Overview of Sentinel Tool Capabilities, Mother-Infant Linkage and Pregnancy Analyses

Sentinel Public Training

Sentinel Operations Center | Harvard Pilgrim Health Care Institute

11/02/2020

Agenda

01 Introduction to Sentinel System and Overview of Analytic Capabilities

Noelle M. Cocoros, DSc, MPH

02 Creation of a Linked Mother-Infant Cohort and Descriptive Pregnancy Analyses

Elizabeth Suarez, PhD

03 Inferential Analyses for Perinatal Exposures

Mayura Shinde, DrPH

Pre-Training Survey

Introduction to the Sentinel System

Noelle M. Cocoros, DSc, MPH

The Sentinel Initiative and Real World Data

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

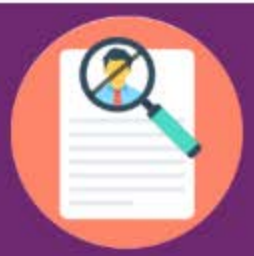
FDA is looking into how real world data like that in Sentinel might help FDA answer these important questions. Much of this real world data comes from health insurance companies and patients themselves.

How does Sentinel work?

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

What kinds of questions?

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



What about privacy?

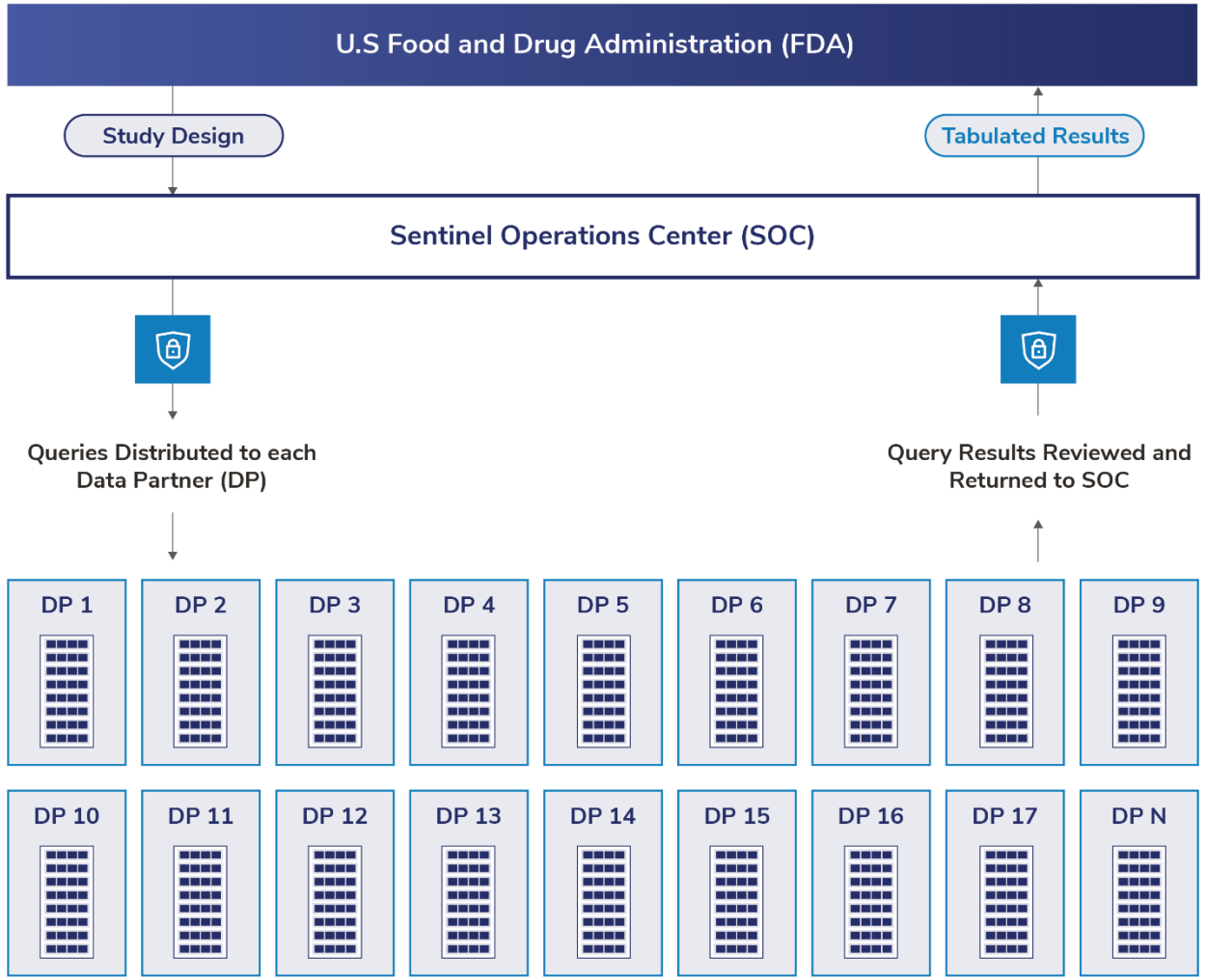
- No one looks at your name, address, phone number, or other information that identifies you.
- For more information please visit sentinelinitiative.org and fda.gov/safety/fdassentinelinitiative/ucm2007250.htm

What happens next?

- FDA may use information from Sentinel to help determine whether medical products are safe and working.
- FDA warns patients and their doctors about bad side effects.
- If you have concerns about your medical products, please contact your doctor.

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

Sentinel is a Distributed Data Network



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

Collaborating Organizations

Lead: Harvard Pilgrim Health Care Institute

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

Data & Scientific Partners

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

Sentinel Data Philosophy

- Predominantly includes claims and a subset of electronic health record (EHR) and registry data
  - 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

Sentinel Data Philosophy

- 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

Sentinel Common Data Model

Administrative Data

Enrollment	Demographics	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 & Provider	Encounter Type & Provider	Encounter Type & Provider
Medical Record Availability	Etc.	Amount Dispensed	Facility	Diagnosis Code & Type	Procedure Code & Type
			Etc.	Principal Discharge Diagnosis	Etc.

Clinical 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/methods-data-tools/sentinel-common-data-model

Single Patient Example Data in Model

DEMOGRAPHIC

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

ENROLLMENT

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

DISPENSING

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

ENCOUNTER

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

DIAGNOSIS

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

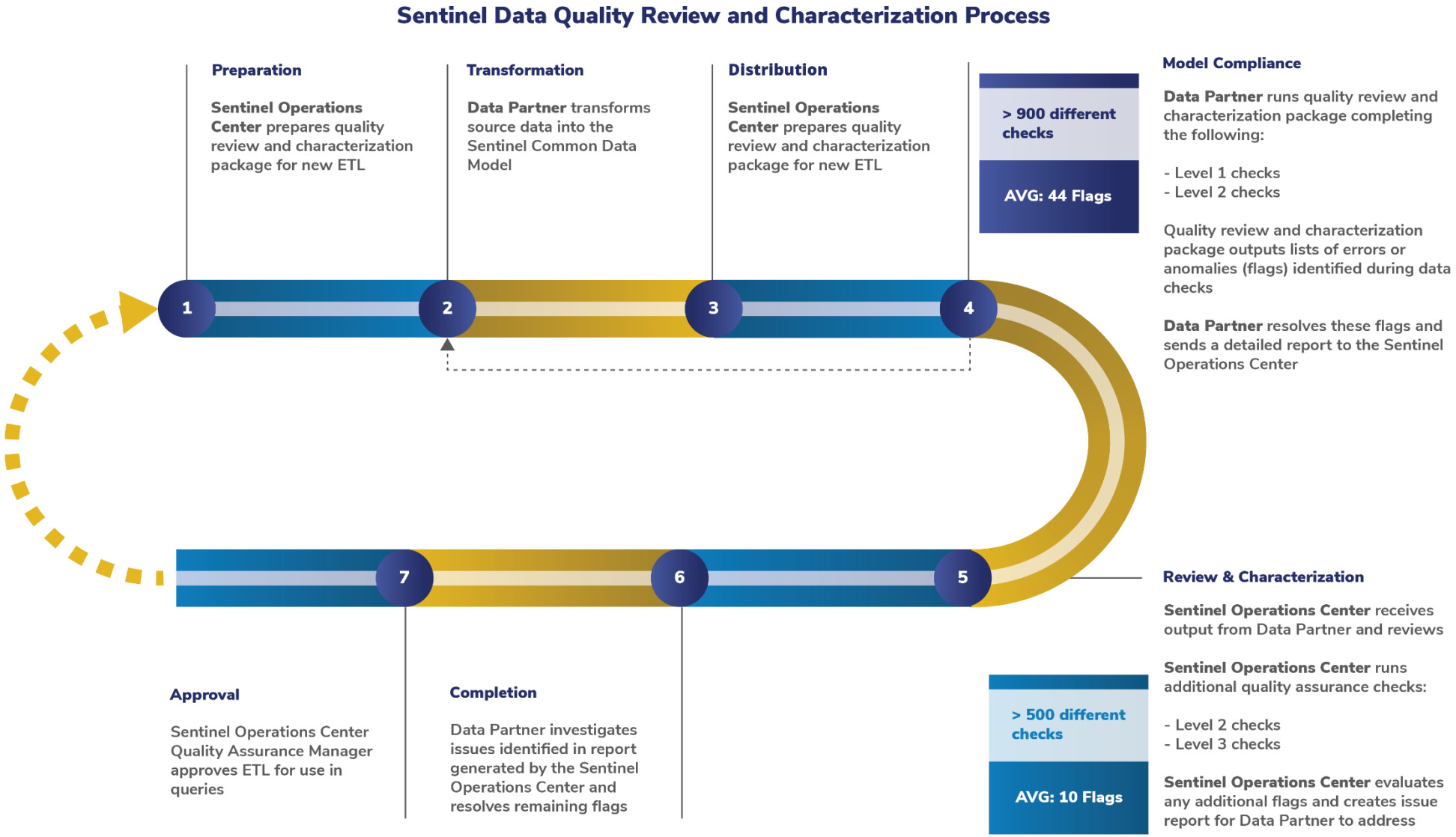
PROCEDURE

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

MOTHER-INFANT LINKAGE

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

Data Quality Review and Characterization Process



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

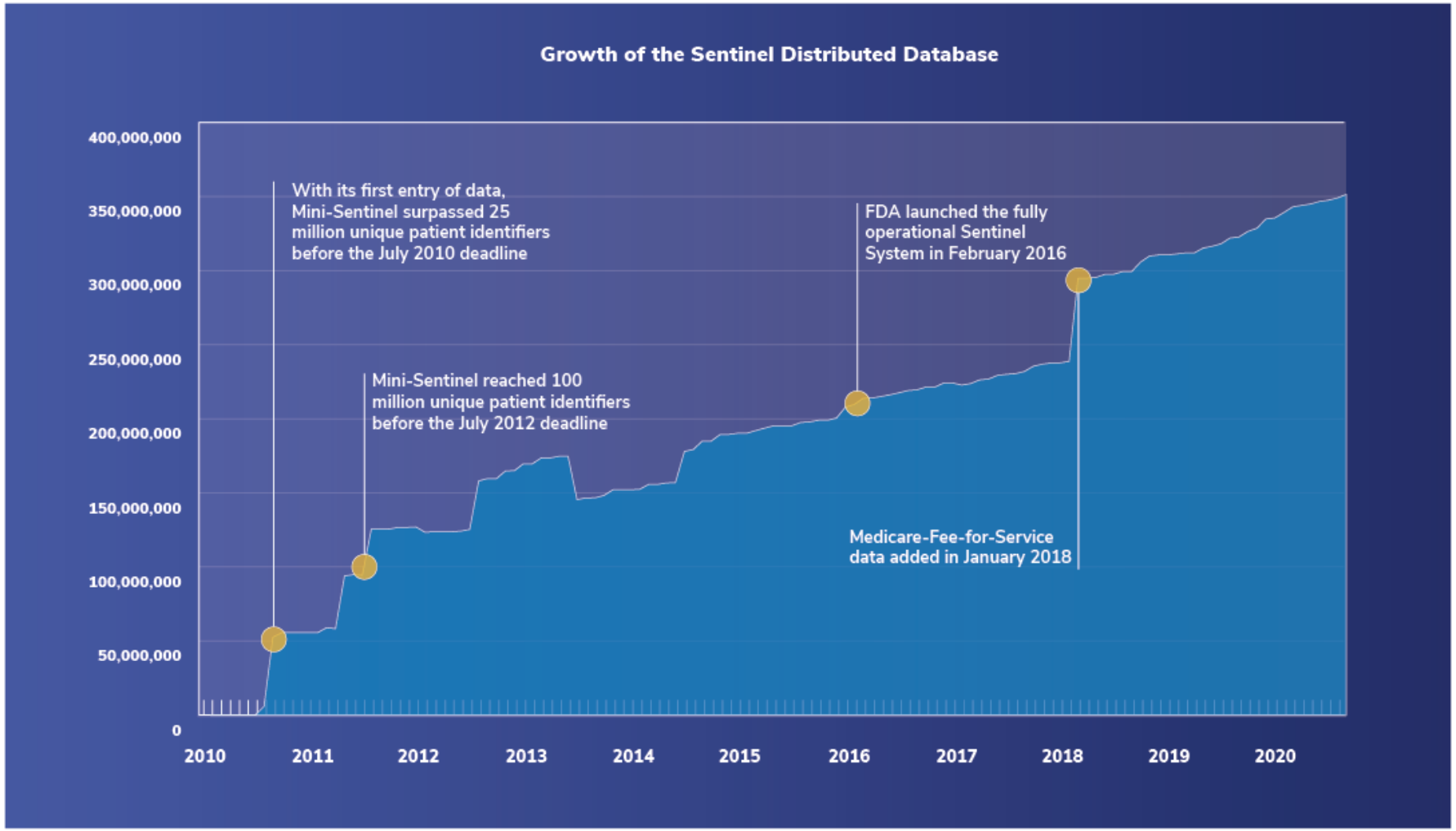
Data Quality Checks and Examples

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

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

Growth of the Sentinel Distributed Database

- A total of 351 unique patient identifiers and 71 million members currently accruing new data



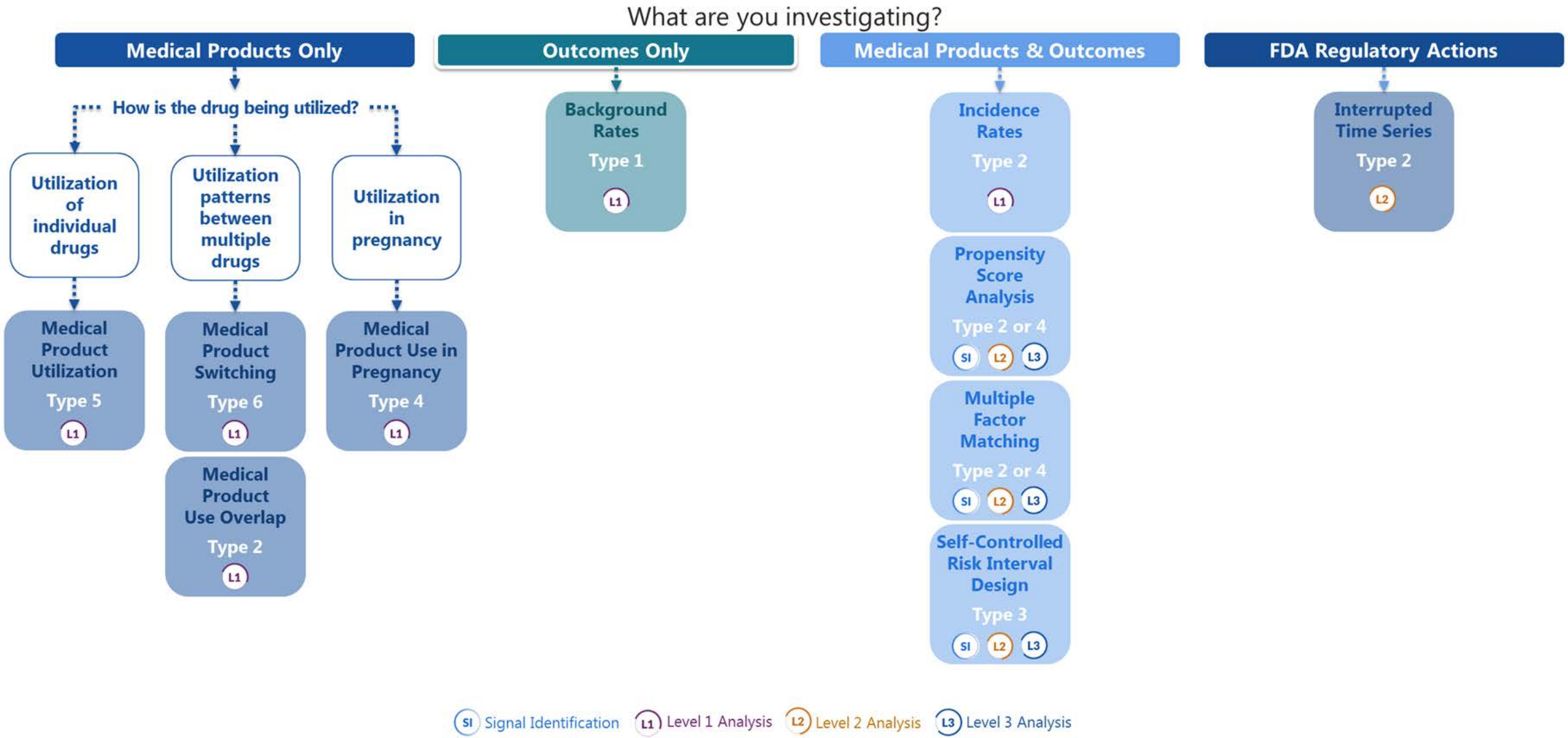
https://www.sentinelinitiative.org/about/key-database-statistics

Overview of Routine Tools Analytic Capabilities

Active Risk Identification and Analysis (ARIA)

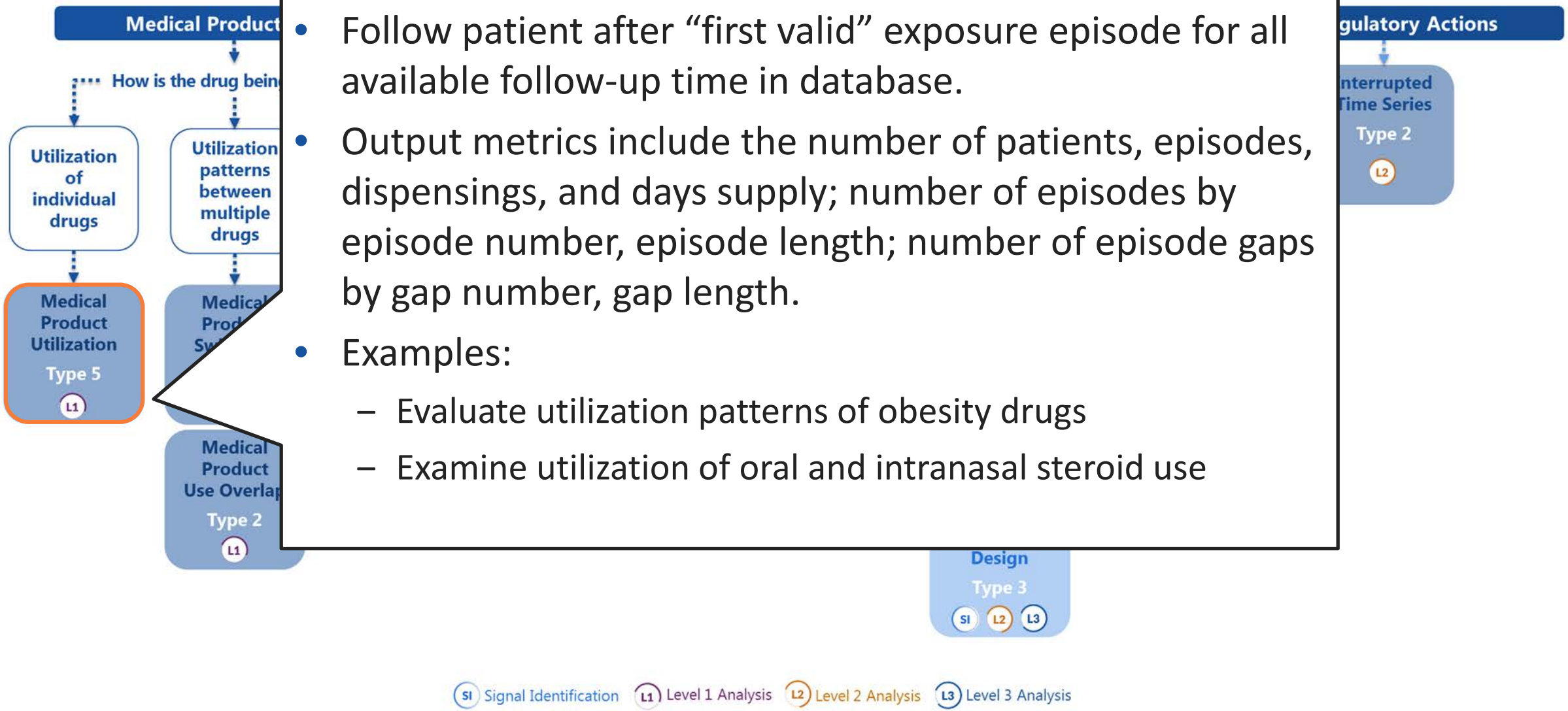
- Template computer programs with standardized questions
- Parameterized at program execution
- Pre-tested and quality-checked
- Standard output

https://www.sentinelinitiative.org/assessments/aria-overview



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

Medical Product Utilization (Type 5)



- Follow patient after "first valid" exposure episode for all available follow-up time in database.
- Output metrics include the number of patients, episodes, dispensings, and days supply; number of episodes by episode number, episode length; number of episode gaps by gap number, gap length.
- Examples:
  - Evaluate utilization patterns of obesity drugs
  - Examine utilization of oral and intranasal steroid use

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

Sinus Stents with Mometasone and Diminished Visual Acuity

Table 1. Descriptive Statistics for Cumulative Length of Treatment Episodes for Oral and Intranasal Steroids in the Sentinel Distributed Database (SDD) between August 1, 2011 and May 31, 2017

		Cumulative Episode Length (Days)				
	Number of Days	Q1	Median	Q3	Mean	Standard Deviation
Oral Steroids						
Episode 1	40,899	7	14	27	27.77	566.13
Episodes 1-2	20,003	17	25	44	46.14	536.70
Episodes 1-3	11,018	25	38	65	66.93	515.22
Episodes 1-4	6,602	35	52	86	88.41	447.26
Episodes 1-5	4,259	45	66	110	111.40	457.77
Episodes 1-6	2,934	56	80	135	134.51	438.79
Intranasal Steroids						
Episode 1	52,763	30	60	144	123.36	1159.80
Episodes 1-2	29,074	60	120	240	192.56	1021.33
Episodes 1-3	18,978	120	180	303	251.71	910.99
Episodes 1-4	13,362	150	225	379	304.29	817.15
Episodes 1-5	9,821	180	270	438	352.61	742.84
Episodes 1-6	7,473	218	319	480	395.14	679.62

sinus surgery and subsequent development of diminished visual acuity, glaucoma, cataracts, or blindness. This request

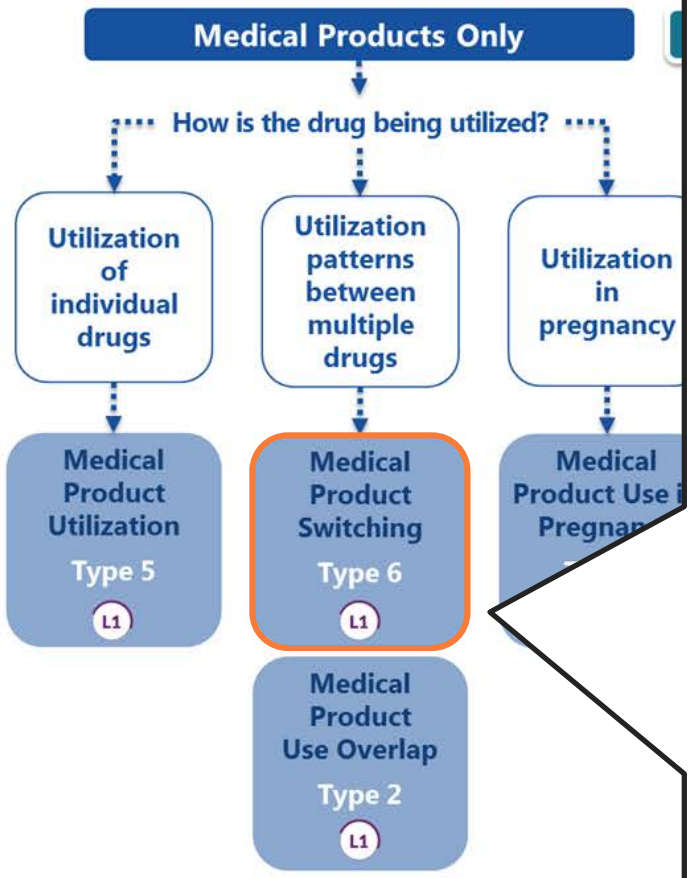
https://www.sentinelinitiative.org/assessments/drugs/sinus-stents-mometasone-and-diminished-visual-acuity

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➔C, A➔B➔A), utilization metrics
- Examples
  - Examine switching patterns for patients receiving sacubitril/valsartan, ACE inhibitors or ARBs



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

Sacubitril/Valsartan, Angiotensin-Converting Enzyme (ACE) Inhibitors, and

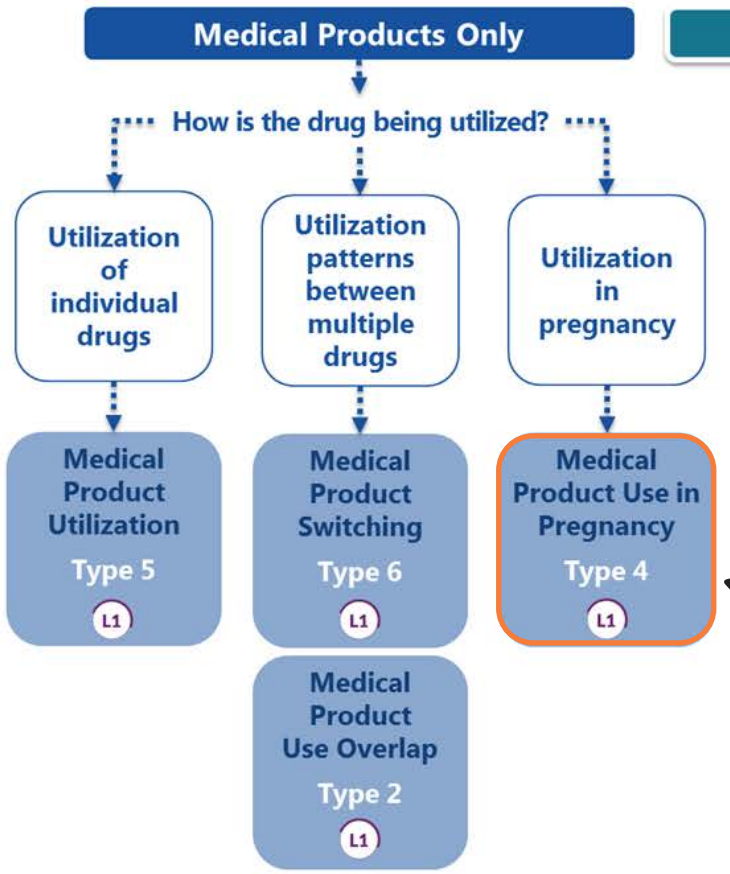
Table 5a. Descriptive Statistics of Time to First Switch for New Users of Angiotensin-Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARBs), and Sacubitril/Valsartan in the Sentinel Distributed Database (SDD) between January 1, 2015 to July 31, 2019

						Percentile (days)									
Switch	Switch Pattern	Switch Episodes	Mean (days)	Standard Deviation (days)	Minimum (days)	1st	5th	10th	25th	50th	75th	90th	95th	99th	Maximum (days)
ACE Inhibitors to Sacubitril/Valsartan	ACE Inhibitors to Sacubitril/Valsartan to ACE Inhibitors	6,628	207.43	243.61	1	4	11	19	40	106	285	558	742	1,090	1527
ACE Inhibitors to Sacubitril/Valsartan	ACE Inhibitors to Sacubitril/Valsartan to ARBs	6,628	207.43	243.61	1	4	11	19	40	106	285	558	742	1,090	1527
ARBs to Sacubitril/Valsartan	ARBs to Sacubitril/Valsartan to ARBs	3,363	194.59	233.52	1	3	10	18	40	100	264	516	713	1,095	1517
ARBs to Sacubitril/Valsartan	ARBs to Sacubitril/Valsartan to ACE Inhibitors	3,363	194.59	233.52	1	3	10	18	40	100	264	516	713	1,095	1517

	Settings
Description	In this analysis we examined counts of new users of sacubitril/valsartan, angiotensin-converting enzyme (ACE)

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

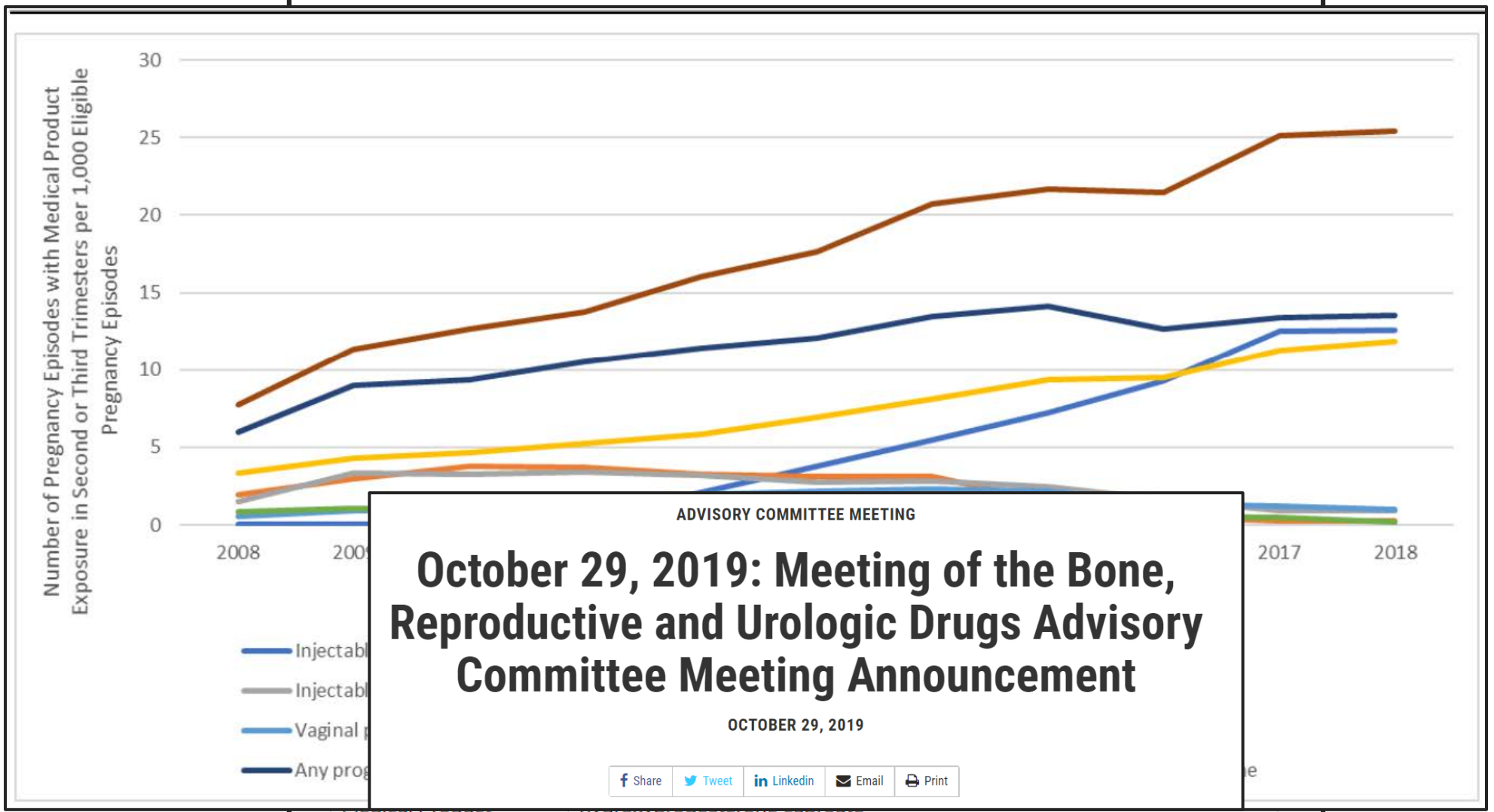
Construct Pregnancy Episodes and Identify Medical Product Use (Type 4)



- 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 hydroxyprogesterone caproate and progesterone among pregnant women

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

Hydroxyprogesterone Caproate and Progesterone Use During Pregnancy



ADVISORY COMMITTEE MEETING

October 29, 2019: Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee Meeting Announcement

OCTOBER 29, 2019

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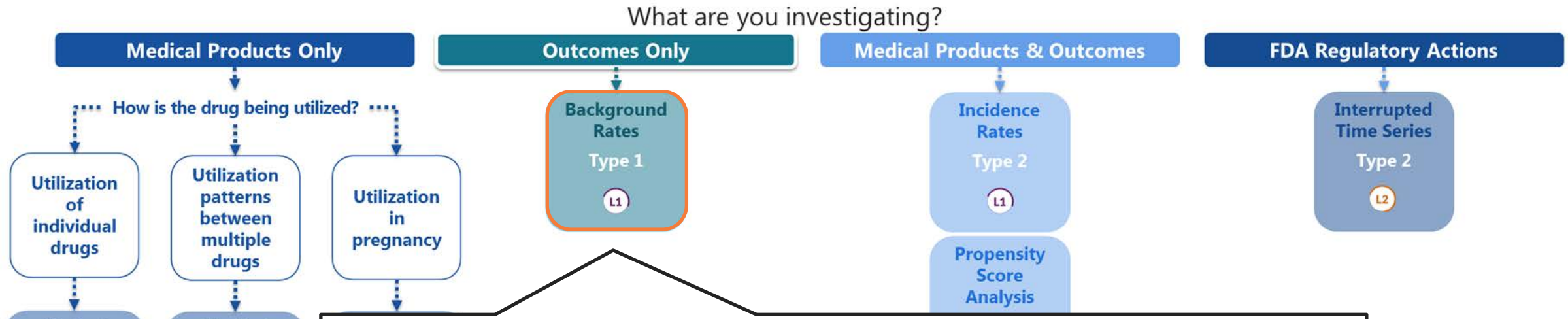
progesterone

https://www.sentinelinitiative.org/assessments/drugs/hydroxyprogesterone-caproate-and-progesterone-use-during-pregnancy
https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-29-2019-meeting-bone-reproductive-and-urologic-drugs-advisory-committee-meeting-announcement



Calculate Background Rates (Type 1)

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

Hypertension in Pediatric Patients: A Descriptive Analysis

Project Title	**Hypertension in Pediatric Patients: A Descriptive Analysis**
Date Posted	Thursday, July 23, 2020
Project ID	cder_mpl1r_wp149

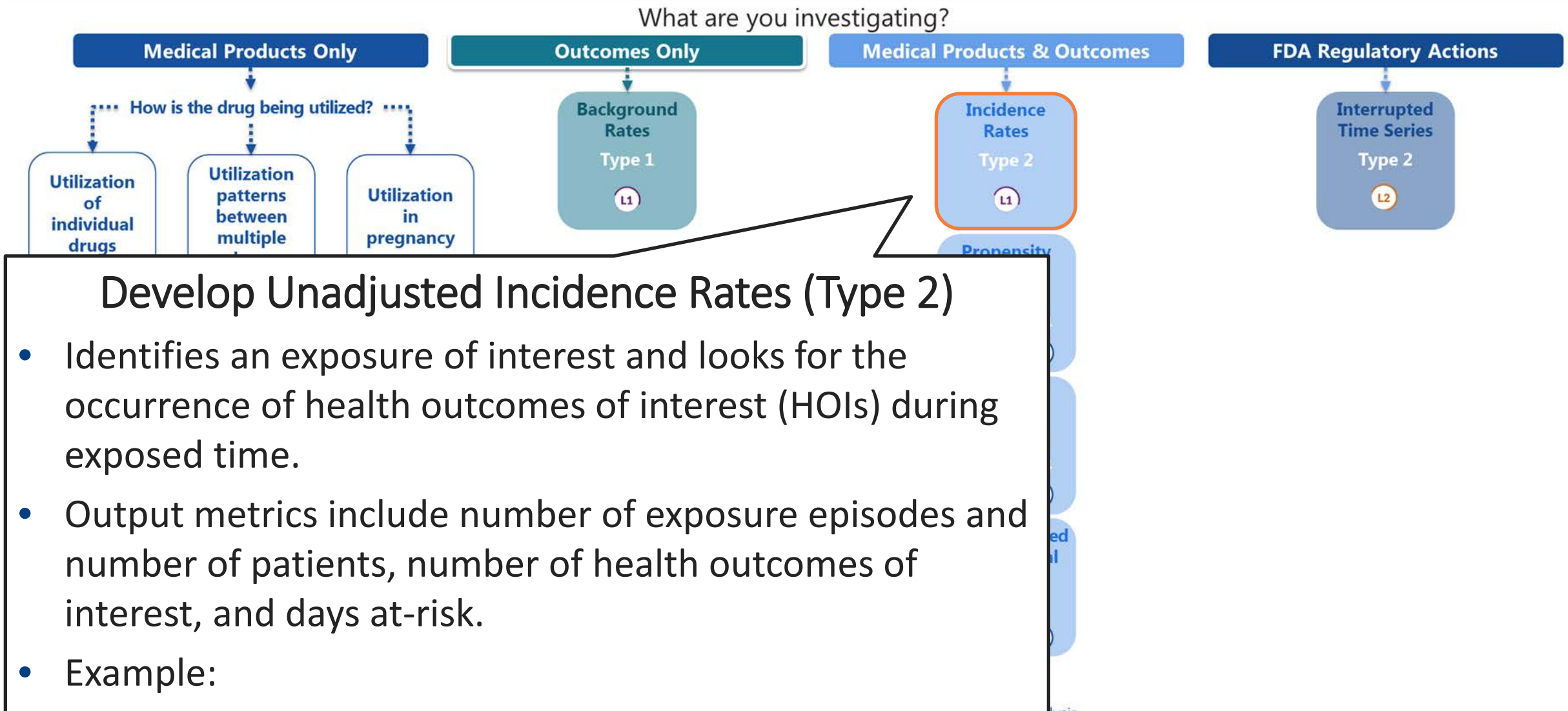
Table 2a. Summary of Members with Pediatric Hypertension in the Sentinel Distributed Database (SDD) between January 1, 2008 and April 30, 2019, by Hypertension Definition[1]

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

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

Population/ Cohort	Individuals 17 years of age and younger
Time Period	January 1, 2008 - April 30, 2019
Assessment Type	Exploratory Analyses
Study Type	Modular Program
Data Sources	Sentinel Distributed Database (SDD)
FDA Center	CDER

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:
  - Mometasone nasal stent implants and Incidence of ocular events

Glaucoma, Cataracts, Diminished Visual

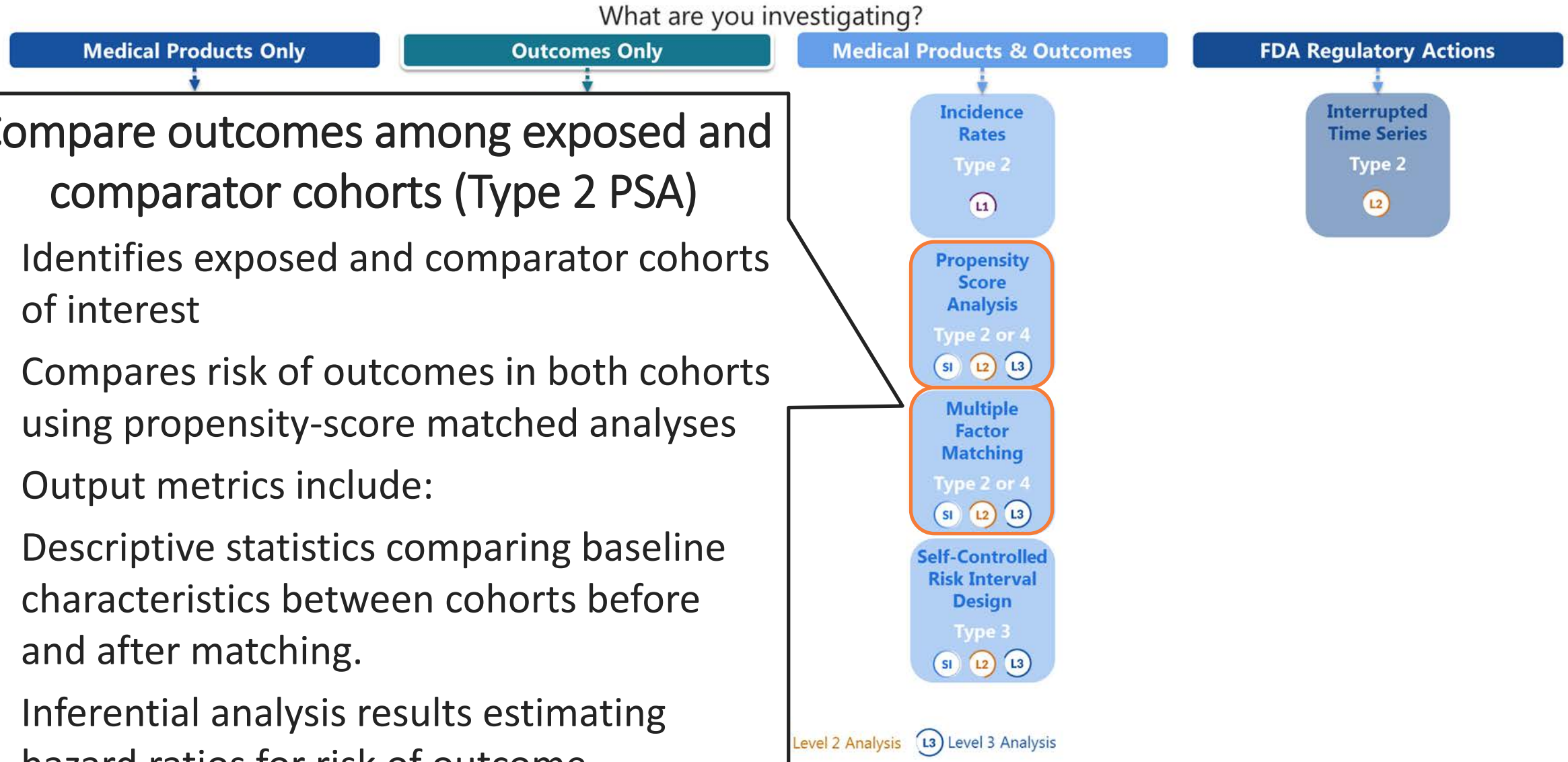
Table 2. Summary of Glaucoma and Cataract Events in Single and Repeat Mometasone Stent Implant Users in the Sentinel Distributed Database (SDD) between January 1, 2016 and September 30, 2019, Overall

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

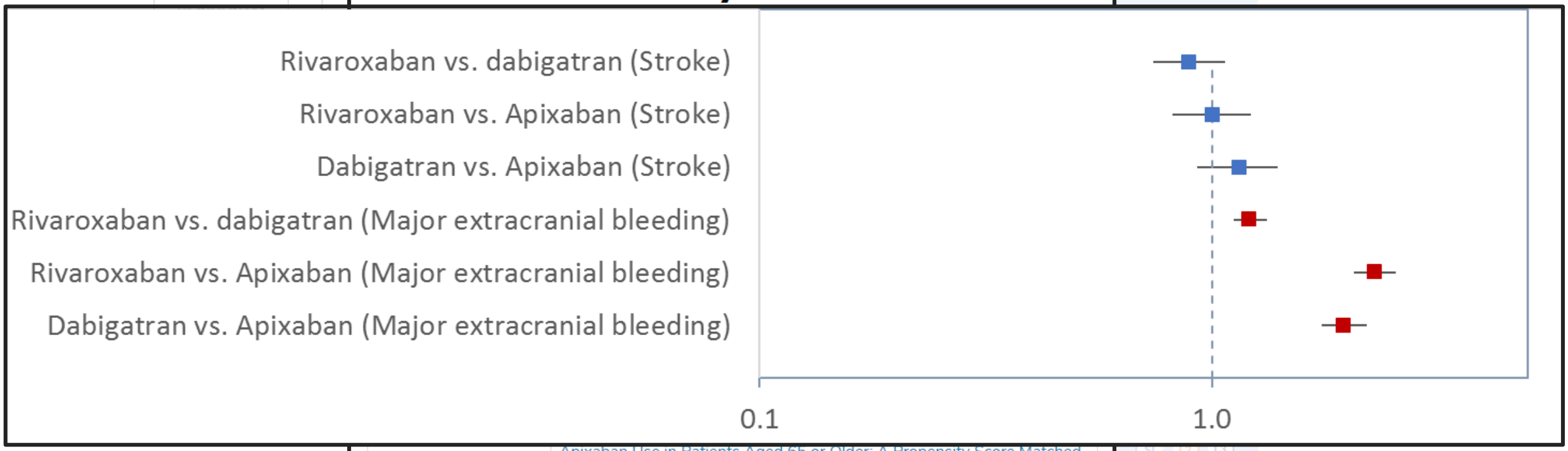
https://www.sentinelinitiative.org/assessments/drugs/adverse-ocular-events-nasal-septal-perforation-mometasone-sinus-implant

Compare outcomes among exposed and comparator cohorts (Type 2 PSA)

- Identifies exposed and comparator cohorts of interest
- Compares risk of outcomes in both cohorts using propensity-score matched analyses
- Output metrics include:
- Descriptive statistics comparing baseline characteristics between cohorts before and after matching.
- Inferential analysis results estimating hazard ratios for risk of outcome



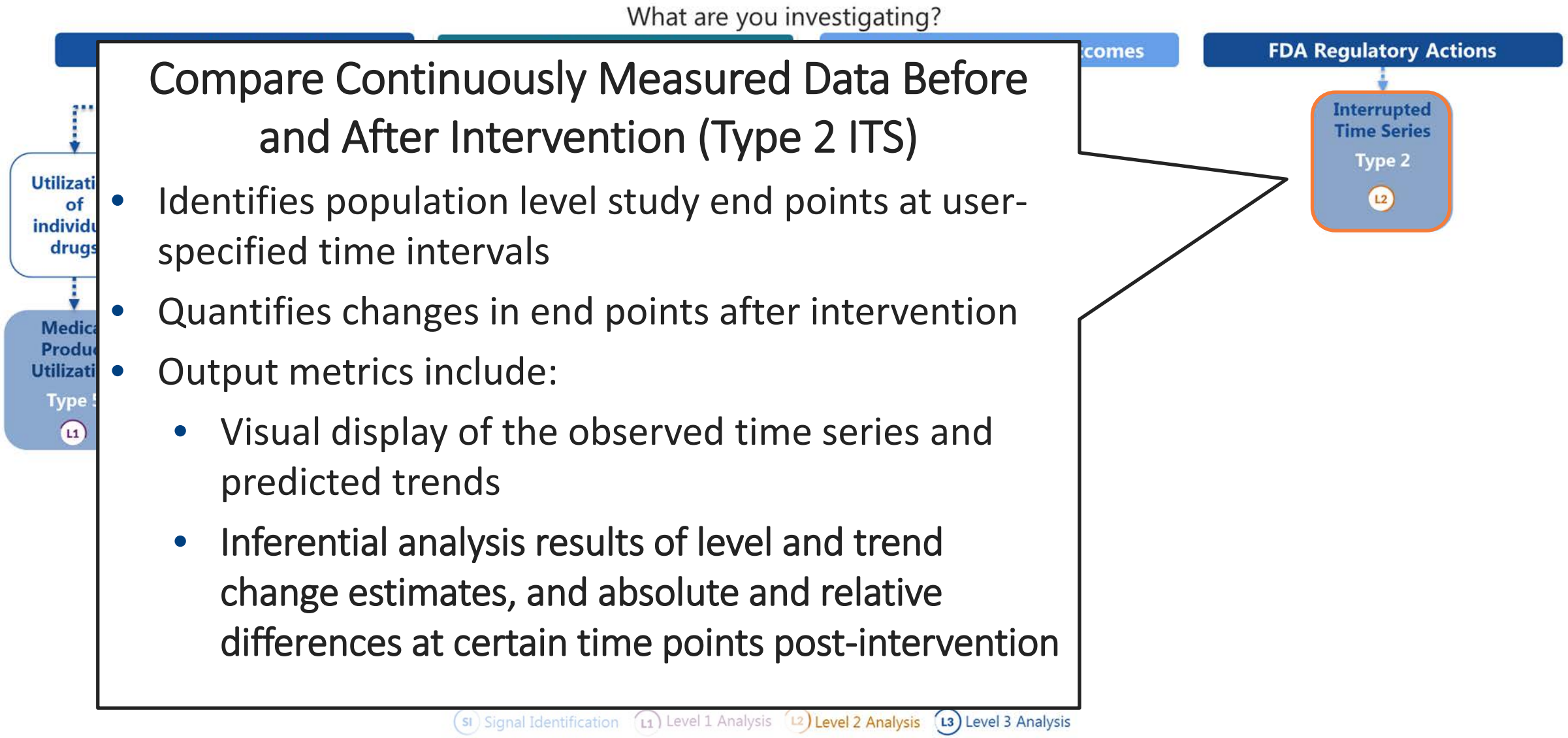
Stroke, Intracranial Hemorrhage, and Bleeding following Dabigatran, Rivaroxaban, and Apixaban Use in Patients Aged 65 or Older: A Propensity Score Matched Analysis



Apixaban Use in Patients Aged 65 or Older: A Propensity Score Matched Analysis"

Thromboembolic Stroke Algorithm Defined in "Stroke, Intracranial Hemorrhage, and Bleeding following Dabigatran, Rivaroxaban, and Apixaban Use in Patients Aged 65 or Older: A Propensity Score Matched Analysis"

https://www.sentinelinitiative.org/assessments/drugs/stroke-intracranial-hemorrhage-bleeding-following-dabigatran-rivaroxaban-apixaban-use-patients-65-older



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

- Identifies population level study end points at user-specified time intervals
- Quantifies changes in end points after intervention
- Output metrics include:
  - Visual display of the observed time series and predicted trends
  - Inferential analysis results of level and trend change estimates, and absolute and relative differences at certain time points post-intervention

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)

SENTINEL ROUTINE QUERYING SYSTEM OVERVIEW

The purpose of this repository is to document version 8.0.3 of the Sentinel Routine Querying System, also known as the Query Request Package (QRP). This system is comprised of cohort identification and analytic modules.

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

COHORT IDENTIFICATION AND DESCRIPTIVE ANALYSIS (CIDA) MODULE

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

CIDA calculates descriptive statistics for the cohort(s) of interest and outputs datasets that may be useful for additional analyses.

CIDA Cohort Identification Strategies

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

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

Downloading Sentinel Analytic Packages

Sentinel

Sentinel Analytic Packages

Overview

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

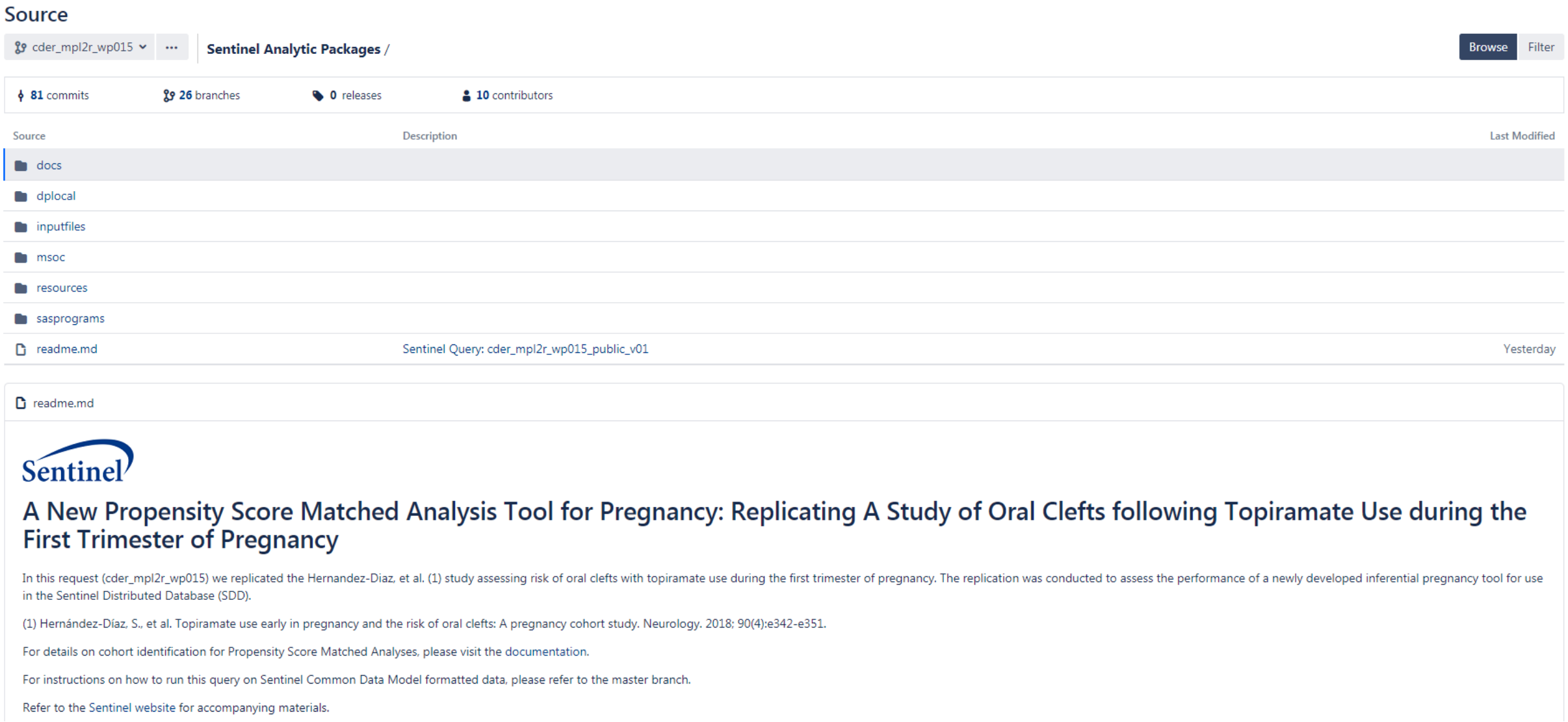
Sentinel's analytic request packages are intended to run on data formatted in accordance with the Sentinel Common Data Model (SCDM). Note that data must be in SAS datasets to use these analytic programs.

Analytic Request Packages Available for Download

Request ID	Summary
cder_mpl2r_wp015	A New Propensity Score Matched Analysis Tool for Pregnancy: Replicating A Study of Oral Clefts following Topiramate Use during the First Trimester of Pregnancy
cder_mpl2p_wp015	Factors Related to the Assignment of Sodium Glucose Cotransporter-2 Inhibitors (SGLT-2i) versus Dipeptidyl Peptidase-4 Inhibitors (DPP-4i)
cder_mpl2p_wp017	Stroke, Intracranial Hemorrhage, and Bleeding following Dabigatran, Rivaroxaban, and Apixaban Use in Patients Aged 65 or Older: A Propensity Score Matched Analysis
cder_mpl2p_wp018	Severe Uterine Bleed following Novel Oral Anticoagulants Use: A Propensity Score Stratified Analysis (an update to cder_mpl2p_wp007)
cder_mpl1r_wp176	Diminished Visual Acuity and Nasal Septal Perforation following Mometasone Sinus Implant Use in Patients with Nasal Polyposis: A Descriptive Analysis (an update to cder_mpl1r_wp157), Part 2
cder_mpl1r_wp172	Glaucoma and Cataracts following Mometasone Sinus Implant Use in Patients with Nasal Polyposis: A Descriptive Analysis (an update to cder_mpl1r_wp157), Part 1
cder_mpl1r_wp157	Glaucoma, Cataracts, Diminished Visual Acuity, and Nasal Septal Perforation following Mometasone Sinus Implant Use in Patients with Nasal Polyposis: A Descriptive Analysis
cder_mpl2p_wp023	Risk of Congenital Cardiac Malformations Following Armodafinil or Modafinil Use: A Propensity Score Matched Analysis
cdrh_mpl2r_wp001	Gynecologic Surgery following Permanent Sterilization: A Propensity Score Matched Analysis
cder_mpl2r_wp011	Acute Myocardial Infarction and Hospitalized Heart Failure following Saxagliptin or Sitagliptin Use: A Propensity Score Matched Analysis, Part 2
cder_mpl2r_wp008	Acute Myocardial Infarction and Hospitalized Heart Failure following Saxagliptin or Sitagliptin Use: A Propensity Score Matched Analysis, Part 1
cder_mpl2p_wp022	Non-Melanoma Skin Cancer following Hydrochlorothiazide Use: A Propensity Score Matched Analysis, Part 4
cder_mpl2p_wp019	Non-Melanoma Skin Cancer following Hydrochlorothiazide Use: A Propensity Score Matched Analysis, Part 3
cder_mpl1p_wp034	Non-Melanoma Skin Cancer following Hydrochlorothiazide Use: A Propensity Score Matched Analysis, Part 2
cder_mpl2p_wp016	Non-Melanoma Skin Cancer following Hydrochlorothiazide Use: A Propensity Score Matched Analysis, Part 1
cder_mpl2p_wp014	Neuropsychiatric Events following Montelukast Use: A Propensity Score Matched Analysis, Part 2

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

Downloading Sentinel Analytic Packages



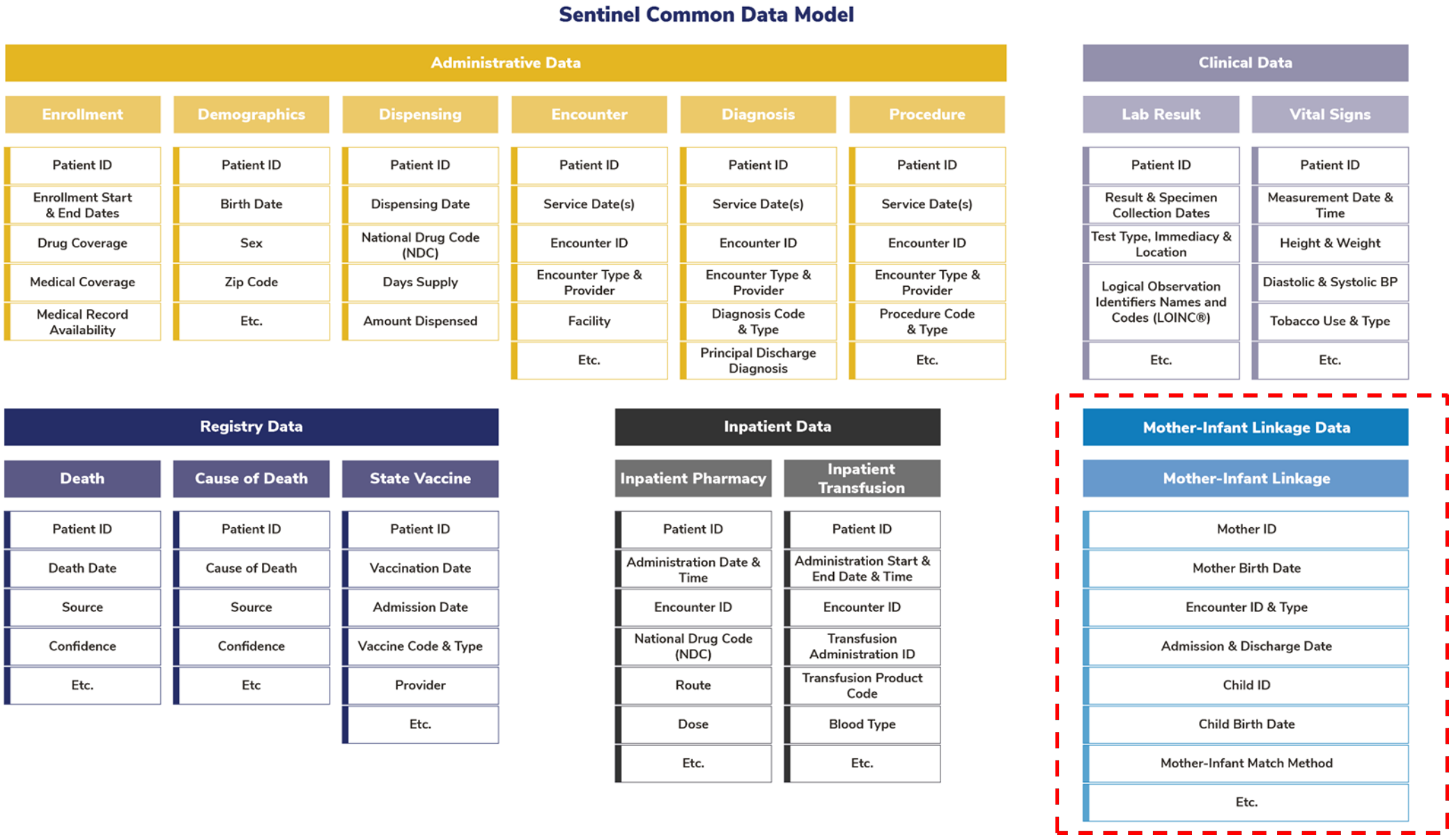
https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_mpl2r_wp015

Part 1 Questions

Creation of a Linked Mother-Infant Cohort

Elizabeth Suarez, PhD

Table in Sentinel Common Data Model



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

Mother-Infant Linkage Table

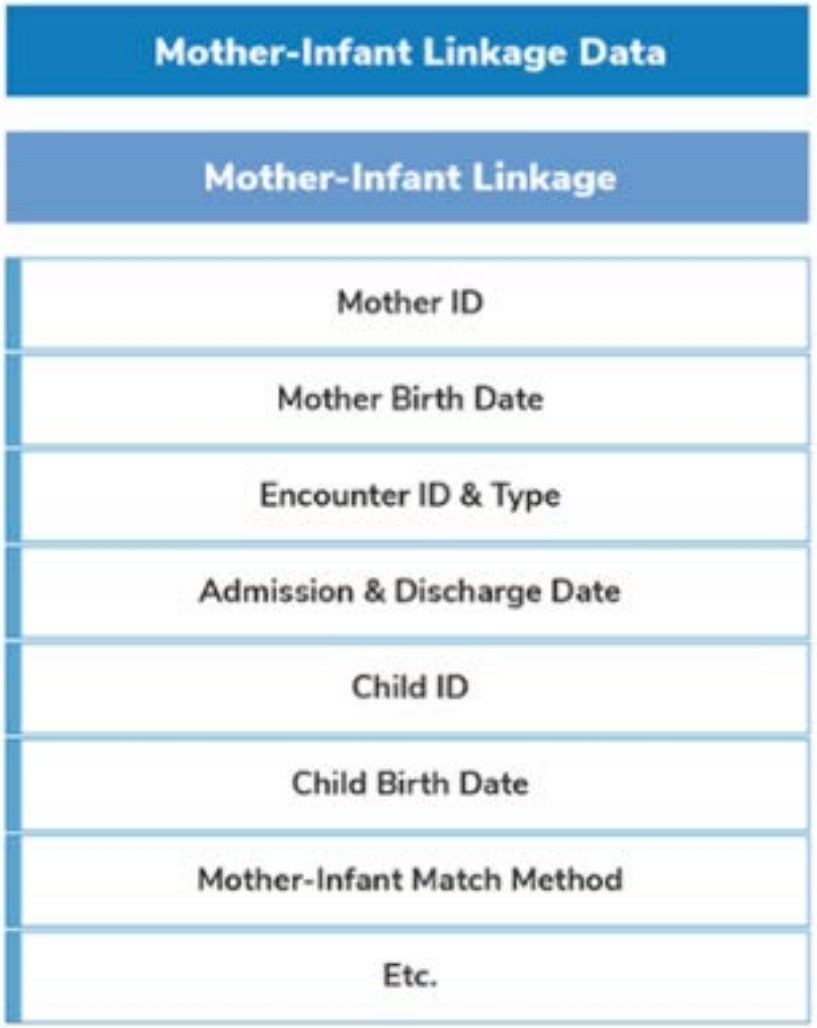


Table in the Sentinel Common Data Model, populated by four Data Partners

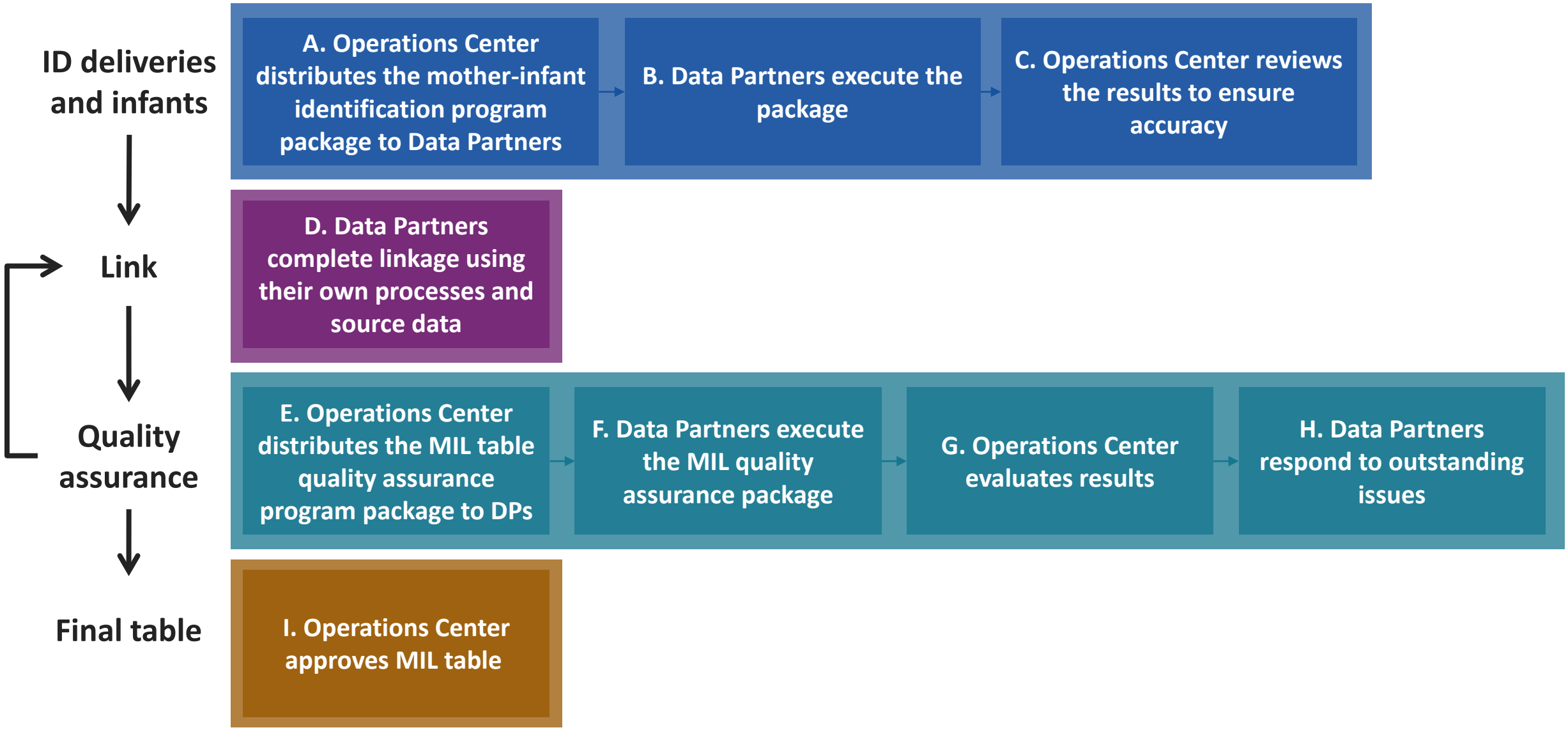
- 3 national claims insurers
- 1 Medicaid data source

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

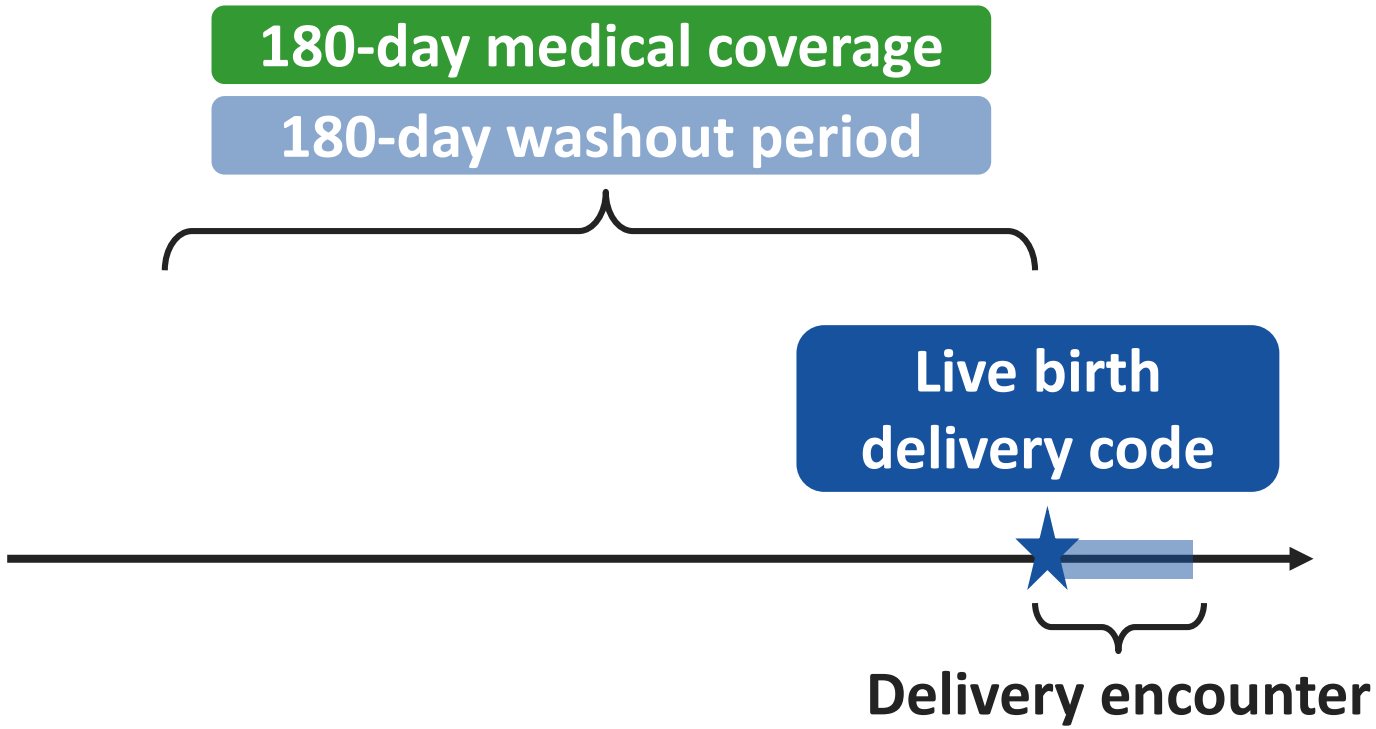
Mother-Infant Linkage Table

- Mother-Infant Linkage Table is only used to identify:
  - deliveries that resulted in a live birth
  - mother-infant pairs
  - certain infant characteristics
- Pregnancies can be selected from linked mother-infant pairs
  - Requester can select infant linking method
- Requesters can look at all deliveries in table or only linked deliveries

Steps for creating the MIL table



Identifying deliveries for the MIL table



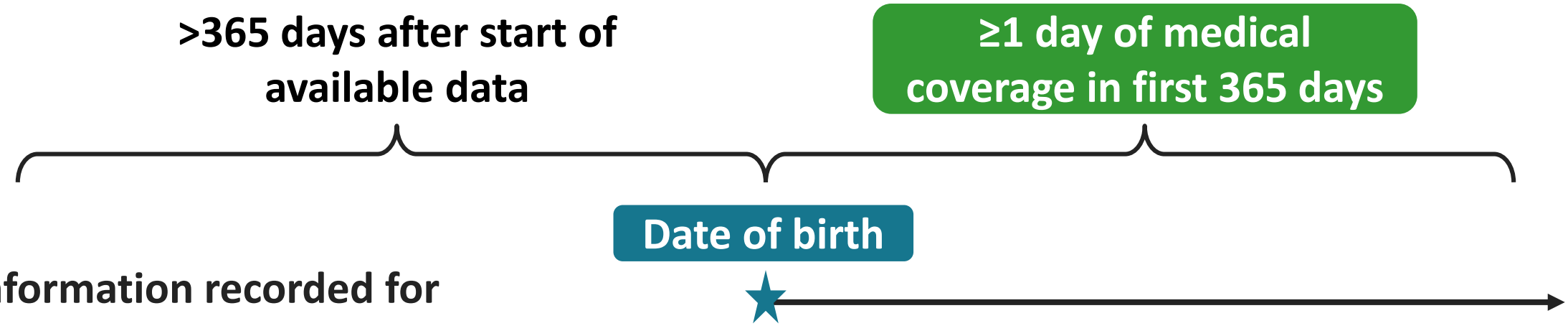
Also required: female, ages 10-54 years at delivery admission

Information recorded for mothers:

- Patient ID
- Birth date
- Age
- ID for delivery encounter
- Delivery encounter type
- Delivery encounter admission date
- Delivery encounter discharge date
- Singleton or multiple delivery

Codes for singleton vs multiple are taken from the delivery encounter

Identifying infants for the MIL table



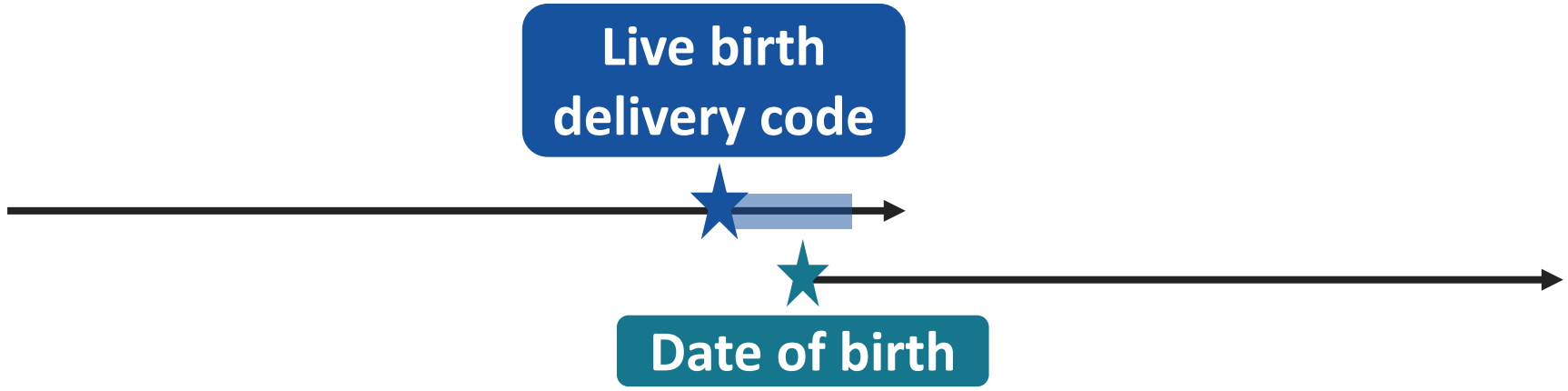
Information recorded for infants:

- Patient ID
- Birth date
- Sex
- Date of first enrollment

Linking mothers to infants

- Linkage process and source data is determined by each Data Partner
- Most matches were *deterministic* and relied on subscriber IDs; *probabilistic* matching was also used by some Data Partners
- Multiple infants could be linked to the single delivery, but only one linkage was allowed per infant

Linking mothers to infants



New variable for MatchMethod:
BC = Birth Certificate
RE = DP maintained birth registry
SI = health plan subscriber or family number
LA = exact or probabilistic last name and address match based upon health plan administrative data
OT = other

Values of MatchMethod if no link is made:
N1 = No subscriber/family IDs available for linkage
N2 = No name/address available for linkage
N3 = Neither subscriber/family IDs nor name/address available for linkage
NA = no linkage

Mother Infant Linkage – Latest Data

Approximately 5 million linked deliveries available in the Sentinel Common Data Model currently – updated regularly

	Total
Deliveries	6,491,060
Linked deliveries	5,108,877
Linkage rate	78.7%

Things that impact linkage rates –

- Mothers and infants insured under different plans
- Requirements for identifying deliveries was strict and require enrollment – an infant may have been identified but not the mother because only part of her pregnancy was observed
- Data partners only linked when they had confidence in the link – more linkages could have been possible with looser criteria, but with the cost of incorrect linkages

Linkage Rates by Birth Types

	Birth type				
	Unknown # of live births	One live birth	Two live births	3+ live births or unspecified multiples	Conflicting codes on # of live births
Deliveries	520,744	5,832,761	110,405	6,030	21,120
Linked Deliveries	165,911	4,832,347	89,166	3,424	18,029
Linkage Rate	31.86%	82.85%	80.76%	56.78%	85.36%

95% of linked deliveries were singleton deliveries

Linkage by age and encounter type

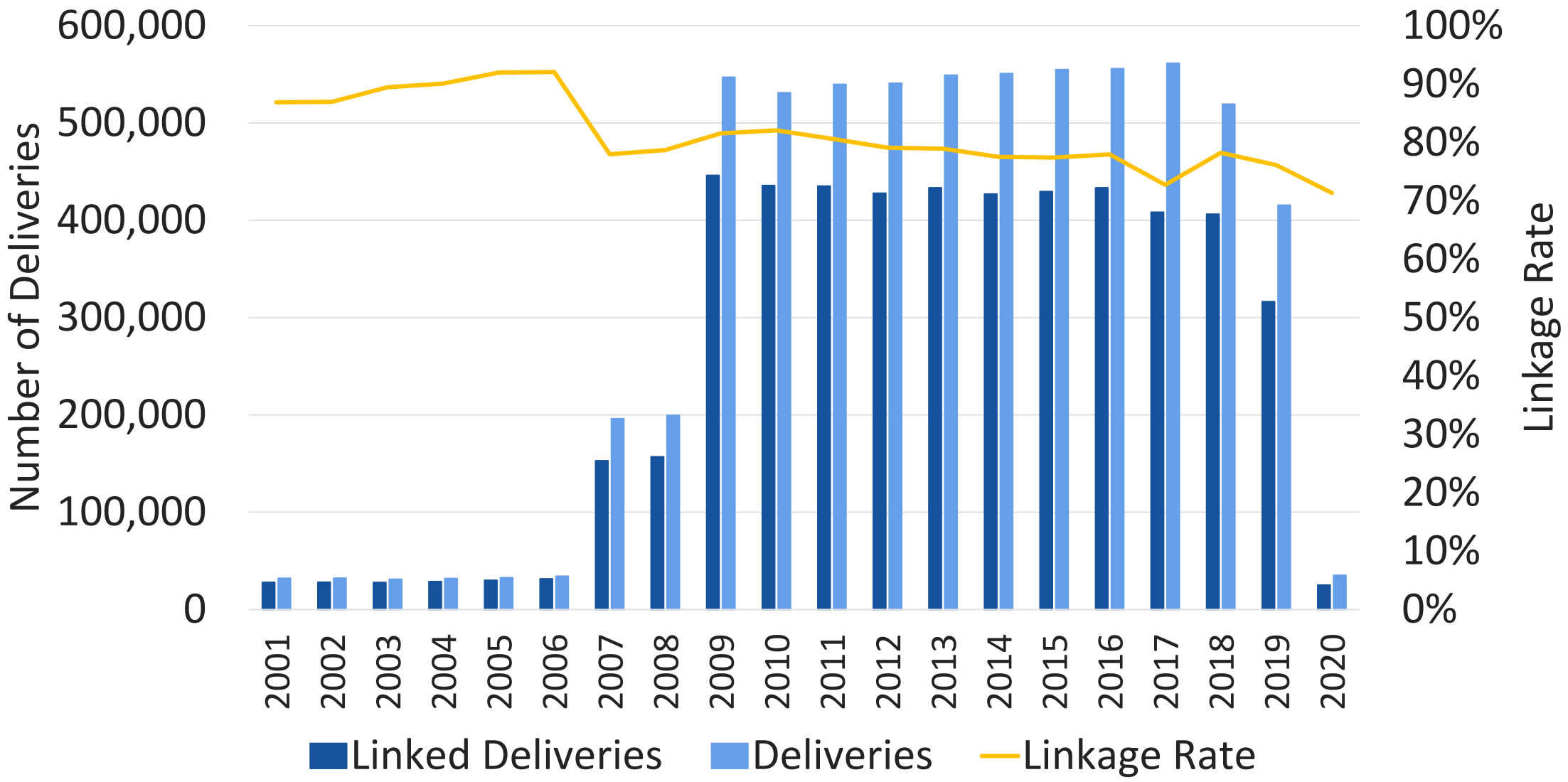
Maternal age at delivery			
	10-19	20-44	45-54
Deliveries	269,671	6,172,895	48,494
Linked Deliveries	125,268	4,968,554	15,055
Linkage Rate	46.50%	80.50%	31.00%

97% of linked deliveries were ages 20-44

99% of linked deliveries were identified in inpatient records

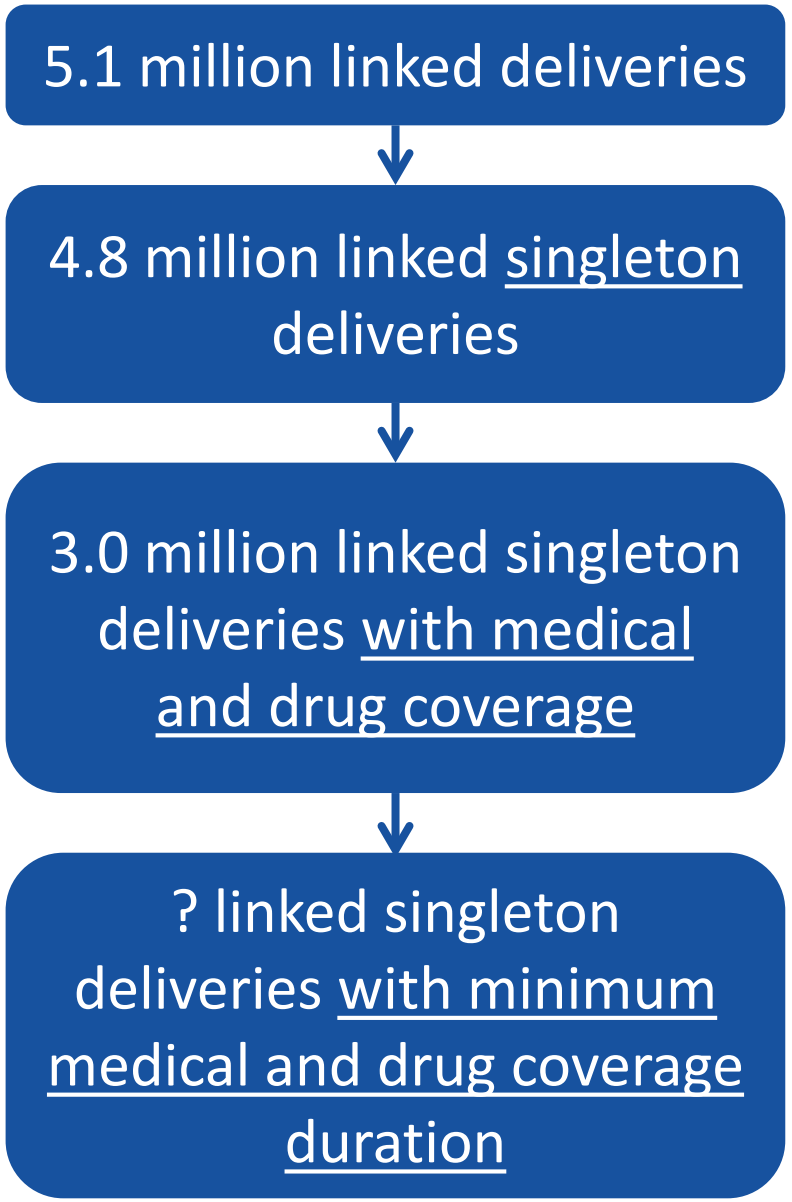
Encounter type of delivery					
	Inpatient Hospital	Emergency Department	Non-Acute Institutional	Ambulatory Visit	Other Ambulatory Visit
Deliveries	6,131,319	8,772	3,140	244,234	103,595
Linked Deliveries	5,050,905	1,154	2,555	28,231	26,032
Linkage Rate	82.40%	13.20%	81.40%	11.60%	25.10%

Linkage Rates By Year



Linked mother-infant sample for analysis

- Singleton deliveries only
  - We currently only analyze singleton deliveries due to the additional complexity of analyzing multiple infants paired with a single mother
- Require drug coverage in addition to medical coverage
  - Inclusion in the MIL table only requires medical coverage
- Require a specific duration of medical and drug coverage prior to delivery for the mother



Duration of enrollment prior to delivery

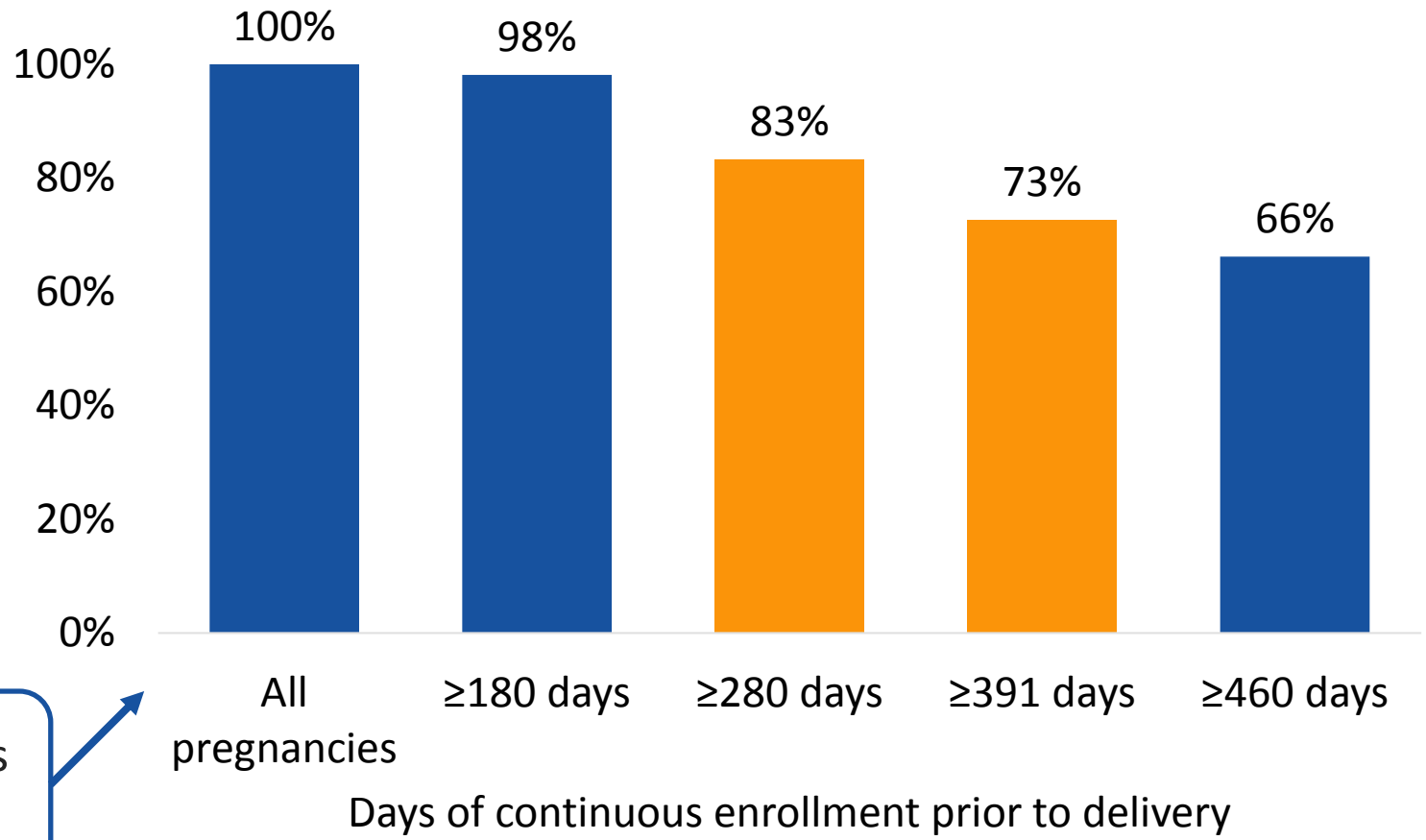
Medical and drug enrollment should be required for:

- The duration of the pregnancy episode, and
- Any pre-pregnancy period used to assess covariates

Cohort size shrinks as more enrollment duration is required

3.0 million linked singleton deliveries with medical and drug coverage

Cohort size after requiring continuous medical and drug coverage prior to delivery



Comparison of Linked and Unlinked Deliveries in the SDD MIL table

- Recently completed an analysis to compare linked and unlinked deliveries in the SDD MIL table
- For this analysis, we required that:
  - Only singleton deliveries were included
  - Mothers had 391 days of medical and drug coverage prior to the delivery date
    - Covers full pregnancy period and a 90-day pre-pregnancy period
  - No additional enrollment required for the matched infants

	Linked	Unlinked
Number of singleton pregnancies	2,175,261	474,858
Number of pregnant patients	1,826,162	441,520

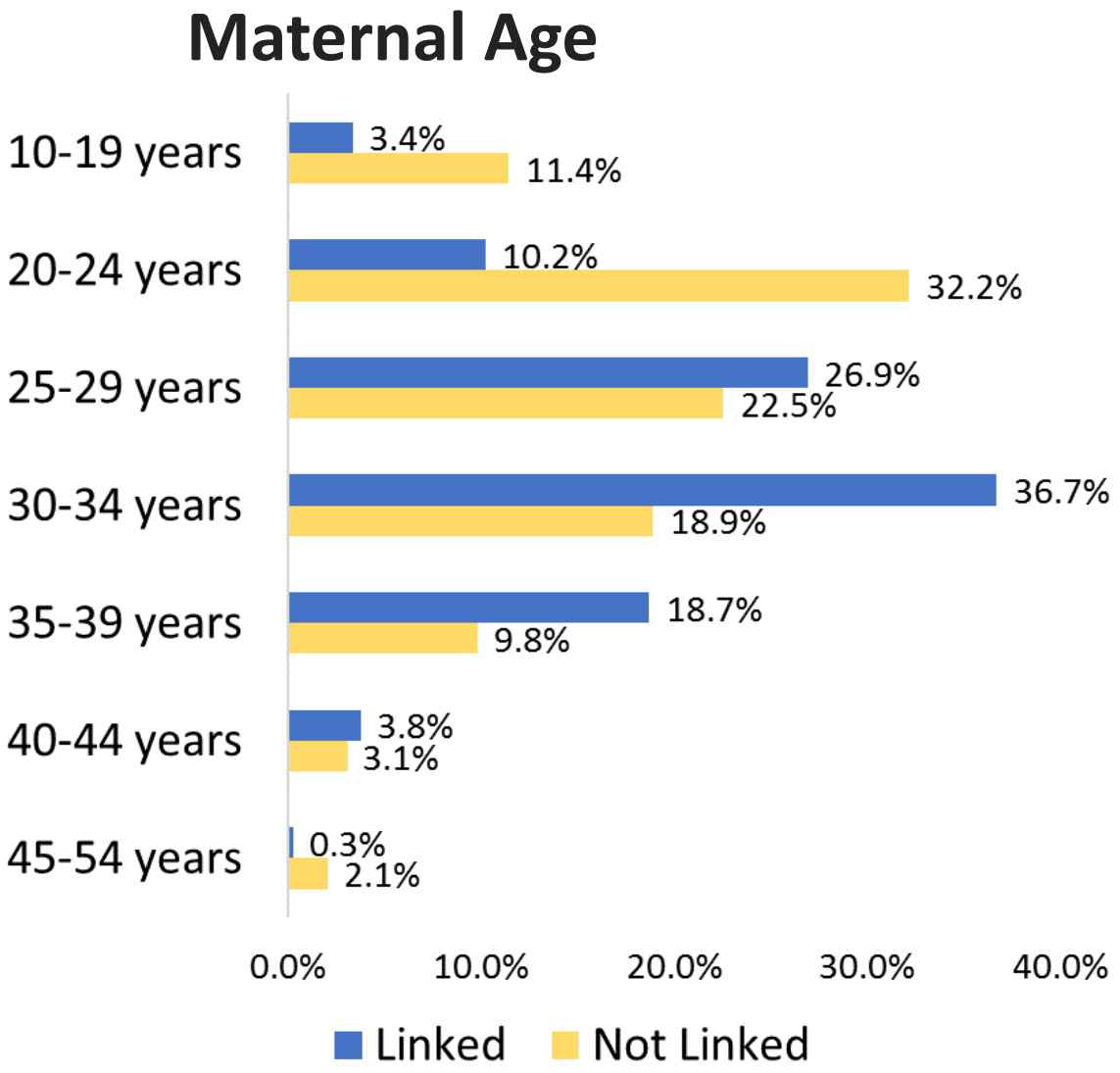
Comparison of Linked and Not Linked Deliveries in the SDD MIL table

Linked deliveries were older than not linked deliveries:

- Mean age (SD):
  - Linked: 31.1 (4.7) years
  - Not linked: 27.7 (7.0) years

Linked deliveries were less likely to be classified as preterm than not linked deliveries:

- Linked: 5.7% preterm
- Not linked: 7.3% preterm

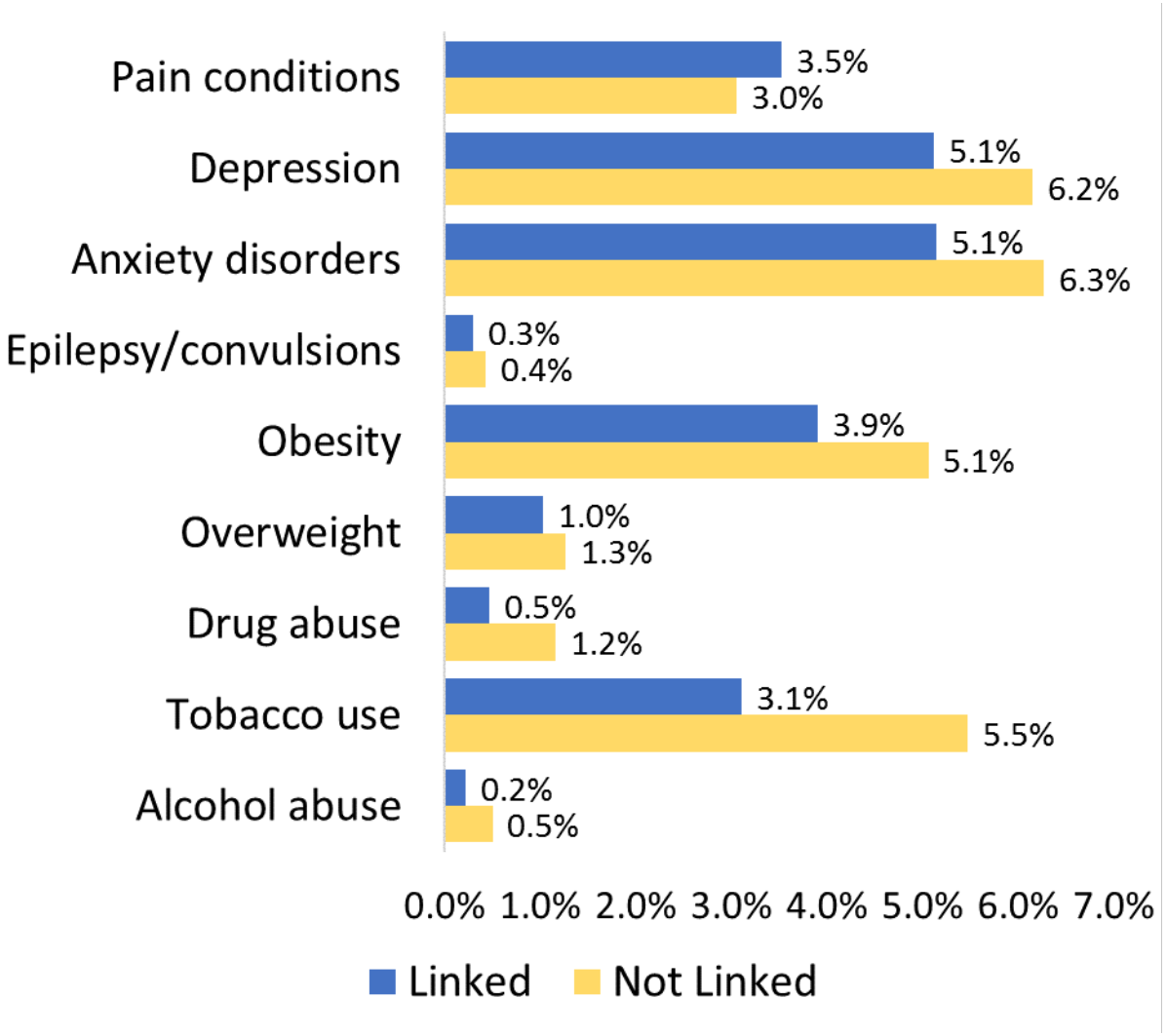


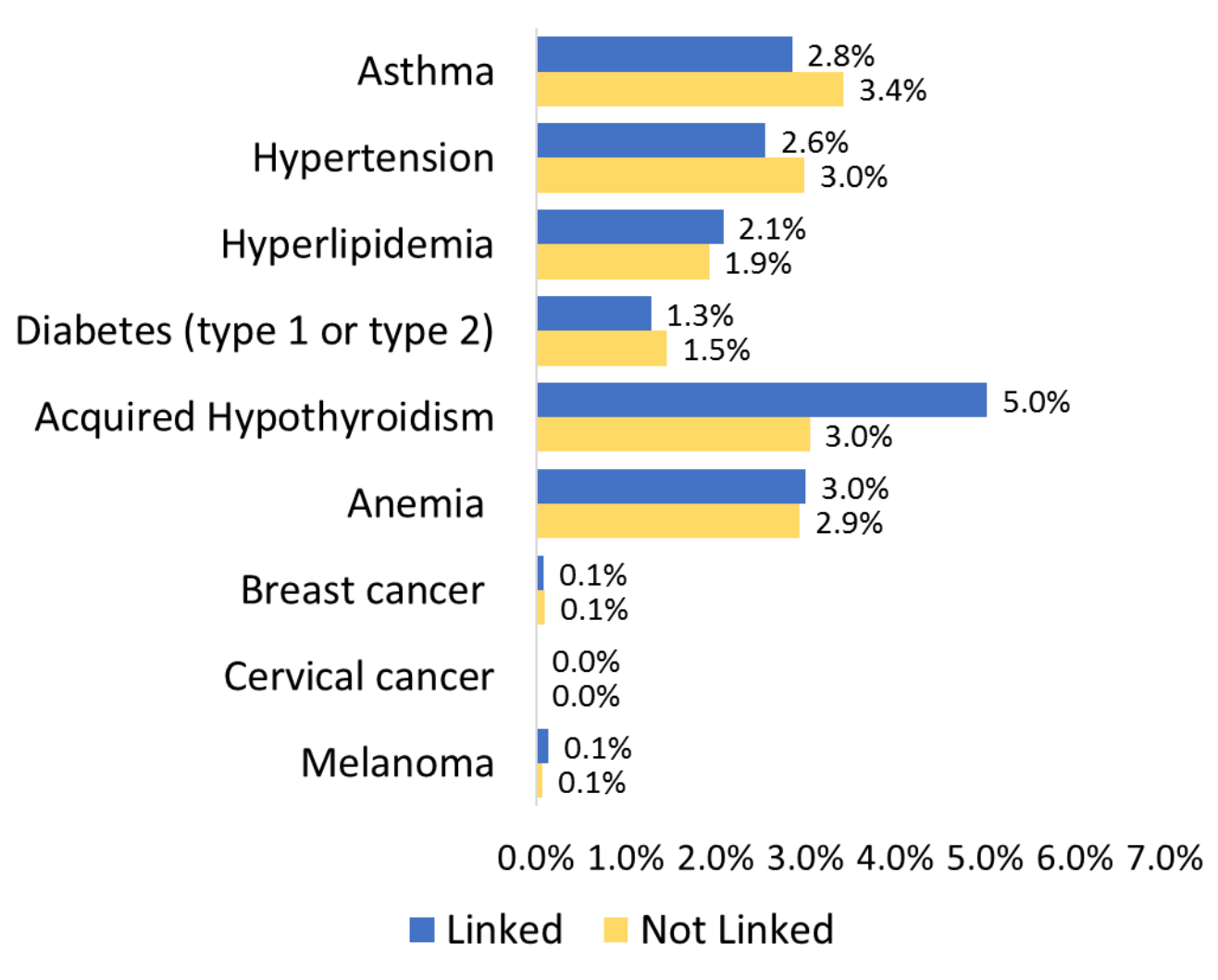
Comparison of Linked and Not Linked Deliveries in the SDD MIL table

	Linked	Not Linked
Race		
American Indian or Alaska Native	0.1%	0.1%
Asian	1.0%	0.4%
Black or African American	2.8%	2.8%
Native Hawaiian or Other Pacific Islander	0.1%	0.0%
White	10.1%	7.5%
Unknown	86.0%	89.1%
Hispanic		
Yes	1.3%	1.5%
No	7.2%	5.7%
Unknown	91.6%	92.8%

	Linked	Not Linked
Health care utilization (90 days prior to pregnancy start)		
Mean number of ambulatory encounters	2.0 (3.1)	1.7 (2.8)
Mean number of other ambulatory encounters	0.3 (0.9)	0.3 (0.9)
Mean number of inpatient encounters	0.0 (0.1)	0.0 (0.2)
Mean number of institutional stay encounters	0.0 (0.0)	0.0 (0.0)
Mean number of emergency department encounters	0.1 (0.4)	0.1 (0.5)

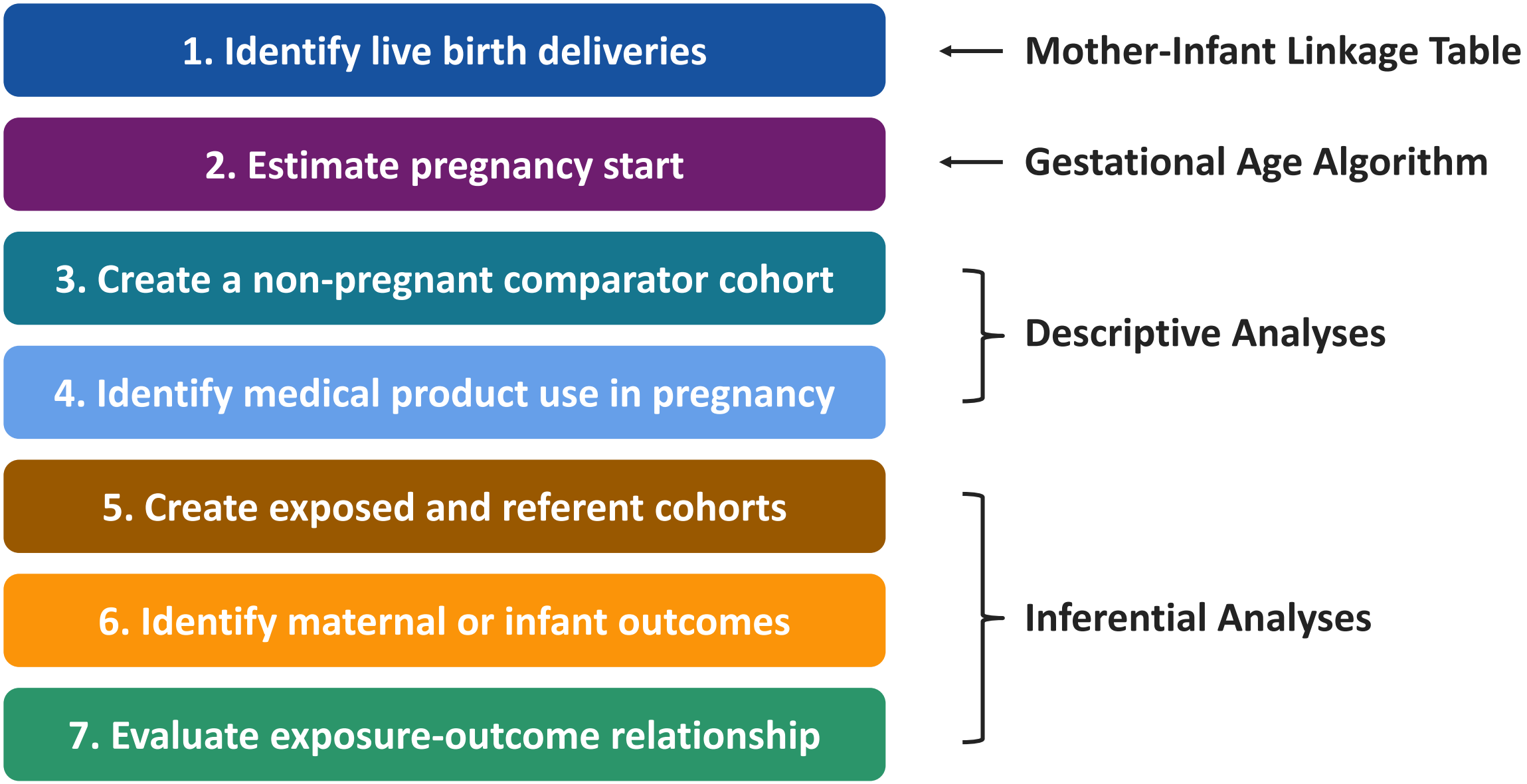
Pre-existing Conditions Among Linked and Not Linked Deliveries





Descriptive Pregnancy Analyses

Creating and analyzing a cohort of deliveries



Creating and analyzing a cohort of deliveries

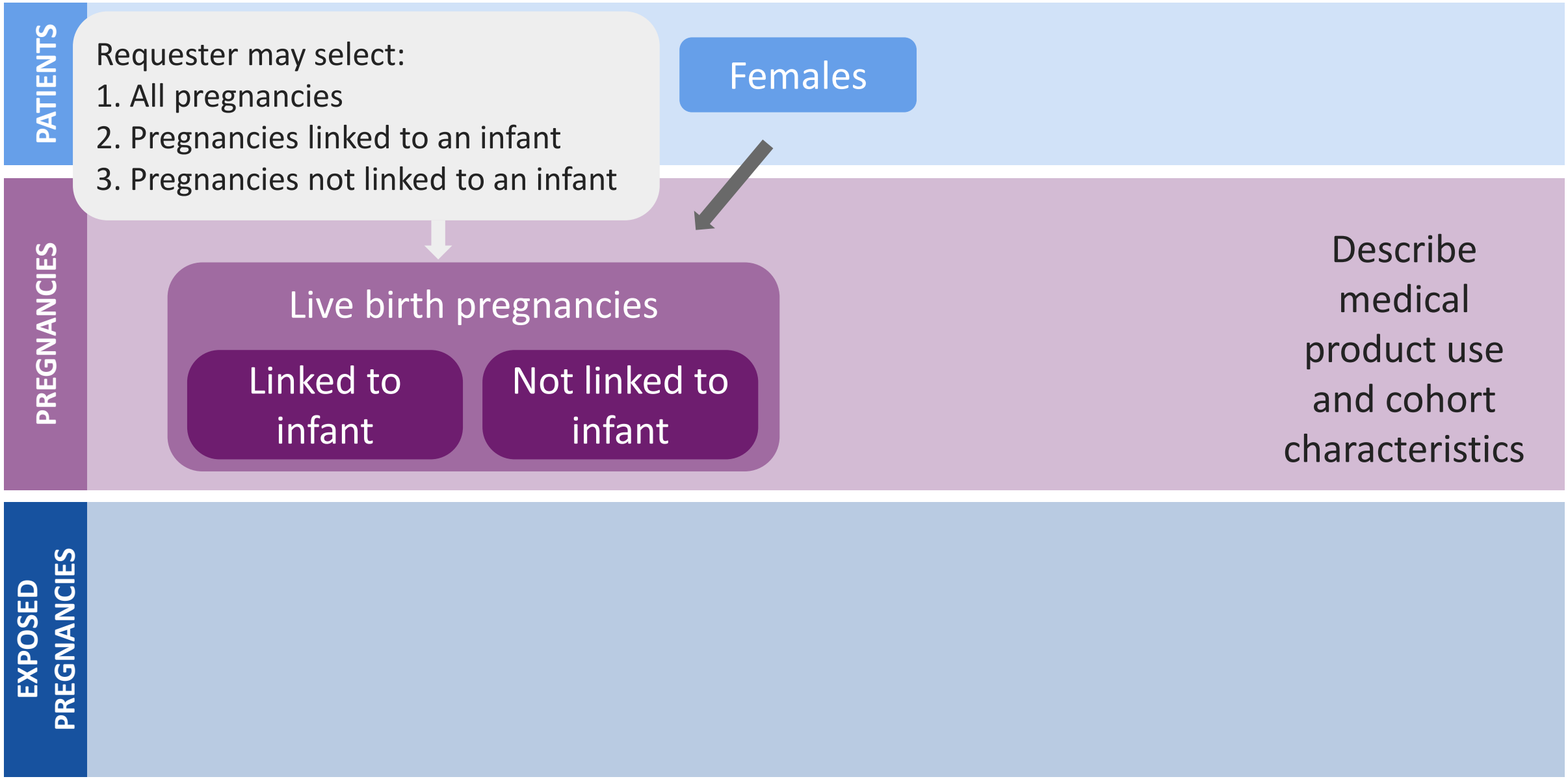
1. Identify live birth deliveries ← **Mother-Infant Linkage Table**
2. Estimate pregnancy start ← Gestational Age Algorithm
3. Create a non-pregnant comparator cohort
4. Identify medical product use in pregnancy

} Descriptive Analyses

5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes
7. Evaluate exposure-outcome relationship

} Inferential Analyses

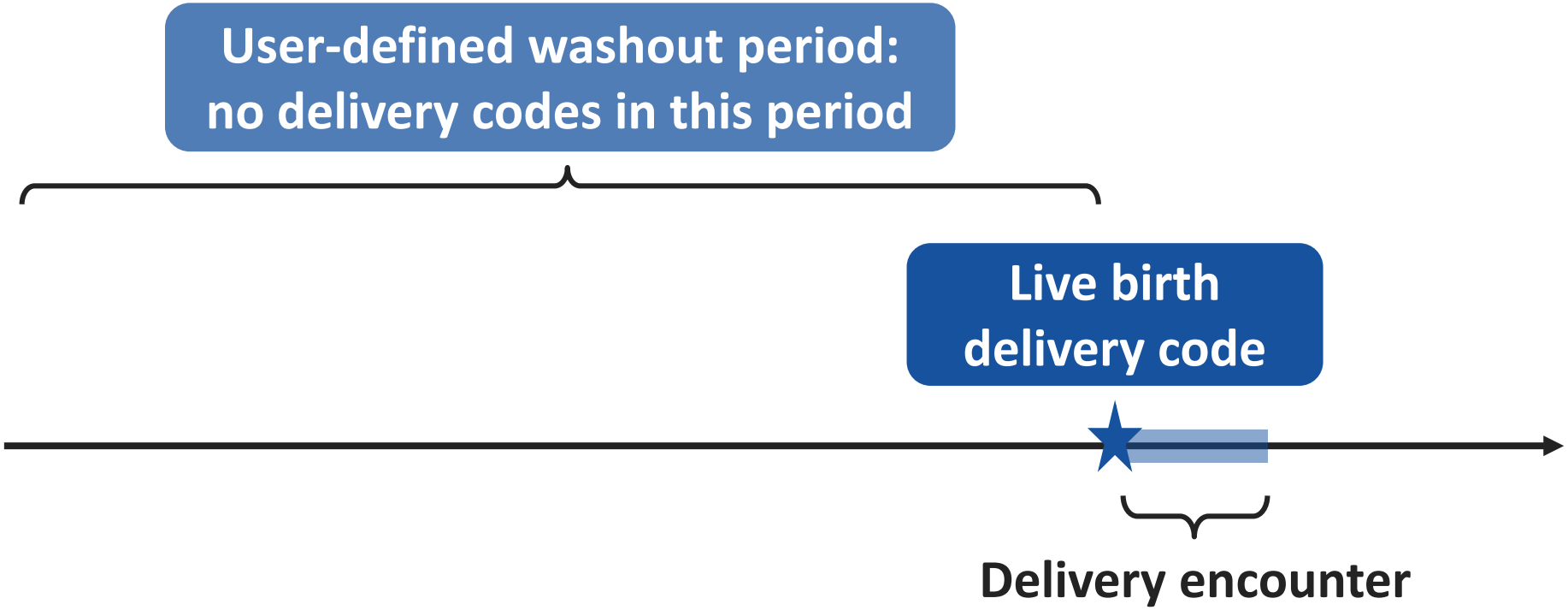
Cohort Selection



Selecting deliveries for analysis

Method	Use case examples	Advantages
Using ICD-9 and ICD-10 codes (without the MIL table)	Any analysis that uses mothers claims only: • Characterizing medication utilization prior to and during pregnancy • Characterizing comorbidities among pregnant women • Conducting an inferential analysis for a maternal outcome	• Does not require having the MIL table in the SCDM • When analyzing the SDD, we can include data from all Data Partners, not just those with a populated MIL table, greatly increasing our sample size
Using the MIL table	Any analysis that requires infant data or knowledge of the linkage status: • Conducting an inferential analysis for an infant outcome • Characterizing medication utilization or comorbidities among deliveries that were linked to infants	• Access to infant data • Ability to select a cohort of linked deliveries, leading to less misclassification of delivery status

Identifying live birth deliveries using ICD-9 and ICD-10 codes



User-specified: Live birth delivery encounter type

Live birth delivery date = admission date for delivery encounter

1. Identify live birth deliveries

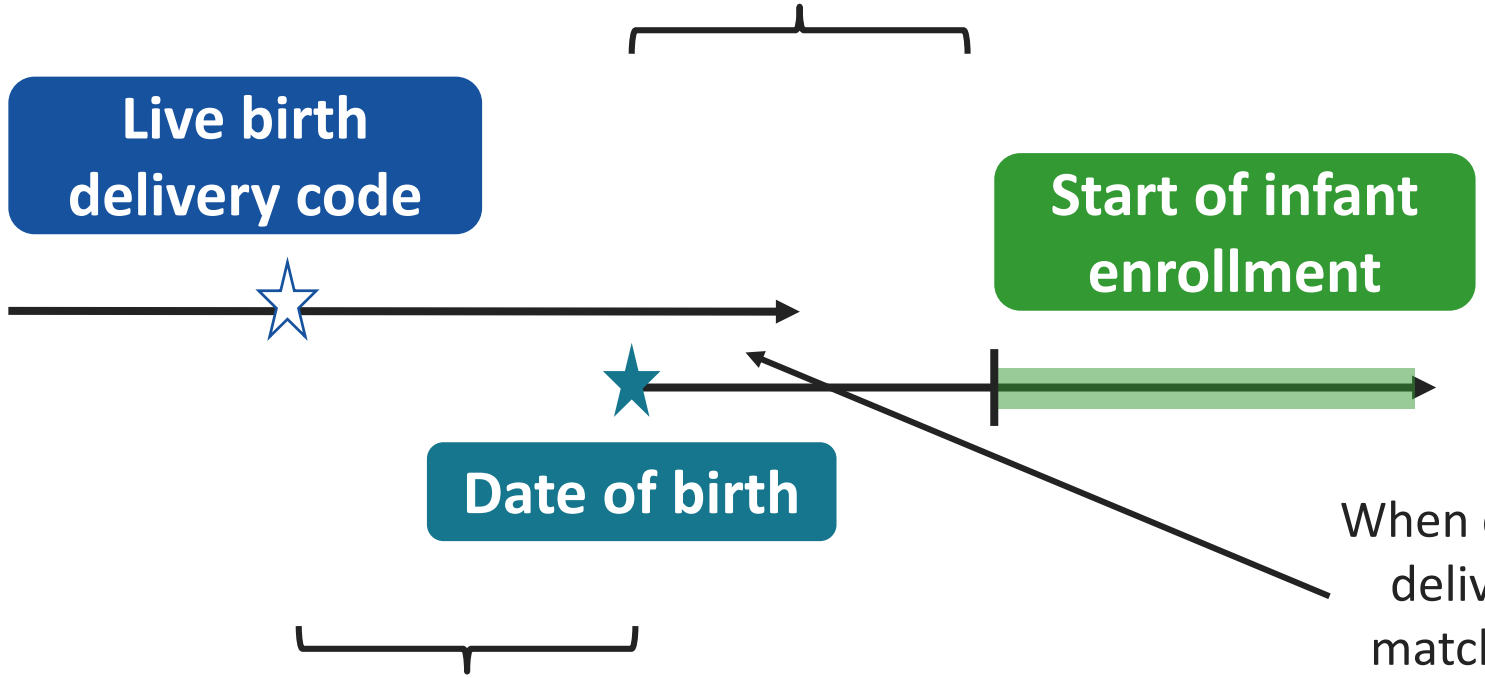
Identifying live birth deliveries from the MIL table

User-specified: MatchMethod

- BC = Birth Certificate
- RE = DP maintained birth registry
- SI = health plan subscriber or family number
- LA = exact or probabilistic last name and address match based upon health plan administrative data
- OT = other

Identifying live birth deliveries from the MIL table

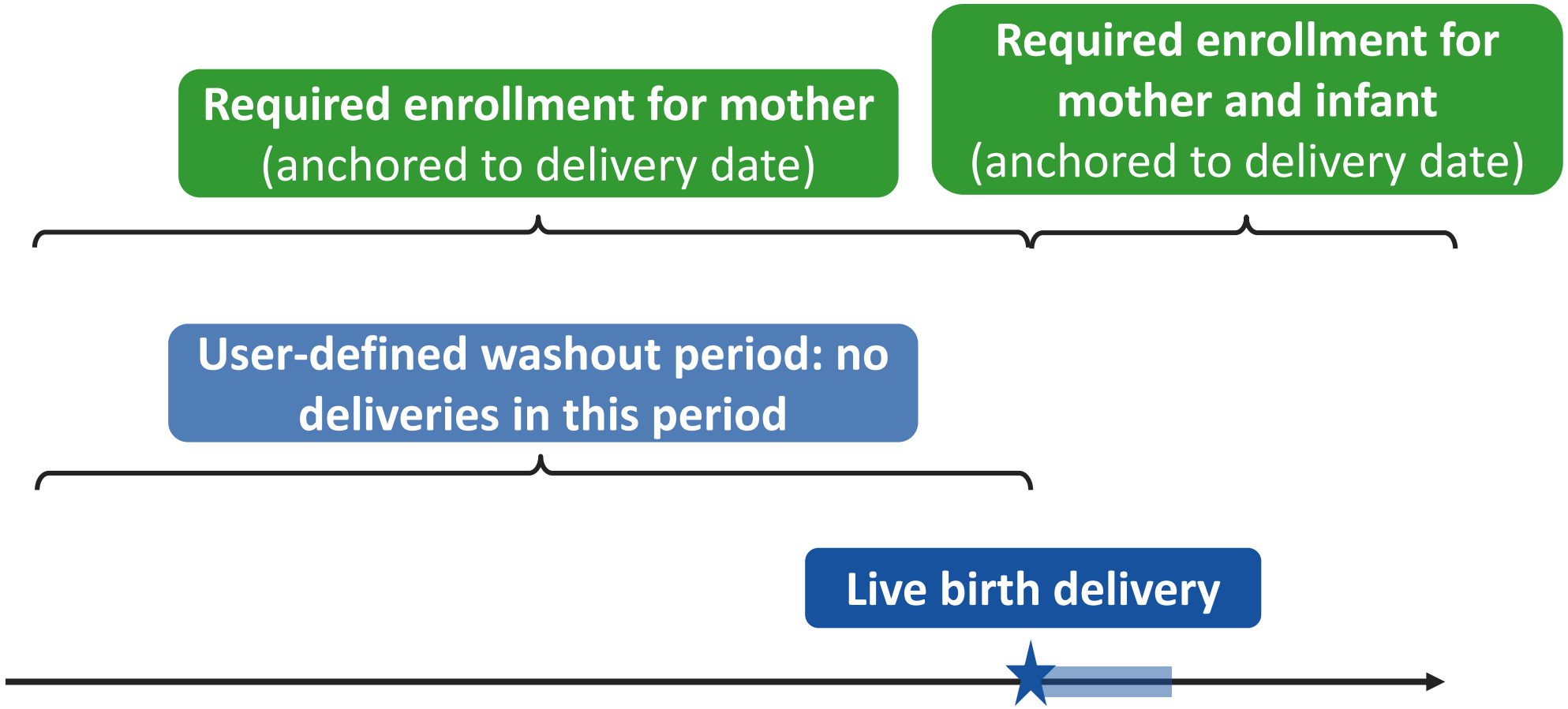
User-specified: maximum number of days between infant's birth date and infant's first enrollment date



User-specified: maximum number of days between mother's delivery admission date and infant's birth date

1. Identify live birth deliveries

Refining the cohort of deliveries



1. Identify live birth deliveries

Creating and analyzing a cohort of deliveries

1. Identify live birth deliveries ← Mother-Infant Linkage Table
2. **Estimate pregnancy start** ← **Gestational Age Algorithm**
3. Create a non-pregnant comparator cohort
4. Identify medical product use in pregnancy

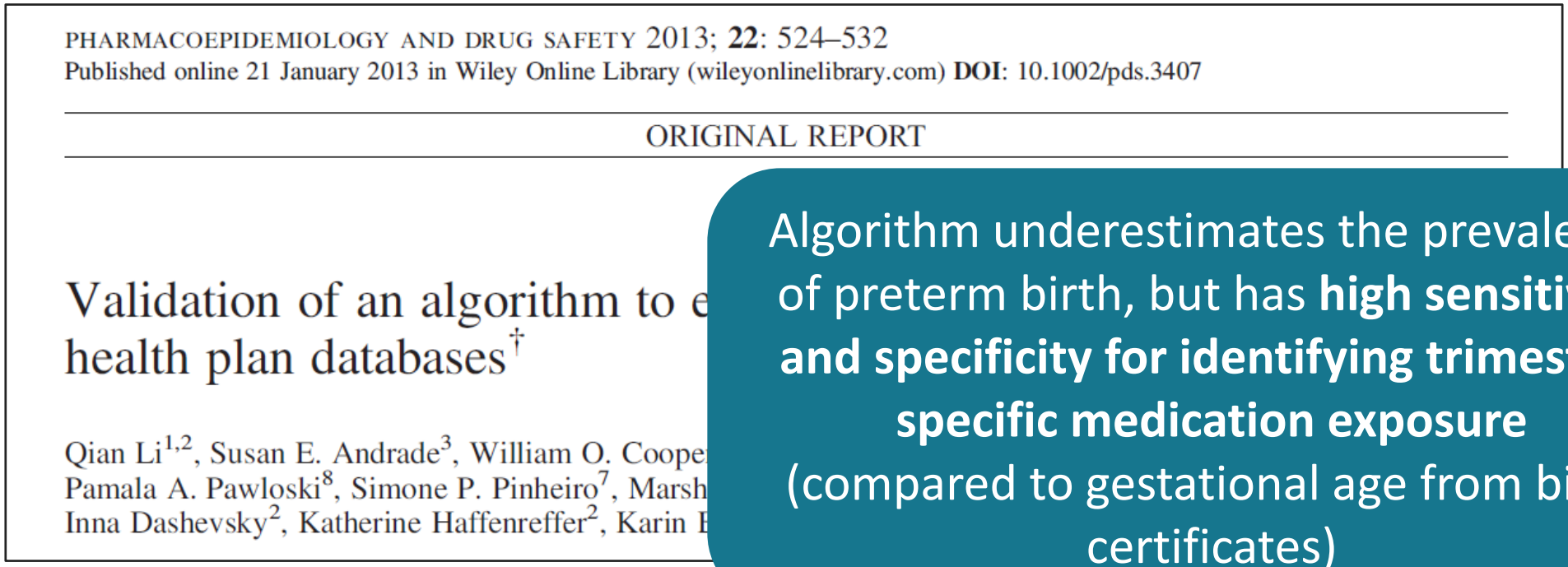
Descriptive Analyses

5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes
7. Evaluate exposure-outcome relationship

Inferential Analyses

Gestational age algorithm

Last menstrual period (LMP) is not available in US insurance claims data, therefore gestational age needs to be estimated



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Published online 21 January 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3407

ORIGINAL REPORT

Validation of an algorithm to e
health plan databases†

Qian Li[1,2], Susan E. Andrade[3], William O. Coope
Pamala A. Pawloski[8], Simone P. Pinheiro[7], Marsh
Inna Dashevsky[2], Katherine Haffenreffer[2], Karin E

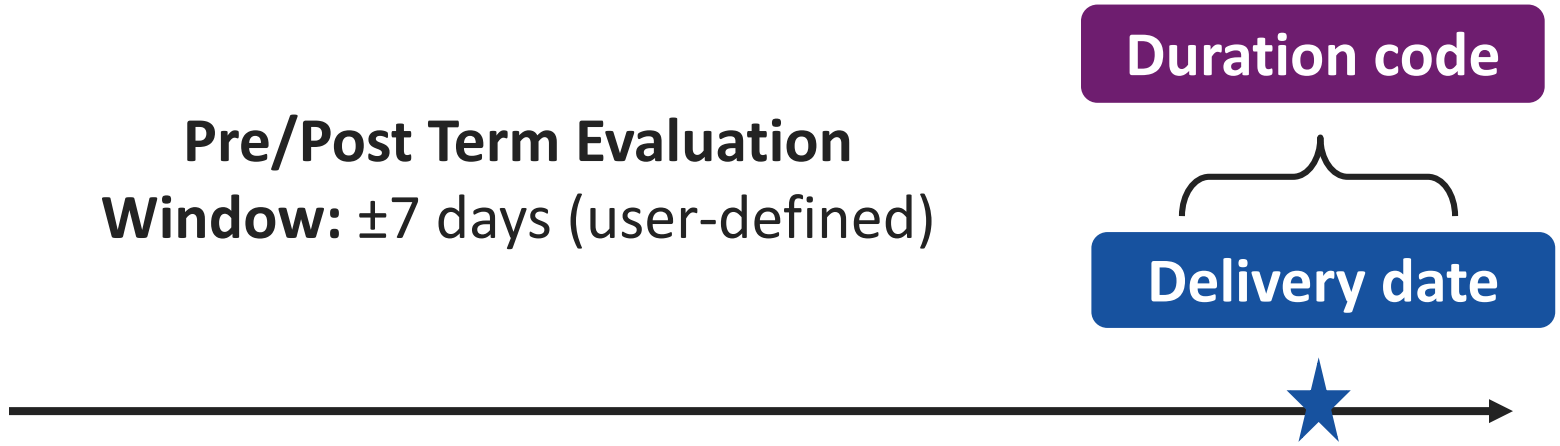
Algorithm underestimates the prevalence of preterm birth, but has **high sensitivity and specificity for identifying trimester-specific medication exposure** (compared to gestational age from birth certificates)

Current algorithm is a modification of this algorithm and includes both ICD-9 and ICD-10 codes

2. Estimate pregnancy start

Identifying gestational duration codes

Pre/Post Term Evaluation
Window: ±7 days (user-defined)



2. Estimate pregnancy start

Examples of ICD-9-CM and ICD-10-CM GA Codes

If multiple conflicting gestational age codes are found in the record, a priority ranking is used to determine the final gestational age:

1. Gestational week specific codes: Z3A codes and P07 codes
2. "Vague" codes that do not specify gestational age but suggest pre-term status
3. "Vague" codes that do not specify gestational age but suggest post-term status

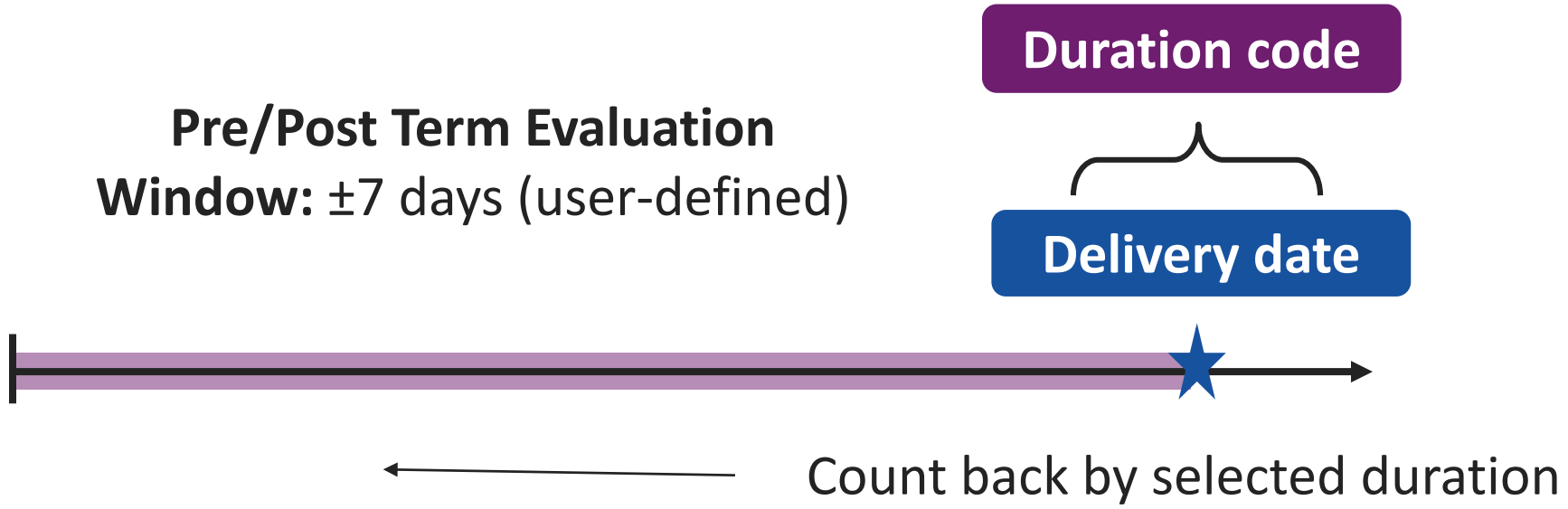
Code	Description	Duration (weeks)	Duration (days)
Z3A.35	35 weeks gestation of pregnancy	35.5	249
644.21	Onset of delivery before 37 completed weeks of gestation	35	245
O480	Post-term pregnancy	41	287

If there are no gestational age codes, a user-defined default gestational age is assigned – typically 273 days

2. Estimate pregnancy start

Identifying duration codes

Pre/Post Term Evaluation
Window: ±7 days (user-defined)



2. Estimate pregnancy start

Creating and analyzing a cohort of deliveries

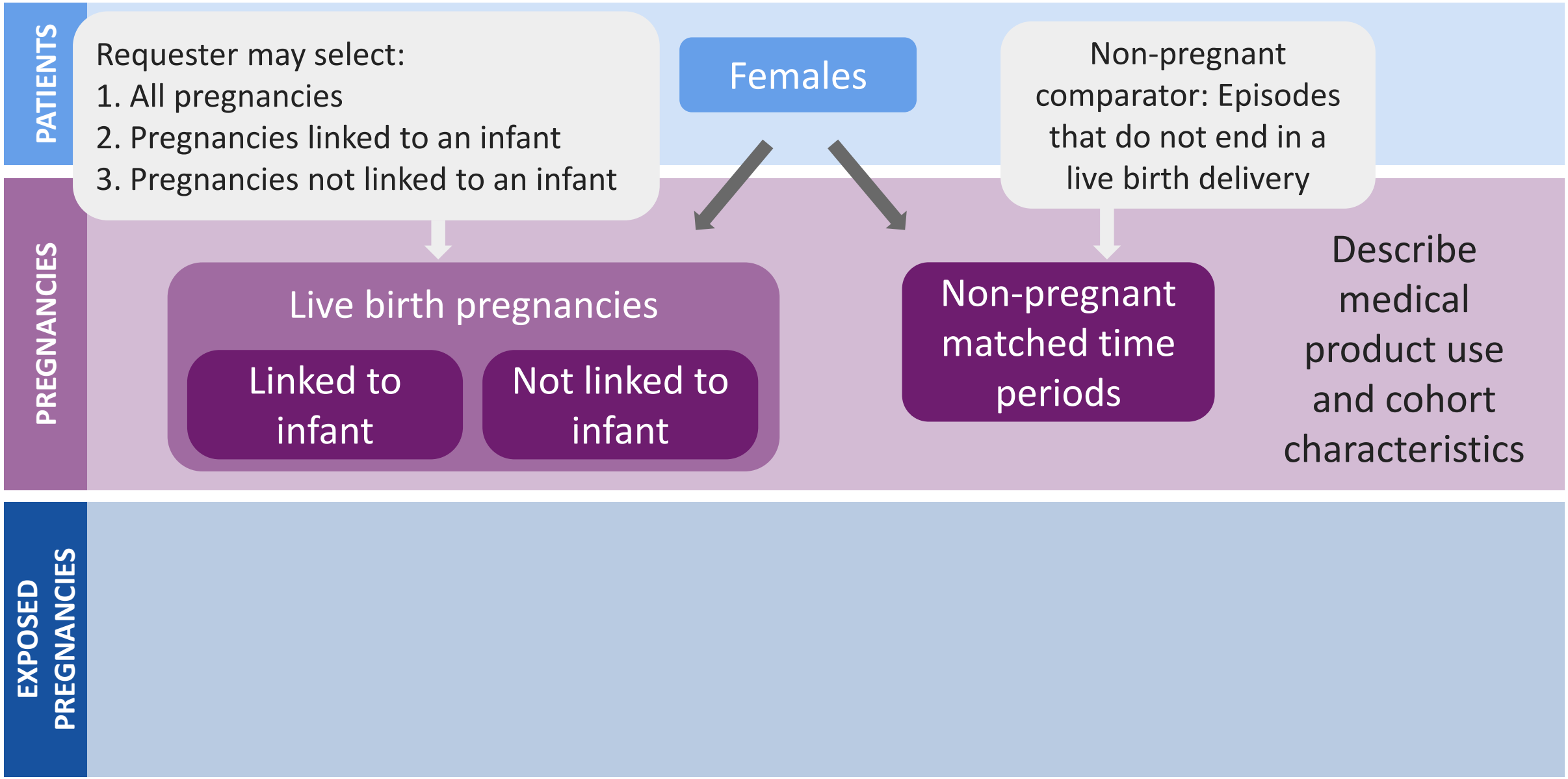
1. Identify live birth deliveries ← Mother-Infant Linkage Table
2. Estimate pregnancy start ← Gestational Age Algorithm
3. Create a non-pregnant comparator cohort
4. Identify medical product use in pregnancy

Descriptive Analyses

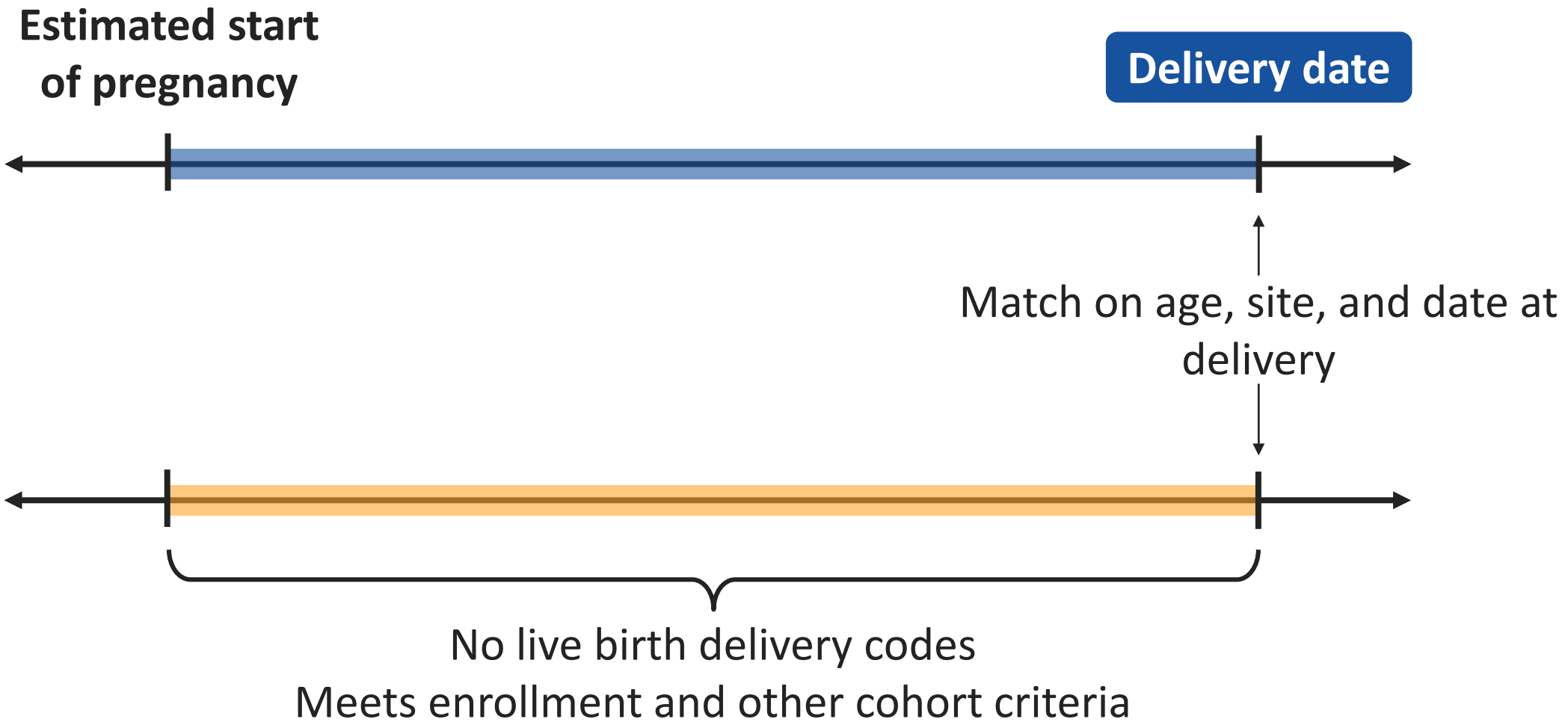
5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes
7. Evaluate exposure-outcome relationship

Inferential Analyses

Cohort Selection



Create non-pregnant comparator cohort



3. Create a non-pregnant comparator cohort

Creating and analyzing a cohort of deliveries

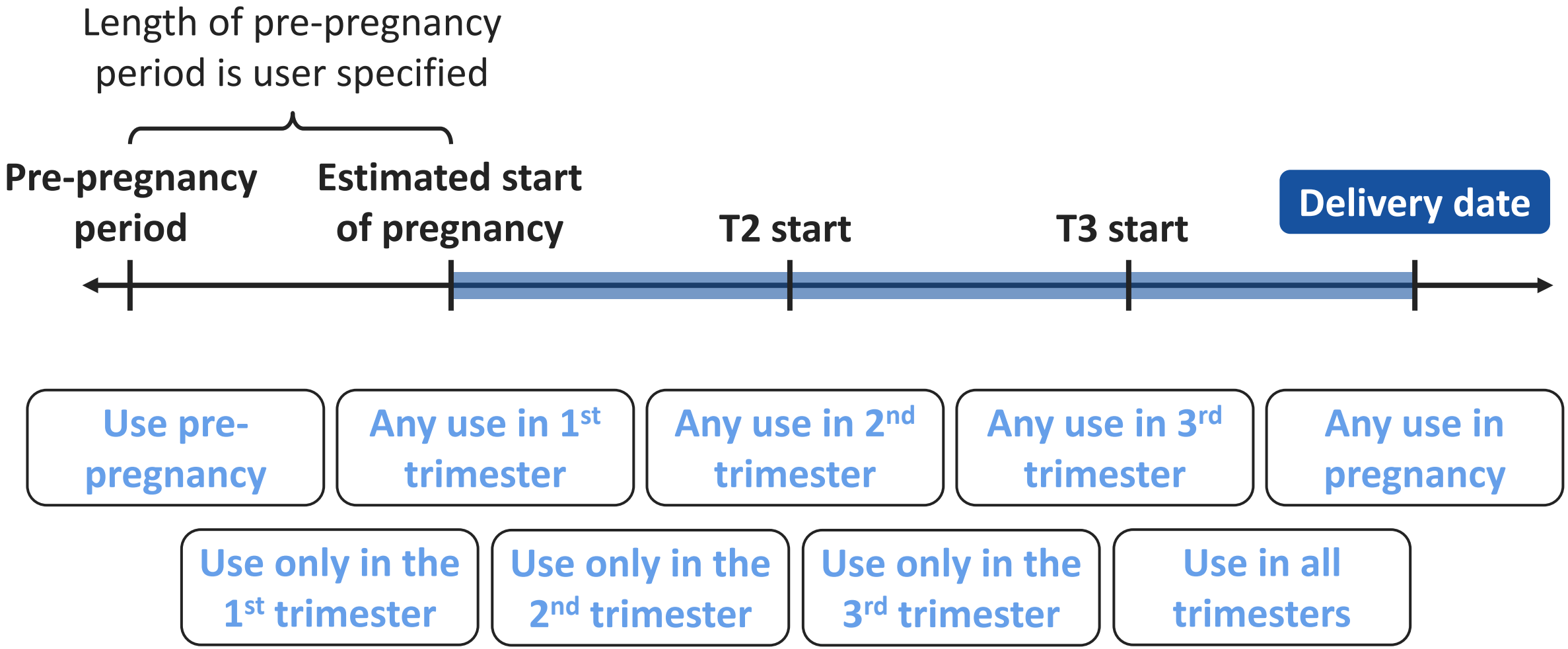
1. Identify live birth deliveries ← Mother-Infant Linkage Table
2. Estimate pregnancy start ← Gestational Age Algorithm
3. Create a non-pregnant comparator cohort
4. Identify medical product use in pregnancy

Descriptive Analyses

5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes
7. Evaluate exposure-outcome relationship

Inferential Analyses

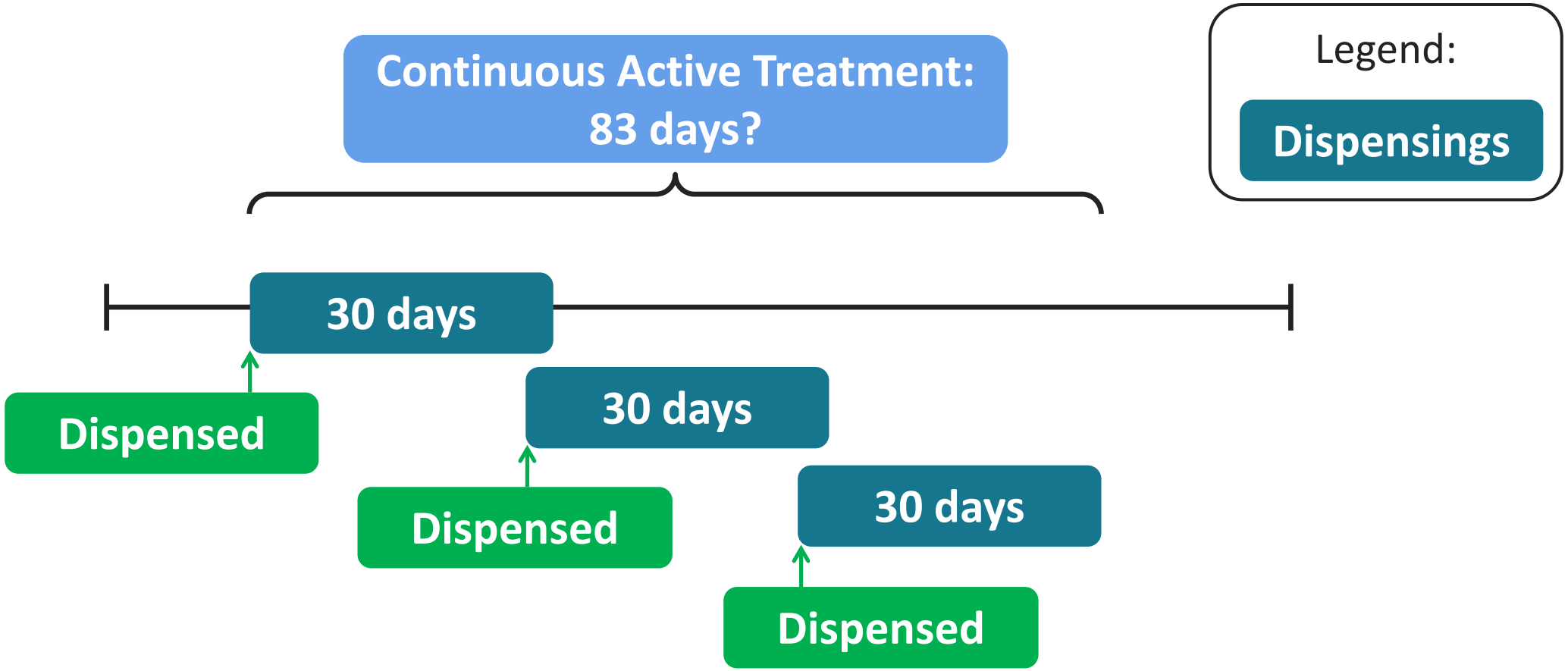
Classifying medical product use by timing during pregnancy



4. Identify medical product use in pregnancy

Creating exposure episodes: stockpiling

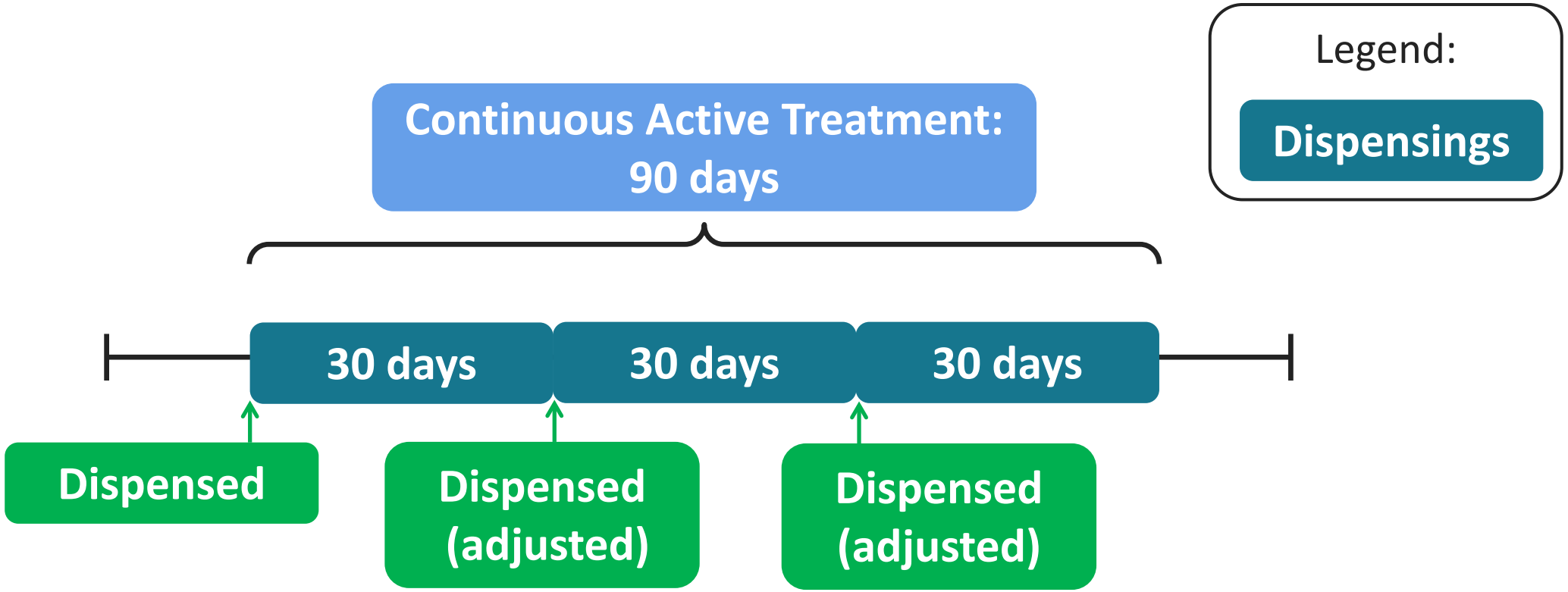
- Patients may refill prescriptions before exhausting previous dispensing's days supply



4. Identify medical product use in pregnancy

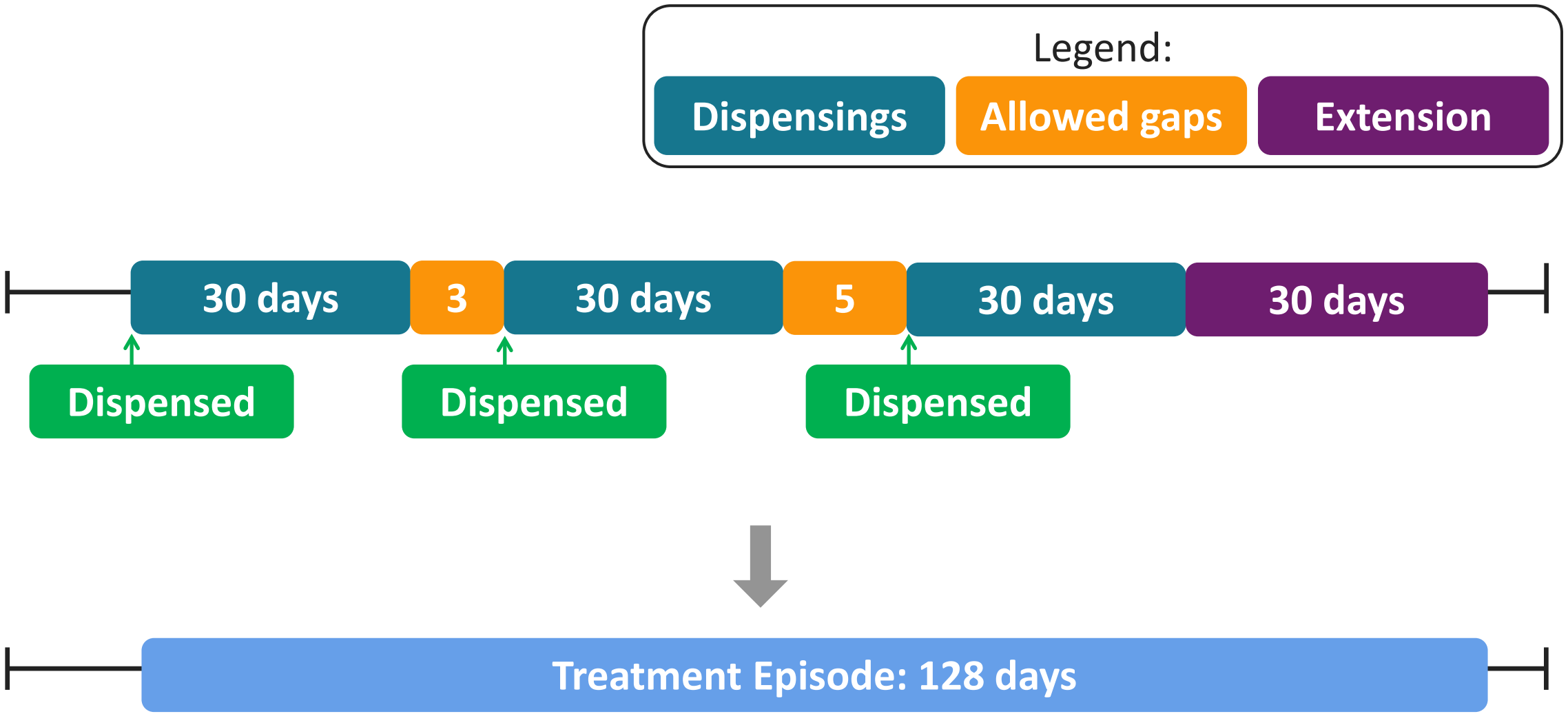
Creating exposure episodes: stockpiling

- Apply stockpiling algorithm to adjust dispensing dates



4. Identify medical product use in pregnancy

Creating exposure episodes: stockpiling



4. Identify medical product use in pregnancy

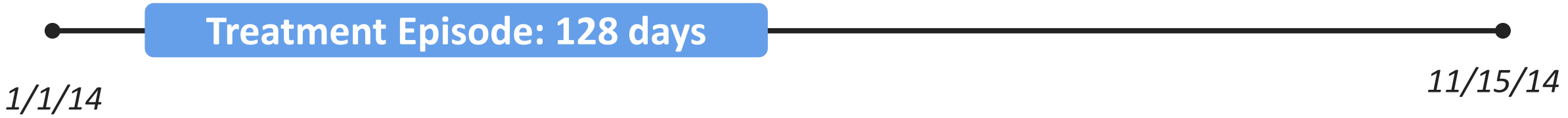
Defining gestational timing of medication exposure

Example patient:

4. Identify medical product use in pregnancy

Defining gestational timing of medication exposure

Example patient:

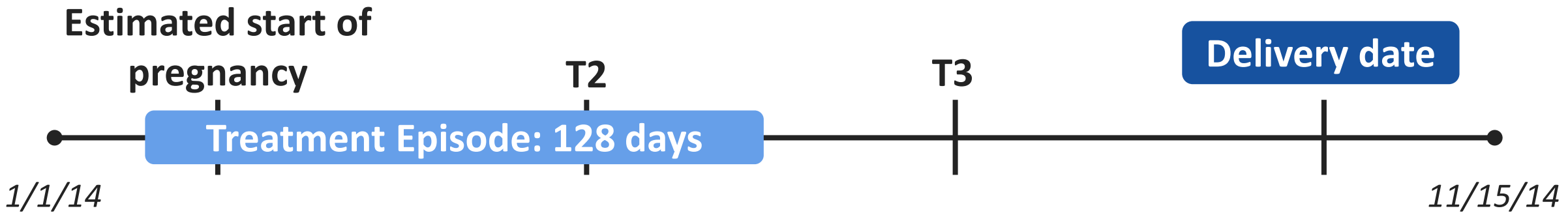


4. Identify medical product use in pregnancy

Defining gestational timing of medication exposure

Example patient:

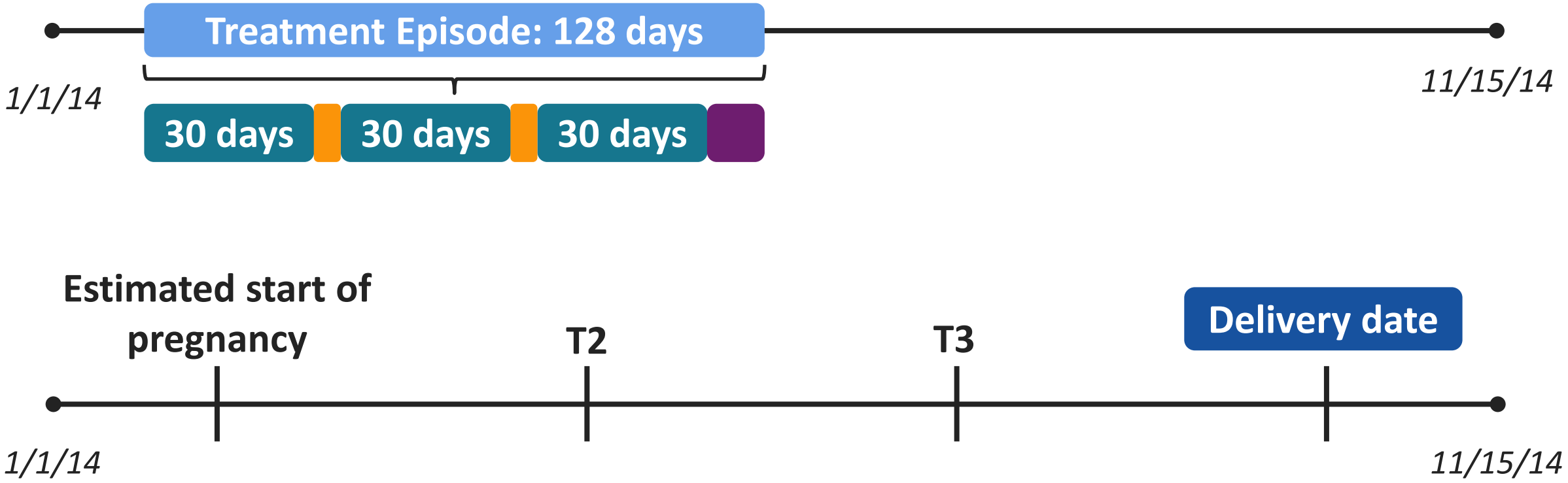
Based on overlapping treatment episode:
- **Exposed pre-pregnancy**
- **Exposed first trimester**
- **Exposed second trimester**



4. Identify medical product use in pregnancy

Defining gestational timing of medication exposure

Example patient:

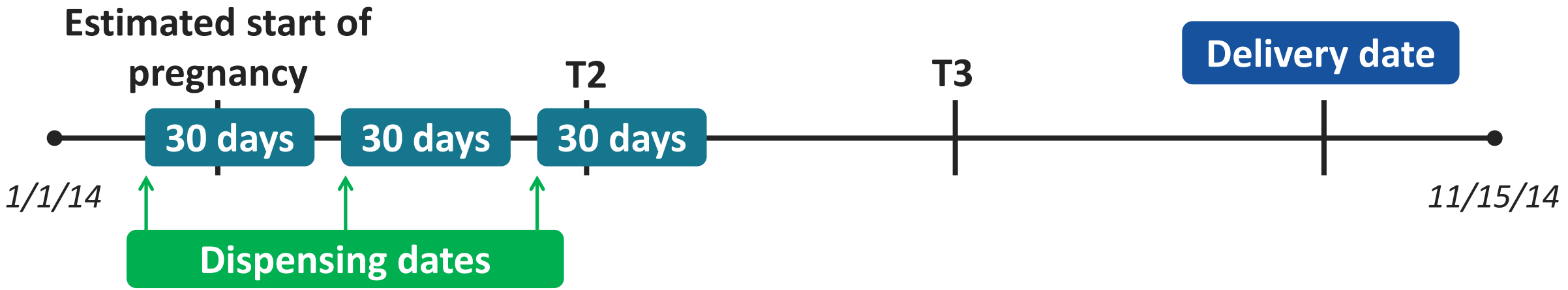


4. Identify medical product use in pregnancy

Defining gestational timing of medication exposure

Example patient:

Based on date of dispensing:
- **Exposed pre-pregnancy**
- **Exposed first trimester**
- **NOT exposed second trimester**



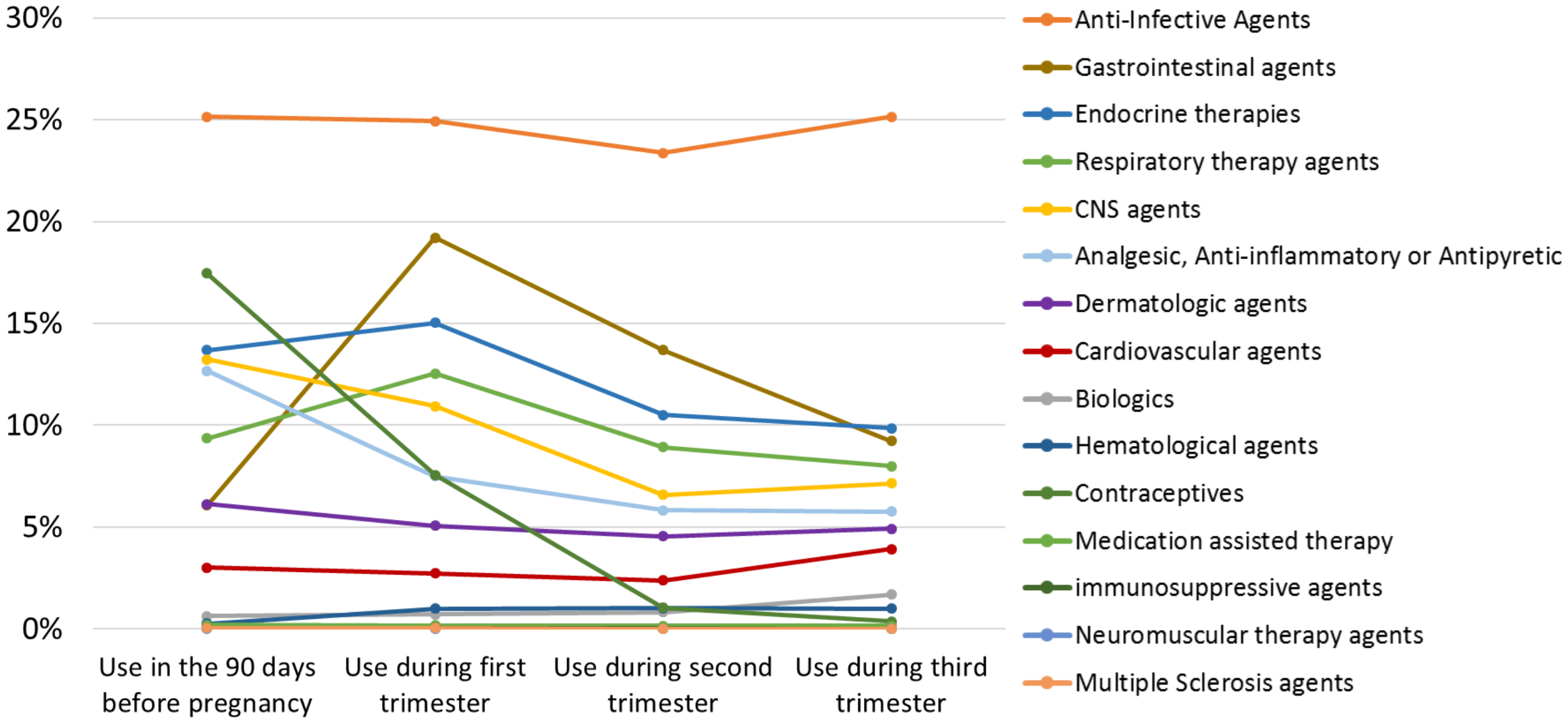
4. Identify medical product use in pregnancy

Characterizing medication exposure – 2 examples

- Example 1: Characterizing medication exposure for all linked deliveries in the MIL table
  - Identify commonly used medication groups during pregnancy
  - Used overlapping medication episode to define gestational timing
- Example 2: Studying utilization of topiramate and lamotrigine
  - Compare utilization during pregnancy and in a matched non-pregnant comparator cohort
  - Inform planned inferential analyses

4. Identify medical product use in pregnancy

Example 1: Medication Use During Pregnancy, Linked Deliveries



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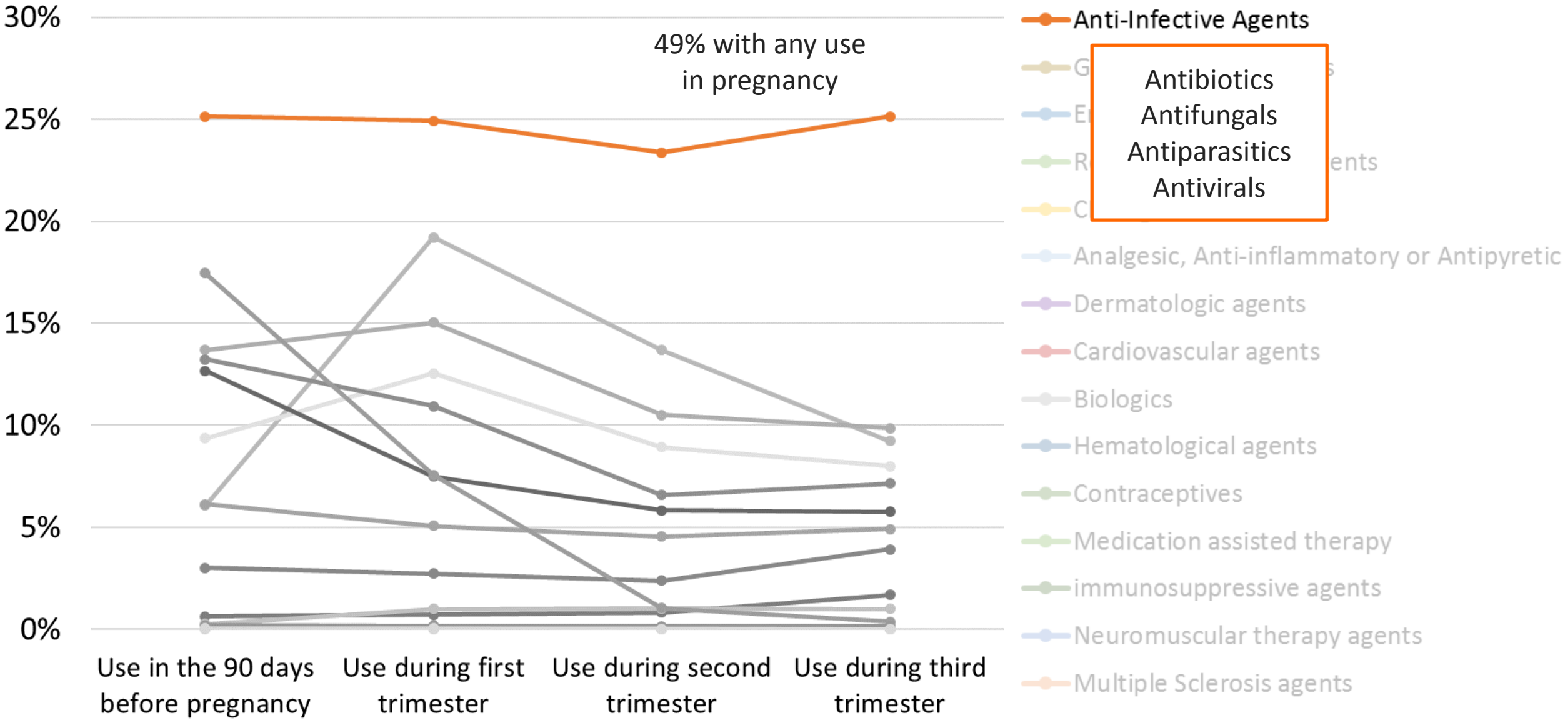

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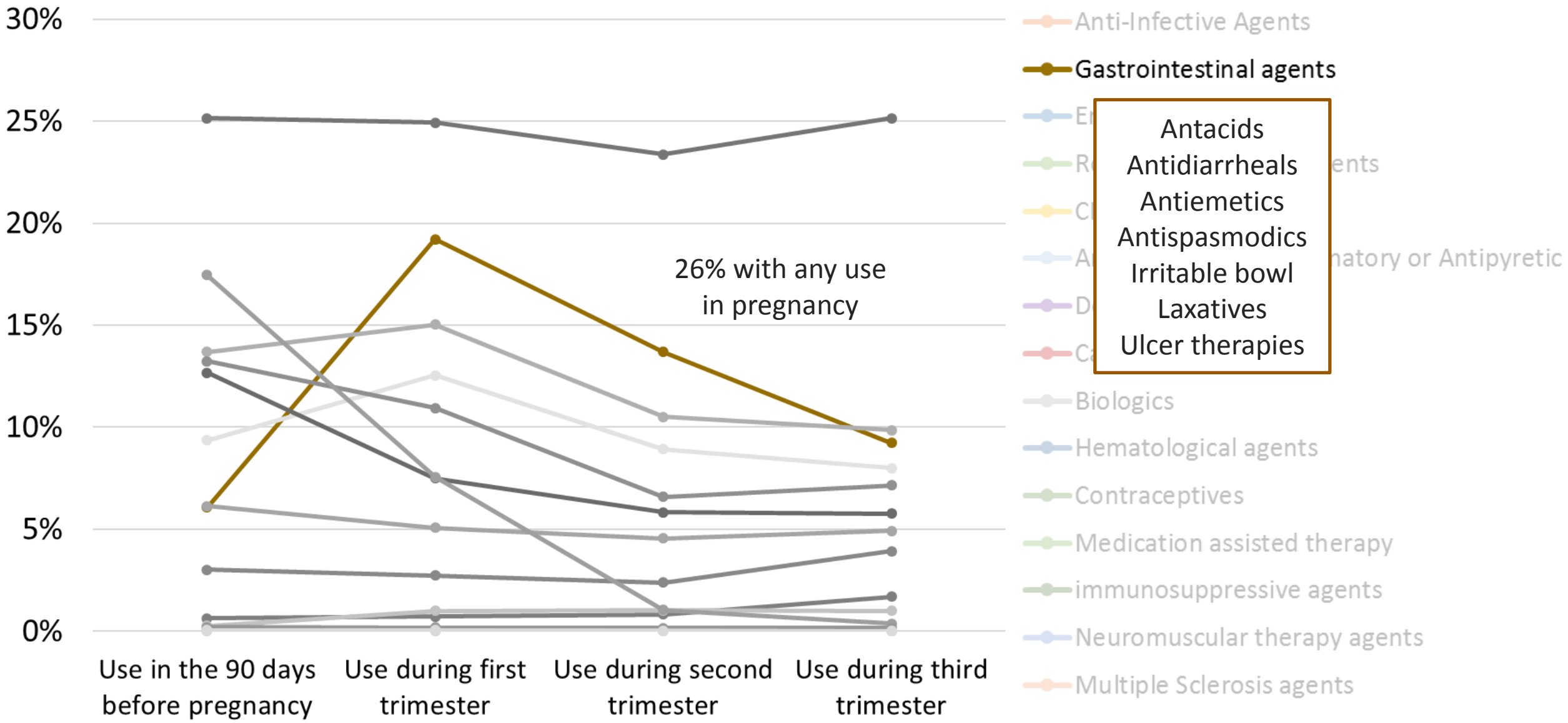
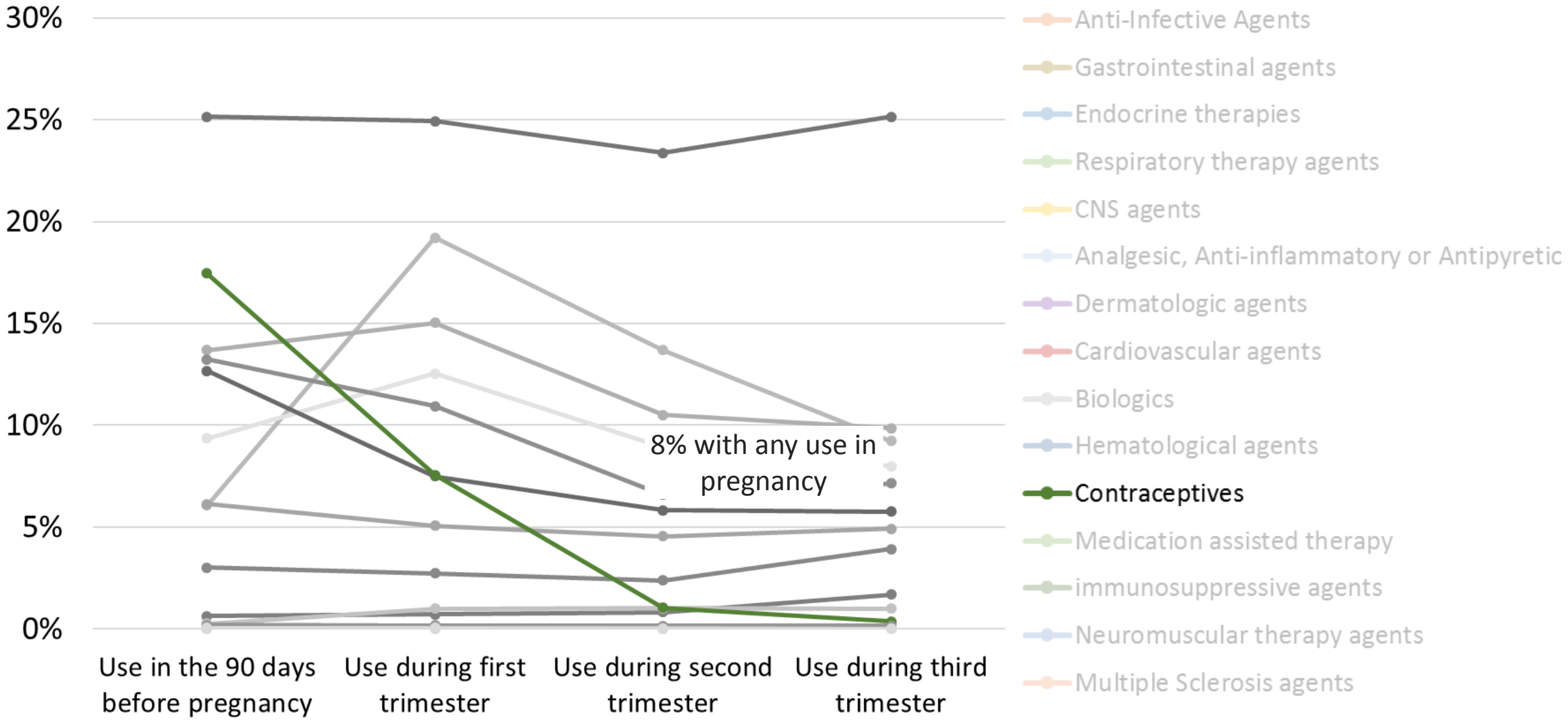
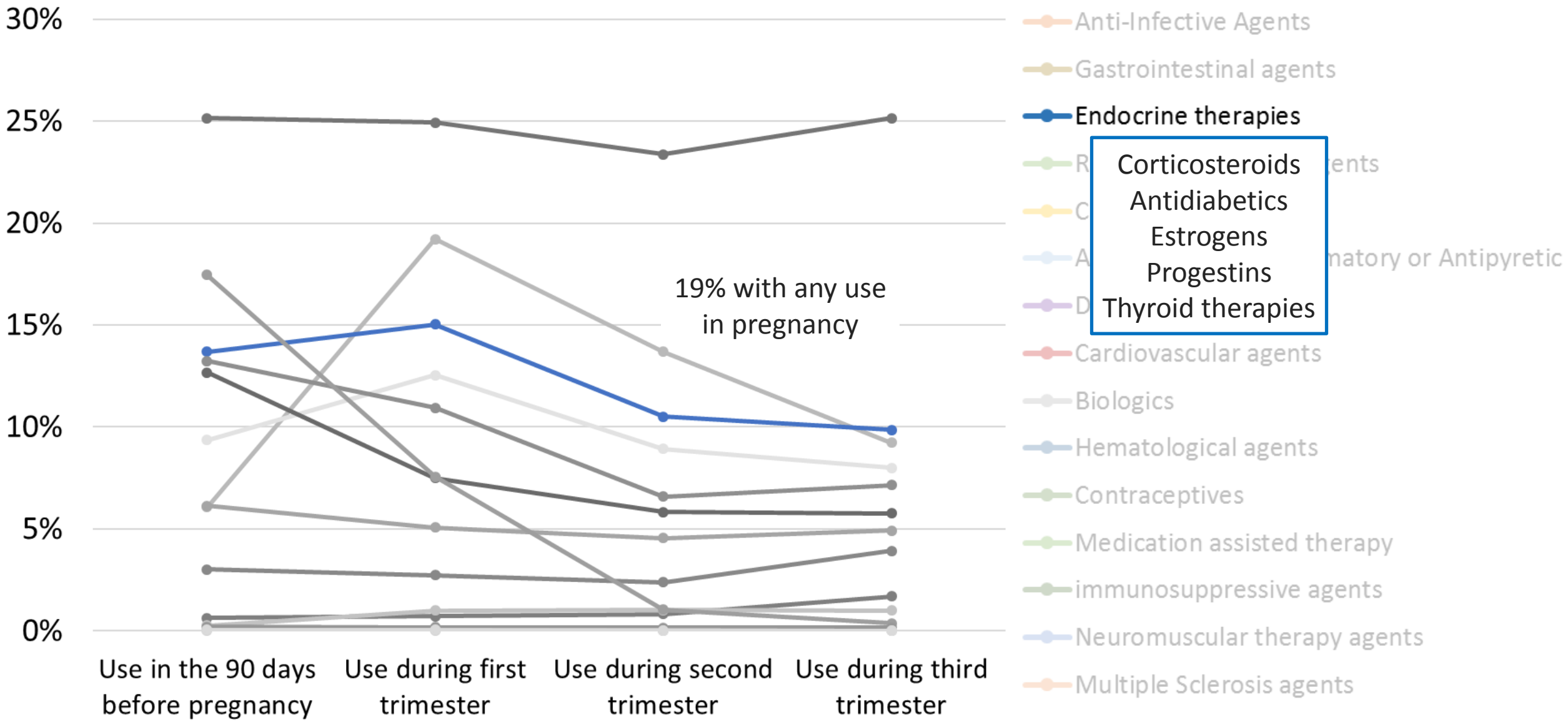


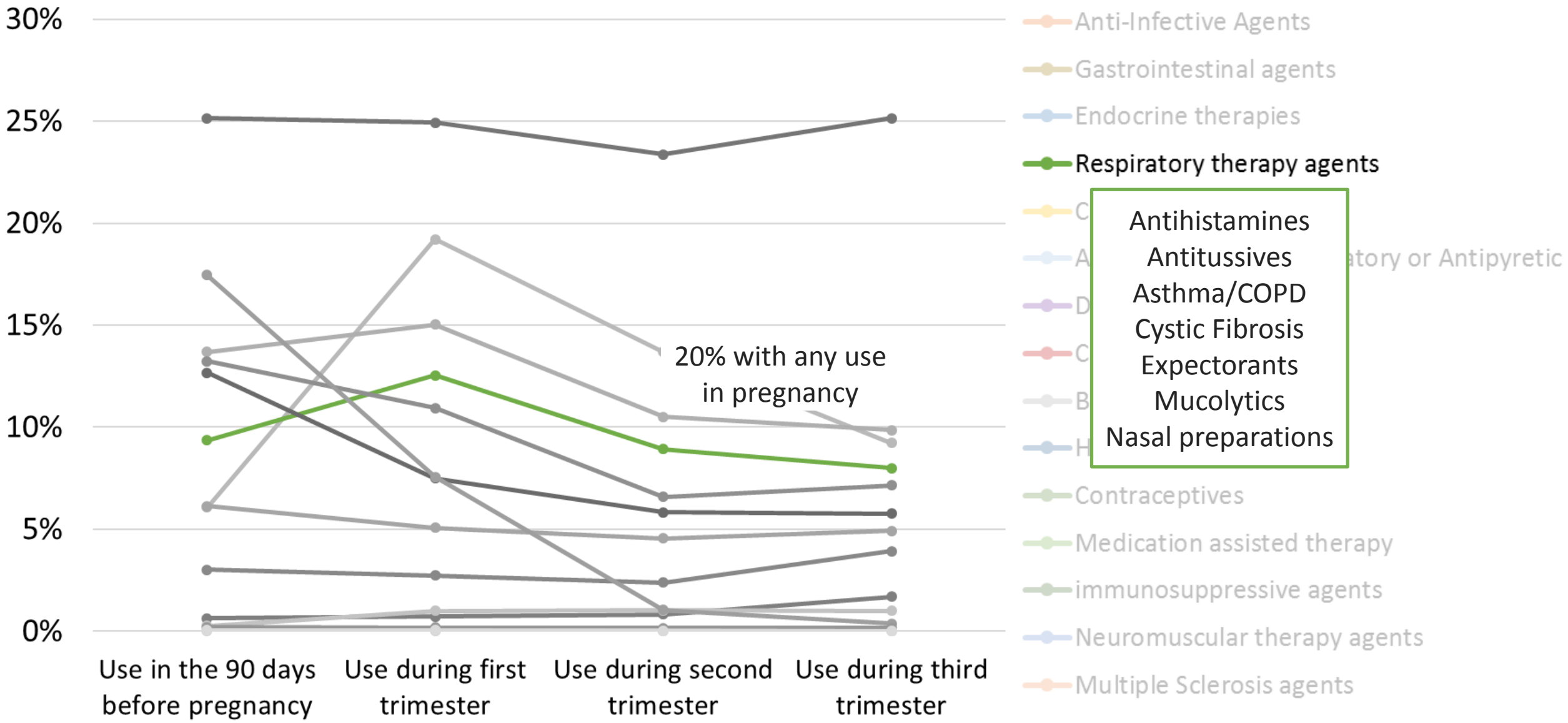
Example 1: Medication Use During Pregnancy, Linked Deliveries



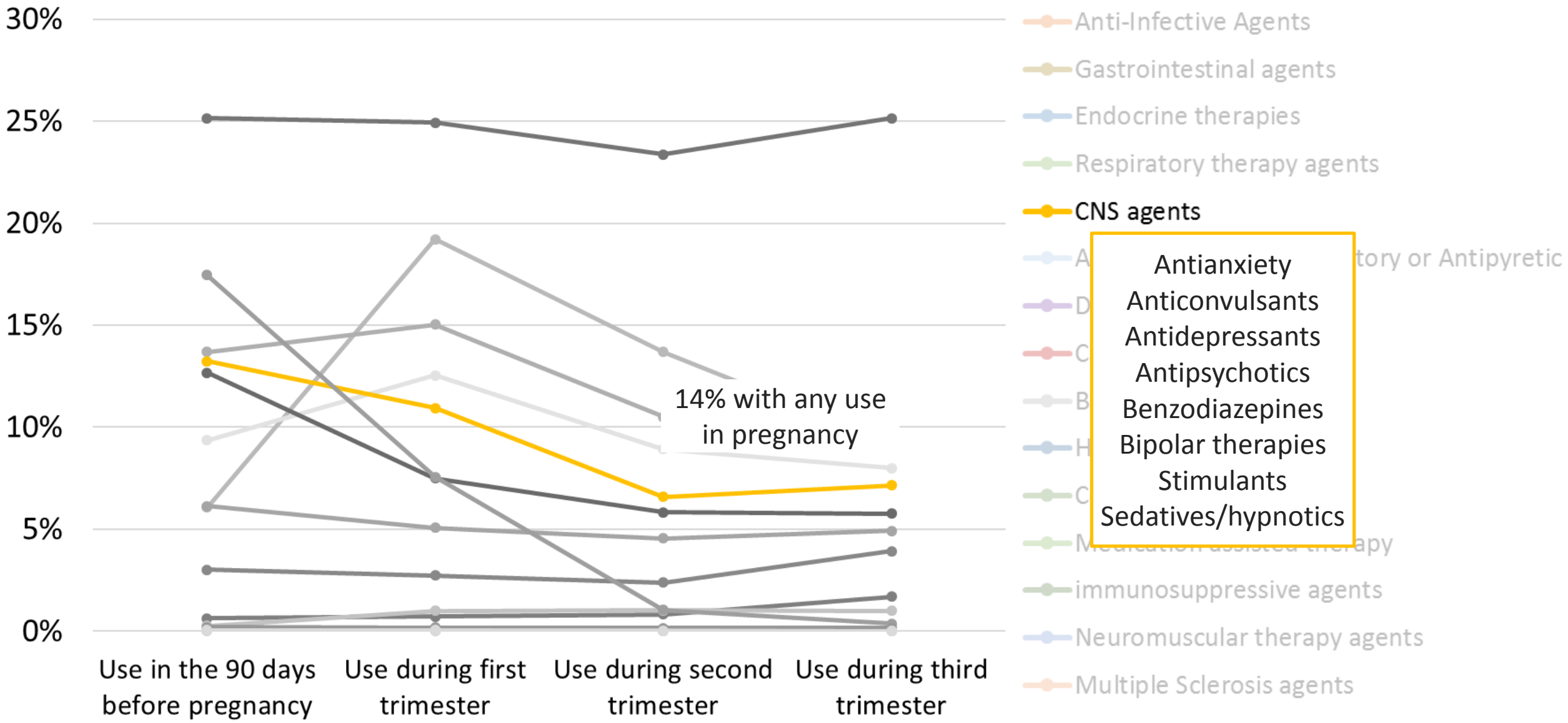
Example 1: Medication Use During Pregnancy, Linked Deliveries



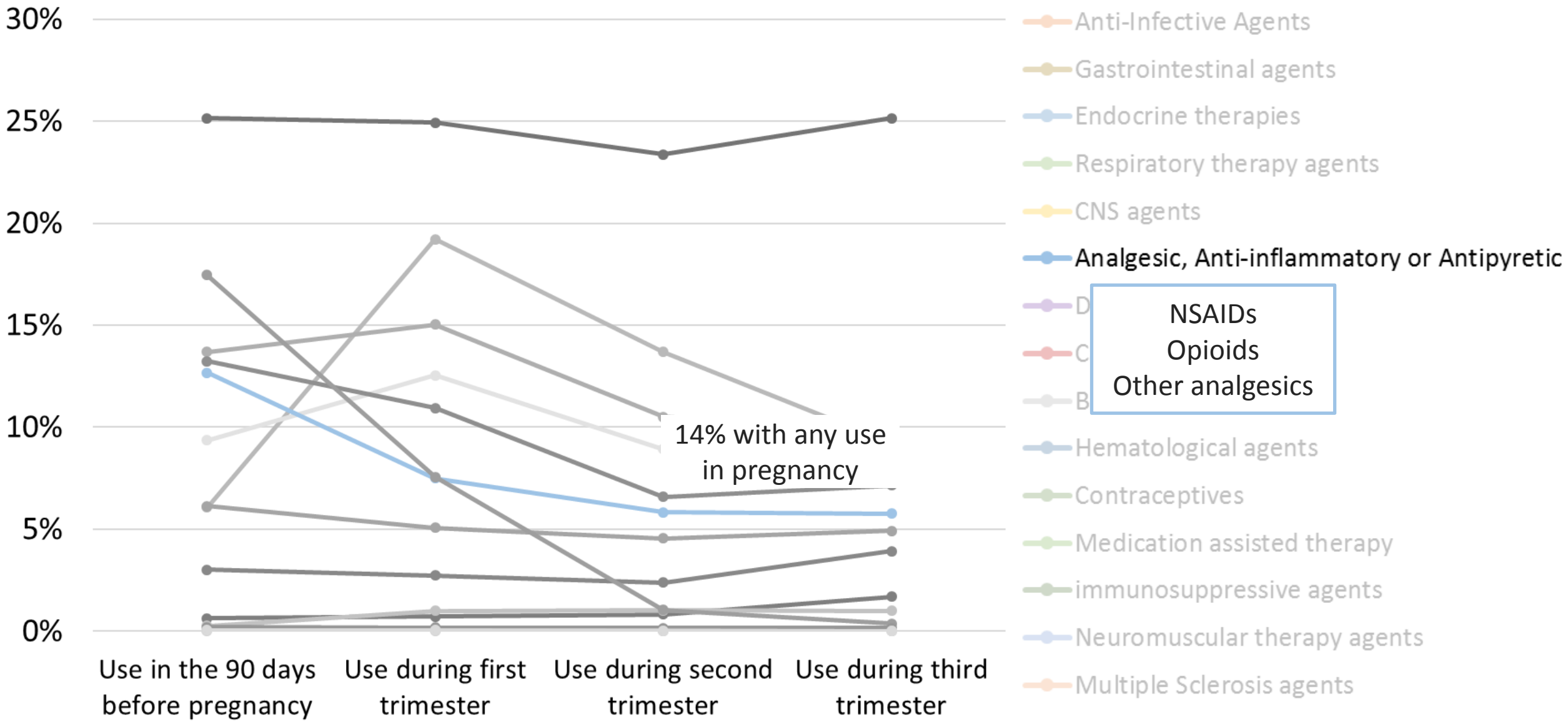
Example 1: Medication Use During Pregnancy, Linked Deliveries



Example 1: Medication Use During Pregnancy, Linked Deliveries



Example 1: Medication Use During Pregnancy, Linked Deliveries



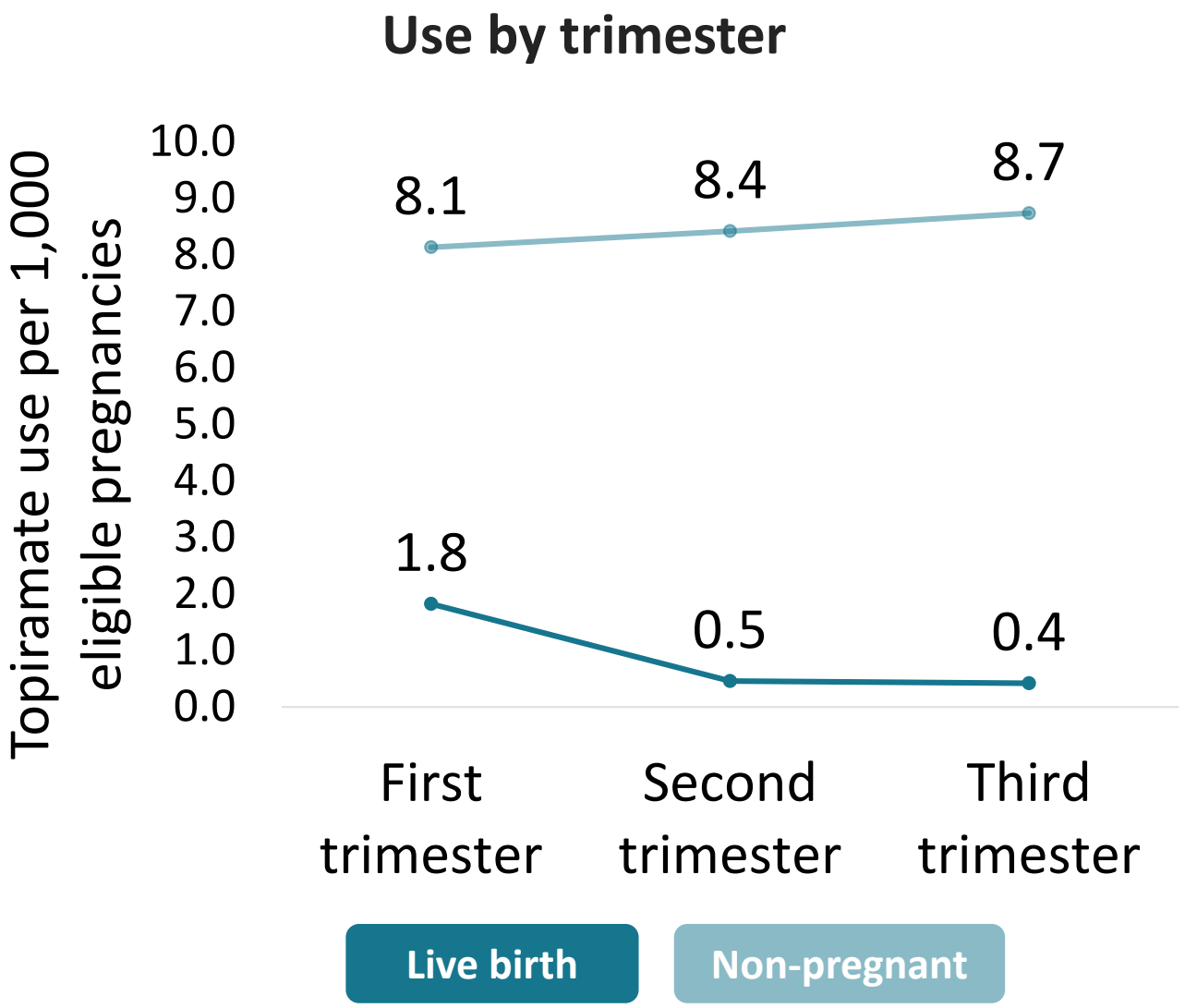
Example 2: Studying utilization of topiramate and lamotrigine

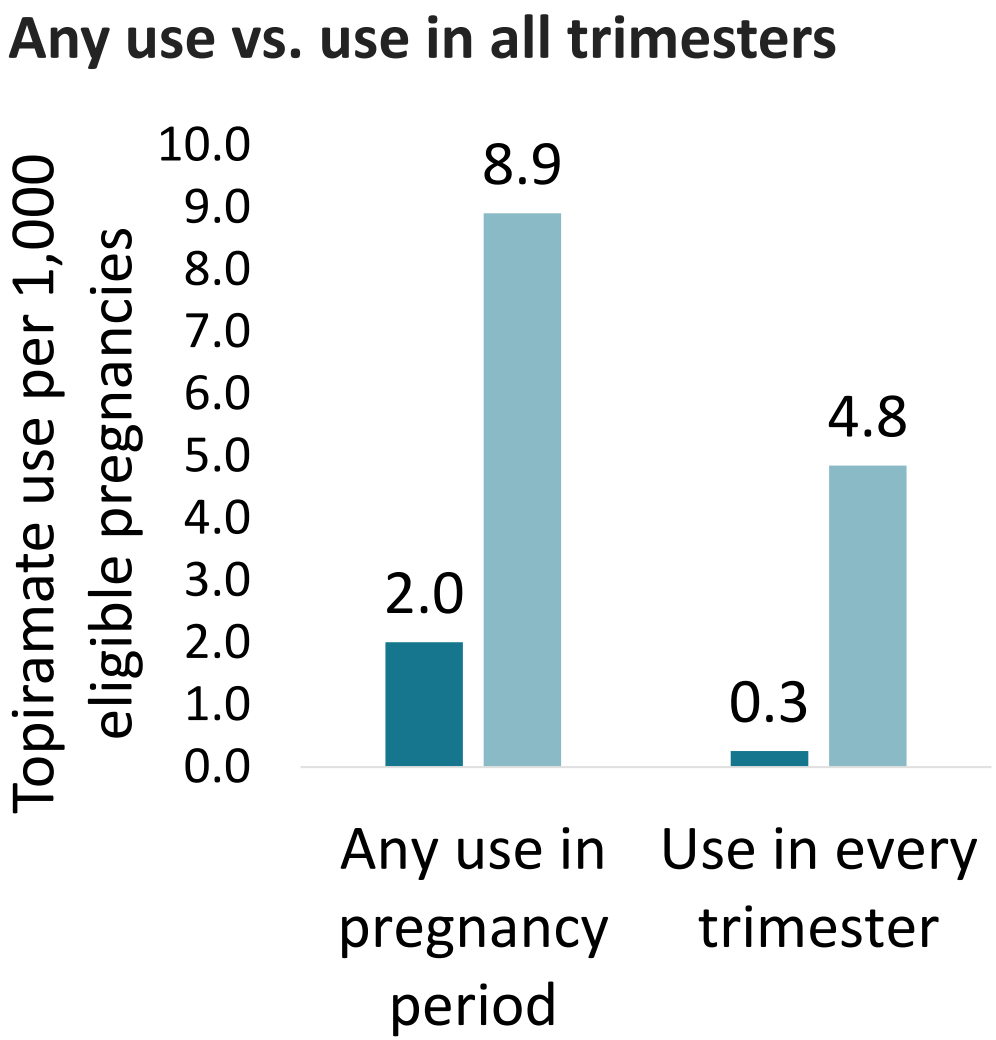
- Study parameters:
  - Study period: January 1, 2000 – September 30, 2015
  - Live births linked to infants, selected from the MIL table
  - Look at utilization of Topiramate and Lamotrigine by trimester

Characteristic	Live Birth Pregnancy Cohort	Non-Pregnant Cohort
Patients, N	1,311,094	1,320,369
Pregnancies, N	1,538,486	1,538,486
Age, years, mean (sd)	30.60 (4.76)	30.60 (4.78)

4. Identify medical product use in pregnancy

Topiramate use

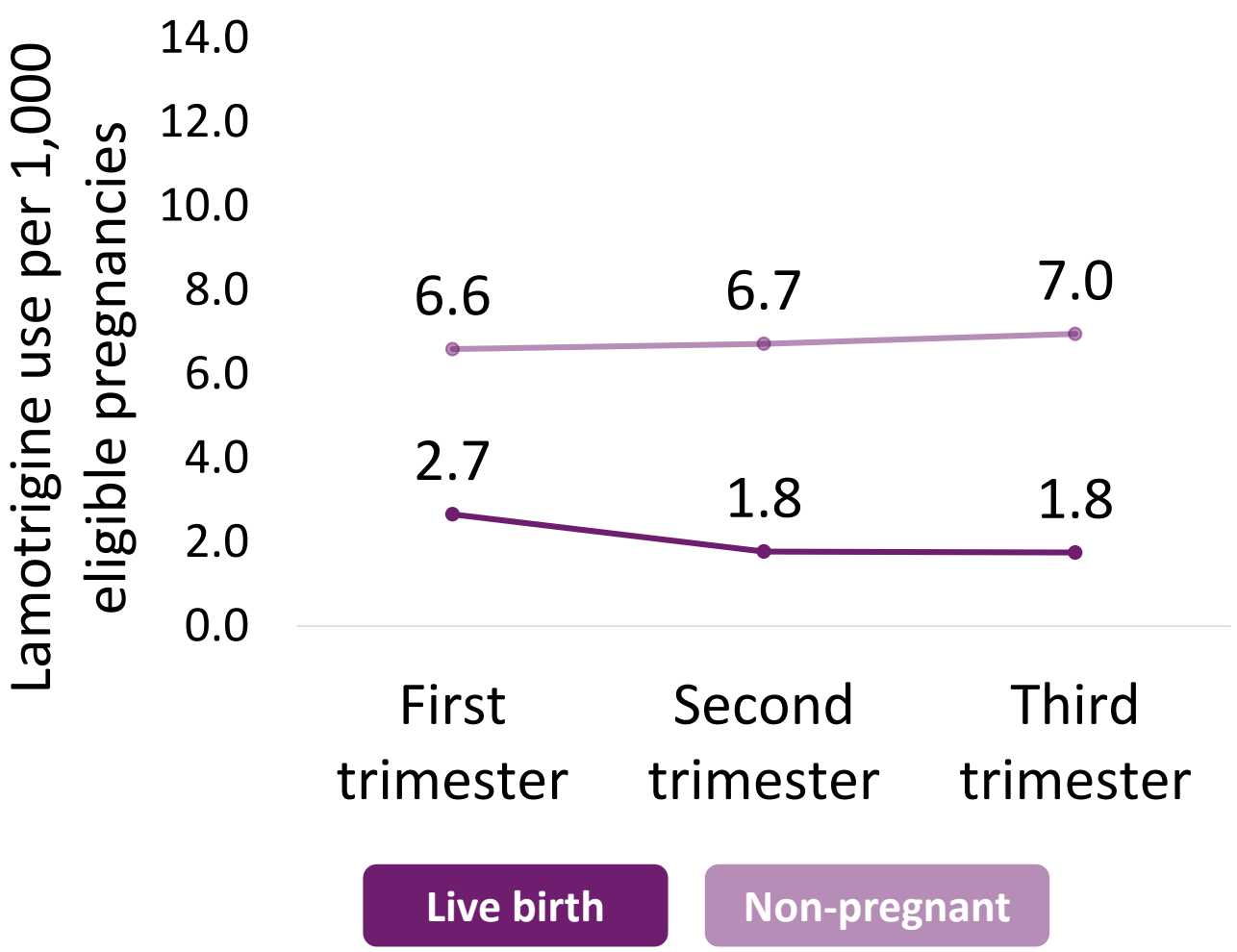




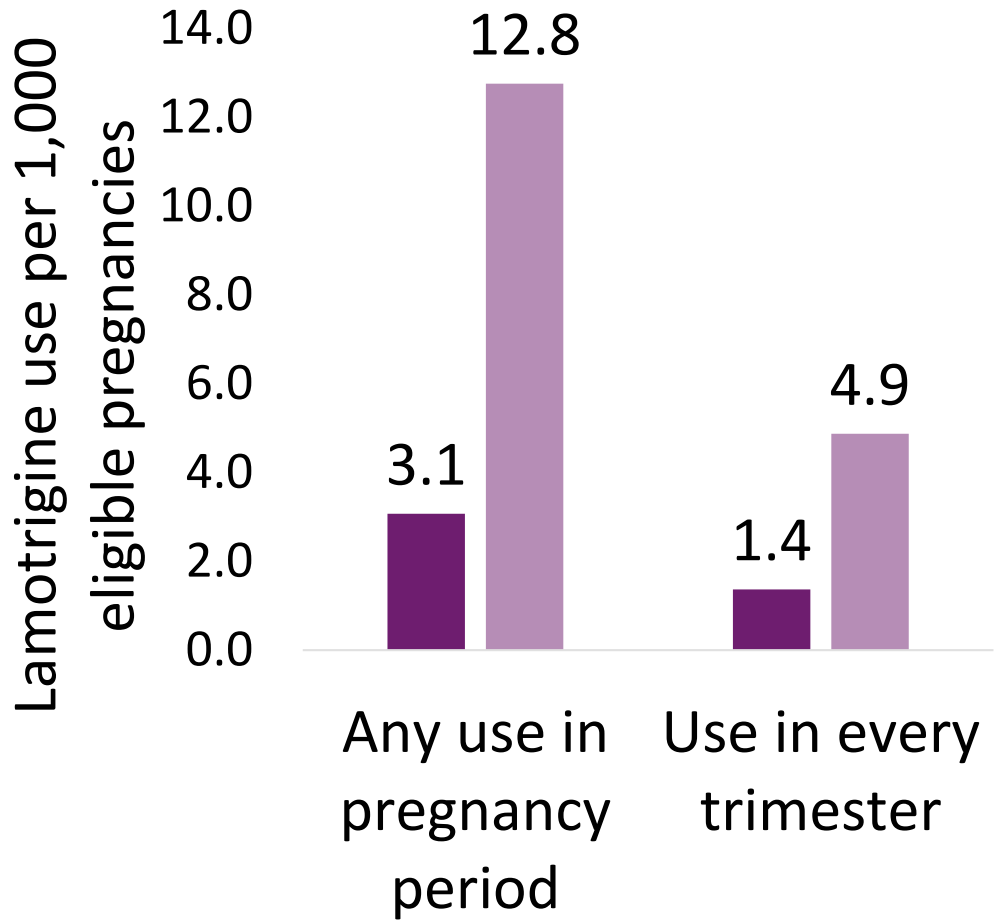
4. Identify medical product use in pregnancy

Lamotrigine use

Use by trimester

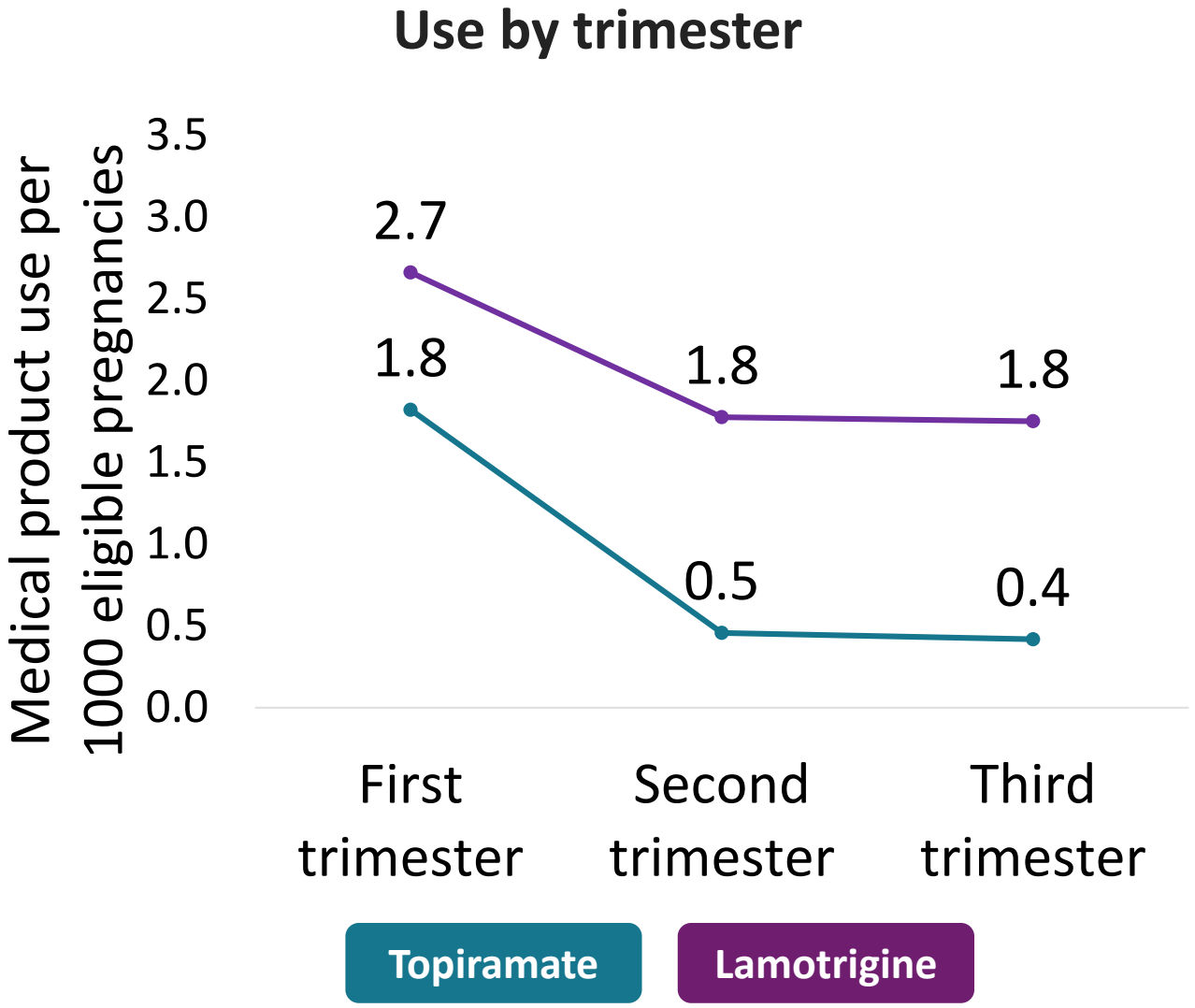


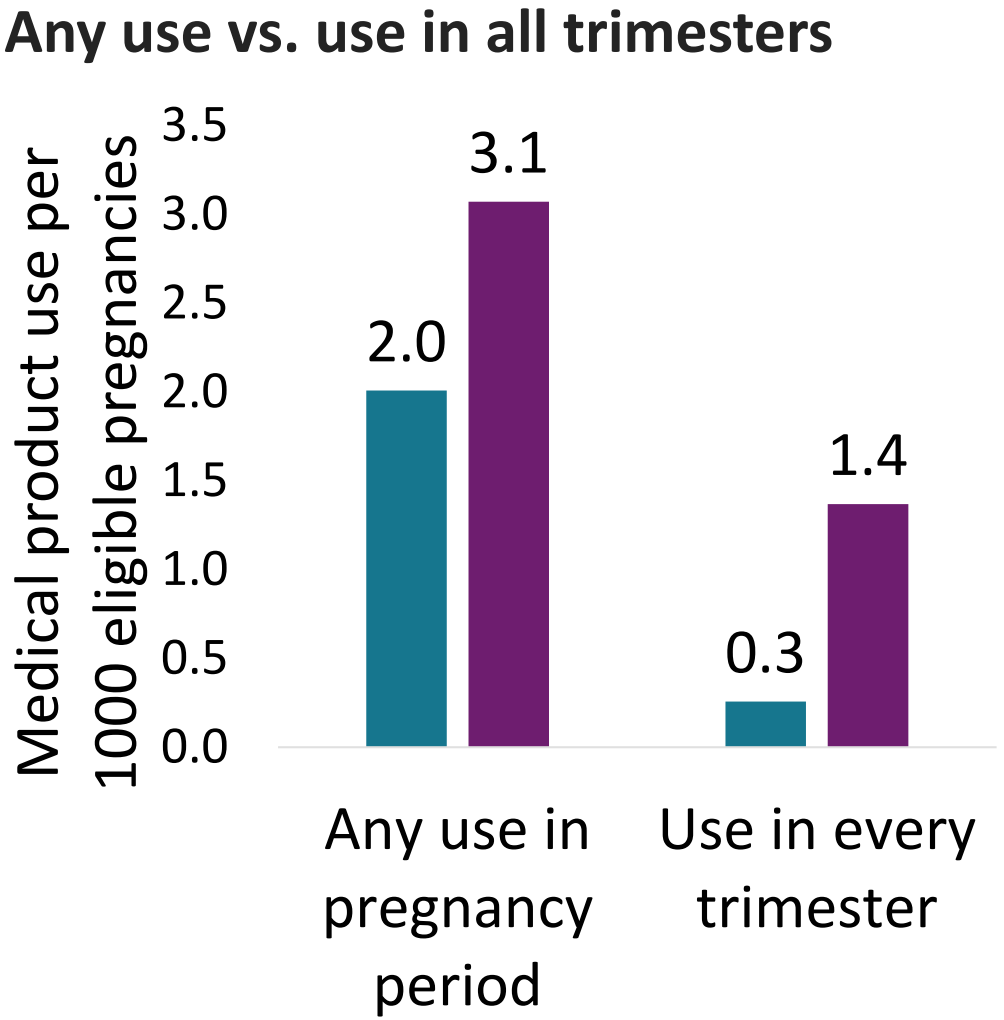
Any use vs. use in all trimesters



4. Identify medical product use in pregnancy

Comparing Topiramate and Lamotrigine use in pregnancy





4. Identify medical product use in pregnancy

Part 2 Questions

Break

10 minutes

Inferential Analyses for Perinatal Exposures

Mayura Shinde, DrPH

Pregnancy Analyses

Use Case: Topiramate Use in Early Pregnancy and Risk of Oral Clefts

Use Case: Topiramate and Oral Clefts

ARTICLE

Topiramate use early in pregnancy and the risk of oral clefts

A pregnancy cohort study

1.3 million pregnancies with a live birth from US Medicaid Analytic Extract from 2000-2010

ni J. Desai, PhD, Jacqueline M. Cohen, PhD,
MD, and Elisabetta Patorno, DrPH

00000004857

Correspondence
Dr. Hernandez-Diaz
shernan@hsph.harvard.edu

Abstract

Objective

To assess the relative risk of oral clefts associated
topiramate during the first trimester for epilepsy

Methods

This population-based study nested in the US 2000–2010 Medicaid Analytic eXtract included a cohort of 1,360,101 pregnant women with a live-born infant enrolled in Medicaid from 3 months before conception through 1 month after delivery. Oral clefts were defined as the presence of a recorded diagnosis in claims during the first 90 days after birth. Women with a topiramate dispensing during the first trimester were compared with those without any

Maternal use of topiramate during the first trimester was associated with an ≈3-fold increased risk of oral clefts after accounting for confounding by clinical characteristics...

Topiramate

- Approved indications:
  - Epilepsy
  - Migraine headaches
- May be used off-label for:
  - Bipolar disorder
  - Chronic weight management
  - Alcohol dependence
- Previous pregnancy classification: Category D

- Fetal Toxicity: use during pregnancy can cause cleft lip and/or palate and being small for gestational age (5.7)

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-risk-oral-clefts-children-born-mothers-taking-topamax-topiramate
https://www.cdc.gov/ncbddd/birthdefects/features/birthdefects-topiramate-keyfindings.html

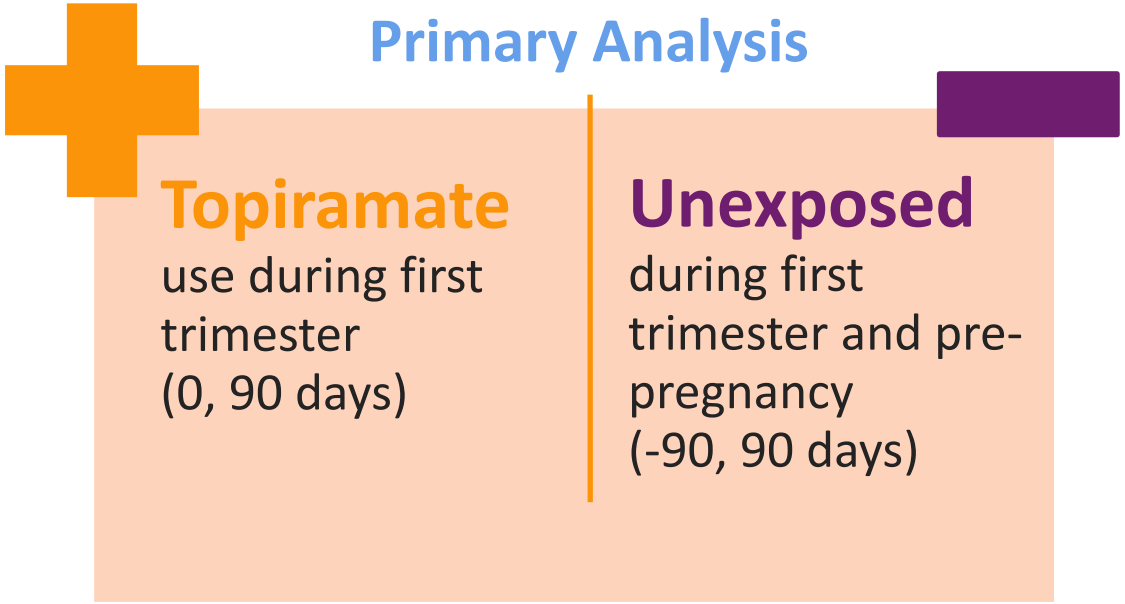
Oral Clefts

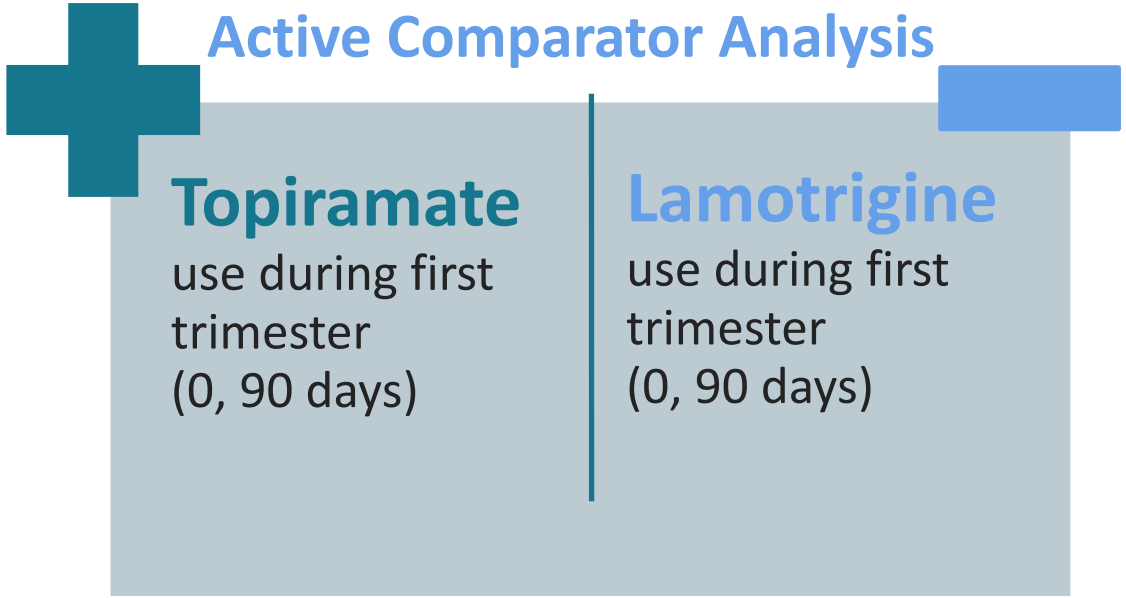
- Cleft lip/cleft palate is second most common birth defects in United States
- Approximately 1 in 1,600 infants is born with cleft lip with cleft palate and 1 in 1,700 with cleft palate
- Risk factors include:
  - Genetics
  - Smoking
  - Diabetes
  - In utero exposures to some medical products, such as antiepileptics

Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A; National Birth Defects Prevention Network. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol. 2010 Dec;88(12):1008-16.
Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, Lupo PJ, Riehle-Colarusso T, Cho SJ, Aggarwal D, Kirby RS. National population-based estimates for major birth defects, 2010–2014. *Birth Defects Research.* 2019; 111(18): 1420-1435.

Use Case Study Parameters

- Objective: To assess the risk of **oral clefts** with topiramate use during the first trimester of pregnancy in the Sentinel Distributed Database (SDD).
  - Study period: January 1, 2000 – September 30, 2015
  - Women, aged 12-55 years
  - No evidence of chromosomal abnormalities and teratogen medication use





Creating and analyzing a cohort of deliveries

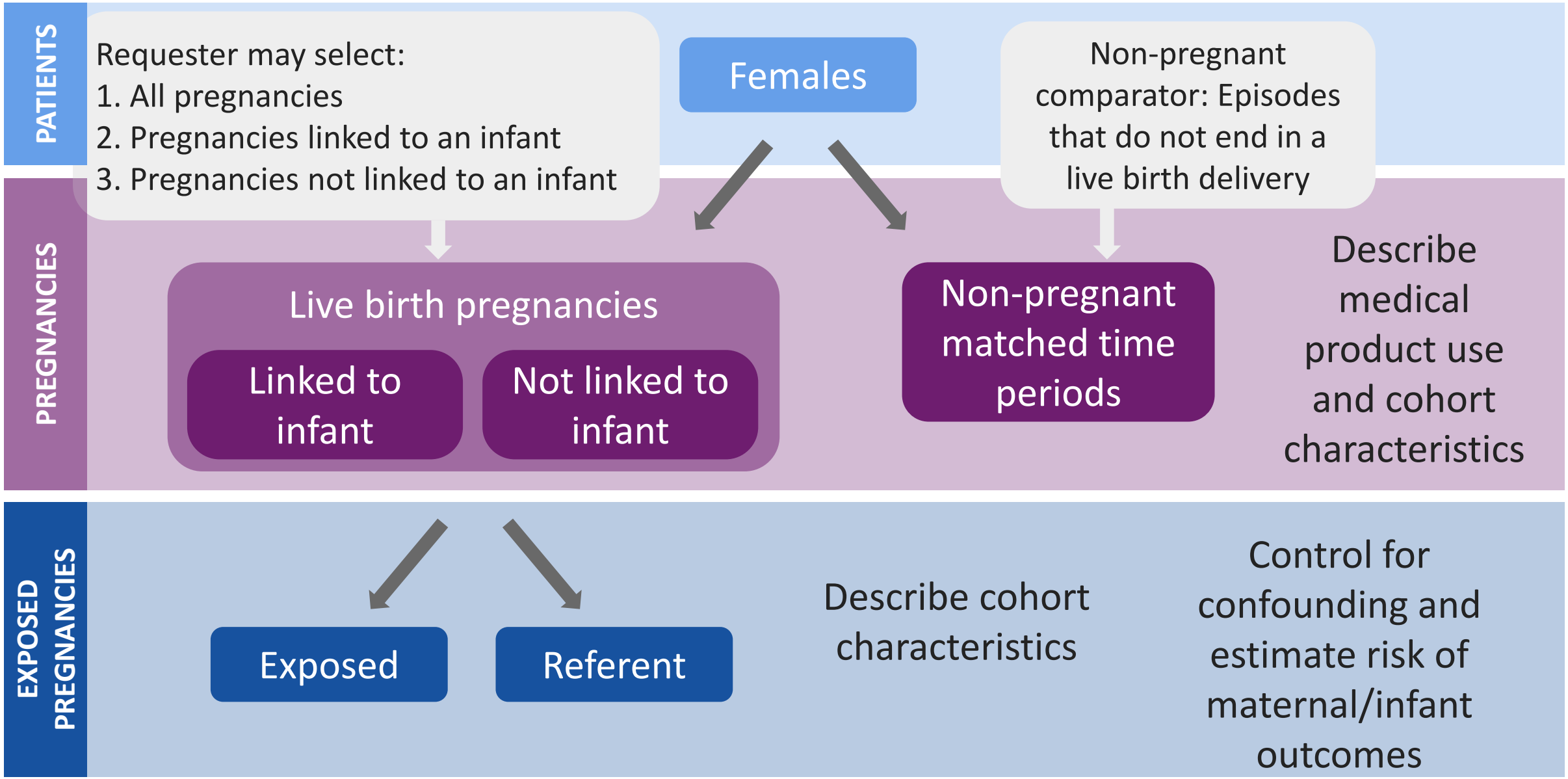
1. Identify live birth deliveries ← Mother-Infant Linkage Table
2. Estimate pregnancy start ← Gestational Age Algorithm
3. Create a non-pregnant comparator cohort
4. Identify medical product use in pregnancy

} Descriptive Analyses

5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes
7. Evaluate exposure-outcome relationship

} **Inferential Analyses**

Cohort Selection

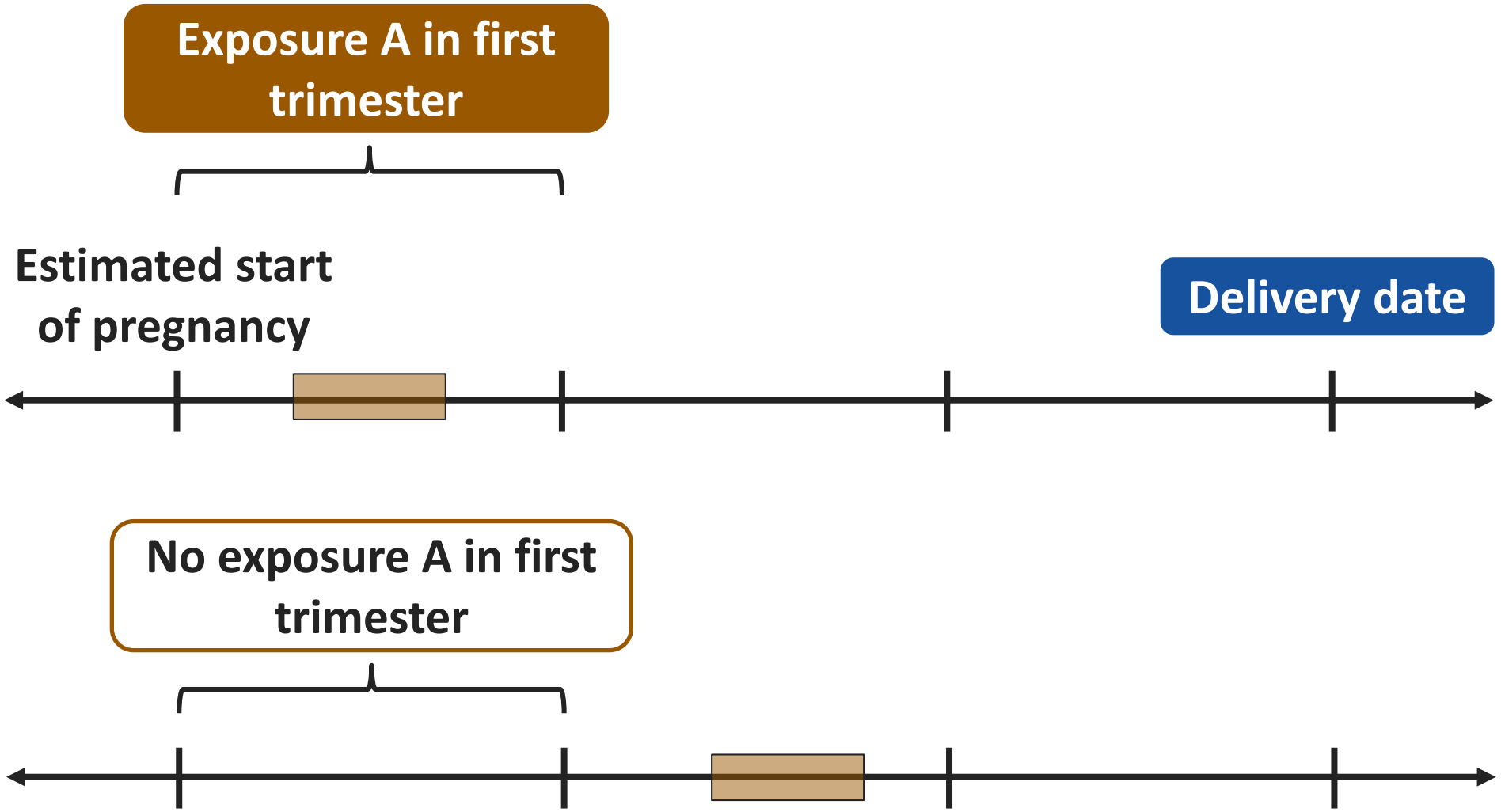


Defining the Exposed and Referent Cohorts

- Exposure is binary
  - A pregnancy may be exposed (yes vs. no) during a specific exposure window
  - Pregnancies are classified as either *exposed* or *unexposed/comparator-exposed*
- The exposure window can be specified in trimesters or gestational weeks
  - E.g. first trimester, or gestational weeks 6-12

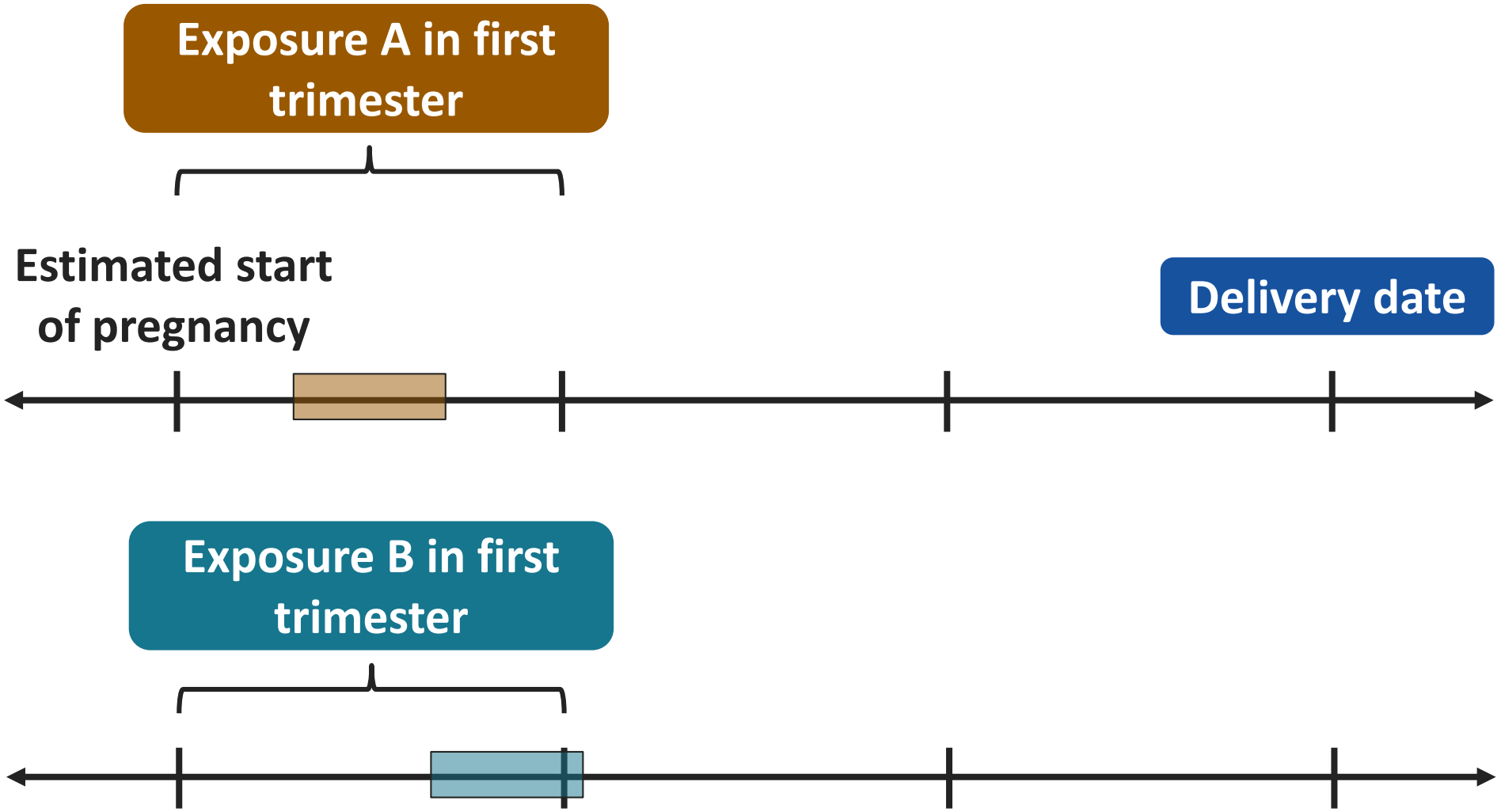
5. Create exposed and referent cohorts

Defining exposed and unexposed referent groups



5. Create exposed and referent cohorts

Defining exposed and comparator exposed referent groups



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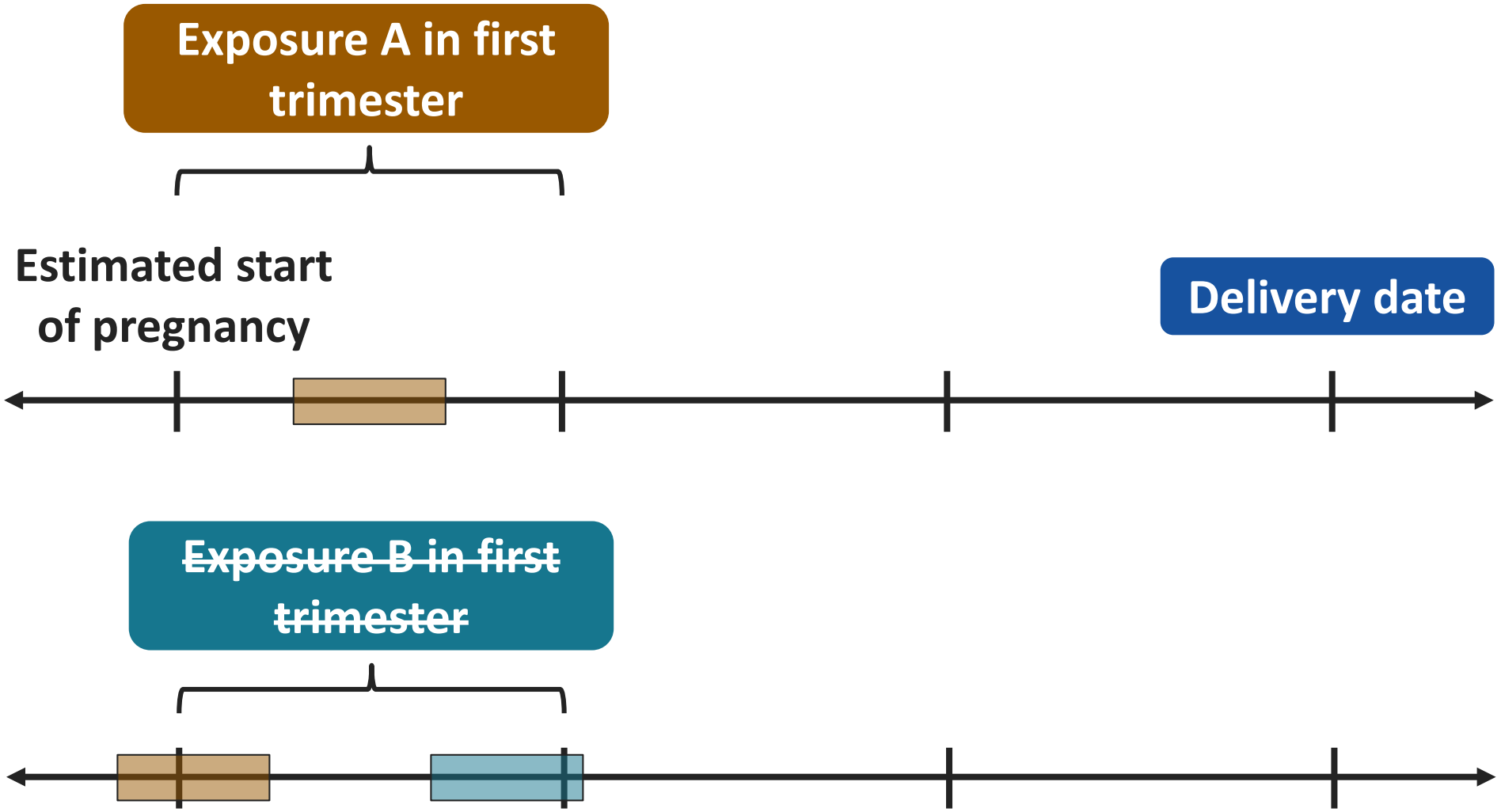
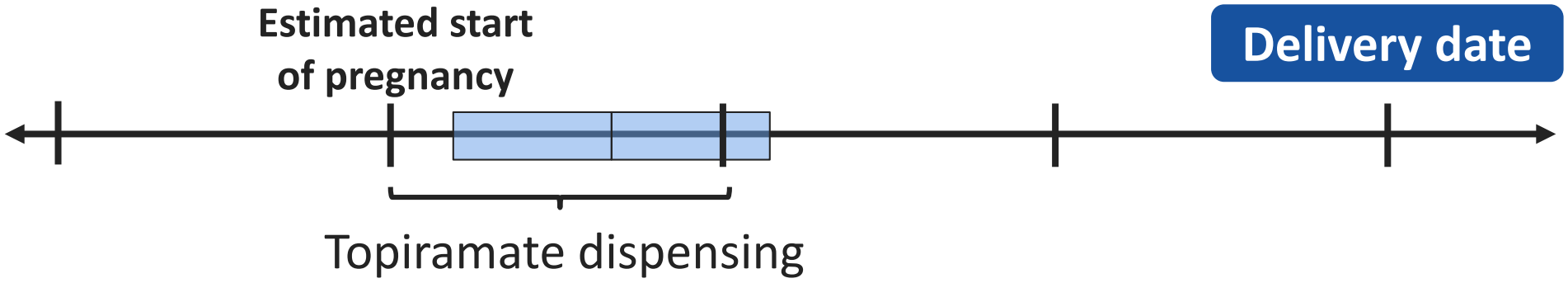
Defining exposed and comparator exposed referent groups



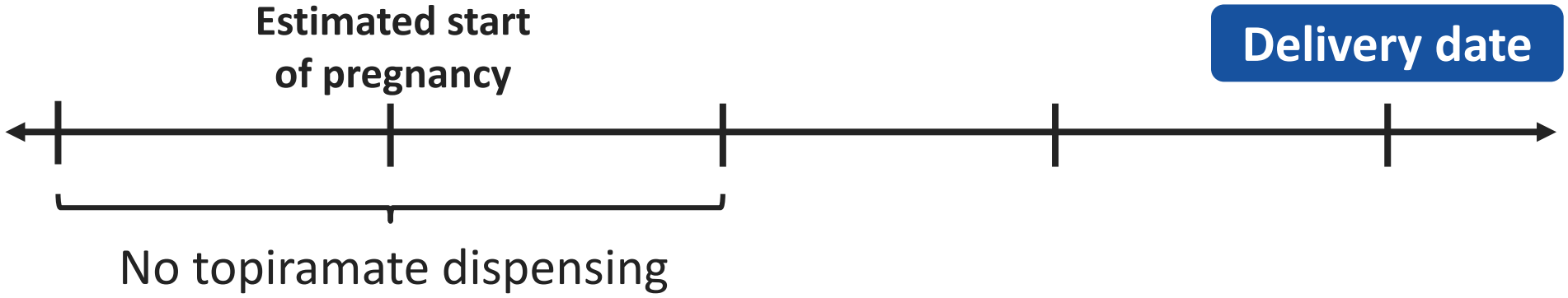
5. Create exposed and referent cohorts

Topiramate study exposure definitions: unexposed comparator

Classified as exposed to topiramate if dispensing date was in the first trimester

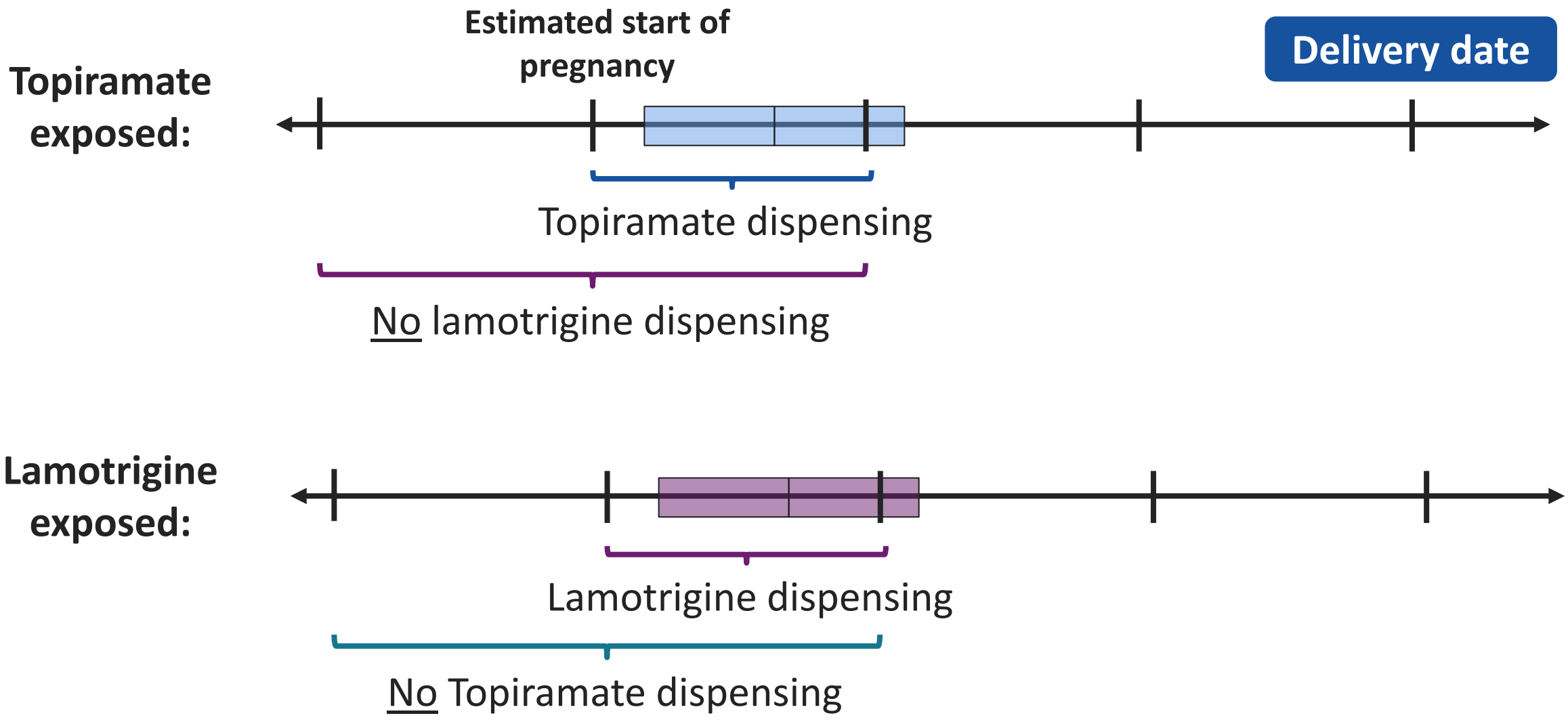


Classified as unexposed to topiramate no dispensing occurred in first trimester or 90 days before pregnancy start



5. Create exposed and referent cohorts

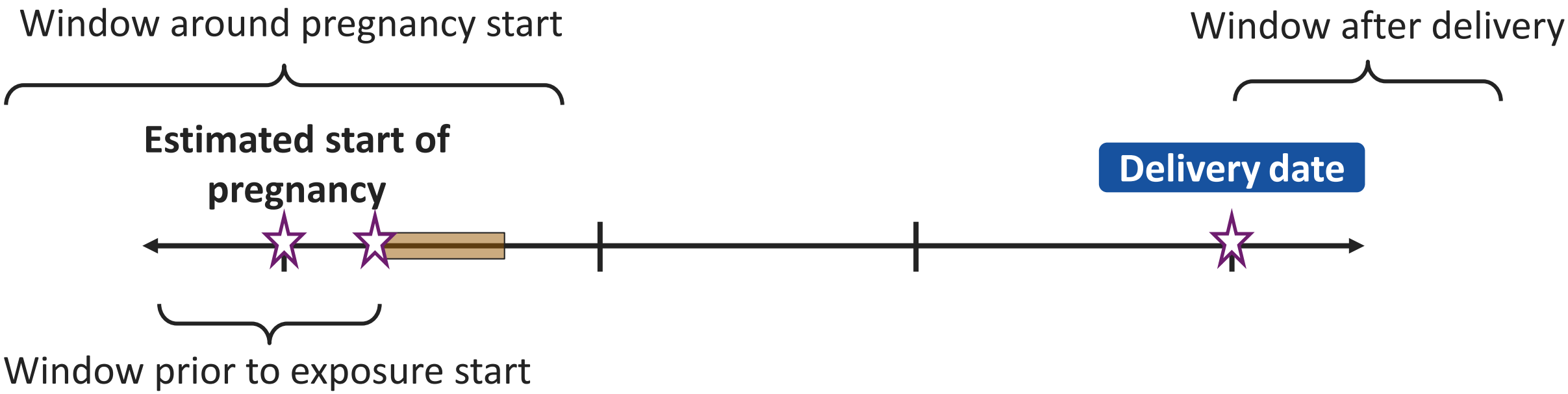
Topiramate study exposure definitions: active comparator



5. Create exposed and referent cohorts

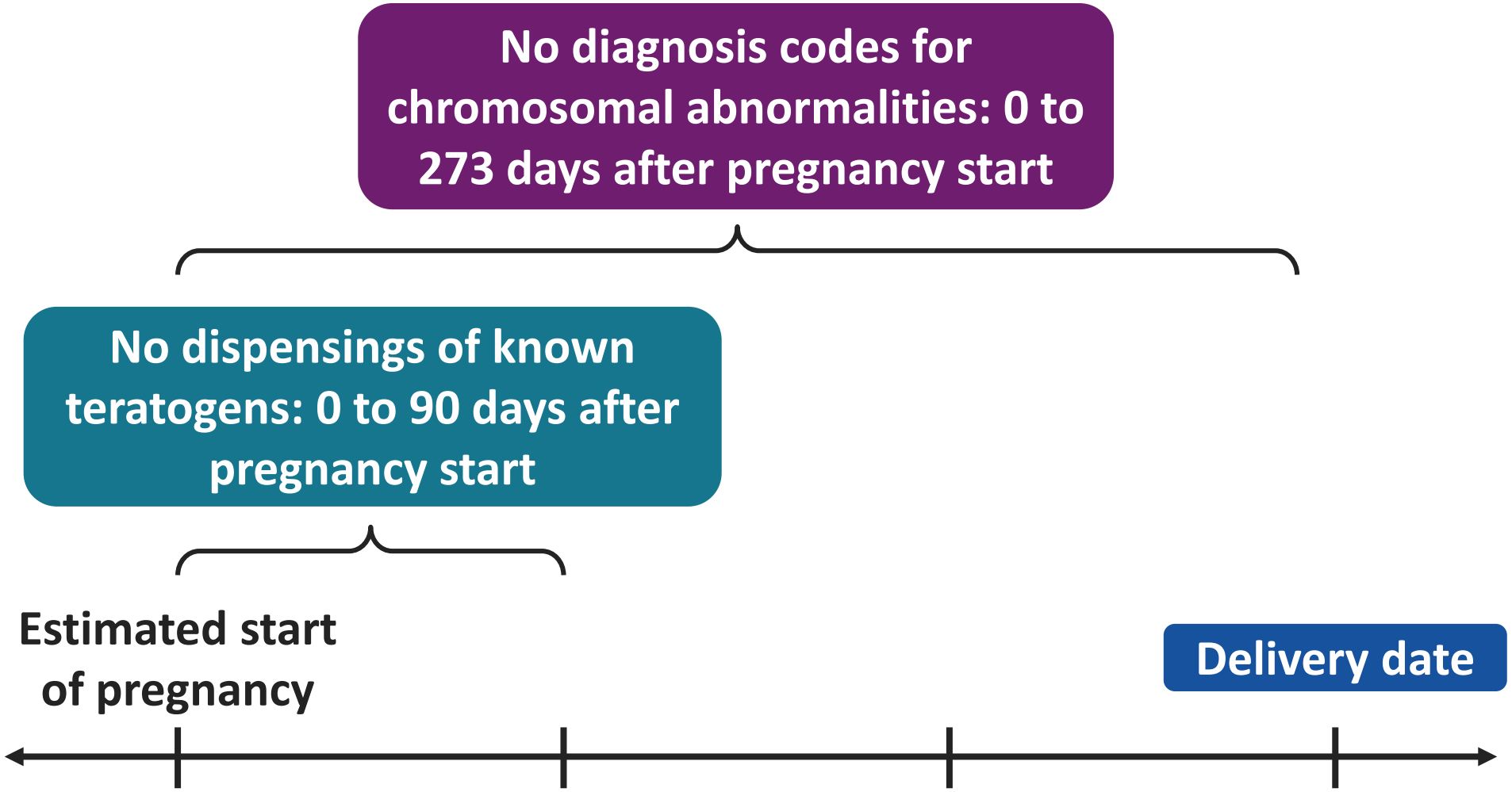
Refine Exposed and Referent Cohorts

- Define window for exclusions/inclusions and covariates



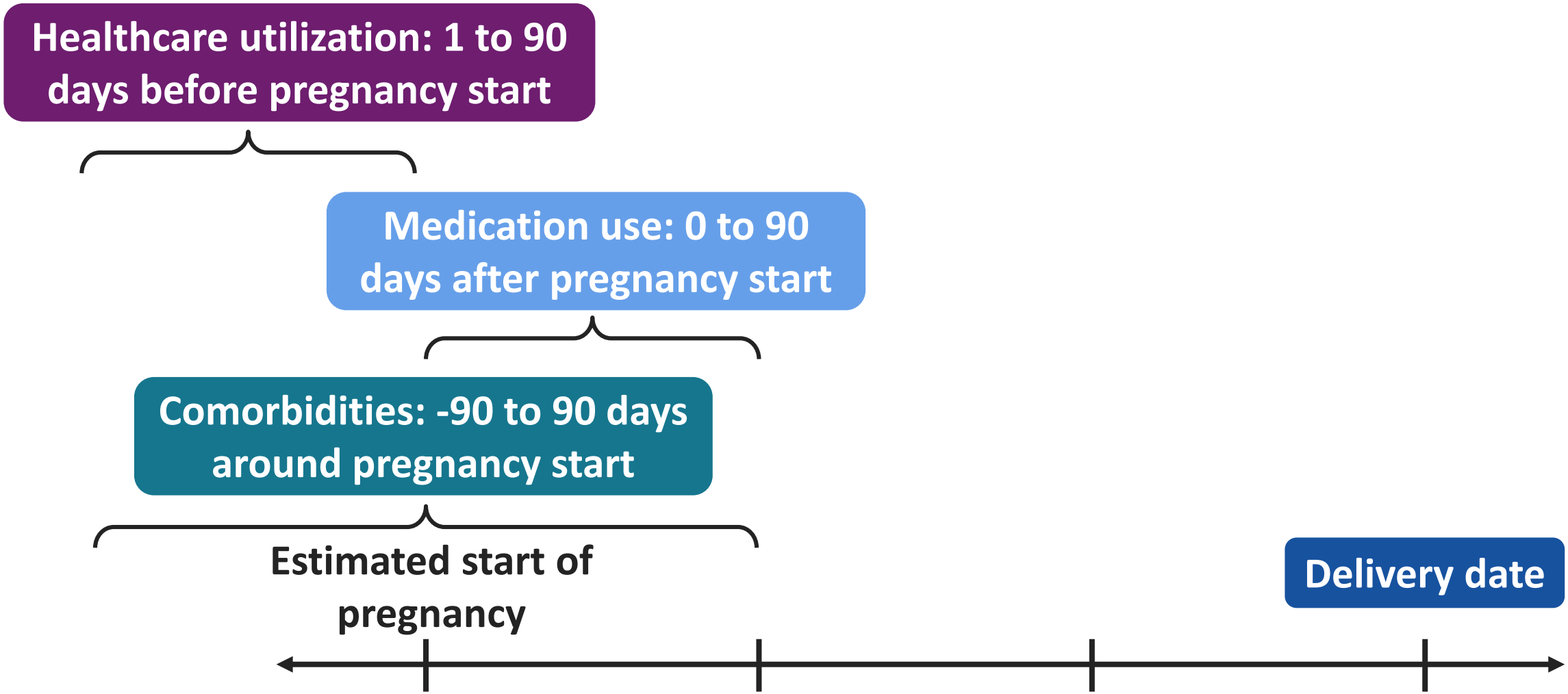
5. Create exposed and referent cohorts

Topiramate study: exclusions



5. Create exposed and referent cohorts

Topiramate study: covariates



5. Create exposed and referent cohorts

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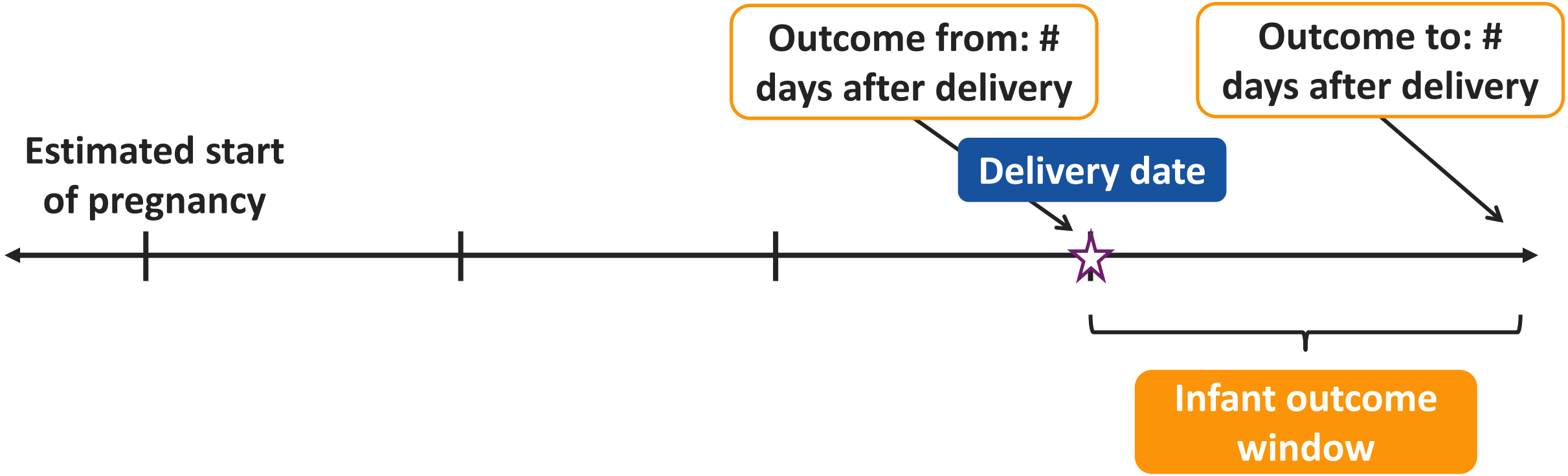
6. Identify maternal or infant outcomes
7. Evaluate exposure-outcome relationship

} **Inferential Analyses**

Defining infant outcomes

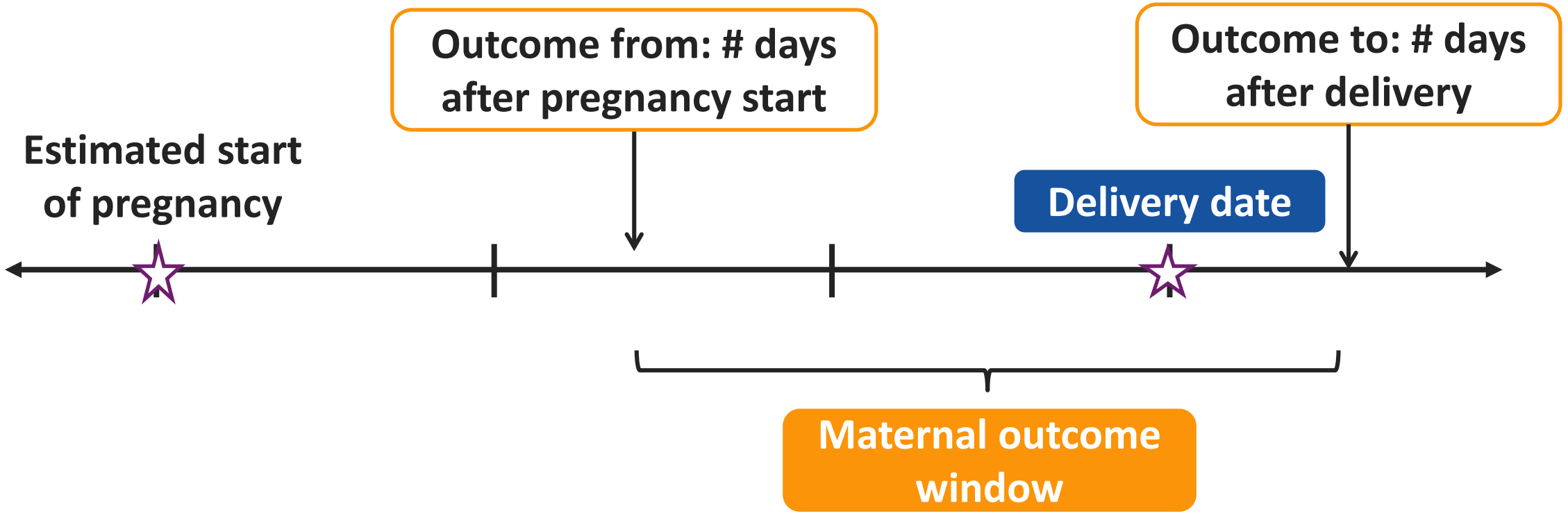
Outcomes are typically assessed after delivery – for example, cardiac defects



6. Identify maternal or infant outcomes

Defining maternal outcomes

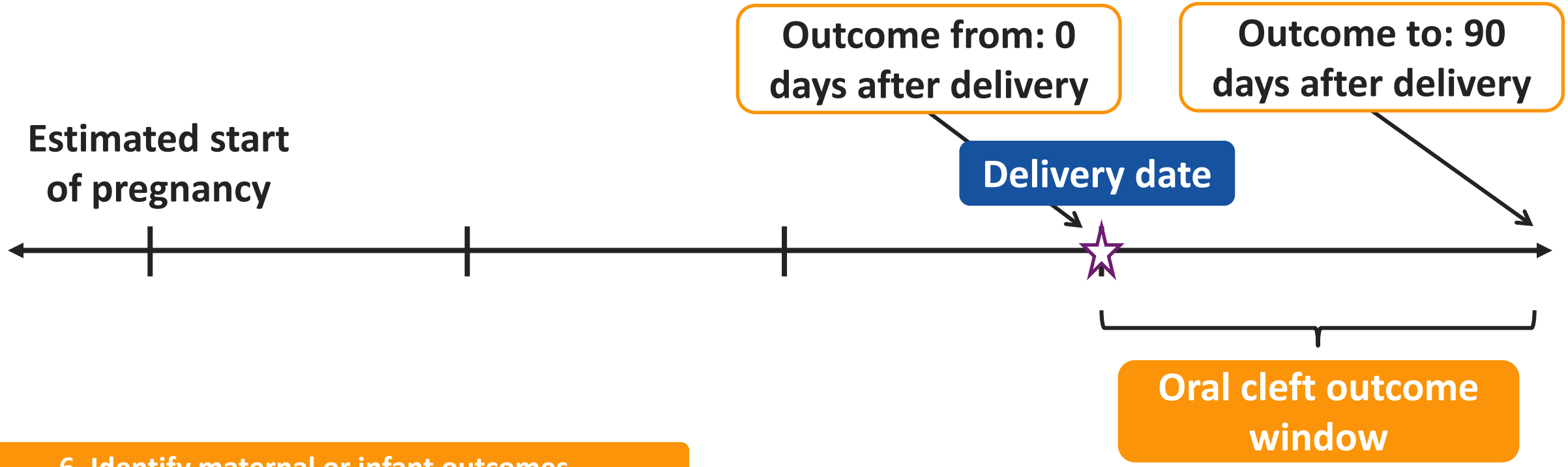
Outcomes occur during gestation and after delivery – for example, gestational hypertensive disorders



6. Identify maternal or infant outcomes

Topiramate study: defining oral clefts

- Infants were classified as having an oral cleft if at least one of the following criteria were met in the mother's or infant's record:
  - ≥2 diagnosis codes for oral clefts, OR
  - 1 diagnosis code and 1 procedure/surgery code for oral clefts



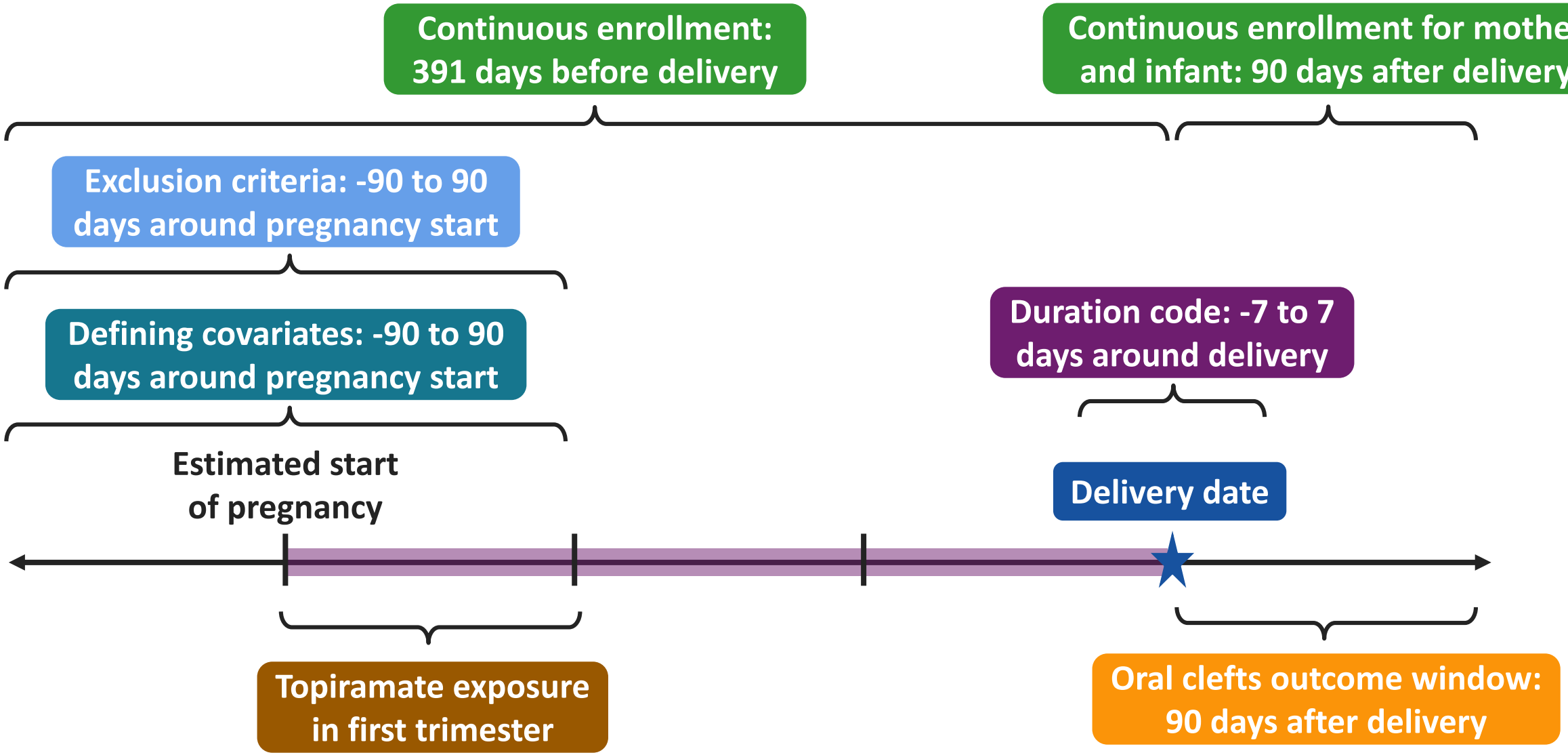
6. Identify maternal or infant outcomes

Maternal vs infant records

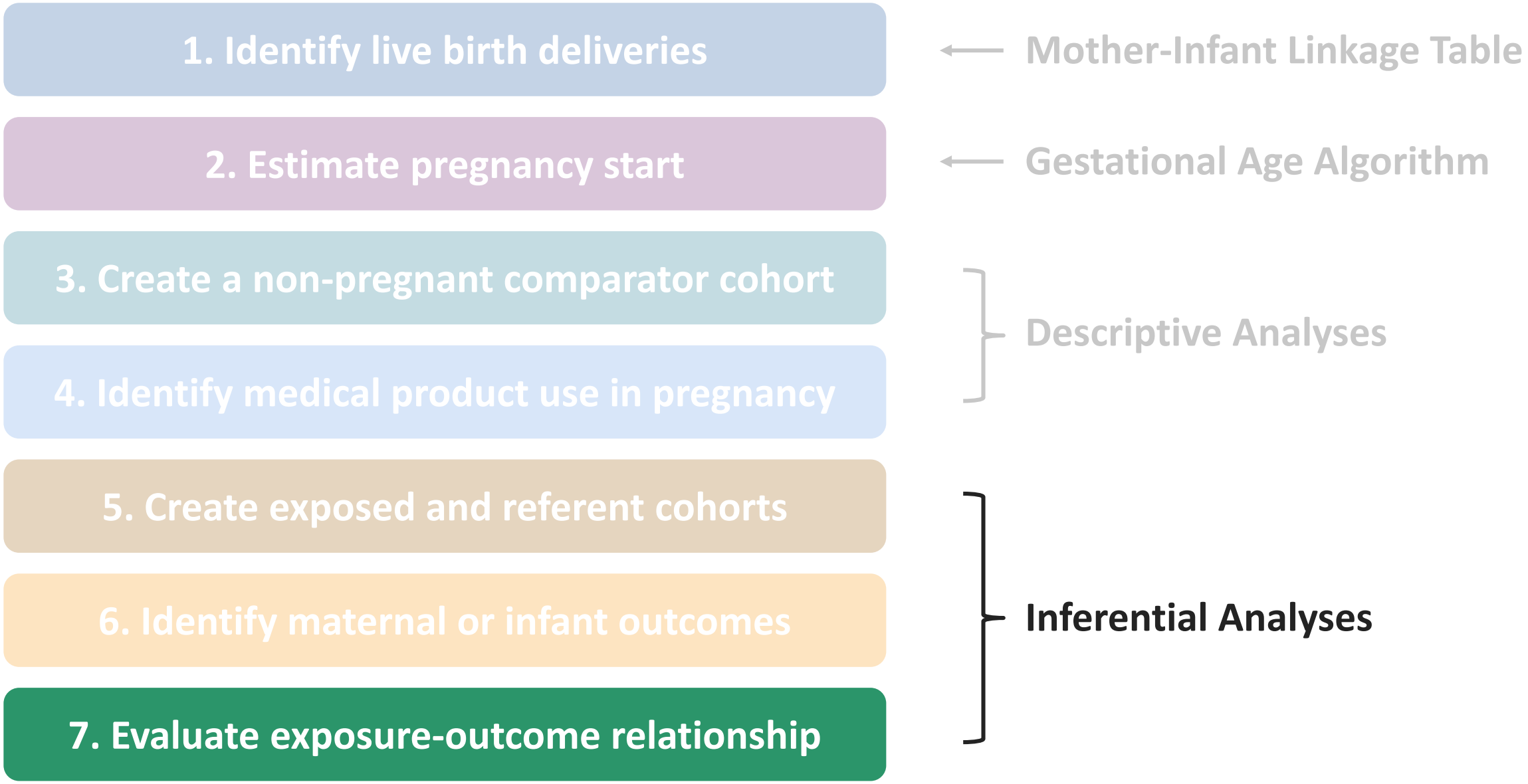
- Infants are typically enrolled under parent's insurance within 30-60 days after delivery
- Before enrollment, claims for the infant may appear on the mother's record
- Therefore, infant outcomes are assessed using claims from both the *infant's record* and the *mother's record*
- To assess outcomes only based on the infant's record would require limiting the cohort to infants that are enrolled at birth – this is very restrictive

6. Identify maternal or infant outcomes

Putting it all together: design diagram for topiramate study



Creating and analyzing a cohort of deliveries

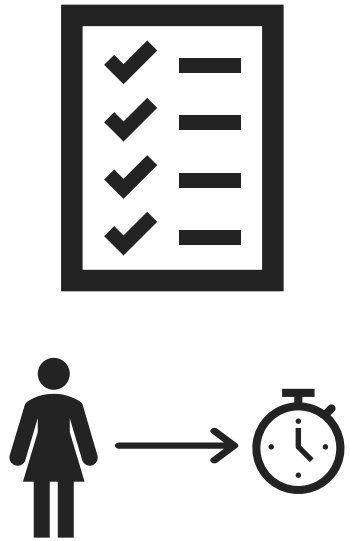


Operational flow at Data Partner site

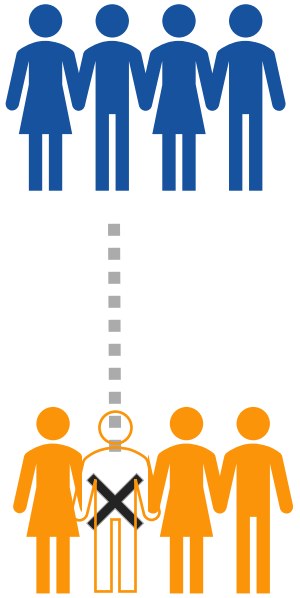
CIDA

PSA Tool

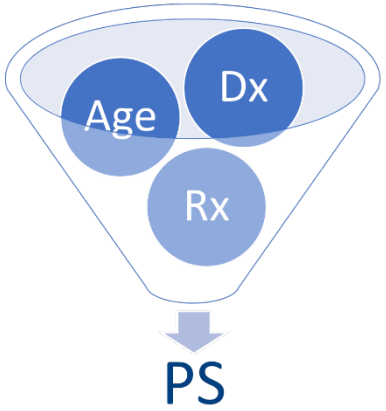
Identify pregnancies of interest



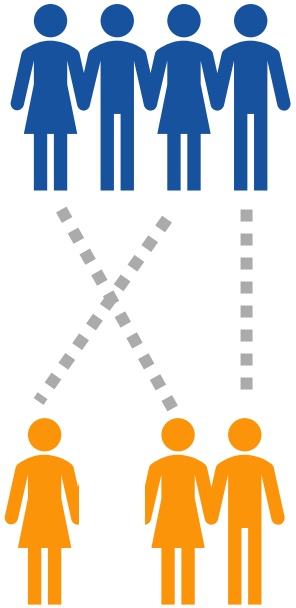
Extract covariate info



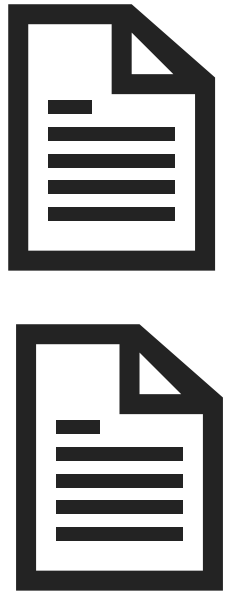
Deduplicate cohorts



Estimate propensity scores



Match or stratify



Generate output files

7. Evaluate exposure-outcome relationship

Operational flow at SOC

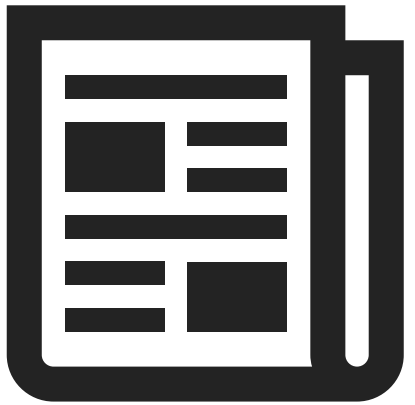
Manual

PSA Local Reporting Tool

Review of returned files

Aggregate DP-specific files

Generate estimates



Create formatted report

7. Evaluate exposure-outcome relationship

Analyzing maternal and infant outcomes

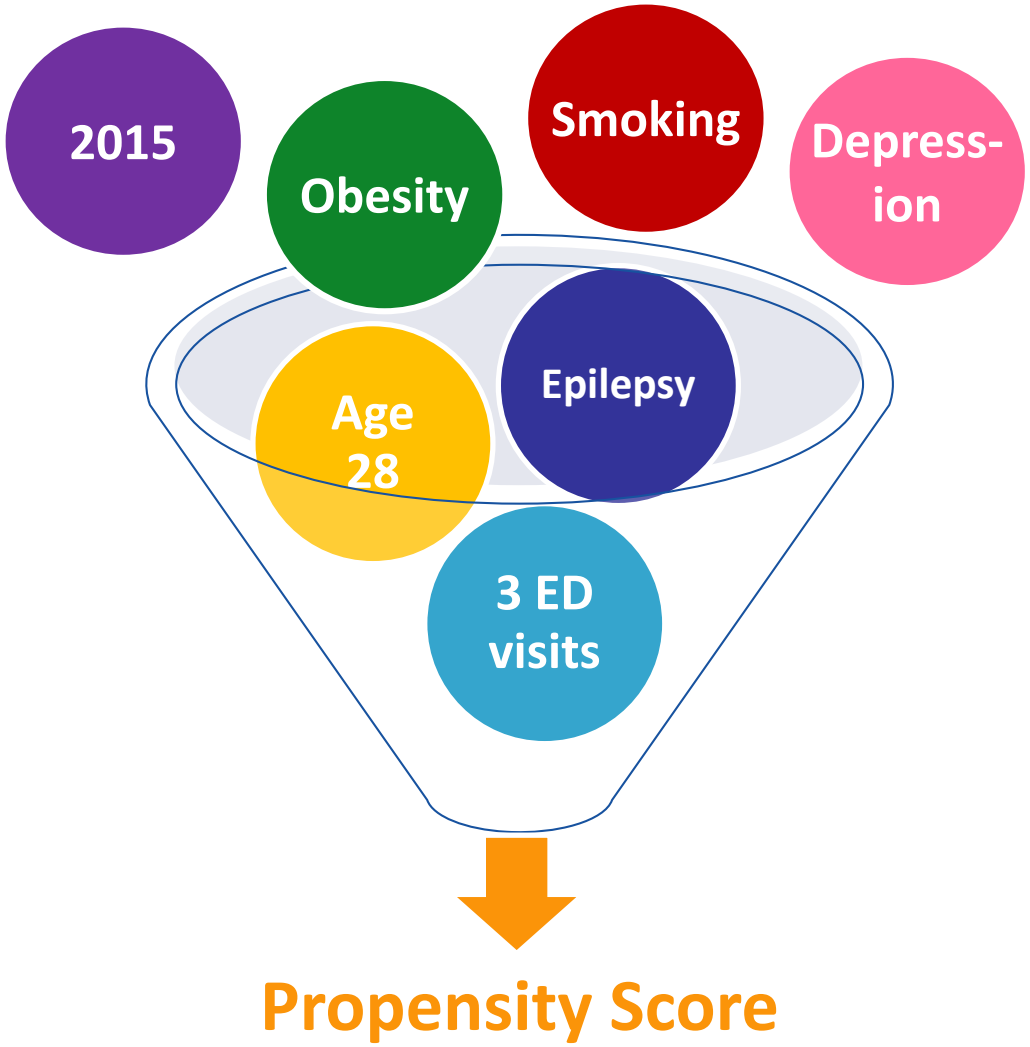
- Single outcome analysis: Logistic regression to estimate the association between an exposure and outcome of interest
- Multiple outcome analysis (signal detection): TreeScan to detect possible safety alerts across a range of infant or maternal outcomes with a single exposure of interest

Methods to Control for Confounding		
	Logistic Regression	**Signal Detection§**
Propensity score matching	Available	Available
Propensity score stratification	Available	
Propensity score weighting (inverse probability and stratification weighting)	Not yet available for pregnancy analyses	
Covariate stratification	Available	

*High-dimensional propensity score approach is available for all propensity score methods
§ Signal detection is still under testing and is not yet available for regulatory decision making

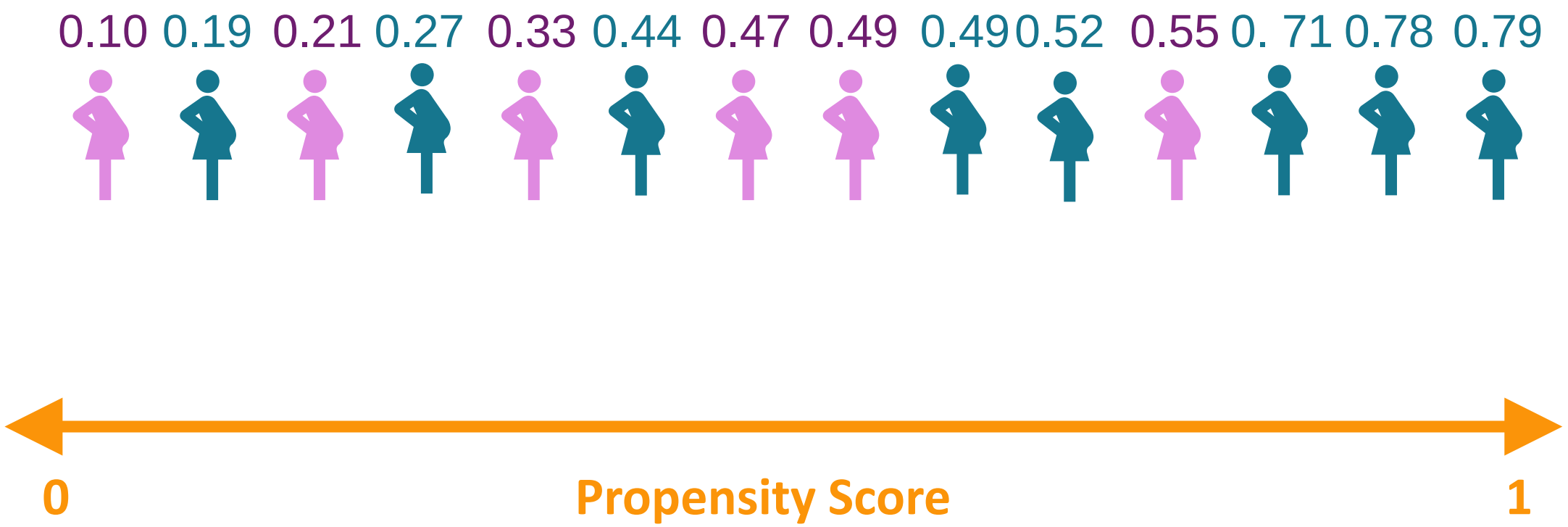
7. Evaluate exposure-outcome relationship

Measure Covariates and Estimate Propensity Score



7. Evaluate exposure-outcome relationship

Propensity Score



7. Evaluate exposure-outcome relationship

Topiramate Study: Propensity Score Models

- PS models optimized for each analysis to maintain sample size
- Full model included:
  - **Demographics**: Age
  - **Treatment indications**: epilepsy/seizure, migraine/headache/bipolar disorder, neuropathic pain, non-neuropathic pain
  - **Comorbidities and lifestyle factors**: obesity, smoking, depression, anxiety, other psychiatric disorders, sleep disorders, fibromyalgia, hypertension, Charlson Comorbidity Index
  - **Medication use**: other anticonvulsants, benzodiazepines, triptans, antipsychotics, antidepressants, antihypertensives, anxiolytics, stimulants, non-insulin diabetics, opioids, other pain, ADHD, hypnotics, teratogens, NSAIDS
  - **Healthcare utilization**: number of inpatient stays, number of ambulatory visits, and number of filled prescriptions

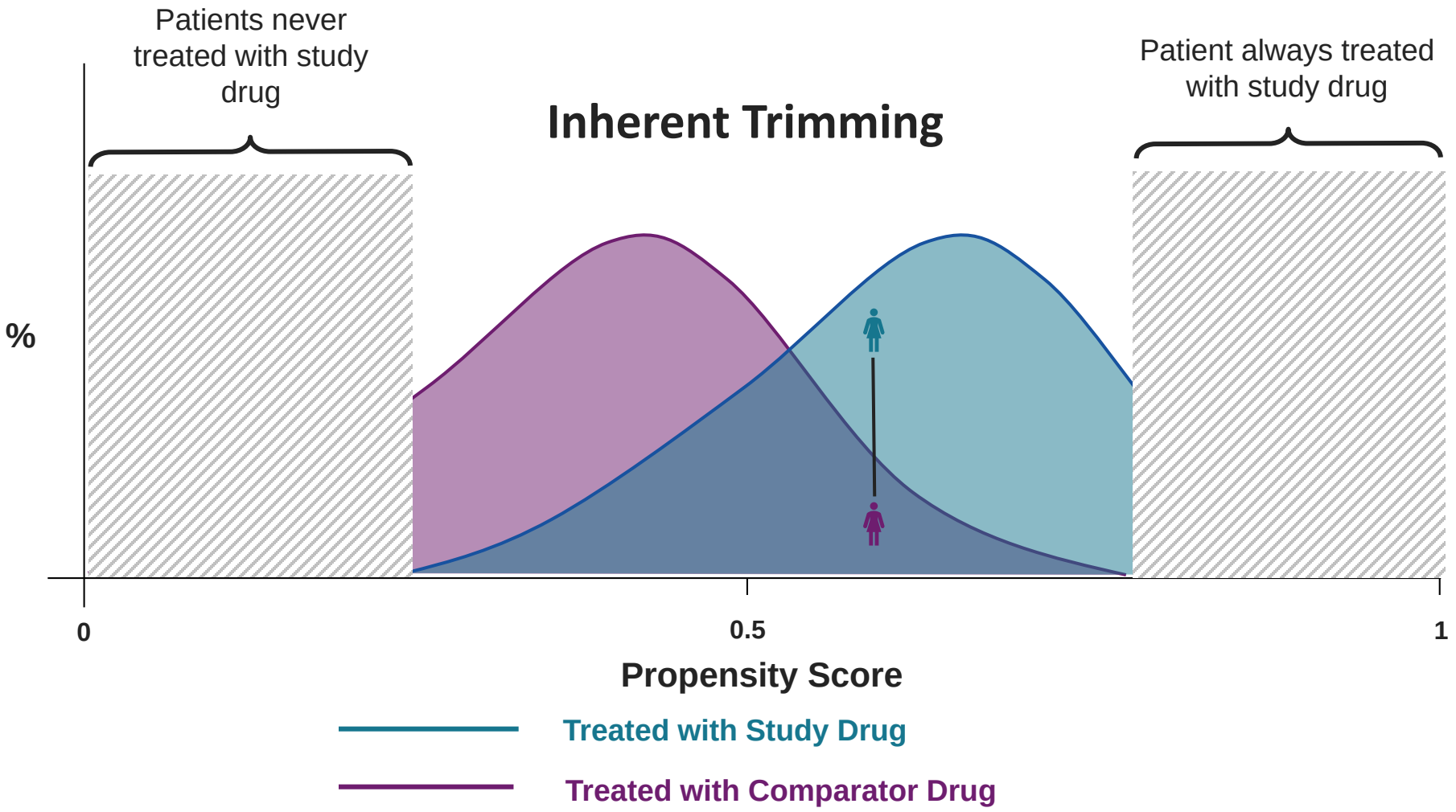
7. Evaluate exposure-outcome relationship

Method 1: Propensity Score Matching

- Algorithm
  - **Optimal nearest neighbor** matching without replacement
    - Calculate differences in PS values between all possible treatment and comparator group pairs
    - Find smallest difference and match, then remove pair
    - Repeat in rounds
- Options
  - 1:1 or 1:M fixed-ratio and variable-ratio matching
  - Matching caliper on natural scale (e.g., 0.01) sets maximum allowable difference

7. Evaluate exposure-outcome relationship

Method 1: Matching on the Propensity Score



7. Evaluate exposure-outcome relationship

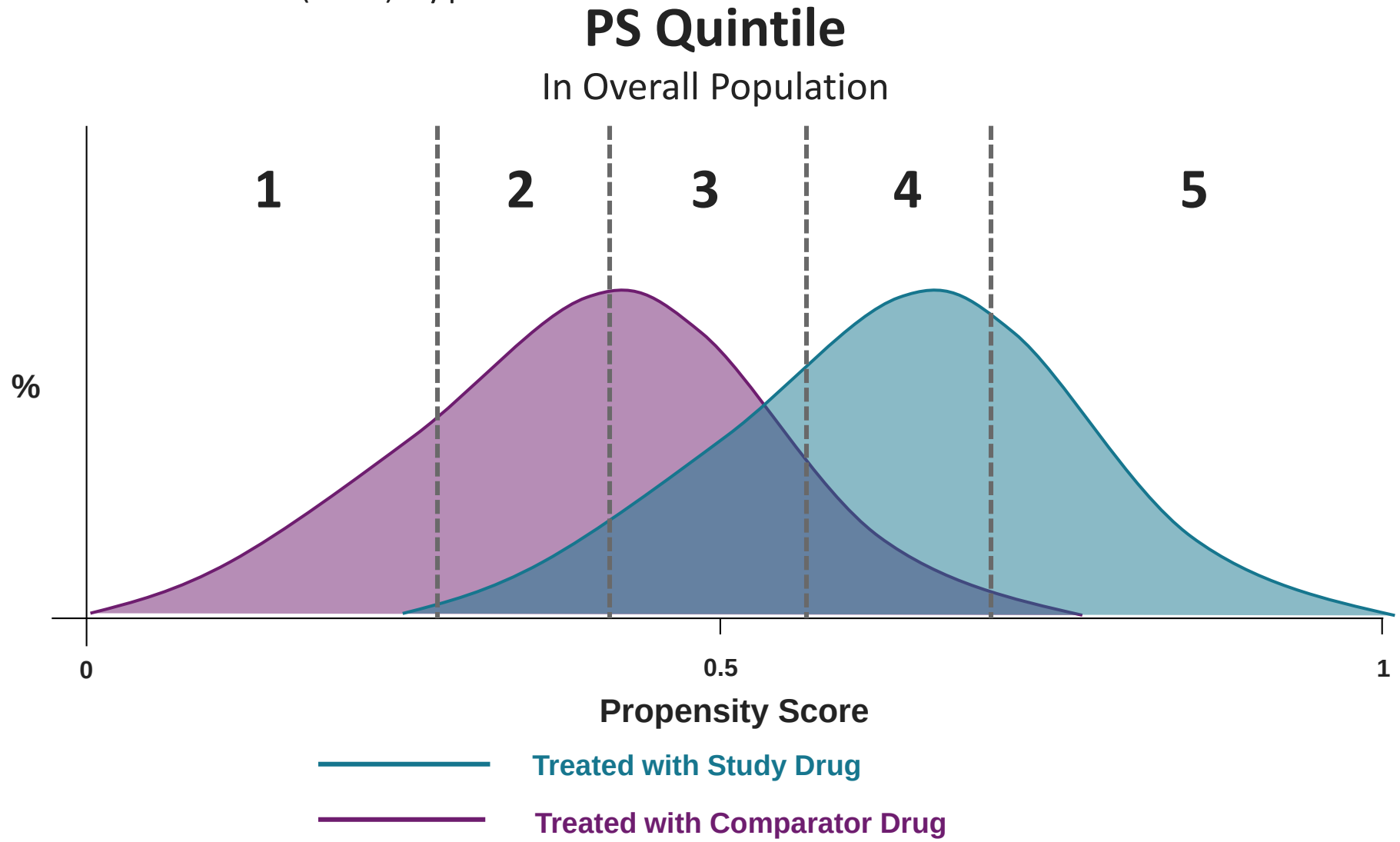
Method 2: Propensity Score Stratification

- Algorithm
  - Group episodes into strata defined by quantile of PS distribution
  - PS percentiles determined for the entire cohort within each Data Partner (which may be quite different in size)
    - ALL pregnancies are retained, there is no trimming
  - Performs an *"Average Treatment Effect"* (ATE) analysis
- Options
  - Number of groups (e.g., 10 for deciles)

7. Evaluate exposure-outcome relationship

Method 2: Stratification on the Propensity Score

Average treatment effect (ATE) type



7. Evaluate exposure-outcome relationship

Estimate Odds Ratios in Matched/Stratified Cohort

Population	Analysis	Output
Unmatched	Site-adjusted logistic regression	Cohort N Number of events Crude risk Crude risk ratio Crude risk difference Odds Ratio 95% Confidence Interval
Matched	Fixed-ratio or variable-ratio matched logistic regression	
Stratified	N strata stratified logistic regression	

7. Evaluate exposure-outcome relationship

Hernandez-Diaz Results

Table 2 Risk at birth of oral clefts among infants exposed to topiramate during the first trimester compared to infants exposed to lamotrigine and to unexposed infants

Oral clefts	Unexposed (n = 1,322,955)	[illegible]	Topiramate (n = 2,425)
Events, n	1,501		<11[b]
Risk (per 1,000)	1.1		4.1
Unadjusted RR (95% CI)	Reference	1.89 (0.85–4.21)	3.63 (1.95–6.76)
PS-adjusted RR (95% CI)		1.89 (0.85–4.21)	2.90 (1.56–5.40)
Unadjusted RR (95% CI)	NA	[illegible]	2.30 (0.69–7.64)[a]
PS-adjusted RR (95% CI)		[illegible]	2.38 (0.71–7.96)[a]

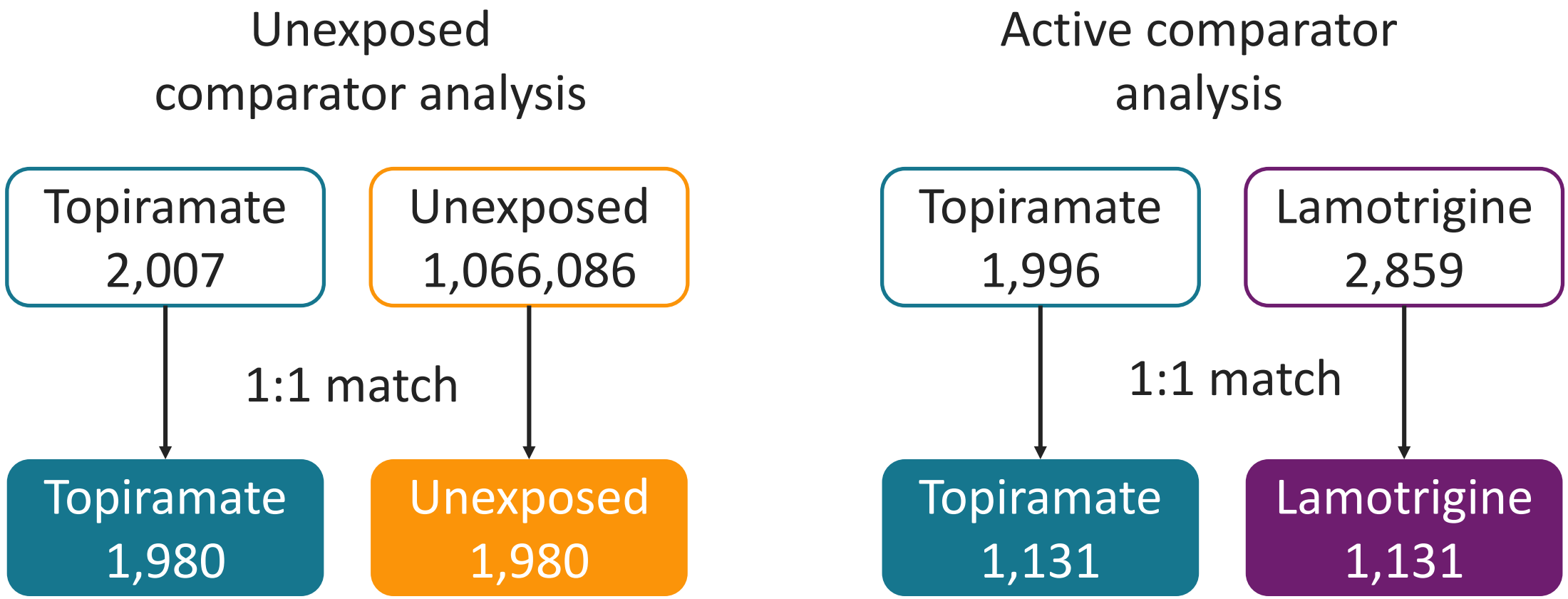
Topiramate vs unexposed:
Adjusted RR: 2.90 (1.56, 5.40)

Topiramate vs lamotrigine:
Adjusted RR: 2.38 (0.71, 7.96)

Abbreviations: CI = confidence interval; NA = not applicable; PS = propensity score
Medicaid Analytic eXtract, 2000 to 2010.
[a] Analyses comparing topiramate and lamotrigine were restricted to patients who did not concomitantly use topiramate and lamotrigine during the 90 days before the last menstrual period through the end of the first trimester.
[b] In accordance with the data-use agreement, we do not report information for frequency cells with less than 11 cases.

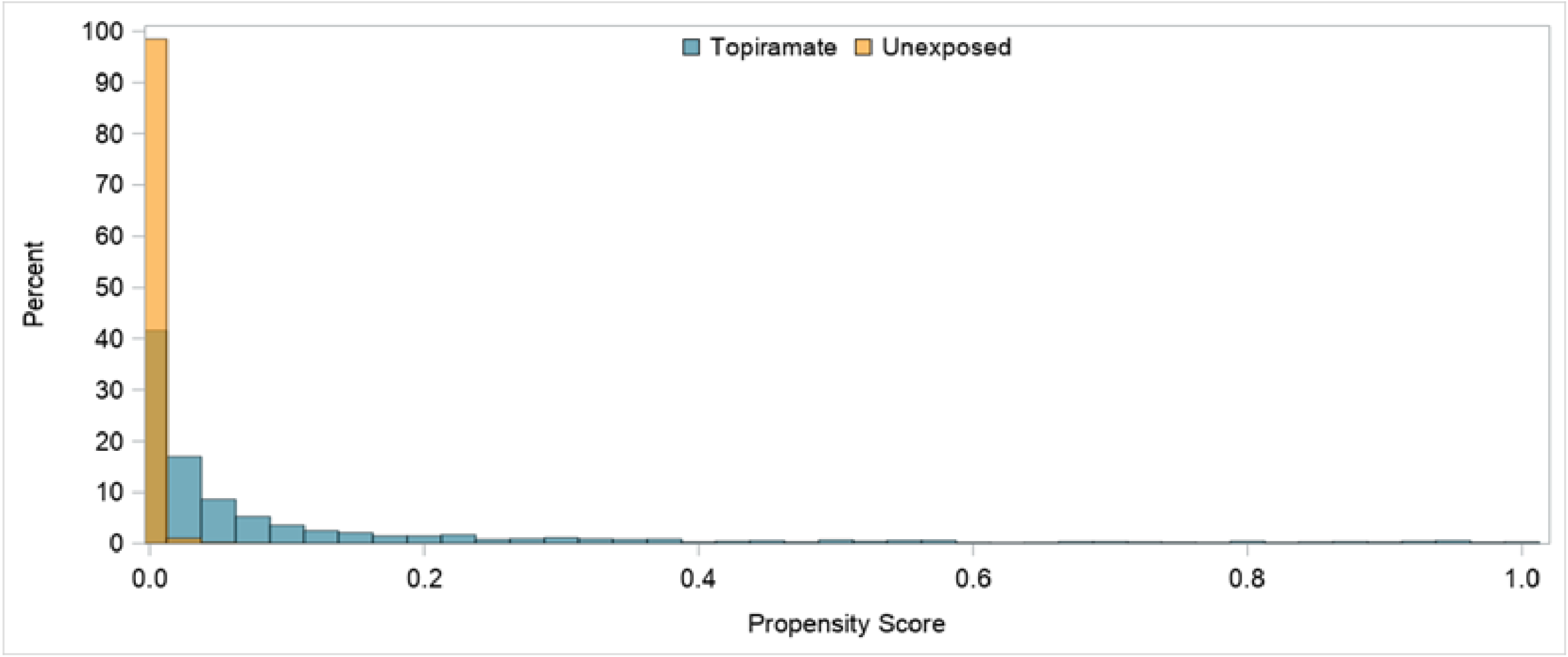
7. Evaluate exposure-outcome relationship

Cohort Sizes: Sentinel Distributed Database study



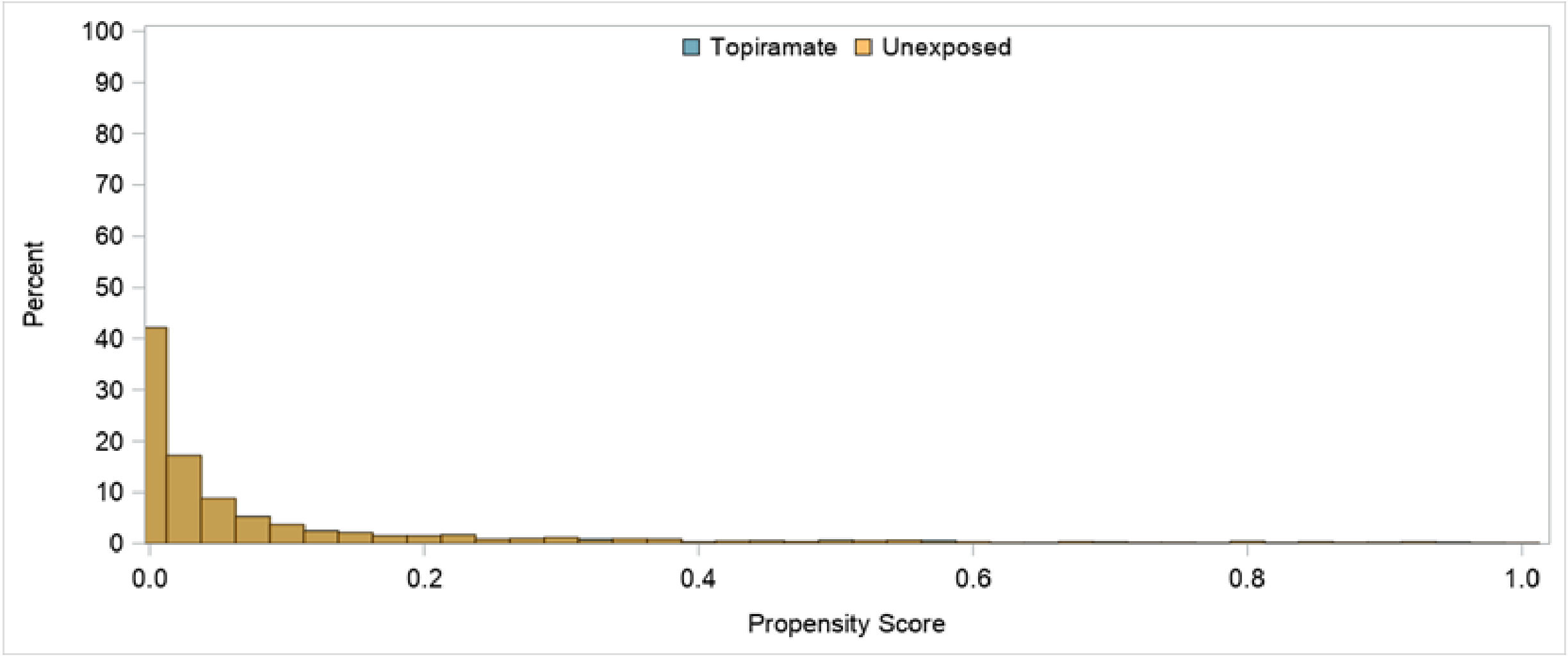
7. Evaluate exposure-outcome relationship

Propensity Score Distribution – Unadjusted, Primary Analyses



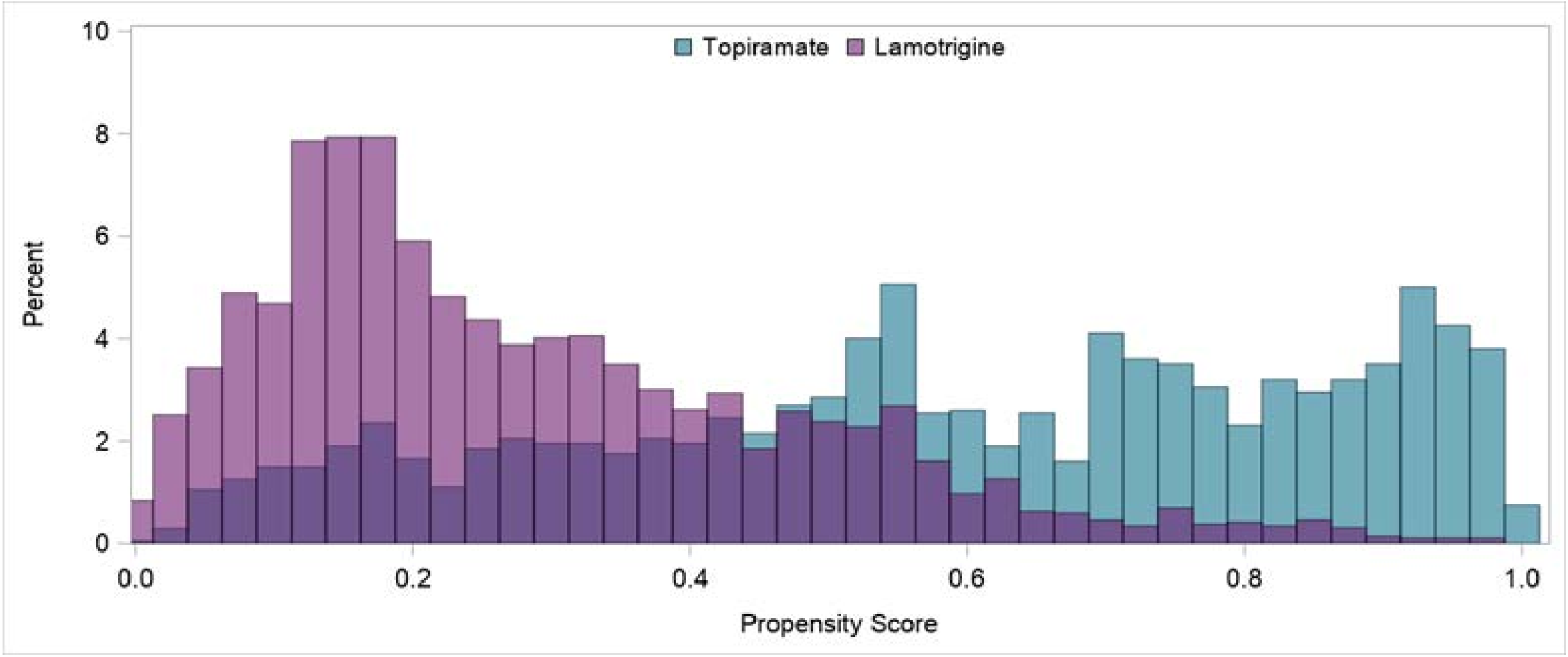
7. Evaluate exposure-outcome relationship

Propensity Score Distribution – Adjusted, Primary Analyses



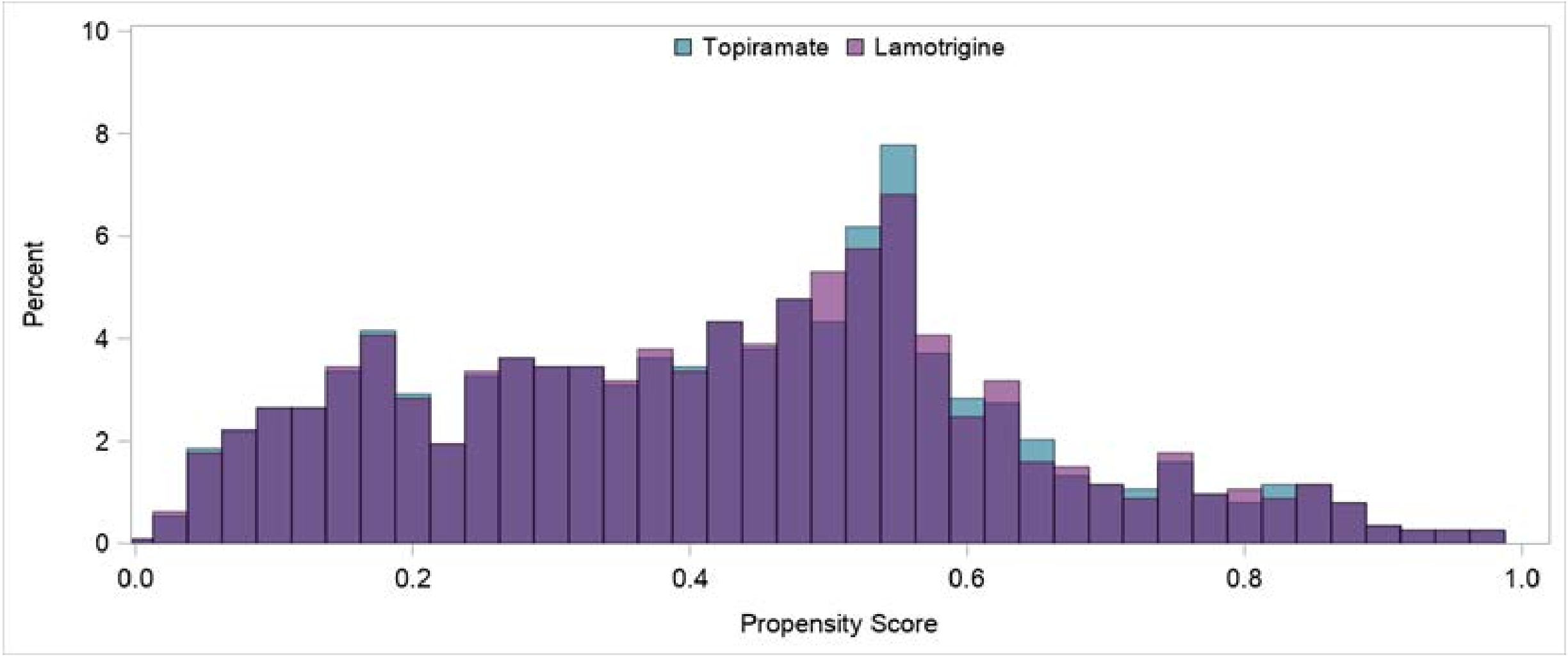
7. Evaluate exposure-outcome relationship

Propensity Score Distribution – Unadjusted, Active Comparator Analyses



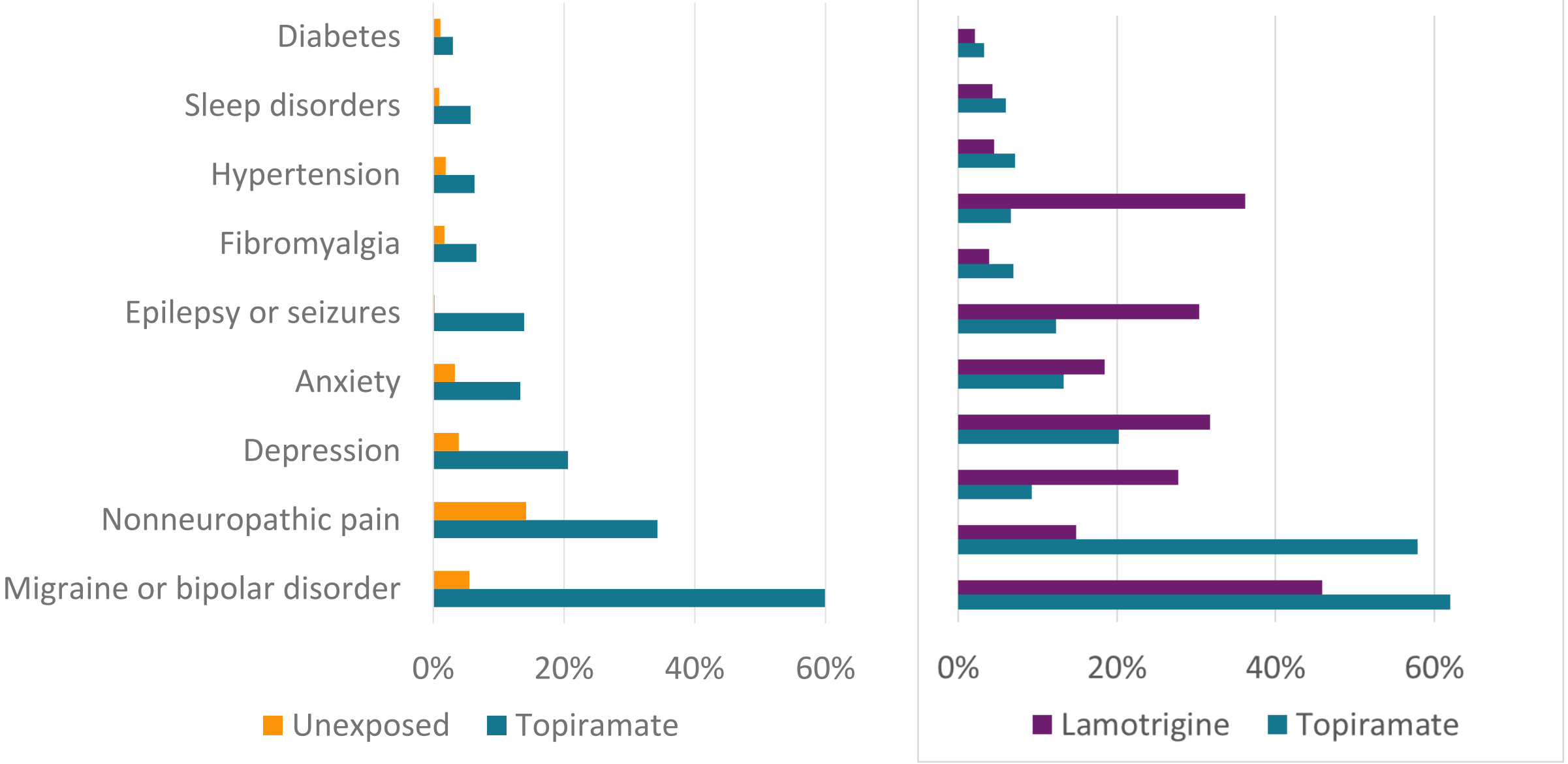
7. Evaluate exposure-outcome relationship

Propensity Score Distribution –Adjusted, Active Comparator Analyses



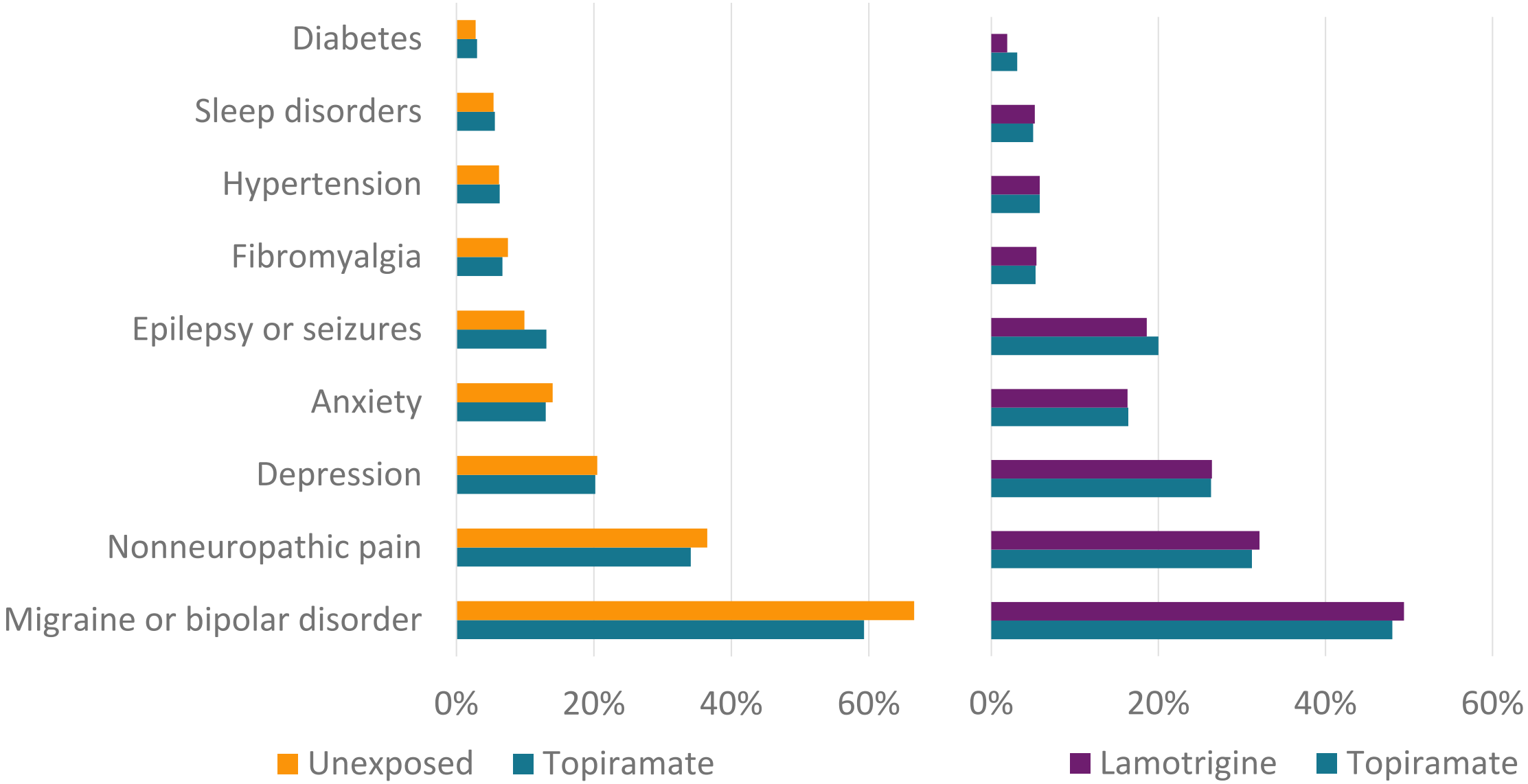
7. Evaluate exposure-outcome relationship

Selected Health Characteristics: Unmatched/Stratified Cohorts



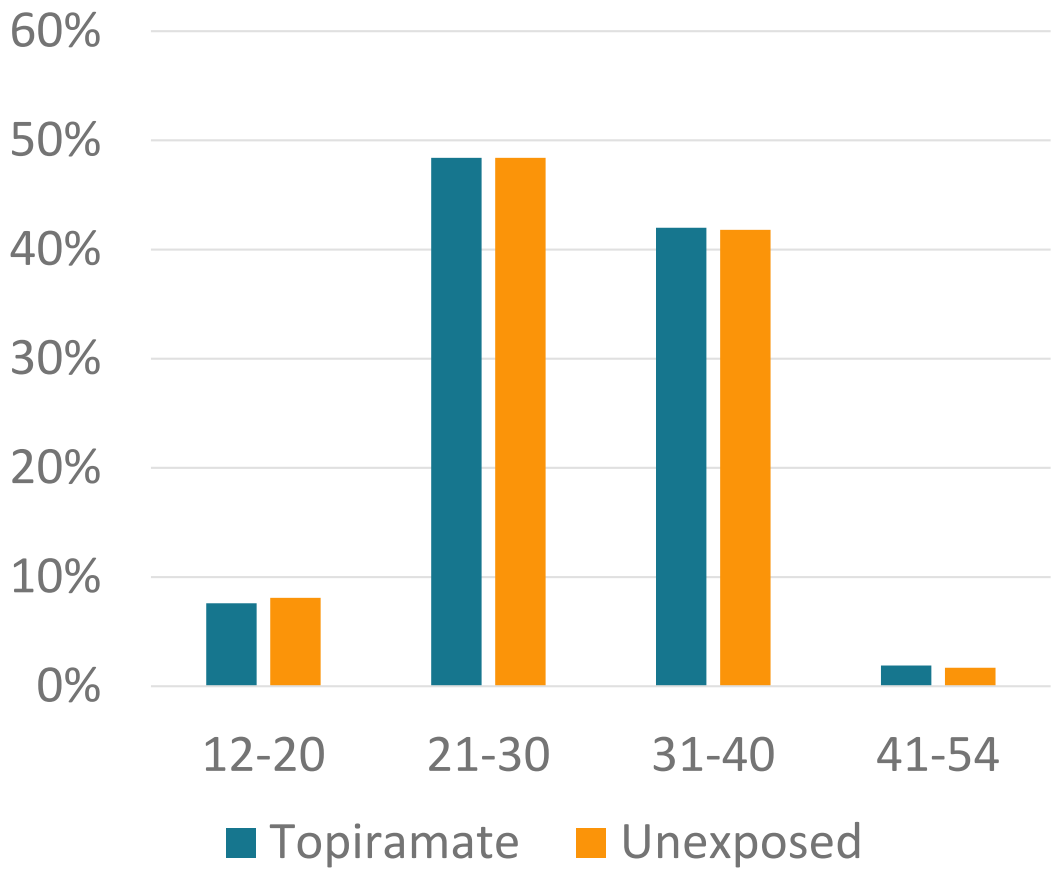
7. Evaluate exposure-outcome relationship

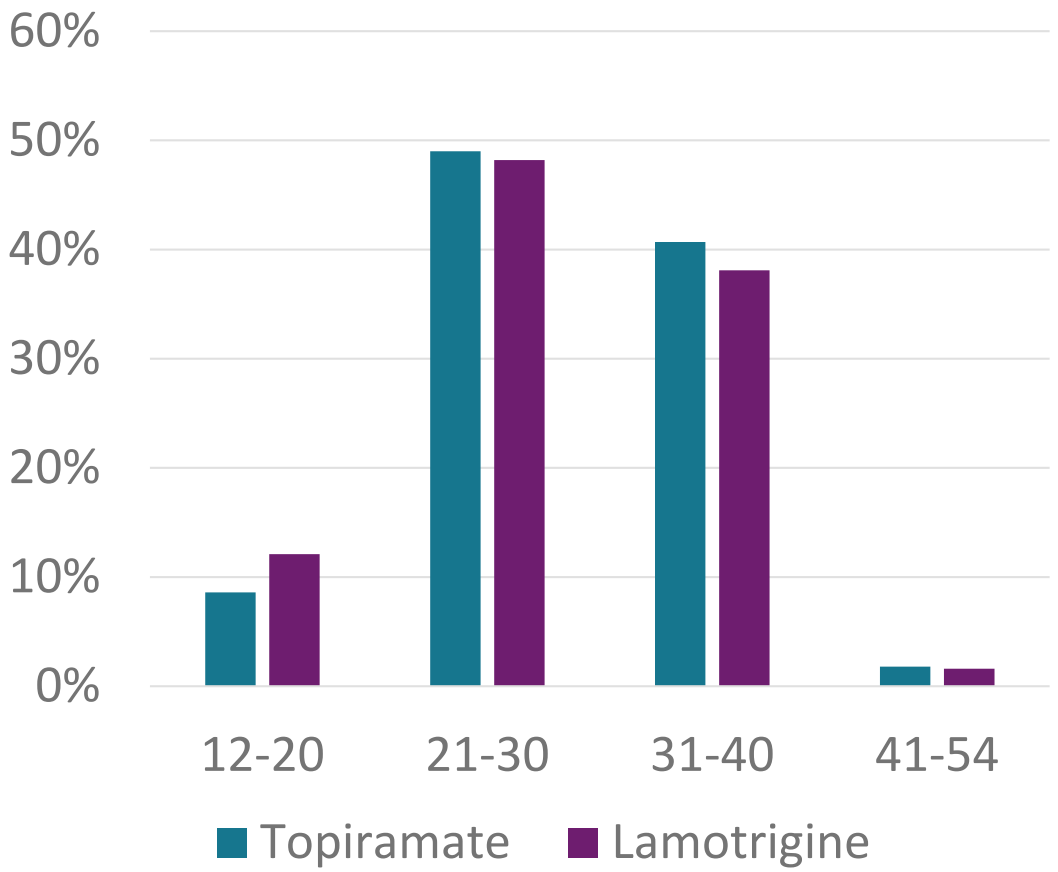
Selected Health Characteristics: Matched Cohorts



7. Evaluate exposure-outcome relationship

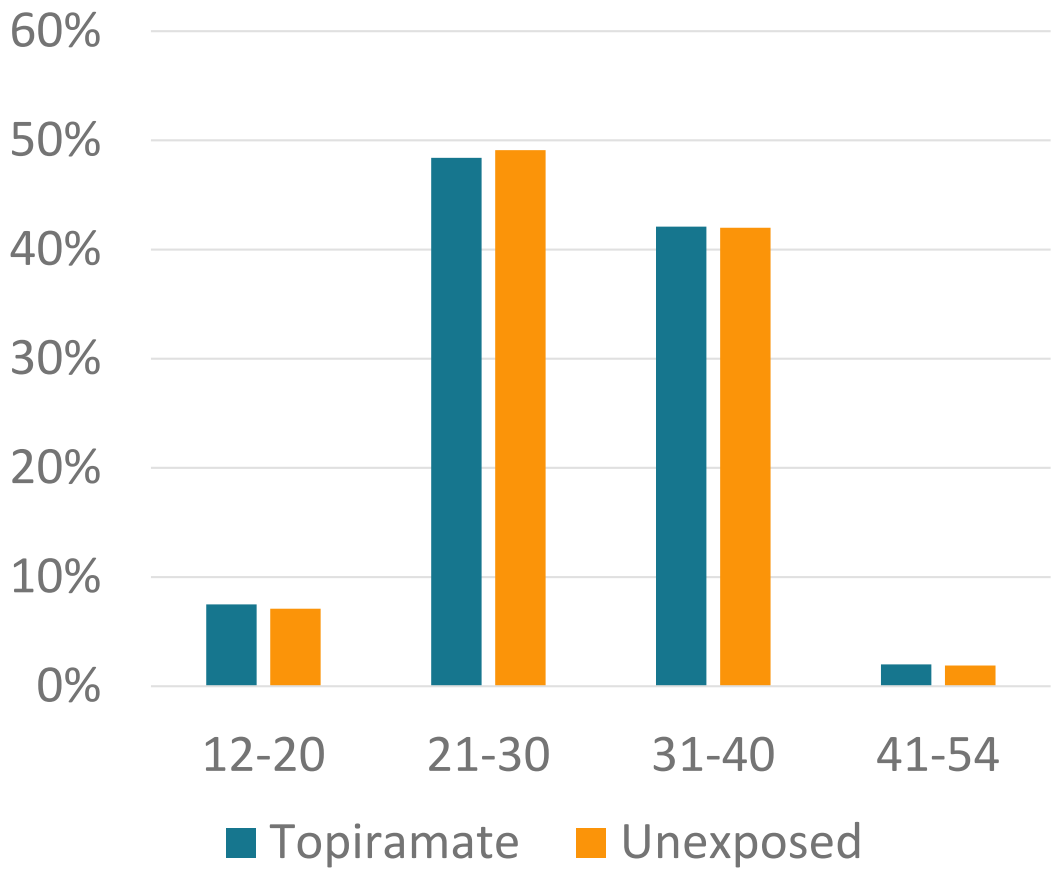
Maternal age (years) at delivery: Unmatched/Stratified Cohorts

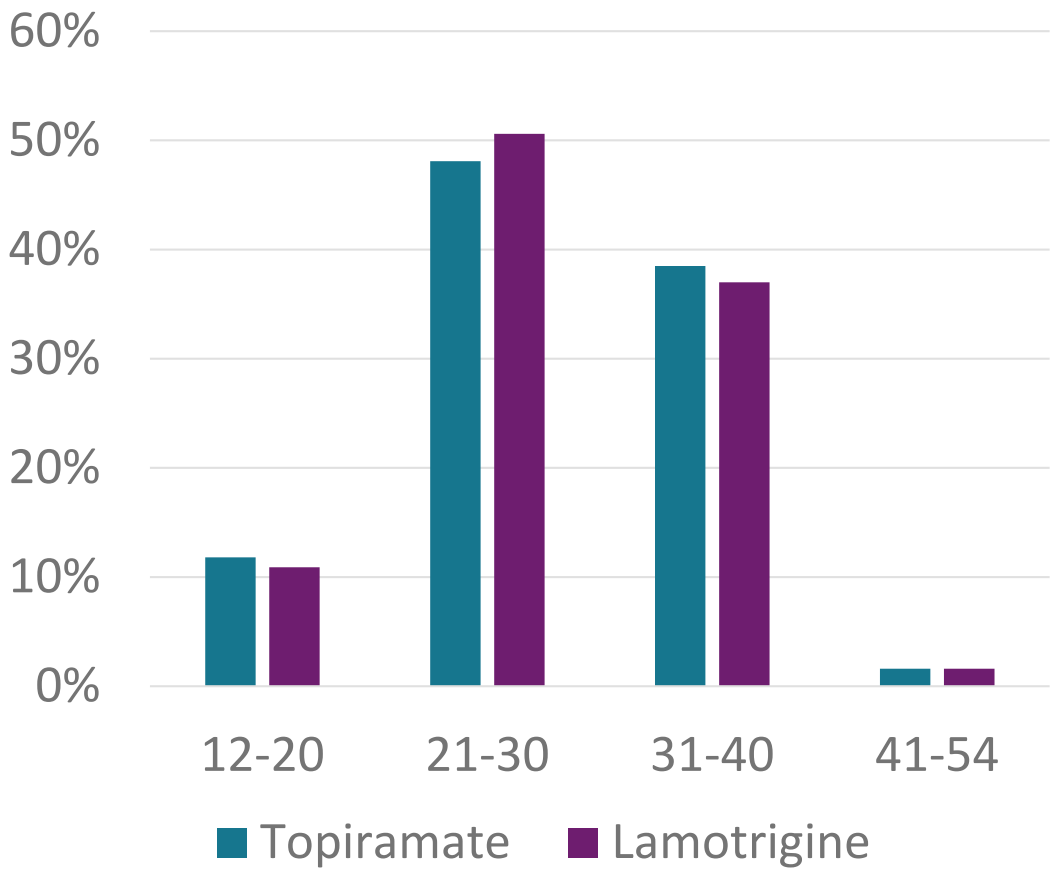




7. Evaluate exposure-outcome relationship

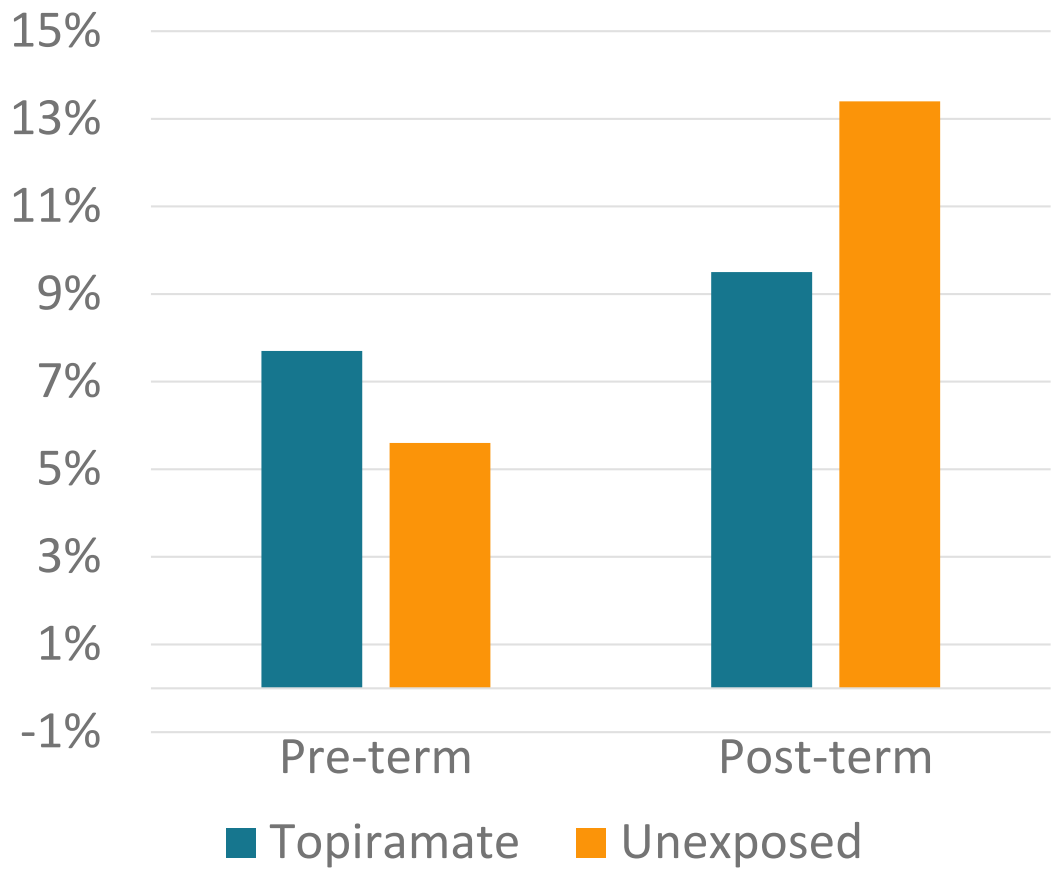
Maternal age (years) at delivery: Matched Cohorts

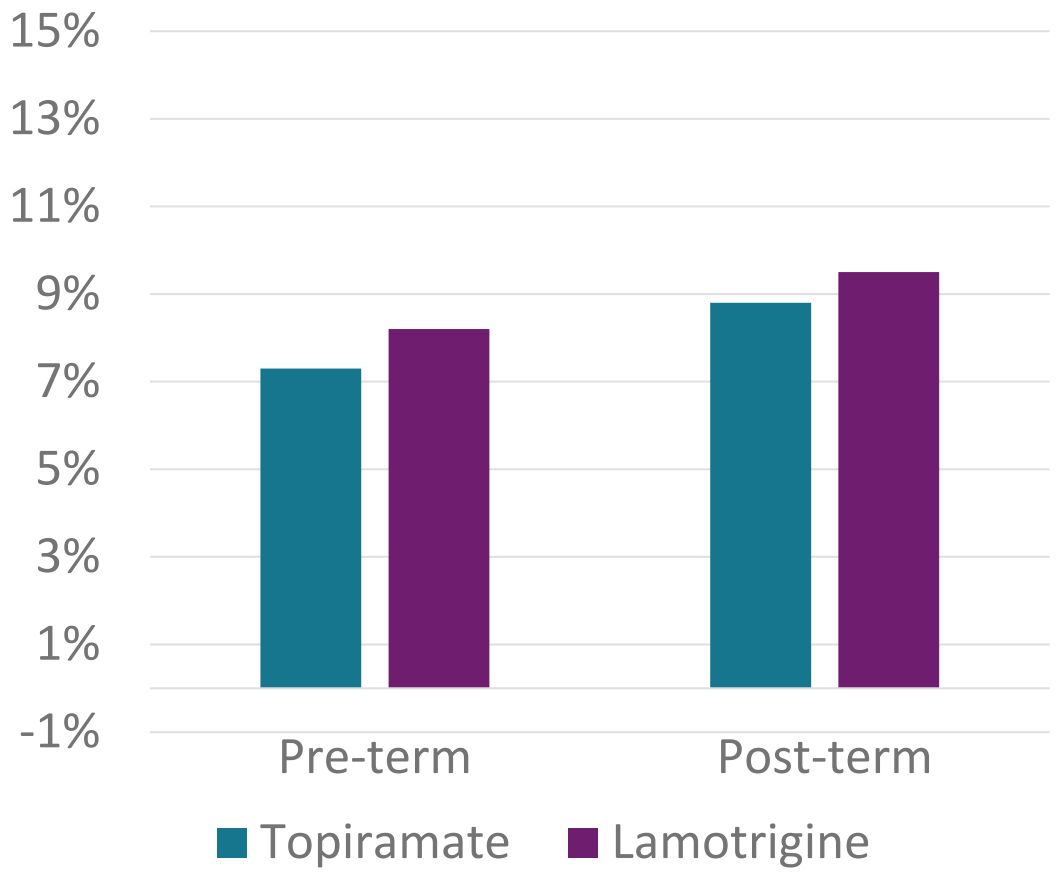




7. Evaluate exposure-outcome relationship

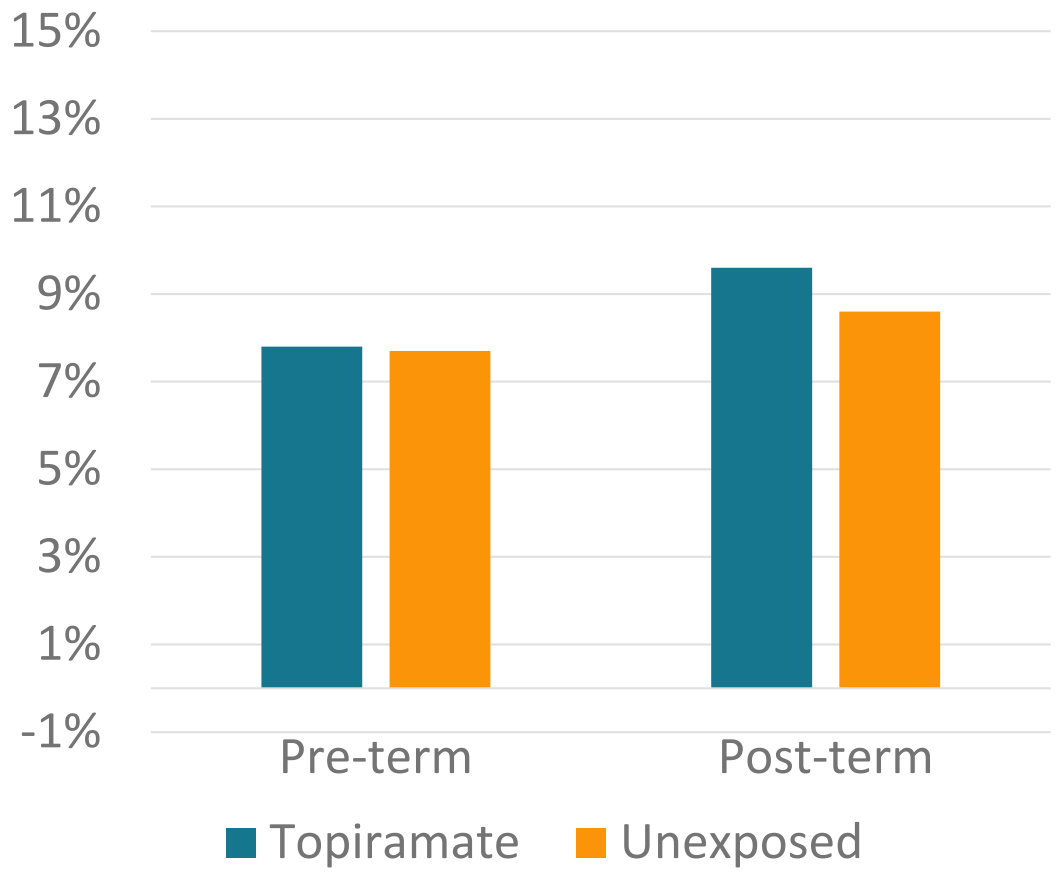
Pre- or post-term delivery codes: Unmatched/stratified cohorts

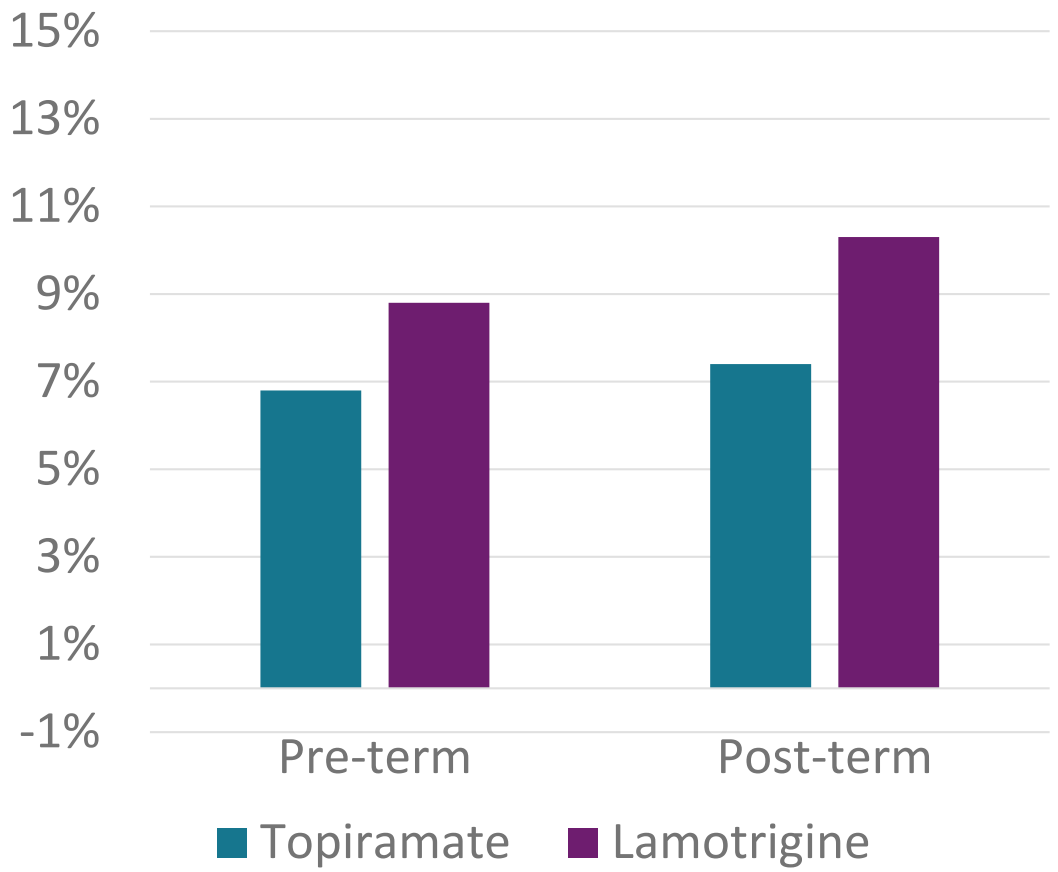




7. Evaluate exposure-outcome relationship

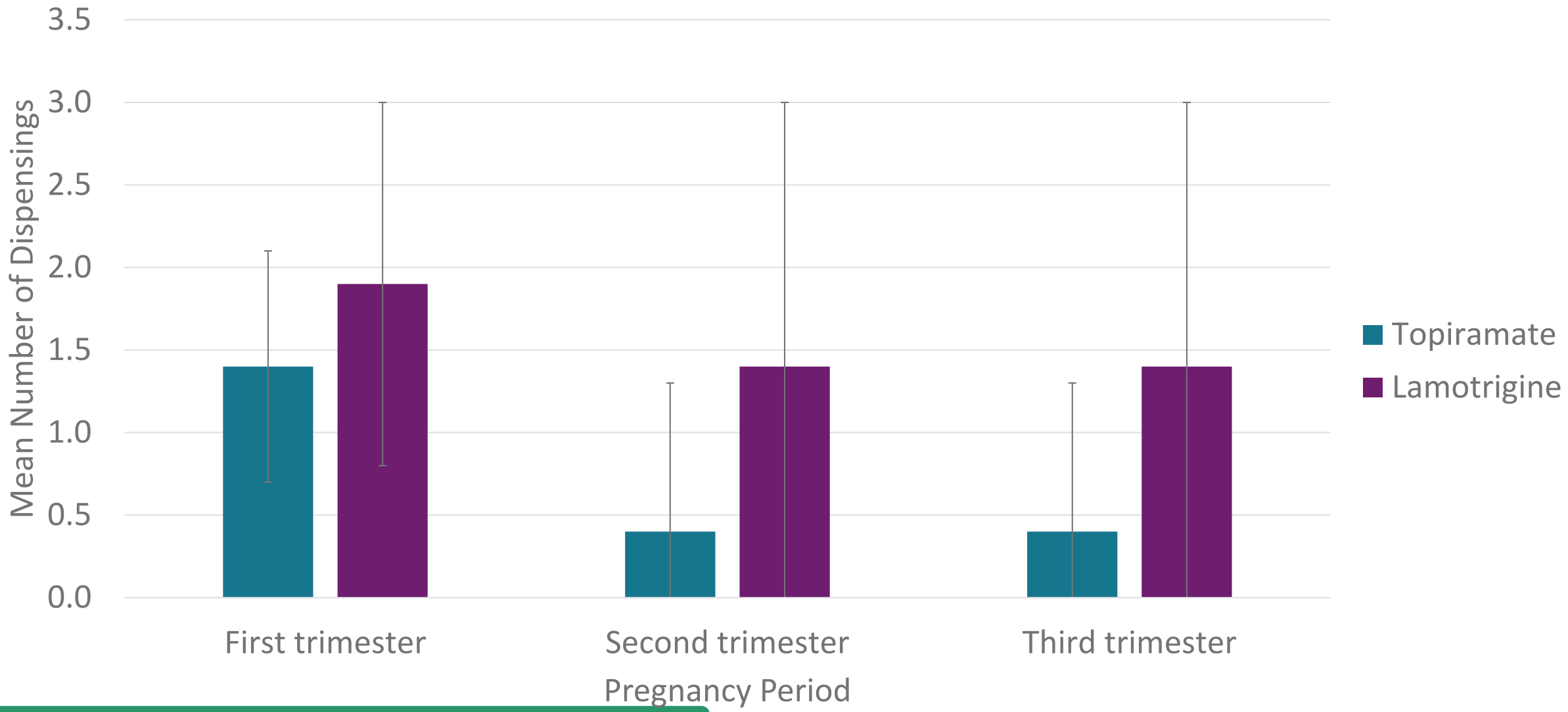
Pre- or post-term delivery codes: Matched cohorts





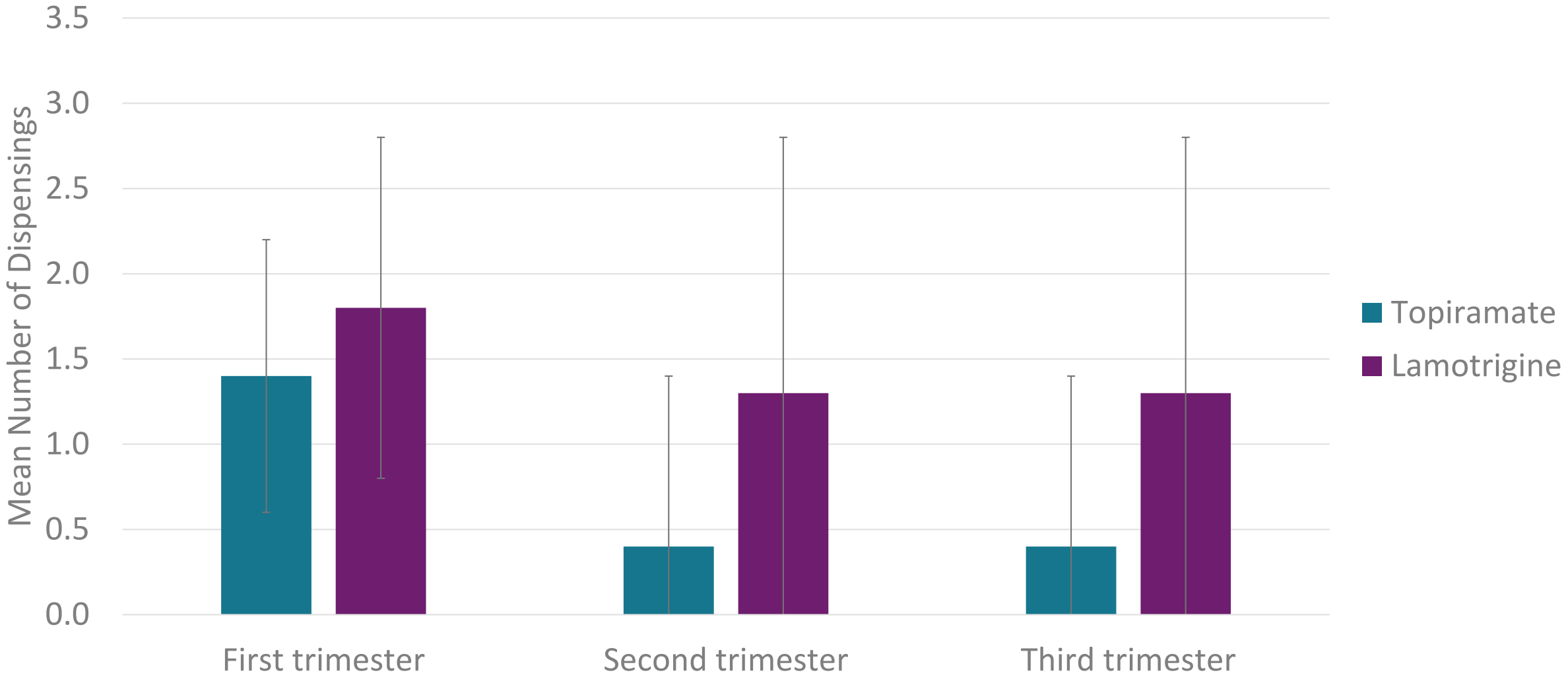
7. Evaluate exposure-outcome relationship

Number of dispensings: Unmatched/stratified cohorts



7. Evaluate exposure-outcome relationship

Number of dispensings: Matched cohorts



7. Evaluate exposure-outcome relationship

Oral Clefts – Unexposed comparator

Topiramate versus unexposed	Cohort	Events	Risk per 1000	OR	95% CI
Crude	Exposed	8	3.99	3.24	(1.62, 6.51)
	Referent	1,314	1.23		
1:1 matched	Exposed	8	4.04	8.03	(1.00, 64.25)
	Referent	1	0.51		
PS stratified	Exposed	8	3.99	2.92	(1.43, 5.93)
	Referent	1,314	1.23		

Hernandez-Diaz et al.:
Topiramate vs unexposed:
Adjusted RR: 2.90 (1.56, 5.40)

7. Evaluate exposure-outcome relationship

Oral Clefts – Lamotrigine comparator

Topiramate versus lamotrigine	Cohort	Events	Risk per 1000	OR	95% CI
Crude	Exposed	8	4.01	1.64	(0.59, 4.53)
	Referent	7	2.45		
1:1 matched	Exposed	3	2.65	0.75	(0.17, 3.36)
	Referent	4	3.54		
PS stratified	Exposed	8	4.01	2.72	(0.75, 9.93)
	Referent	7	2.45		

Hernandez-Diaz et al.:
Topiramate vs lamotrigine:
Adjusted RR: 2.38 (0.71, 7.96)

7. Evaluate exposure-outcome relationship

Conclusions

Topiramate and Oral Clefts

- Our study suggests that topiramate exposure during the first trimester increases the risk of oral clefts when compared to no topiramate exposure
  - Confirms previous findings of association between topiramate and oral clefts
- When comparing topiramate exposure to lamotrigine exposure, results were also suggestive of an increase in risk, but results were more variable
  - Propensity score matching was unable to balance the topiramate and lamotrigine cohorts on key indication variables that were not included in the propensity score
- 1:1 matching resulted in exclusion of a large proportion of the unexposed population and only one oral cleft case in the unexposed group, leading to imprecise estimates

Performance of the Sentinel Tools for Pregnancy Outcomes

- The new Sentinel tool allows for inferential analysis of maternal and infant outcomes following perinatal exposures
- We replicated a published study using our parameterized tools
  - Estimates of oral cleft risk were similar to published estimates
  - The estimate of the association between topiramate and oral clefts was similar to published estimates
- Flexibility of pregnancy tool allows for a variety of analyses with different methods for controlling confounding including propensity score matching and stratification

Limitations of the topiramate analysis

- Limited to singleton live born infants
  - Multiple gestation deliveries are included in the MIL Table
  - Identification of non-live birth pregnancy outcomes, and methods to estimate the pregnancy duration, are currently under development
- Exposure, outcome, and covariate misclassification is possible when using insurance claims data
  - Outcomes of interest should be validated in similar data sources
  - Sensitivity analyses should be employed to evaluate potential exposure misclassification
  - Validated algorithms for covariates should also be used, when available

How can the FDA – and others – leverage the new functionalities described today?

- FDA now has access to a large network of 5.1 million (and growing) linked mother-infant pairs
  - This supplements existing use of registry data
- FDA and others with data in the Sentinel Common Data Model format and mother-infant linked data can:
  - Conduct inferential analyses to examine infant and maternal outcomes following maternal exposures during pregnancy

Bird ST, Gelperin K, Taylor L, Sahin L, Hammad H, Andrade SE, Mohamoud MA, Toh S, Hampp C. Enrollment and Retention in 34 United States Pregnancy Registries Contrasted with the Manufacturer's Capture of Spontaneous Reports for Exposed Pregnancies. Drug Saf. 2018 Jan;41(1):87-94. doi: 10.1007/s40264-017-0591-5. PMID: 28840499.

Completed Mother-Infant Linkage Analyses

- Topiramate and oral clefts replication study
  - Available at https://www.sentinelinitiative.org/methods-data-tools/methods soon
- Characterizing the Mother-Infant Linkage Table
  - Maternal characteristics: available at https://www.sentinelinitiative.org/assessments soon
  - Infant characteristics ongoing
- Armodafinil or modafinil and cardiac malformations
  - https://www.sentinelinitiative.org/assessments/drugs/risk-congenital-cardiac-malformations-following-armodafinil-or-modafinil-use

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- Jenni Li

Data Partners

- Aetna
- HealthCore, Inc.
- Harvard Pilgrim Health Care
- Humana, Inc., Healthcare Research
- OptumInsight, Inc.
- Vanderbilt University Medical Center

Thank You

Questions?

Post-Training Evaluation