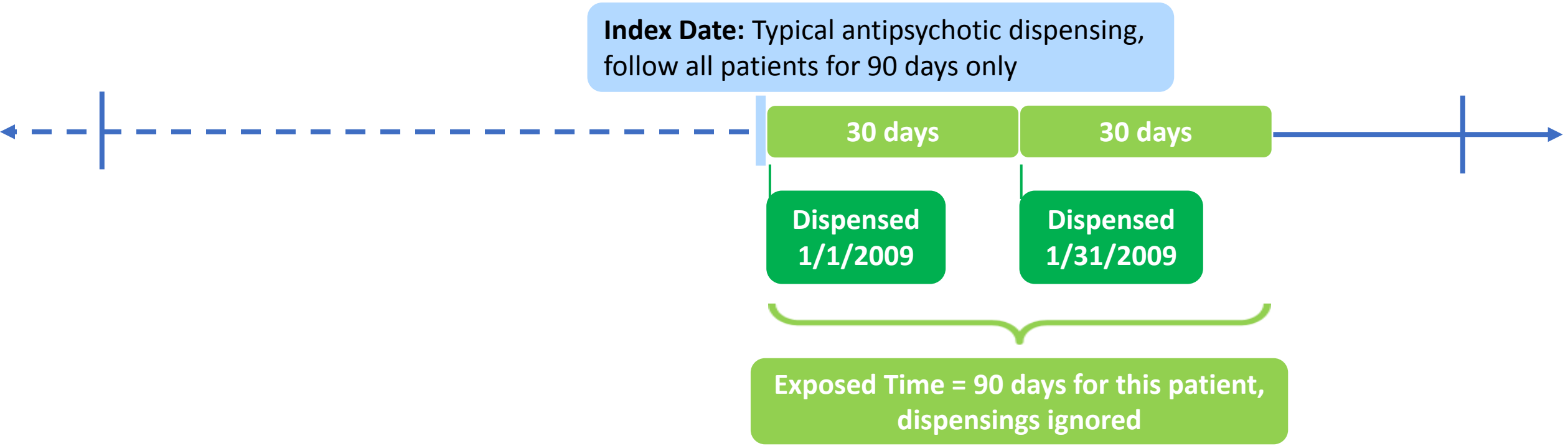
Exposure Episodes: As Treated vs. Intent-to-Treat

- **As treated analysis**: Creating exposure episodes based on dispensing days supplied



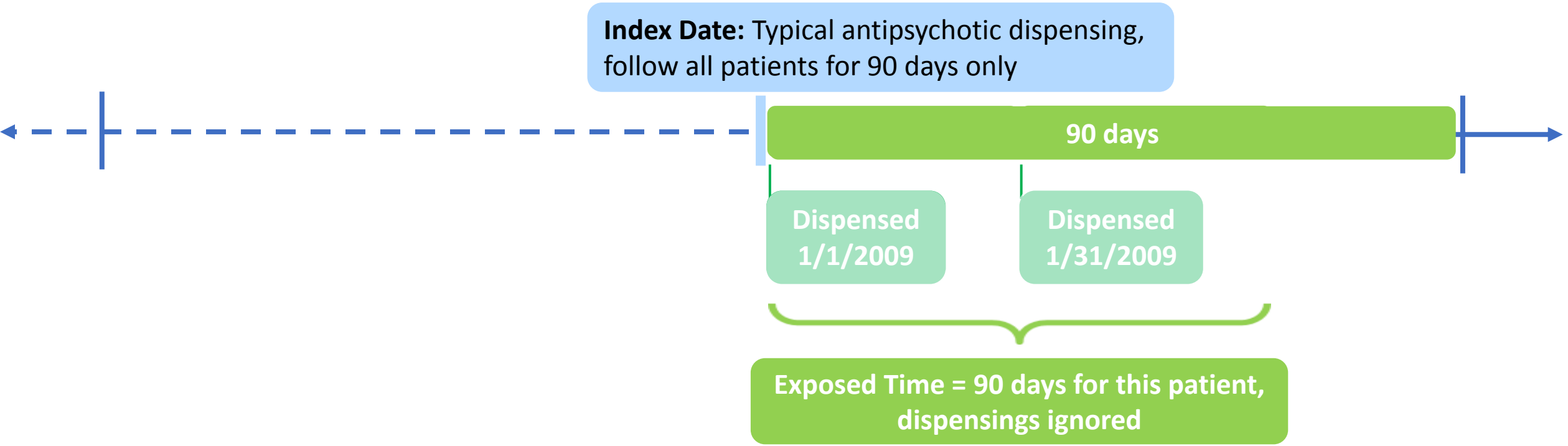
Exposure Episodes: As Treated vs. Intent-to-Treat

- **Intent to treat**: Requester-defined number of days after exposure initiation that is considered "exposed time"



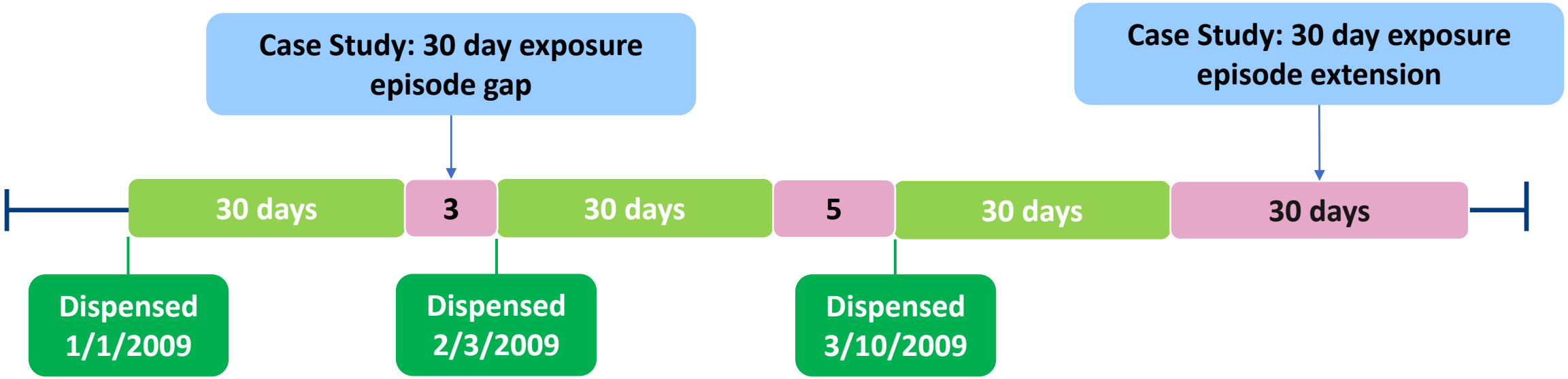
Exposure Episodes: As Treated vs. Intent-to-Treat

- **Intent to treat**: Requester-defined number of days after exposure initiation that is considered "exposed time"



Exposed Time: Concatenating Dispensings

1. **Stockpiling** is used to evaluate early refilling behavior, same day dispensings
   - Defaulted in Query Builder to keep any overlapping dispensings
2. **Gaps** are bridged to deal with late refill behavior
3. **Extension** days are added after any episode gaps have been bridged



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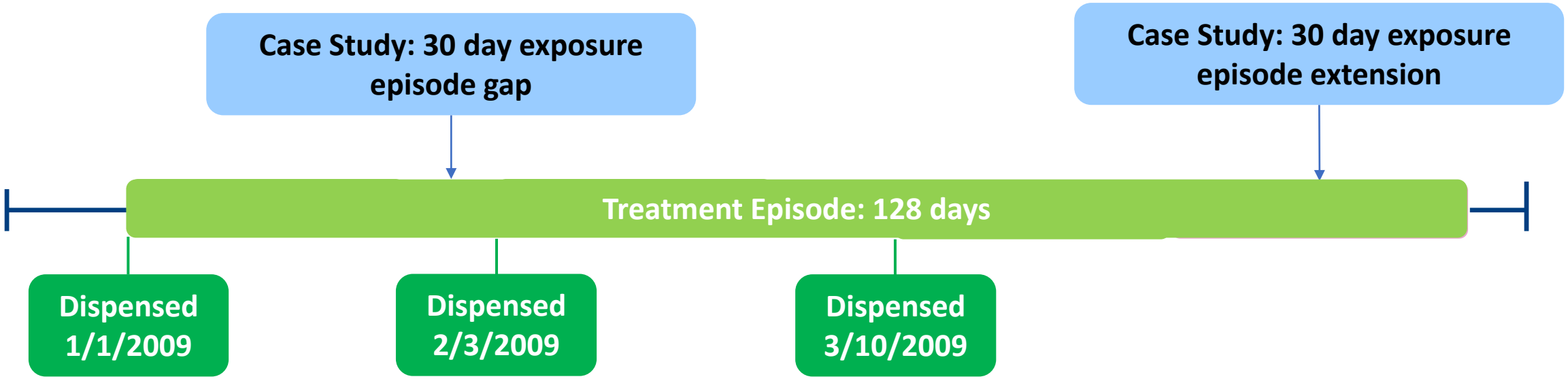


Maximum Exposure Episode Duration

- Truncates episodes after a requester-specified number of exposed days.
- Applied after any gaps are bridged and extension days added to the length of the exposure episode.
- It does not require enrollment.

If maximum episode duration of 120 days is applied, episode would be truncated at 120 days

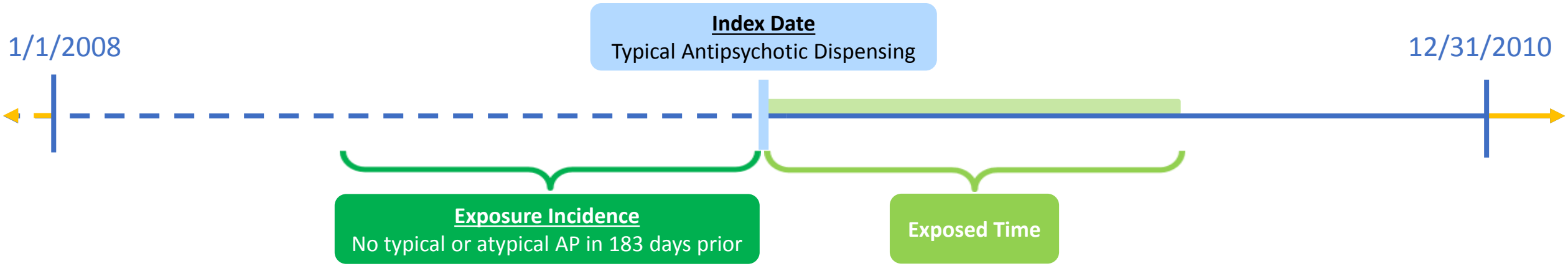
Exposed Time

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions



Scenario 1

Specifications: Exposed Time

	Exposure										
	Group	Index Exposure	Cohort definition	Incident exposure washout period	Incident w/ respect to:	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Minimum days supplied	Maximum exposure episode duration	Censor treatment episode at evidence of:
1	typ_IS	Typical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
2	typ_ICH	Typical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
3	atyp_IS	Atypical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
4	atyp_ICH	Atypical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics

Defining a Follow-up Period

Sentinel

Design overview	Study Design	• Retrospective new-user cohort of 4 unique analysis groups
	Study Population	• 2008-2010 • 18-65 years, 6-months prior continuous insurance eligibility • Exclude use of any AP in the previous 183 days, OR dementia in 183 days prior to AP initiation
	Exposures	• New users of typical vs atypical AP • Do not allow for cohort re-entry • Incident with respect to all typical and atypical AP in prior 6mo
	Follow-up	• Duration of exposure (30-day gap); default stockpiling
	Censoring	• Identify events that will result in truncation of exposed time
	Outcomes	• Identify and define main outcomes of interest
Analysis	Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Defining Censoring Criteria

Sentinel

Design overview

Study Design	• Retrospective new-user cohort of 4 unique analysis groups
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Follow-up	• Duration of exposure (30-day gap); default stockpiling
Censoring	• Identify events that will result in truncation of exposed time
Outcomes	• Identify and define main outcomes of interest

Analysis

Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Censoring

- Required: first occurrence of disenrollment, outcome event
- Optional: user-defined codes, death, Data Partner end date, query end date

Specifications: Censoring Parameters

	Exposure									
Group	Index Exposure	Cohort definition	Incident exposure washout period	Incident w/ respect to:	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Minimum days supplied	Maximum exposure episode duration	Censor treatment episode at evidence of:
1 typ_IS	Typical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
2 typ_ICH	Typical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
3 atyp_IS	Atypical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics
4 atyp_ICH	Atypical Antipsychotics	First valid exposure episode during query period	183 days	Typical and atypical antipsychotics	30 days	30 days	1	1	None	Death; DP end date; Query end date; Atypical antipsychotics

Defining Censoring Criteria

Sentinel

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	Follow-up	• Duration of exposure (30-day gap); default stockpiling
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	Outcomes	• Identify and define main outcomes of interest
Analysis	Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Defining an Outcome

Sentinel

Design overview	Study Design	• Retrospective new-user cohort of 4 unique analysis groups
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	Outcomes	• Identify and define main outcomes of interest
Analysis	Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Three Elements to Define Outcome Events

- Event Identification – any combination of code(s) and care-setting(s)
  - Must be during the “at-risk” follow-up period
- Event Incidence or Washout Period - number of days before index that a user is required to have no evidence of the event
  - Requires enrollment
  - Can require no evidence of related events
- Blackout (Induction) Period – number of days after index before the “at risk” follow-up period begins (e.g., follow-up begins on Day 1 not Day 0)
  - Outcomes that occur in this period are not counted and those episodes are excluded

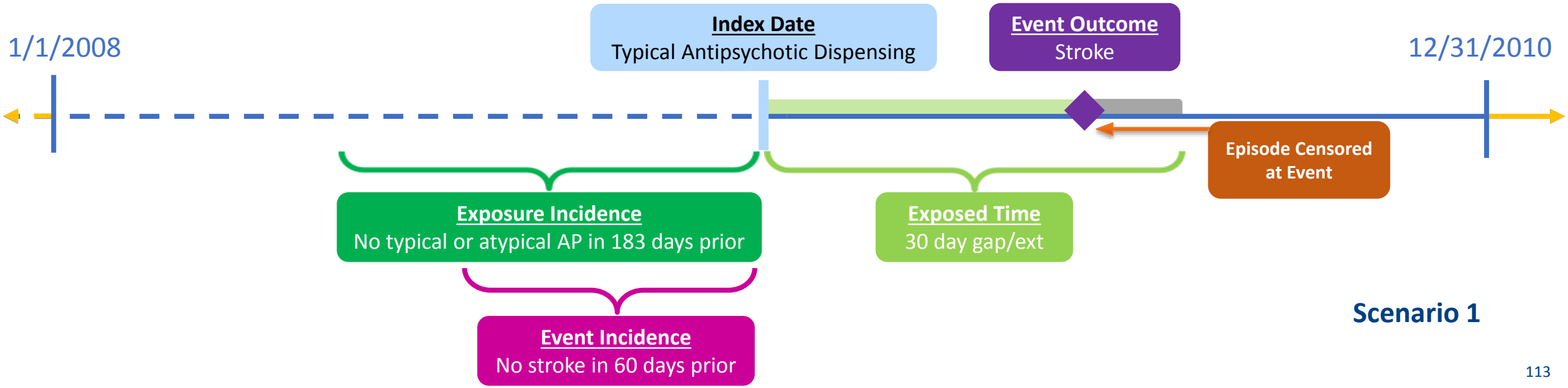
Outcome: Ischemic Stroke

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions



Scenario 1

Specifications: Outcomes

	Event Outcome						
Group	Event	Care setting	Principal diagnosis position	Event washout conditions	Event washout care setting	Event washout period	Blackout period
1 typ_IS	Ischemic stroke	Inpatient hospital stay	Principal	Stroke (ischemic stroke and intracranial hemorrhage)	Any care setting	60	1
2 typ_ICH	Intracranial hemorrhage	Inpatient hospital stay	Principal	Stroke (ischemic stroke and intracranial hemorrhage)	Any care setting	60	1
3 atyp_IS	Ischemic stroke	Inpatient hospital stay	Principal	Stroke (ischemic stroke and intracranial hemorrhage)	Any care setting	60	1
4 atyp_ICH	Intracranial hemorrhage	Inpatient hospital stay	Principal	Stroke (ischemic stroke and intracranial hemorrhage)	Any care setting	60	1

Defining an Outcome

Sentinel

Design overview	Study Design	• Retrospective new-user cohort of 4 unique analysis groups
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	Censoring	• First occurrence of outcome, Rx for comparator, disenrollment, death, or end of query period
	Outcomes	• Ischemic stroke or ICH, primary inpatient diagnosis
Analysis	Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Defining Descriptive Analysis Elements

Sentinel

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	Censoring	• First occurrence of outcome, Rx for comparator, disenrollment, death, or end of query period
	Outcomes	• Ischemic stroke or ICH, primary inpatient diagnosis
Analysis	Analysis	• Descriptive: Identify and define baseline covariates and covariate windows; select stratifications of interest • Inferential: Identify comparator groups, define matching criteria

Covariates

- Covariates can be identified using any combination of NDCs (dispensings), diagnosis codes, or procedure codes
  - Can specify care-setting, number of occurrences
  - Can use complex Boolean logic (AND, OR)
- Evaluation windows must be selected for each covariate
  - Evaluation windows don't have to be the same for every covariate
  - The evaluation windows are relative to day 0 (index date)
  - Evaluation windows can be open-ended (anytime in the patient's enrollment history before or after the index date)
- One set of covariates is used for all scenarios
- Covariates will contribute to the baseline table, may or may not be used in propensity score estimation

Covariates

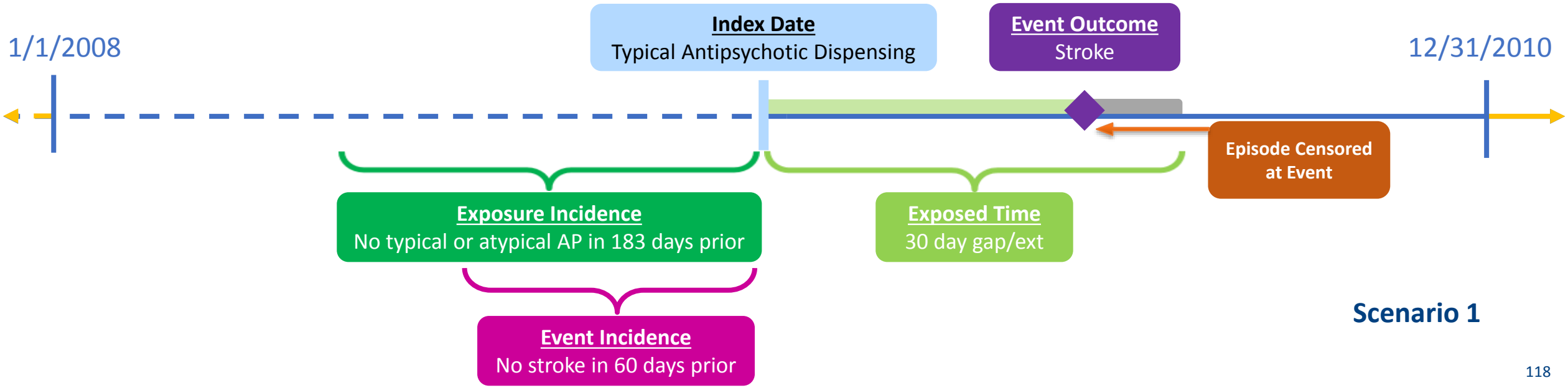
Covariate Evaluation Window
183 days to 1 day prior to index

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions



Scenario 1

Specifications: Covariates

Covariates					
Covariate	Care setting	Principal diagnosis position	Evaluation period start	Evaluation period end	Number of instances the covariate should be found in evaluation period
Acute myocardial infarction	Any	Any	-183	-1	1
Diabetes	Any	Any	-183	-1	1
Heart failure	Any	Any	-183	-1	1
Hypercholesterolemia	Any	Any	-183	-1	1
Hypertension	Any	Any	-183	-1	1
Kidney failure	Any	Any	-183	-1	1
Transient ischemic attack	Any	Any	-183	-1	1
Depression	Any	Any	-183	-1	1
Anxiety	Any	Any	-183	-1	1
Bipolar	Any	Any	-183	-1	1
Schizophrenia/psychotic disorder	Any	Any	-183	-1	1
Substance abuse	Any	Any	-183	-1	1

Defining Descriptive Analysis Elements

Sentinel

Design overview

Study Design	• Retrospective new-user cohort of 4 unique analysis groups
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Follow-up	• Duration of exposure (30-day gap); default stockpiling
Censoring	• First occurrence of outcome, Rx for comparator, disenrollment, death, or end of query period
Outcomes	• Ischemic stroke or ICH, primary inpatient diagnosis

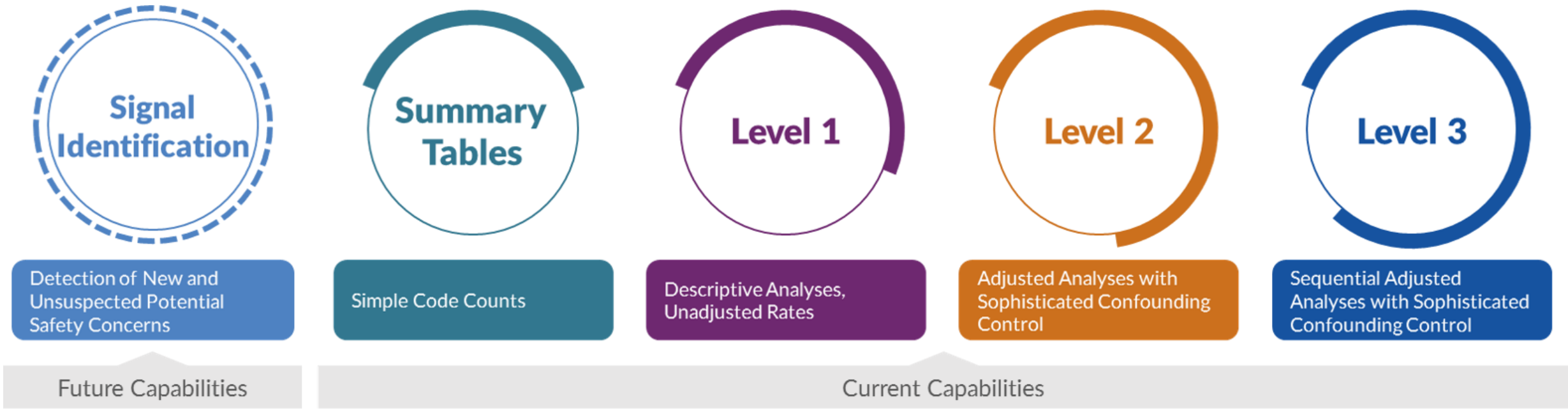
Analysis

Analysis	• Baseline table of cardiovascular and psychiatric risk factors in 183 days prior to AP initiation

Finishing an Incidence Rates Query (Type 2, Level 1)

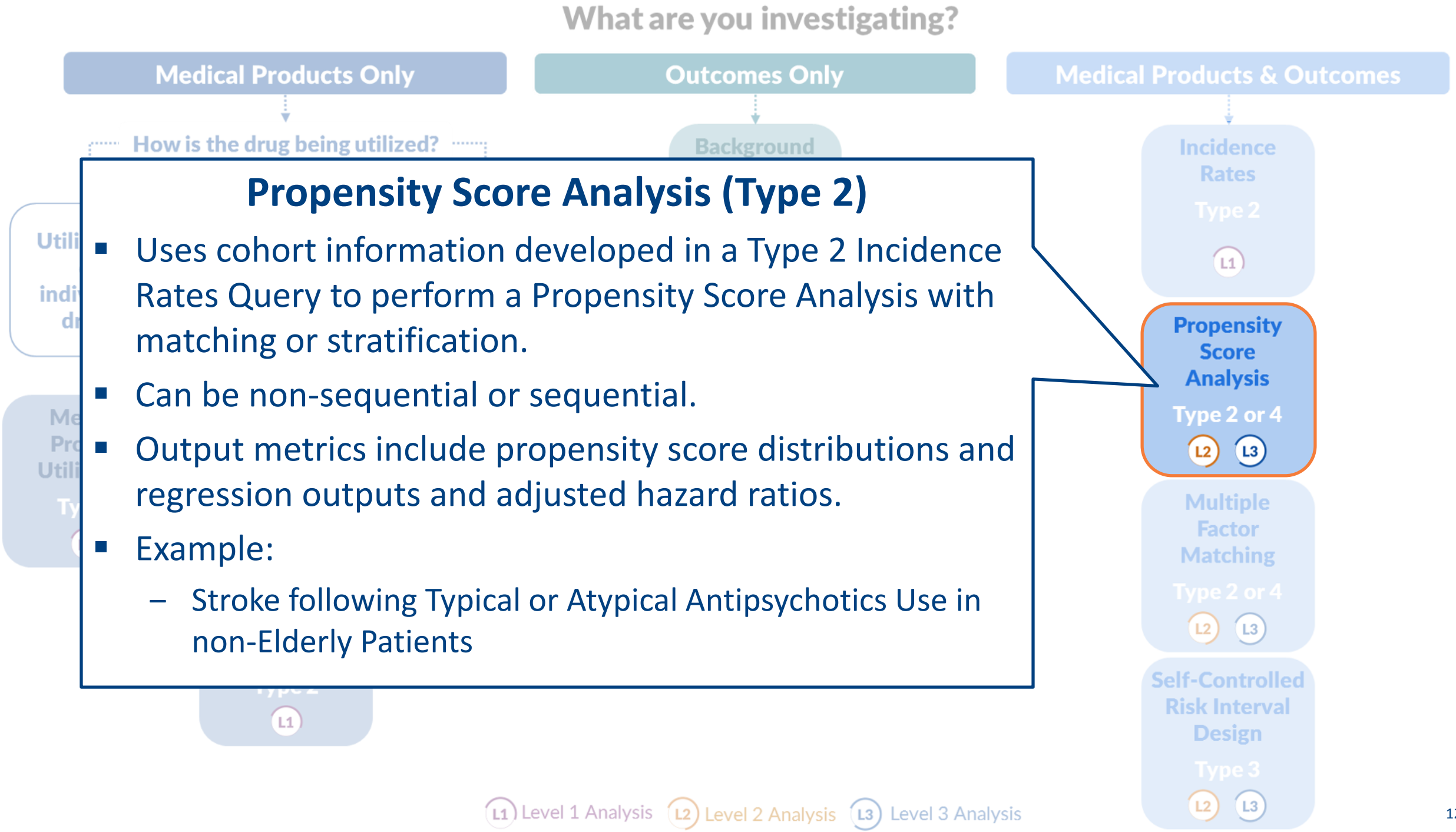
- Produces unadjusted incidence rates that can be used in sample size calculations
  - FDA often requests that outcome counts be combined among exposure groups to remain blinded.
- Baseline Covariates Table provides a sense of unmatched cohorts
  - Early warning on rare covariates that are unlikely to need adjustment but can generate problems in propensity score estimation
- Stratifications can inform the potential for effect modification

Active Risk Identification and Analysis (ARIA)



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

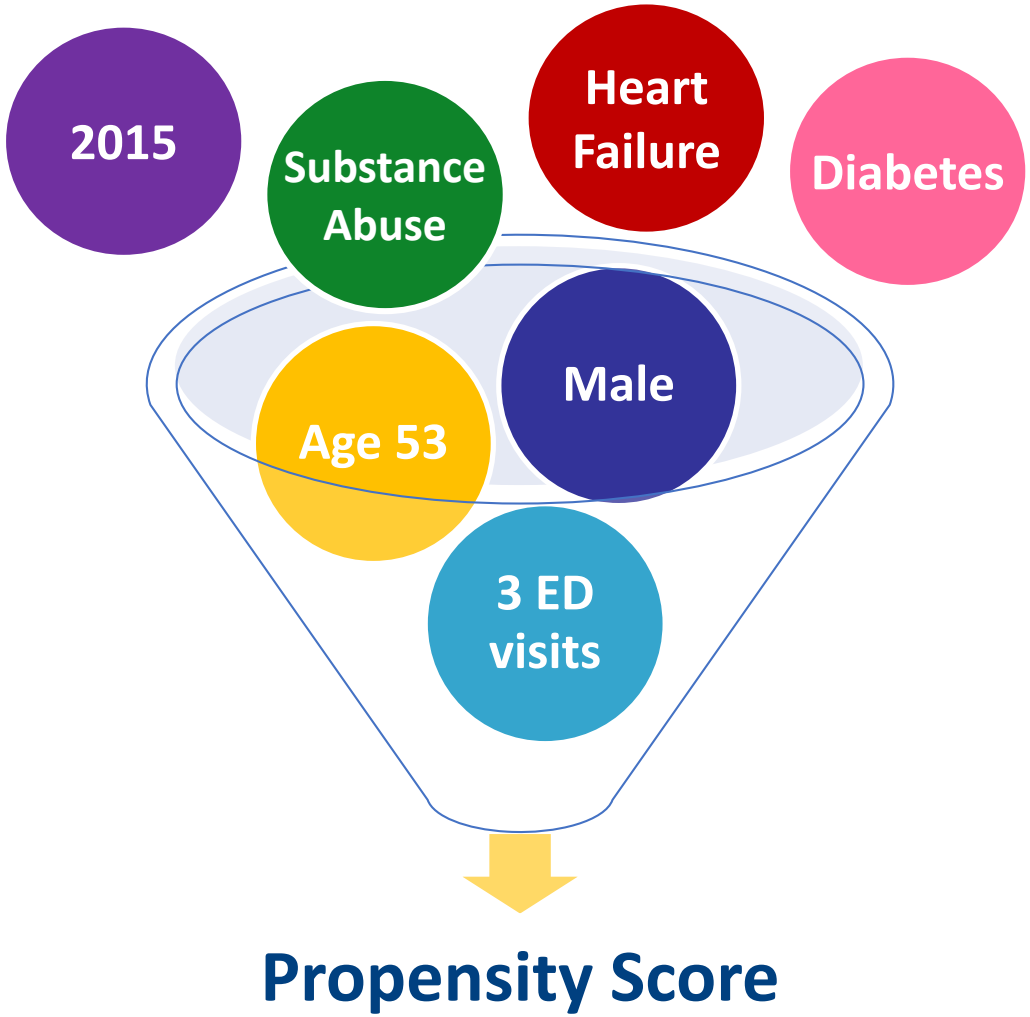
https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria



Propensity Score Analysis (Type 2)

- Uses cohort information developed in a Type 2 Incidence Rates Query to perform a Propensity Score Analysis with matching or stratification.
- Can be non-sequential or sequential.
- Output metrics include propensity score distributions and regression outputs and adjusted hazard ratios.
- Example:
  - Stroke following Typical or Atypical Antipsychotics Use in non-Elderly Patients

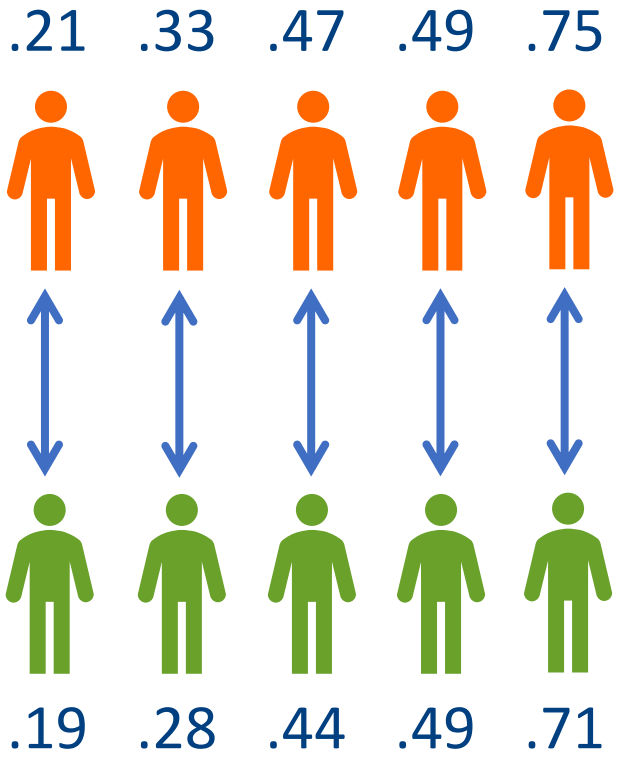
Propensity Score (PS): A Brief Summary



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

Propensity Score Matching Parameters

- Matching Ratio: Fixed 1:1 or variable 1:*n* (*n*≤10)
- Caliper
  - Maximum distance allowed between two matched patients' PS
  - Natural scale of PS (e.g., 0.01, 0.05)
- Nearest Neighbor



Specifications: Propensity Score

* **Query period:**	1/1/2008 - 12/31/2010
Coverage requirement:	Medical and Drug
Pre-index enrollment requirement:	183 days
Post-index enrollment requirement:	0
Enrollment gap:	45 days
Age groups:	18-39, 40-54, 55-65 years
* **Stratifications:**	Age group, Sex, Calendar Year
Censor output categorization:	0-364, 365-729, 730-1094, 1095+ days
* **Envelope macro:**	Reclassify encounters during inpatient stay as inpatient
Propensity score analysis:	1:1 matching
Propensity score caliper:	0.05

*** Global Parameters**

Defining Inferential Analysis Elements

Sentinel

Design overview

Study Design	• Retrospective new-user cohort of 4 unique analysis groups
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Exposures	• New users of typical vs atypical AP • Do not allow for cohort re-entry • Incident with respect to all typical and atypical AP in prior 6mo
Follow-up	• Duration of exposure (30-day gap); default stockpiling
Censoring	• First occurrence of outcome, Rx for comparator, disenrollment, death, or end of query period
Outcomes	• Ischemic stroke or ICH, primary inpatient diagnosis

Analysis

Analysis	• Baseline table of cardiovascular and psychiatric risk factors in 183 days prior to AP initiation • Cox proportional hazards, 1:1 PS matching, caliper=0.05

Propensity Score Match Design Diagram

Sentinel

Propensity Score
- 1:1 Matching
- Caliper: 0.05
- Age, Sex
- Recorded History Parameters

Covariate Evaluation Window
183 days to 1 day prior to index

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
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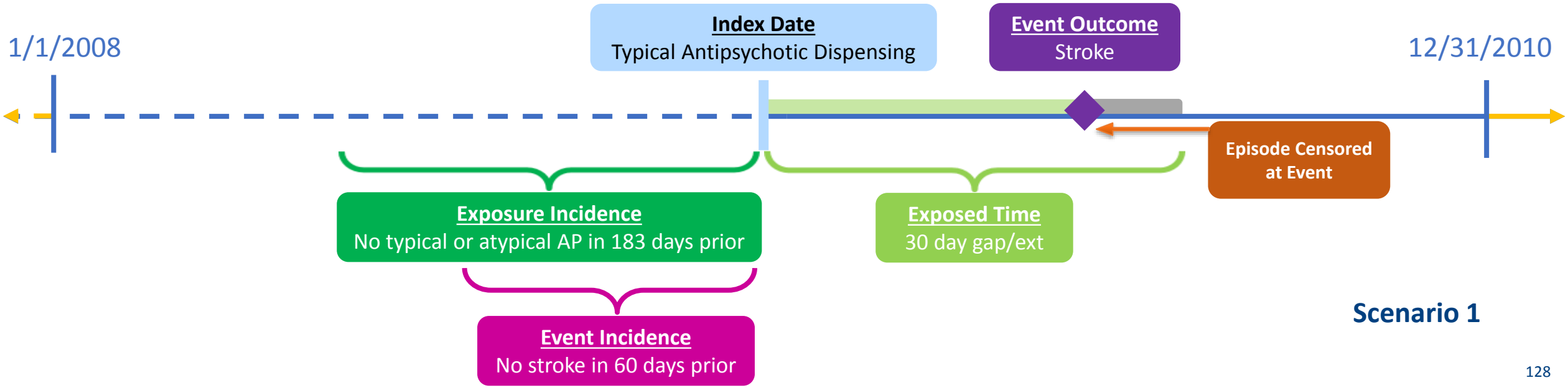


Scenario 1

Defining Clinical Concepts with Codes

Defining Clinical Concepts: Code Lists

- Code categories and code types must be in Sentinel Common Data Model

- In this example, we need codes for:
  - **Exposures:** Typical antipsychotics, atypical antipsychotics
  - **Incidence criteria:** Typical antipsychotics, atypical antipsychotics
  - **Exclusion:** Dementia
  - **Outcome:** Ischemic stroke, intracranial hemorrhage
  - **Covariates:** History of acute myocardial infarction, diabetes, heart failure, hypercholesterolemia, hypertension, kidney failure, transient ischemic attack, depression, anxiety, bipolar, schizophrenia/psychotic disorder, substance abuse

Defining Clinical Concepts: Code Lists

Code	Code Category	Code Type	Description
433.01	Diagnosis	ICD-9	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Diagnosis	ICD-9	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Diagnosis	ICD-9	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Diagnosis	ICD-9	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Diagnosis	ICD-9	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Diagnosis	ICD-9	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434.01	Diagnosis	ICD-9	Cerebral thrombosis with cerebral infarction
434.11	Diagnosis	ICD-9	Cerebral embolism with cerebral infarction
434.91	Diagnosis	ICD-9	Cerebral artery occlusion, unspecified, with cerebral infarction
436	Diagnosis	ICD-9	Acute, but ill-defined, cerebrovascular disease

Specifications | Covariates | Stockpiling | Atypical antipsychotics | Typical antipsychotics | Ischemic Stroke | Intracranial Hemorrhage

Code lists are included in specifications in tabs

Defining Clinical Concepts: Care Setting

- Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded
- Possible care settings include:
  - Inpatient hospital stay (IP)
  - Non-acute institutional stay (IS)
  - Emergency department encounter (ED)
  - Ambulatory visit (AV)
  - Other ambulatory visit (OA)
  - Any care setting

Defining Clinical Concepts: Principal Diagnosis

- Diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital
  - Any
  - Principal
  - Secondary
  - Unknown
- Sentinel CDM only populates principal diagnosis position for inpatient (IP) and institutional (IS) stays

Wrap-Up Morning Session

- We walked through designing, specifying, and implementing a Medical Product Utilization Query using the Sentinel Query Builder (i.e., a simplified, web-based interface that produces a CIDA SAS package).
- We walked through designing and specifying an Incidence Rates Query and a Propensity Score Matched Analysis building on that.
- We focused on design diagrams and specifications.

This afternoon:

- Session A: Review results of implemented query on SynPUFs data. Review other completed queries in the Sentinel Distributed Database.
- Session B: Create a CIDA SAS Package from specifications and execute it against formatted SynPUFs data.

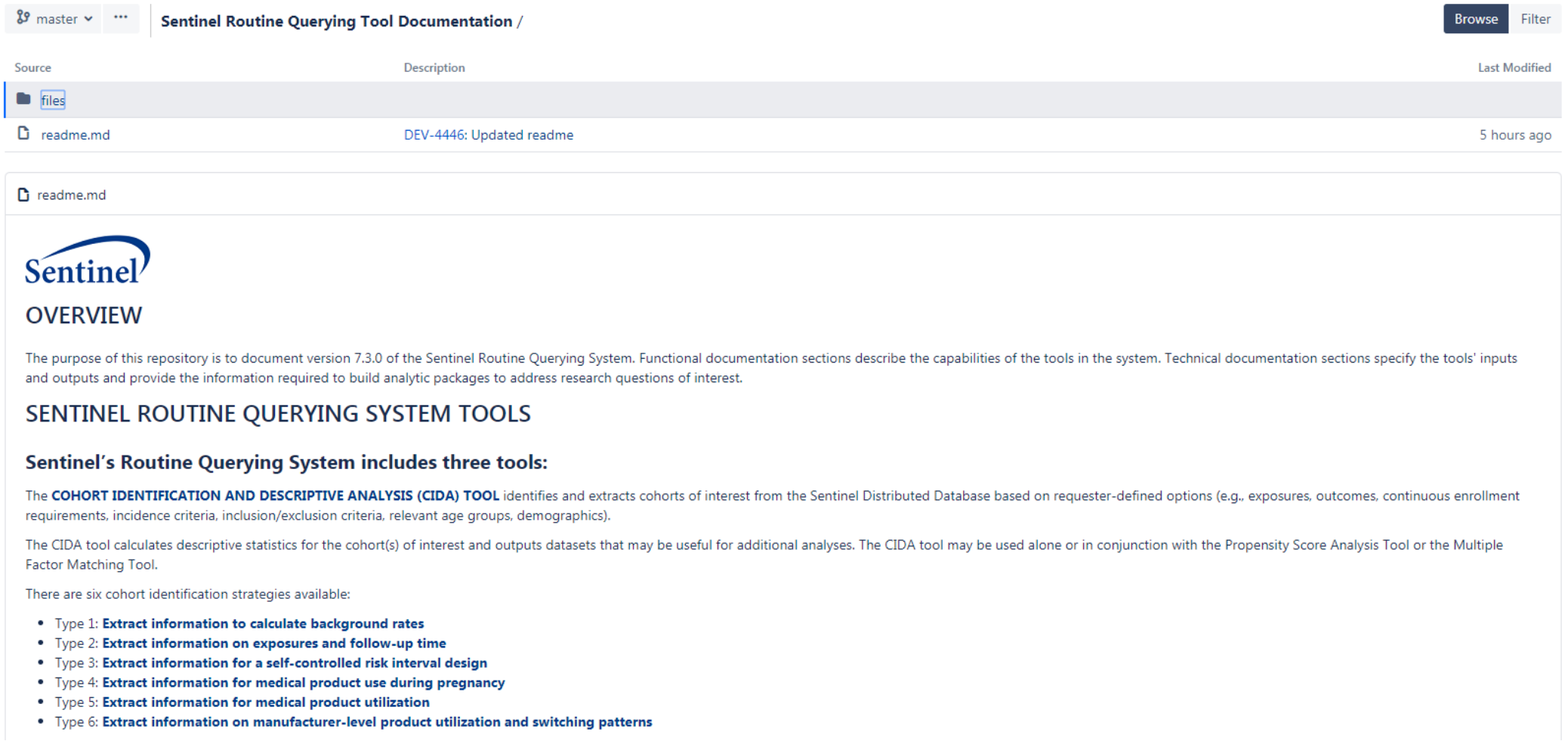
Questions?

info@sentinelsystem.org

Resources

Documentation on Git

- Sentinel is now using Git to post updated versions of CIDA and the accompanying documentation



master ··· **Sentinel Routine Querying Tool Documentation /** Browse Filter

Source	Description	Last Modified
files		
readme.md	DEV-4446: Updated readme	5 hours ago

readme.md

Sentinel

OVERVIEW

The purpose of this repository is to document version 7.3.0 of the Sentinel Routine Querying System. Functional documentation sections describe the capabilities of the tools in the system. Technical documentation sections specify the tools' inputs and outputs and provide the information required to build analytic packages to address research questions of interest.

SENTINEL ROUTINE QUERYING SYSTEM TOOLS

Sentinel's Routine Querying System includes three tools:

The **COHORT IDENTIFICATION AND DESCRIPTIVE ANALYSIS (CIDA) TOOL** identifies and extracts cohorts of interest from the Sentinel Distributed Database based on requester-defined options (e.g., exposures, outcomes, continuous enrollment requirements, incidence criteria, inclusion/exclusion criteria, relevant age groups, demographics).

The CIDA tool calculates descriptive statistics for the cohort(s) of interest and outputs datasets that may be useful for additional analyses. The CIDA tool may be used alone or in conjunction with the Propensity Score Analysis Tool or the Multiple Factor Matching Tool.

There are six cohort identification strategies available:

- 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**

Functional Documentation by Type

COHORT IDENTIFICATION AND DESCRIPTIVE ANALYSIS (CIDA) TOOL

Calculate background rate (Type 1)	Exposures and follow-up time (Type 2)	Self-controlled risk interval (SCRI) design (Type 3)	Pregnancy episodes and identify medical product use (Type 4)	Medical product utilization (Type 5)	Manufacturer-level product utilization and switching patterns (Type 6)
Functional Documentation					
Background Rate Calculation Cohort Identification Strategy	Exposures and Follow-up time Cohort Identification Strategy	Self Controlled Risk Interval (SCRI) Design Cohort Identification Strategy	Pregnancy Episodes Cohort Identification Strategy	Medical Product Utilization Cohort Identification Strategy	Manufacturer-Level Product Utilization and Switching Patterns Cohort Identification Strategy
Cohort Definition Options	Cohort Definition Options	Cohort Definition Options	Cohort Definition Options	Cohort Definition Options	Cohort Definition Options
National Drug Code Processing and the Stockpiling Algorithm	Creation and Retention of First Valid Episodes	National Drug Code Processing and the Stockpiling Algorithm	National Drug Code Processing and the Stockpiling Algorithm	National Drug Code Processing and the Stockpiling Algorithm	National Drug Code Processing and the Stockpiling Algorithm
Defining Complex Algorithms	National Drug Code Processing and the Stockpiling Algorithm	Defining Complex Algorithms	Defining Complex Algorithms	Defining Complex Algorithms	Defining Complex Algorithms

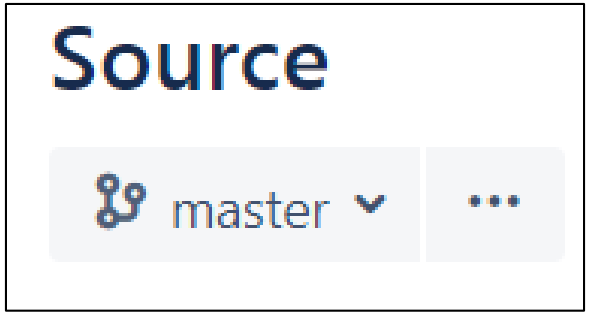
Technical Documentation by Type

COHORT IDENTIFICATION AND DESCRIPTIVE ANALYSIS (CIDA) TOOL

Calculate background rate (Type 1)	Exposures and follow-up time (Type 2)	Self-controlled risk interval (SCRI) design (Type 3)	Pregnancy episodes and identify medical product use (Type 4)	Medical product utilization (Type 5)	Manufacturer-level product utilization and switching patterns (Type 6)
Technical Documentation					
Program Package and Execution	Program Package and Execution	Program Package and Execution	Program Package and Execution	Program Package and Execution	Program Package and Execution
Main Program Parameters	Main Program Parameters	Main Program Parameters	Main Program Parameters	Main Program Parameters	Main Program Parameters
Lookup Tables	Lookup Tables	Lookup Tables	Lookup Tables	Lookup Tables	Lookup Tables
Input Files	Input Files	Input Files	Input Files	Input Files	Input Files
Output Files	Output Files	Output Files	Output Files	Output Files	Output Files

Downloading or Cloning CIDA

- Download:
  - Navigate to the qrp repository
  - Click the button with the three dots in the top left corner



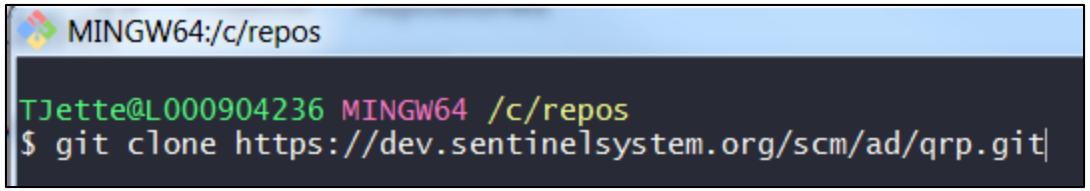
  - Choose the, “Download” option from the drop down menu

Downloading or Cloning CIDA

- Cloning:
  - Navigate to the qrp repository
  - Click the clone button under, “Actions” on the left hand menu bar

  - Copy the clone URL that is displayed

  - Open a Git terminal, type, “git clone” and paste the copied URL after the word clone



Note: You may alternatively copy the clone URL from this presentation → https://dev.sentinelsystem.org/scm/ad/qrp.git

Query Period

- Period in which CIDA looks for exposures and events of interest
- Query Start Date
  - Defines when CIDA will start evaluating presence of index-defining codes
  - Pre-index criteria, such as baseline characteristics and washout assessments, can occur prior to the query start date
- Query End Date
  - Defines when CIDA will stop evaluating presence of index-defining codes
  - Option to either end follow-up here, or continue assessing for health outcomes of interest beyond query end date

Enrollment

- Coverage type
  - At least medical; At least drug; Both medical and drug coverage
- Enrollment gap
  - Number of days that will be bridged between two consecutive enrollment periods to create a “continuously enrolled” period
  - 45 days is typical recommendation
- Length of enrollment prior to index
  - Number of days of continuous enrollment required before the index date

Demographics

- CIDA allows users to limit cohorts of interest to certain categories of:
  - Age
  - Sex
  - Race
  - Ethnicity
- All demographic limitations are based on Sentinel Common Data Model approved values

Inclusion and Exclusion Criteria

- Characteristics used to define additional cohort inclusion/exclusion criteria

- Evaluation Period Start/End
  - Number of days relative to index where a patient is required to have evidence of (for inclusions) or no evidence of (for exclusions) a condition
  - Enrollment is enforced for exclusion evaluation periods

- Code days
  - Required number of days a code must be found to meet inclusion or exclusion criteria

Index Definition

- Cohort-defining event (either a procedure, diagnosis, or dispensing) or combination of those

- All other parameters are defined relative to index
  - Enrollment
  - Exposure washout period
  - Inclusion and exclusion evaluation period
  - Covariate assessment window
  - Outcome washout period

How Many Valid Index Dates?

- Cohort re-entry is a key consideration.
  - **No cohort re-entry**
    - First valid exposure episodes during query period (Cohort Definition 01)
  - **Cohort re-entry**
    - All valid exposure episodes during query period (Cohort Definition 02)
  - **Cohort re-entry until event of interest occurs**
    - All valid exposure episodes during query period until outcome of interest occurs (Cohort Definition 03)
- Cohort identification that will later support Propensity Score adjusted inferential analyses should be set to “No cohort re-entry.”

Index Incidence Criteria

- "Incident with respect to"
  - Exposures or events for which patients must have no evidence during a specified time period, to be considered 'new'
- Washout Period
  - Number of days a patient is evaluated for incidence criteria
  - Continuous enrollment is required during the washout period
  - A prevalent cohort has a 0-day washout period

Exposure Episodes

- Exposed time can be either
  - pre-defined (intent to treat analysis)
  - assessed using dispensings' days supply (as-treated analysis)

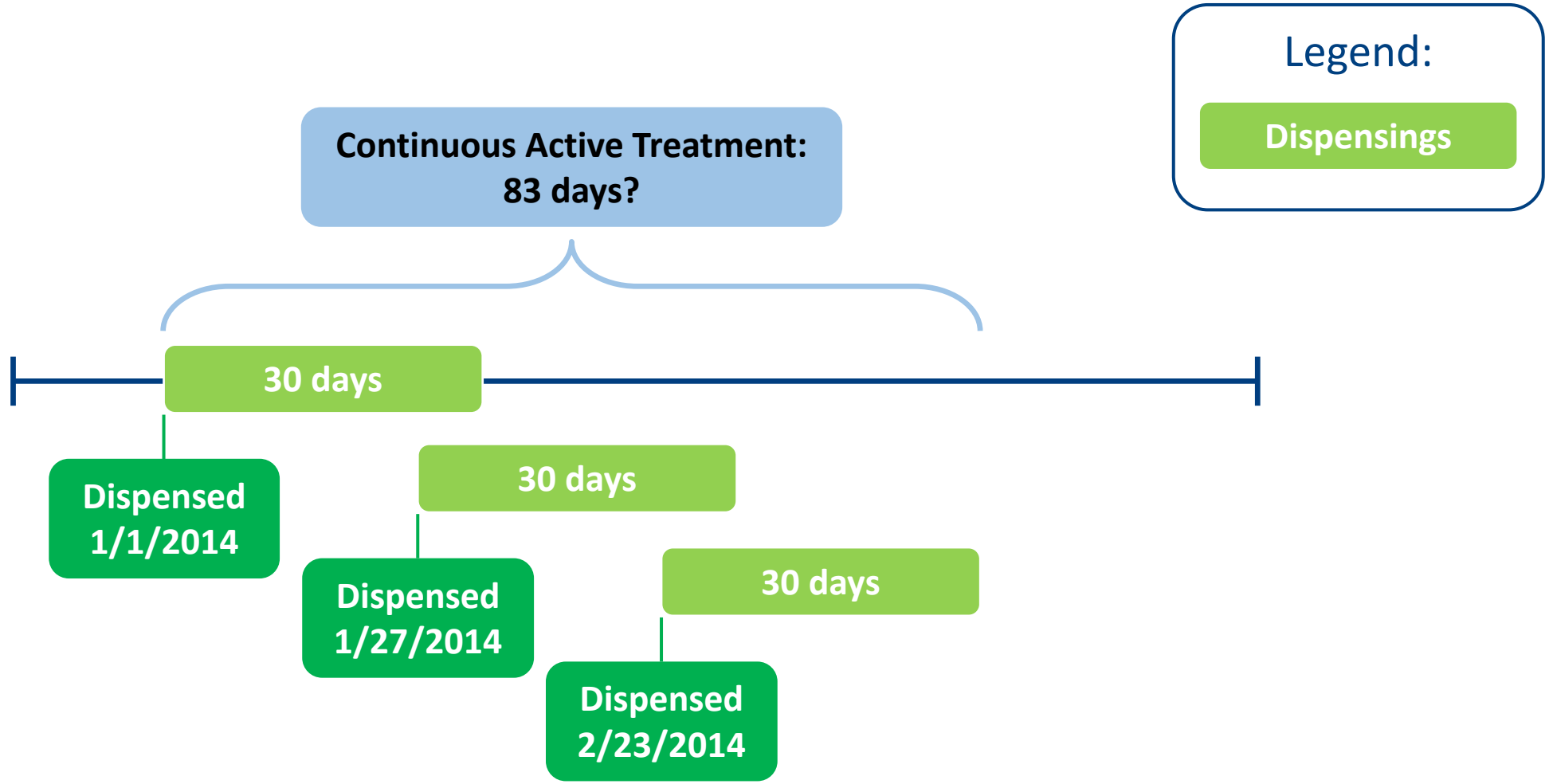
- An outcome needs to occur within an exposed time window (episode) to be captured

Exposure Episodes: Stockpiling

- Some patients may refill their prescription before the end of the days supply of their previous prescription
  - Creates an overlap in days supply
  - The stockpiling algorithm evaluates outpatient pharmacy dispensing dates and adjusts them to reflect active treatment days

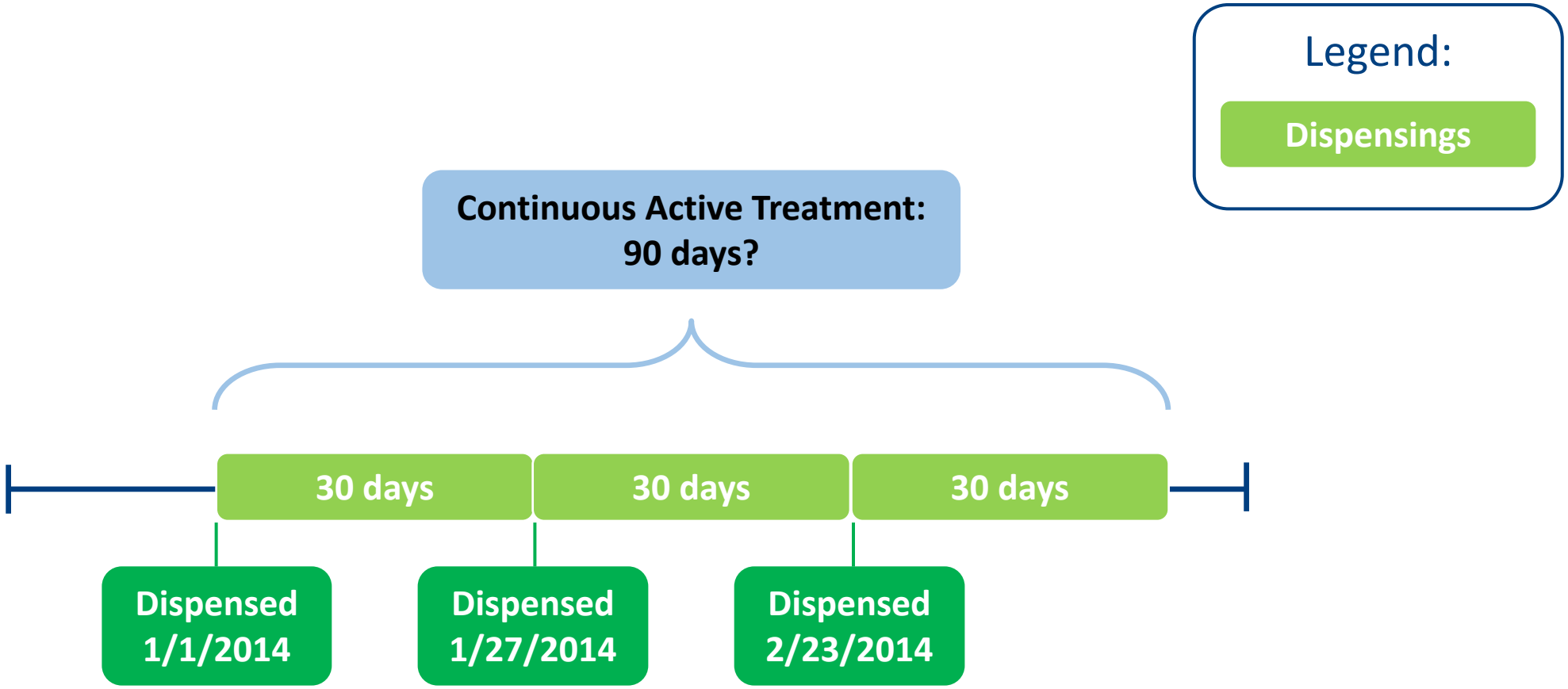
Exposure Episodes: Stockpiling

- Example: Patients may refill prescriptions before exhausting previous dispensing's days supply



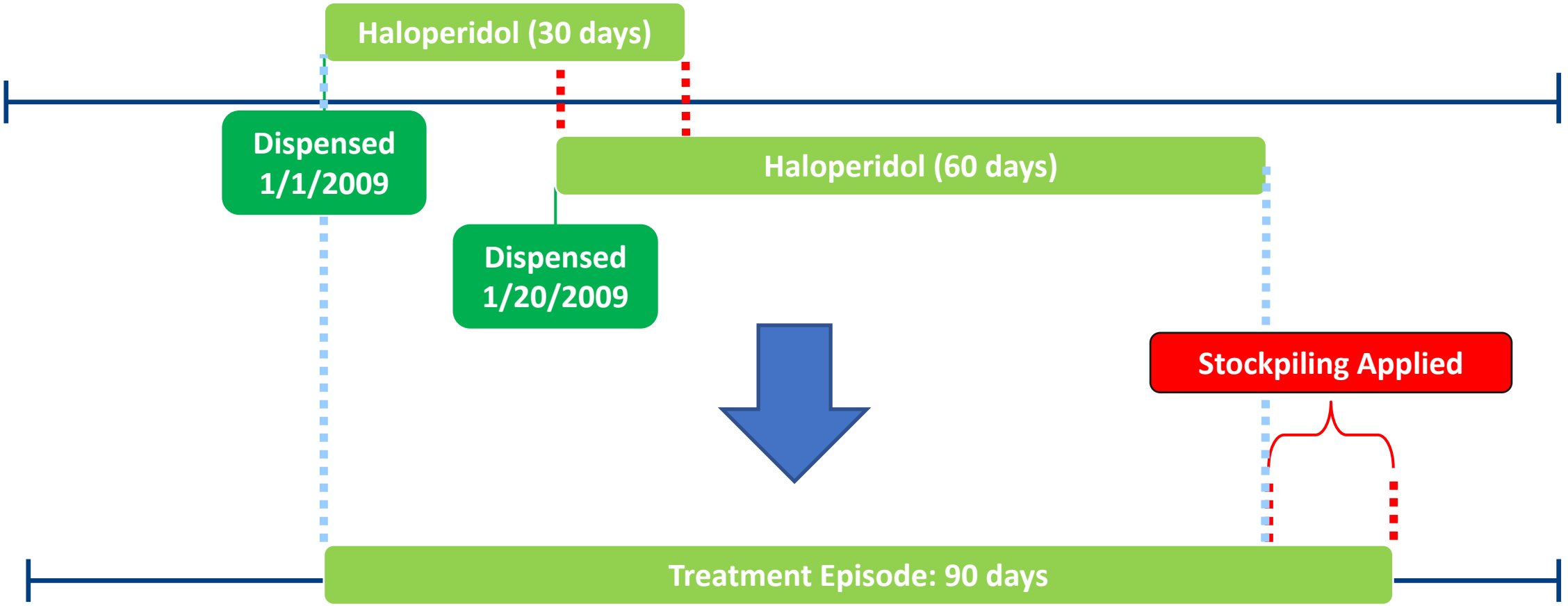
Exposure Episodes: Stockpiling

- Example: Apply stockpiling algorithm to adjust dispensing dates



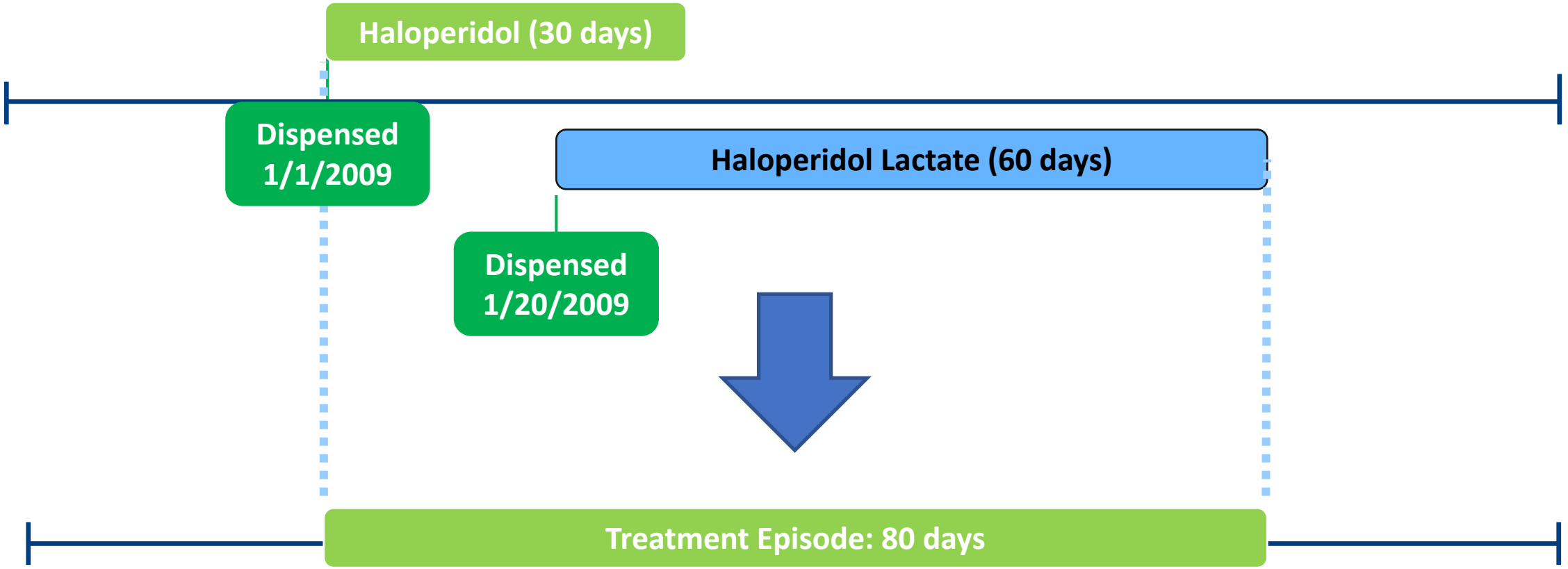
Exposure Episodes: Stockpiling

- Default stockpiling for two overlapping dispensings with the same generic name



Exposure Episodes: Stockpiling

- Stockpiling algorithm doesn't account for overlapping dispensings with different generic names
- Scenario:



Exposure Episodes

- Overlapping and abutting claims are automatically bridged
  - ("as treated" in CIDA lingo)

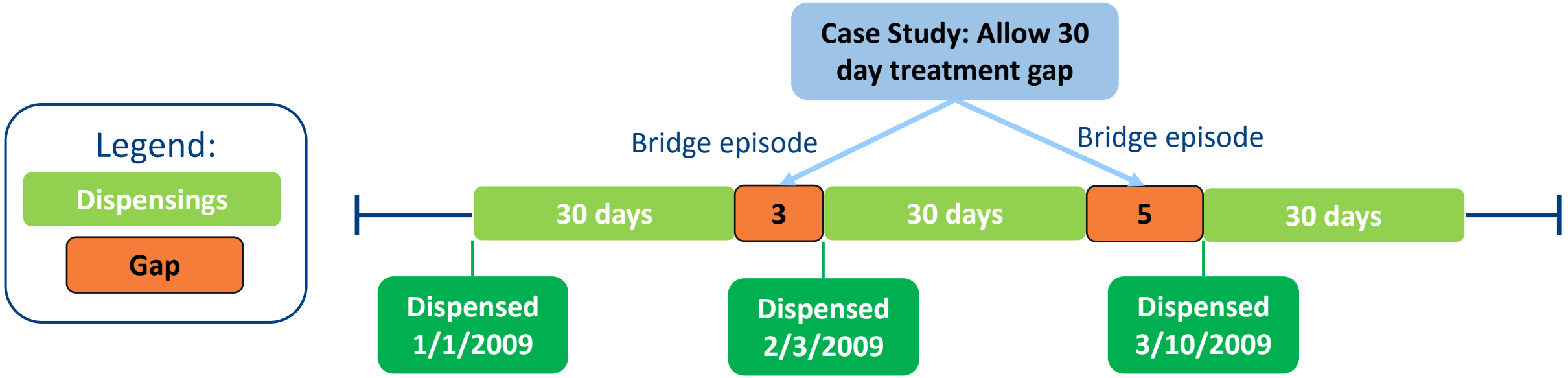
- **Episode gap:** allows a requester-defined allowed number of days between two consecutive claims to consider them as part of the same treatment episode

- **Exposure extension:** after creating episodes, **exposure extension parameter** is applied

Treatment Episode Gap: Requester Defined

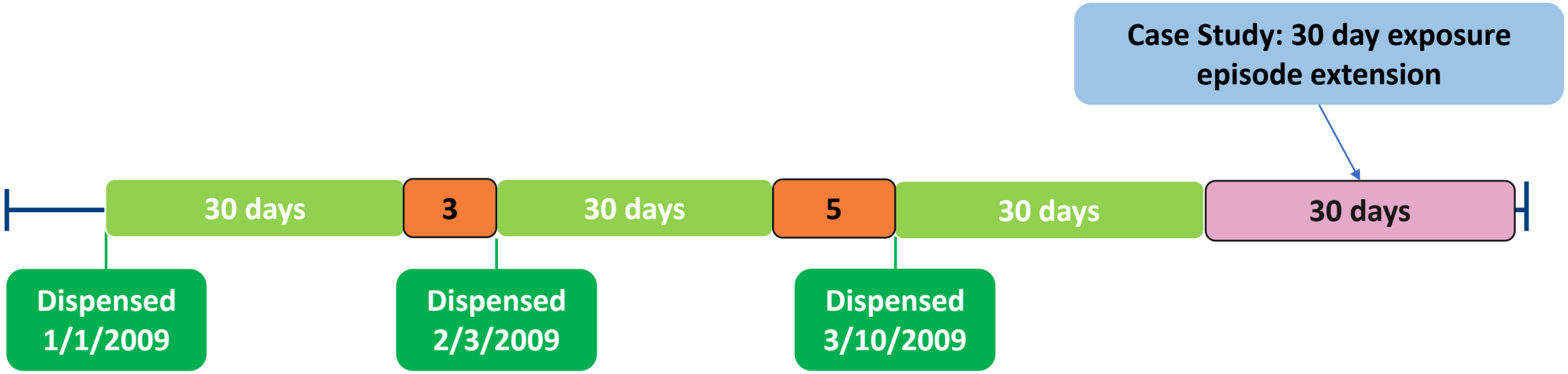
- Number of allowable days between two (or more) consecutive exposure claims (dispensings/procedures) to be considered the same treatment episode

- Two options:
  - ***Fixed number of days:*** typical scenario
  - ***Percentage episode gap:*** % of the previous dispensing's days supplied

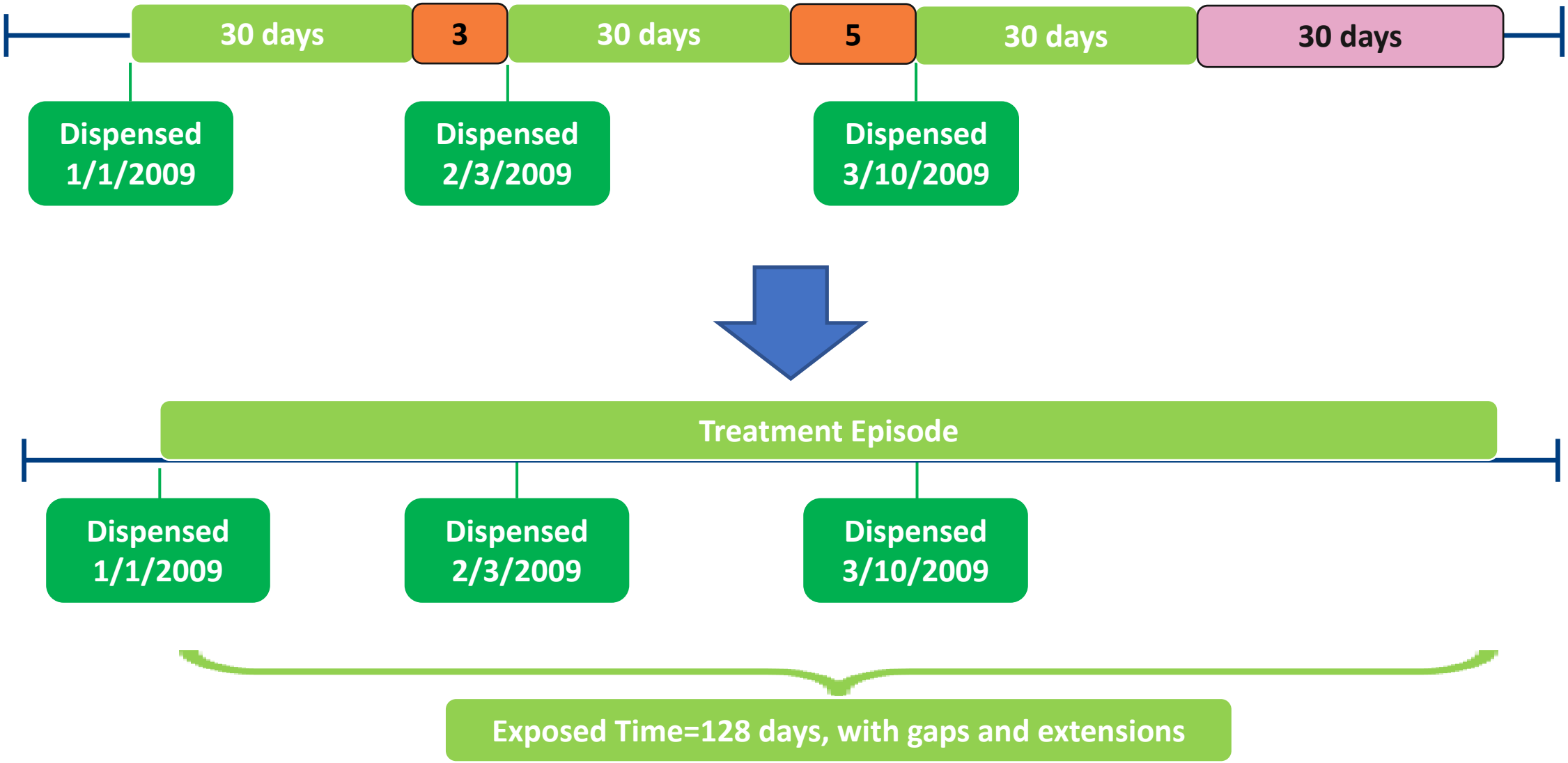


Exposure Episode Extension: Requester Defined

- Number of days to extend the length of an exposure episode
- Exposure episode can be extended after the last day of supply of the treatment episode's last dispensing
- Extension days are added after any episode gaps have been bridged



Full Treatment Episode



Maximum Exposure Episode Duration: Requester Defined

- Truncates episodes after a requester-specified number of exposed days

- Applied after any gaps are bridged and extension days added to the length of the exposure episode

If maximum episode duration of 120 days is applied, episode would be truncated at 120 days

Three Elements to Define Outcome Events

- Event Identification – any combination of code(s) and care-setting(s)
  - Must be during the “at-risk” follow-up period
- Event Incidence or Washout Period - number of days before index that a user is required to have no evidence of the event
  - Requires enrollment
  - Can require no evidence of related events
- Blackout (Induction) Period – number of days after index before the “at risk” follow-up period begins (e.g., follow-up begins on Day 1 not Day 0)
  - Outcomes that occur in this period are not counted and those episodes are excluded

Covariates

- Covariates can be identified using any combination of NDCs (dispensings), diagnosis codes, or procedure codes
  - Can specify care-setting, number of occurrences
  - Can use complex Boolean logic (AND, OR)
- Evaluation windows must be selected for each covariate
  - Evaluation windows don't have to be the same for every covariate
  - The evaluation windows are relative to day 0 (index date)
  - Evaluation windows can be open-ended (anytime in the patient's enrollment history before or after the index date)
- One set of covariates are used for all scenarios

Covariates

- Caresettings must be selected for each covariate and they can vary across covariates or individual codes
- The user can specify a minimum number of occurrences of a code used to define a condition; these codes must occur on different days
- Covariates can be used in combination (covariate 1 and covariate 2, covariate 1 and not covariate 2 or covariate 3)

Propensity Score Parameters: Overview

- Specify covariates for inclusion in the propensity score estimation model
  - Age, sex, year of exposure initiation
  - Any clinical concept that can be defined using a list of codes available in the distributed database
  - Healthcare utilization metrics (number of inpatient, outpatient, emergency dept. encounters)
  - Drug utilization metrics (number of dispensings, unique generics dispensed)
- Define the matching ratio
  - Fixed 1:1 matching or variable 1:*n* (*n*≤10) matching
- Define caliper as any value between 0 and 1
  - Maximum distance allowed between two matched patients' PS
  - Natural scale of PS (e.g., 0.01, 0.05)

Questions?

info@sentinelsystem.org