Sentinel

Sentinel Mother-Infant Linkage and Pregnancy Analyses

Canadian Mother-Child Cohort (CAMCCO) Active Surveillance – 1st Team and Stakeholders Symposium

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February 20, 2020

Agenda

- Sentinel Overview
- Introduction to Cohort Identification and Analysis (CIDA)
- Creating a cohort of deliveries
  1. Identify live birth deliveries
  2. Estimate pregnancy start
  3. Create a non-live birth comparator cohort
  4. Identify medical product use in pregnancy
  5. Create exposed and referent cohorts
  6. Identify maternal or infant outcomes

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

Lead: Harvard Pilgrim Health Care Institute

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

Data & Scientific Partners

HealthCore
Anthem
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
CMS Centers for Medicare & Medicaid Services
CAPriCORN
GPC Greater Plains Collaborative
Booz | Allen | Hamilton
Marshfield Clinic Research Institute
Harvard T.H. Chan School of Public Health
Rutgers
NYC-CDRN New York City Clinical Data Research Network
UF College of Pharmacy University of Florida
Vanderbilt University Medical Center
The Meyers Primary Care Institute
Kaiser Permanente
Kaiser Permanente Washington Health Research Institute
OneFlorida Clinical Research Consortium
REACHnet Research Action for Health Network
IBM Watson Health
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

- 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.	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/sentinel/data/distributed-database-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	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

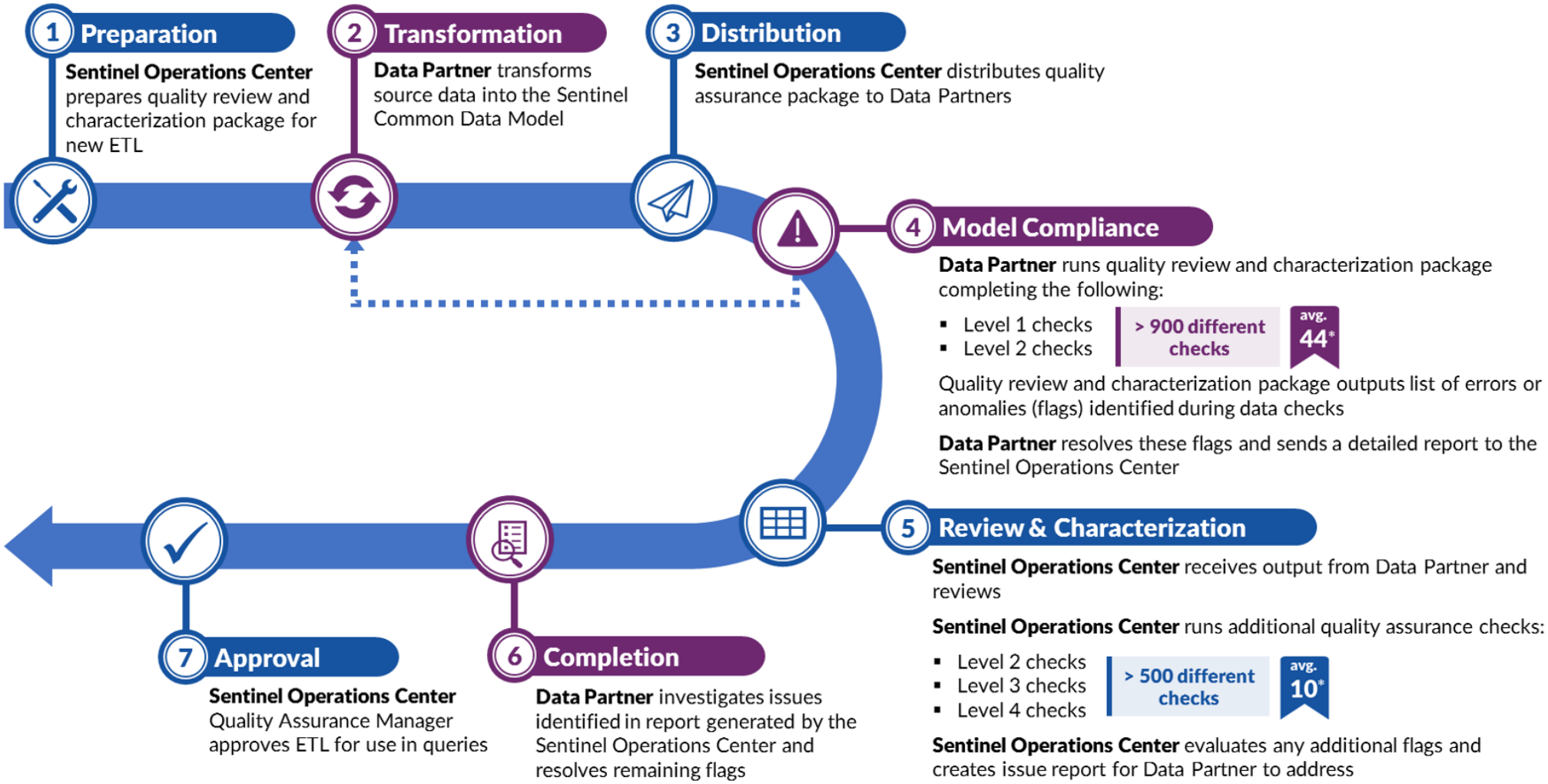
PROCEDURE

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

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



* 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

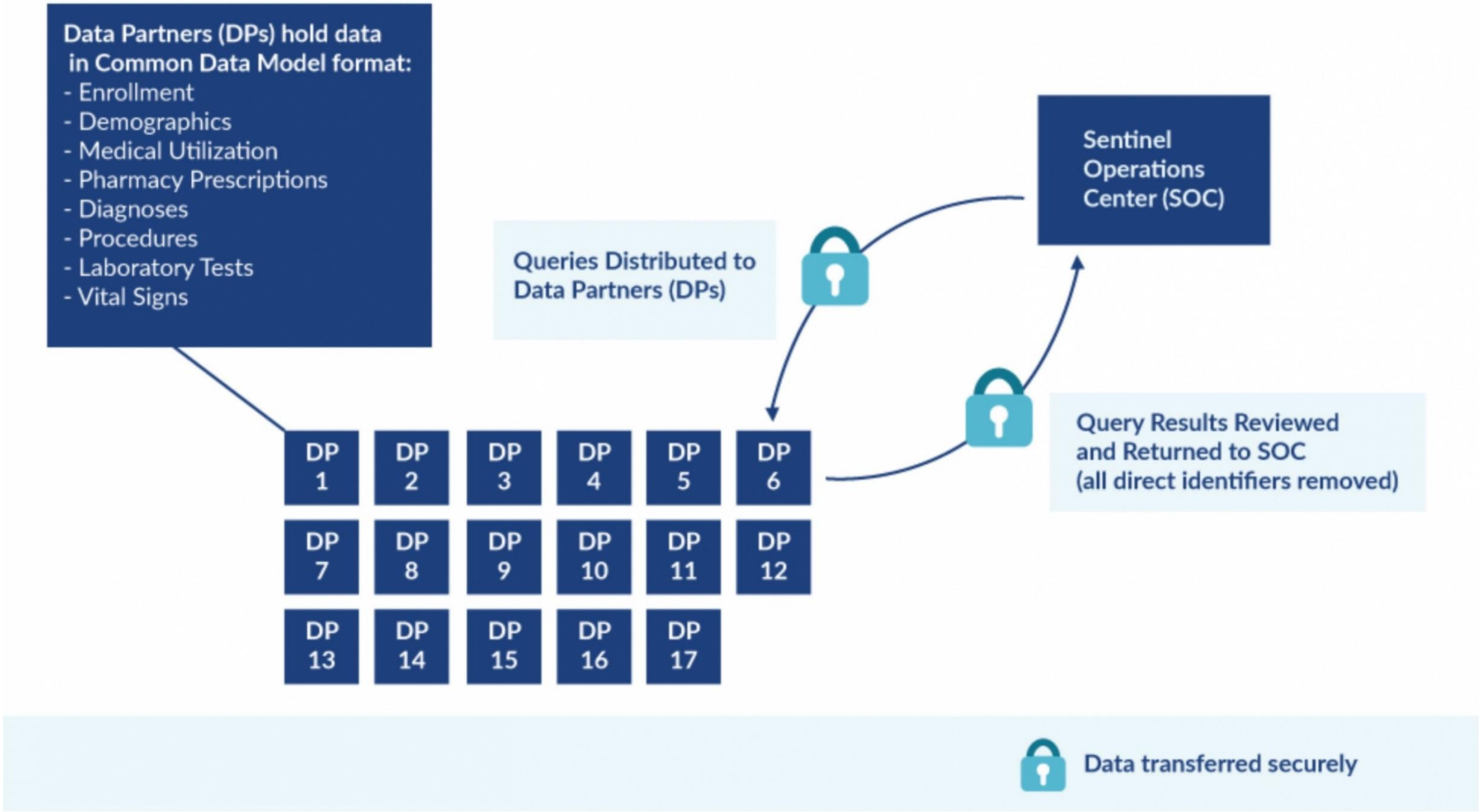
Level 1 Checks	**Completeness** ✓ Admission date is not missing value **Validity** ✓ Admission date is in date format	Sentinel Common Data Model Compliance
Level 2 Checks	**Accuracy** ✓ Admission date occurs before the patient's discharge date **Integrity** ✓ Admission date occurs within the patient's 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

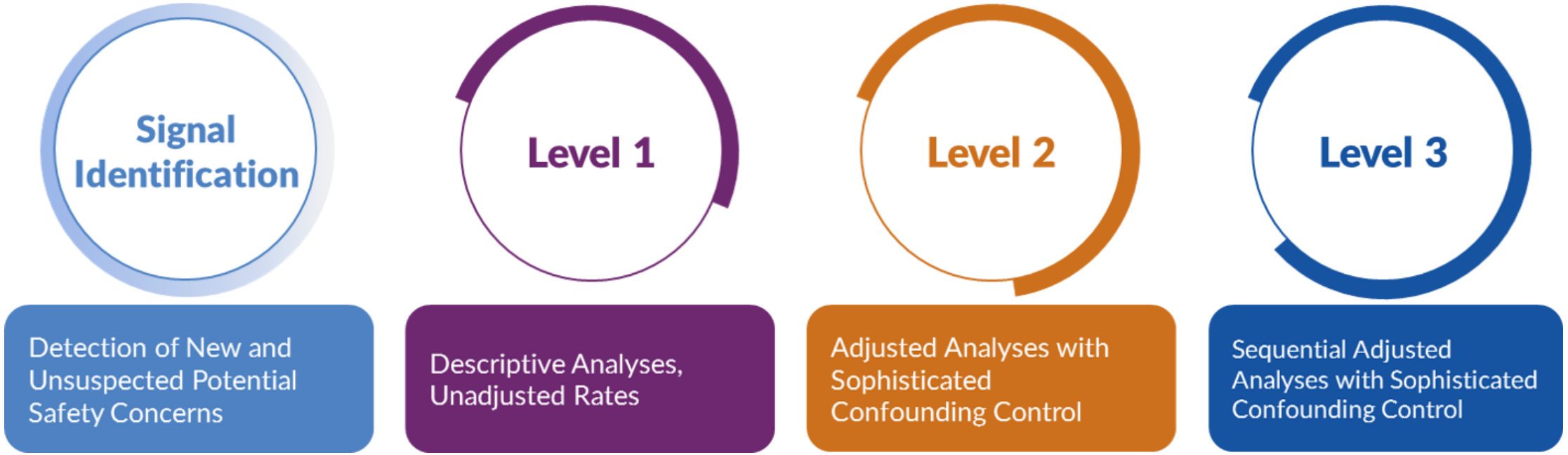
Sentinel Data Queries: Routine Querying Tools

Sentinel is a Distributed Data Network



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

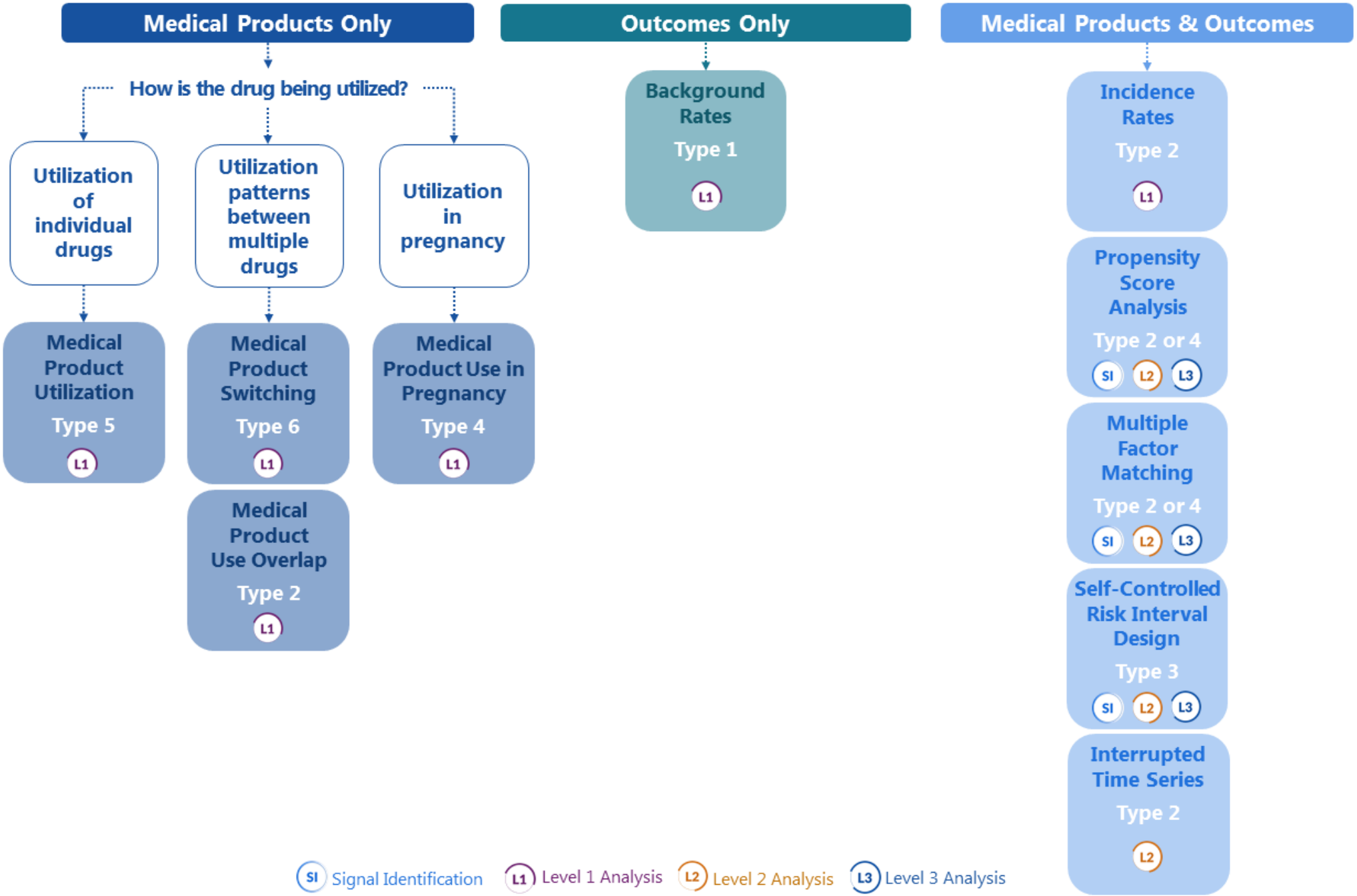
Active Risk Identification and Analysis (ARIA)

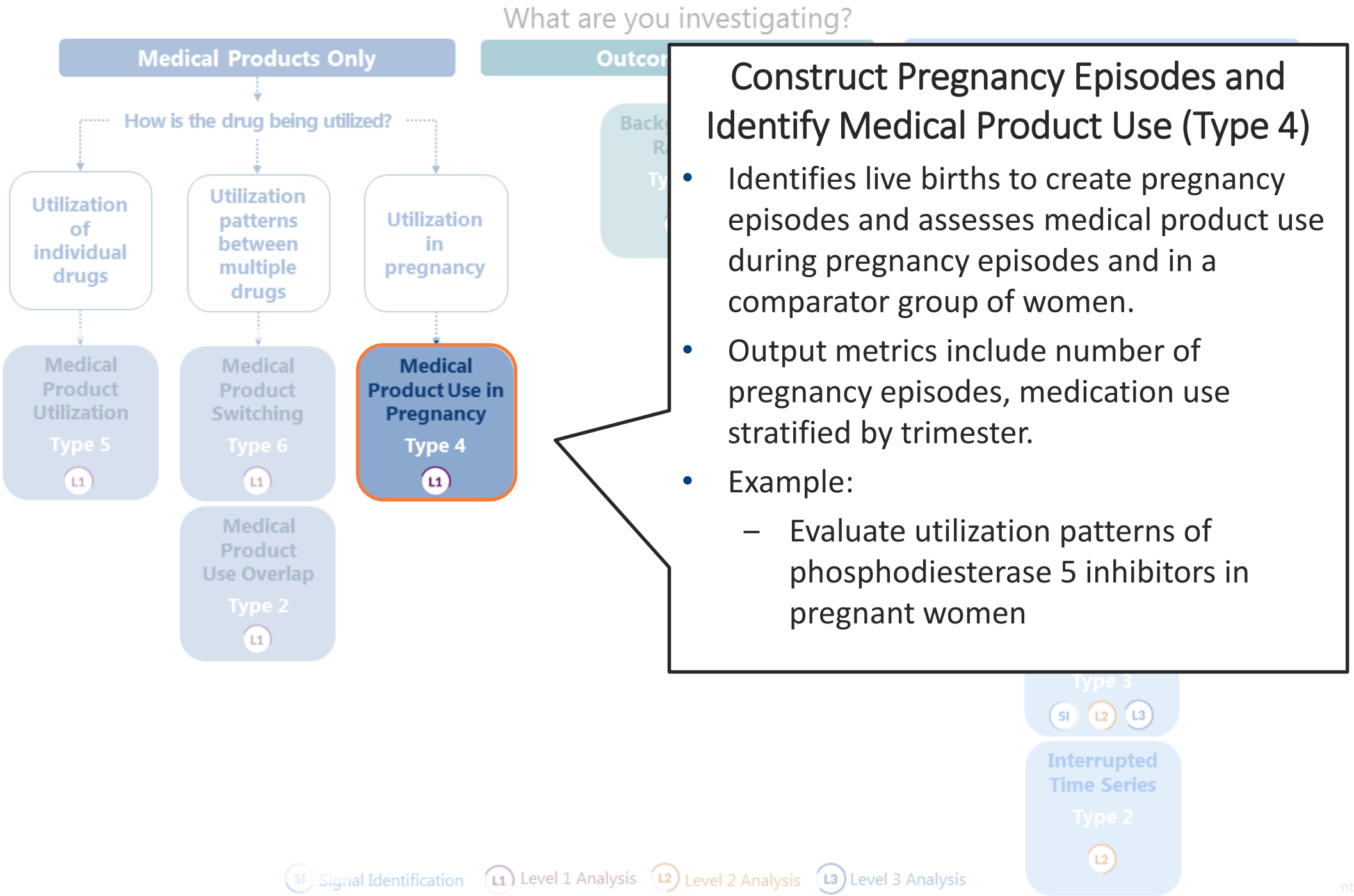


- Template computer programs with standardized questions
- Parameterized at program execution
- Pre-tested and quality-checked
- Standard output

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

What are you investigating?




What are you investigating?
Medical Products Only
How is the drug being utilized?
Utilization of individual drugs
Utilization patterns between multiple drugs
Utilization in pregnancy
Medical Product Utilization
Type 5
L1
Medical Product Switching
Type 6
L1
Medical Product Use in Pregnancy
Type 4
L1
Medical Product Use Overlap
Type 2
L1
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
Type 3
SI
L2
L3
Interrupted Time Series
Type 2
L2
SI Signal Identification
L1 Level 1 Analysis
L2 Level 2 Analysis
L3 Level 3 Analysis

What are you investigating?

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-pde-5-inhibitor-utilization-among-women

PDE5 Inhibitor use among women with live birth deliveries

Table 1a. Summary of Pregnancy Episodes with Prevalent Phosphodiesterase Type 5 (PDE5) Inhibitor Use among Women with Live Birth Deliveries in the Sentinel Distributed Database between January 1, 2001 and March 31, 2018, by Pregnancy-Related Time Period

Total Number of Eligible Pregnant Women: 2,776,562										
			Number of Pregnancy Episodes with Product Use							
	During Any Period[1]	**90 Days Before Pregnancy Start**	**Any Trimester**	**1st Trimester**	**2nd Trimester**	**3rd Trimester**	**All Trimesters**	**Only During 1st Trimester**	**Only During 2nd Trimester**	**Only During 3rd Trimester**
Number of Eligible Pregnancy Episodes	3,373,369	3,373,369	3,373,369	3,373,369	3,373,369	3,368,587	3,368,587	3,373,369	3,373,369	3,368,587
Any PDE5 Inhibitor	139	91	96	88	21	21	16	71	3	4
Sildenafil	127	83	85	81	13	12	10	70	2	2
Tadalafil	14	8	12	7	8	10	6	1	1	3
Vardenafil	1	1	0	0	0	0	0	0	0	0
Avanafil	0	0	0	0	0	0	0	0	0	0

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

PDE5 Inhibitor use among women with live birth deliveries

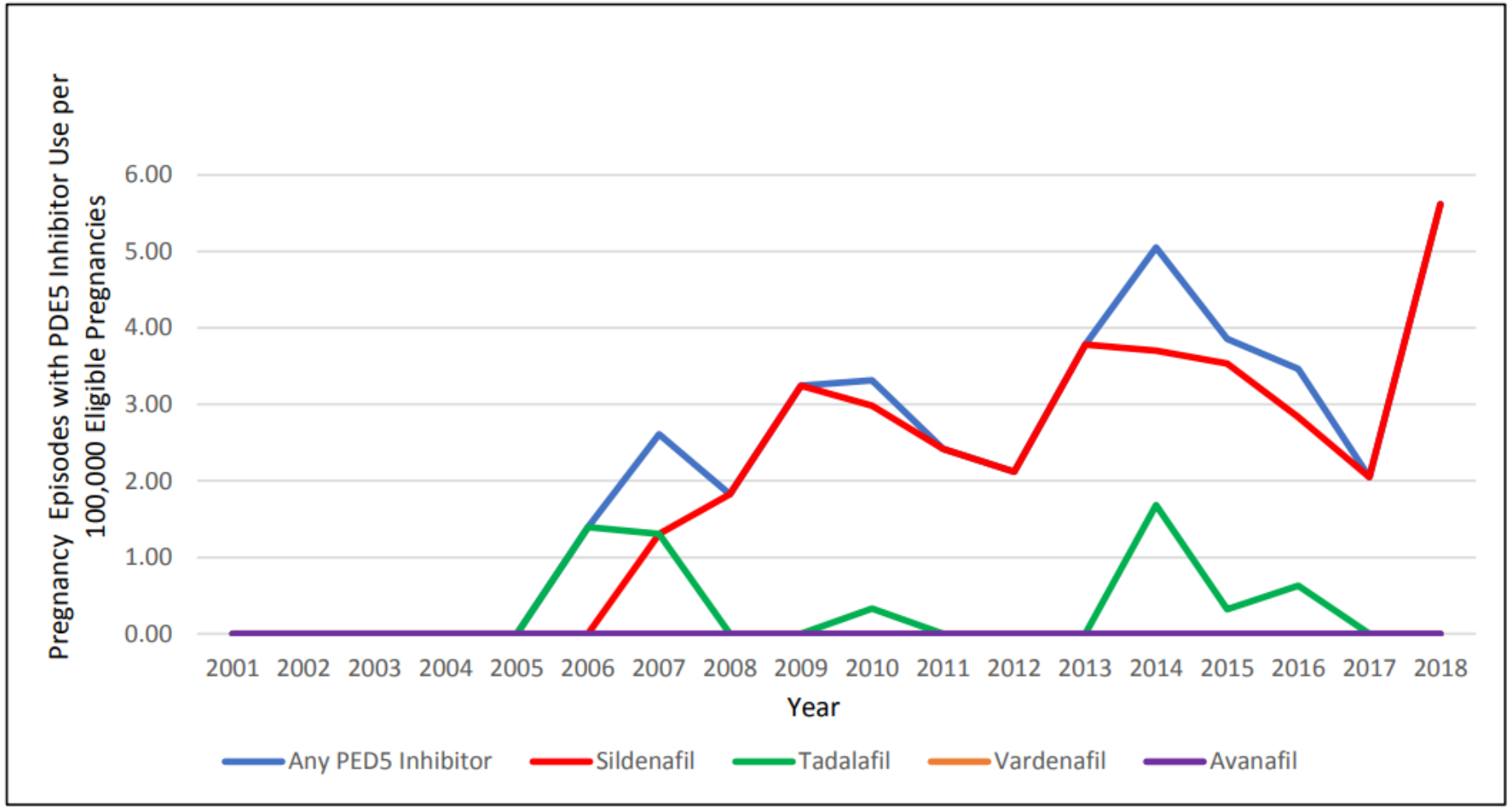
Table 4. Percentage of Prevalent Episodes of Phosphodiesterase Type 5 (PDE5) Inhibitor Use with Related Conditions and Indications Among Women with Live Birth Deliveries in the Sentinel Distributed Database between January 1, 2001 and March 31, 2018

	Any PDE5 Inhibitor	Sildenafil	Tadalafil	Vardenafil	Avanafil
Total Episodes[1]	148	133	18	1	0
Conditions and Indications[2]					
Cardiovascular implications	3.4%	2.3%	11.1%	0.0%	0.0%
Cutaneous implications	9.5%	9.8%	5.6%	0.0%	0.0%
Gastrointestinal implications	0.0%	0.0%	0.0%	0.0%	0.0%
Neurological implications	2.0%	0.8%	11.1%	0.0%	0.0%
Pulmonary arterial hypertension	15.5%	10.5%	61.1%	0.0%	0.0%
Pulmonary implications	2.0%	1.5%	11.1%	0.0%	0.0%
Reproductive implications	38.5%	37.6%	50.0%	0.0%	0.0%
Sexual implications	2.7%	3.0%	0.0%	0.0%	0.0%
Urogenital implications	4.7%	3.8%	16.7%	0.0%	0.0%
Fetal growth retardation	25.0%	26.3%	16.7%	0.0%	0.0%
Preeclampsia	31.1%	29.3%	50.0%	0.0%	0.0%
Diabetes	6.1%	6.8%	0.0%	0.0%	0.0%
Lupus	6.8%	5.3%	16.7%	0.0%	0.0%
None of the conditions of interest	35.1%	35.3%	22.2%	100.0%	0.0%

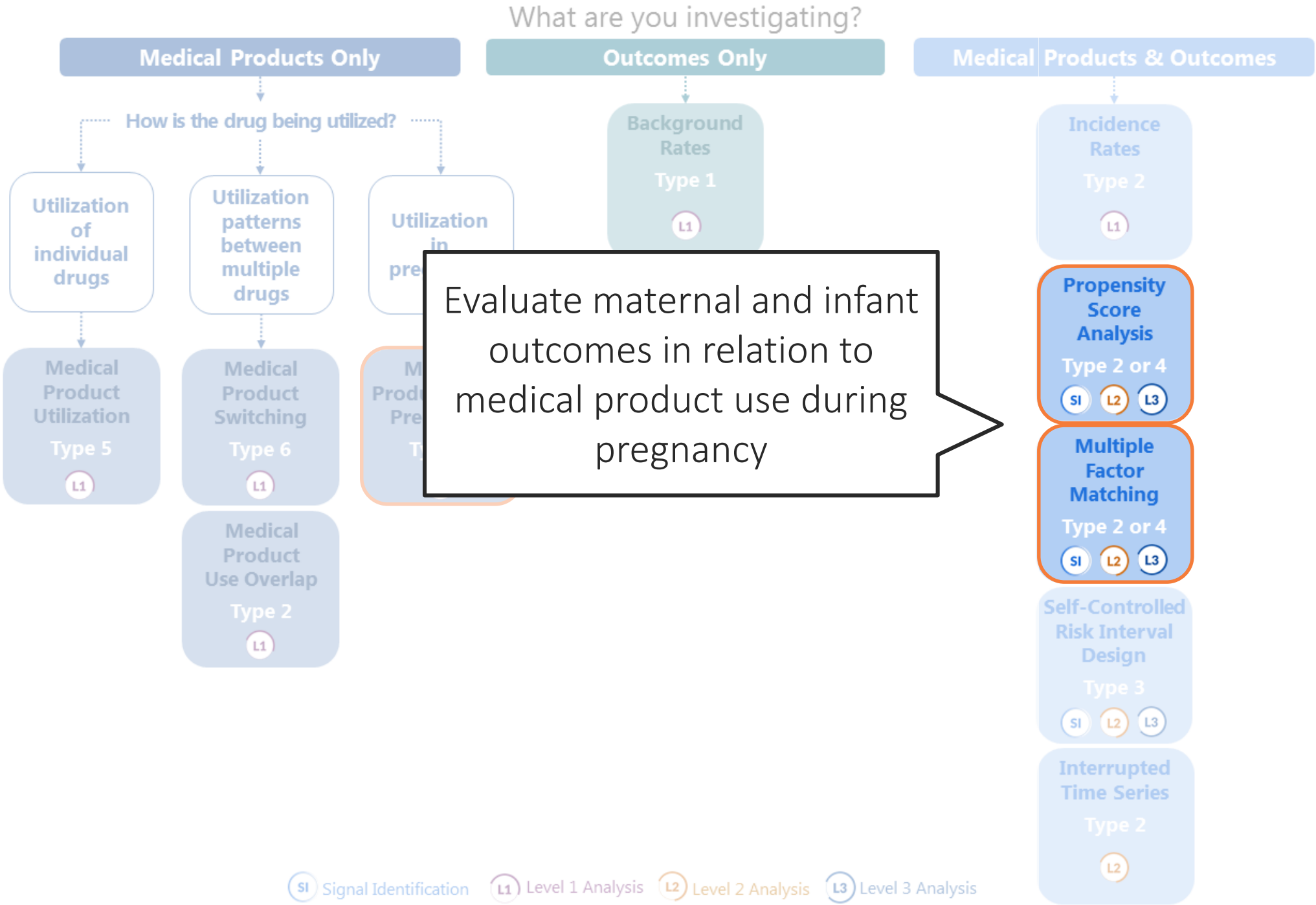
https://www.sentinelinitiative.org/drugs/assessments/phosphodiesterase-type-5-pde-5-inhibitor-utilization-among-women

PDE5 Inhibitor use among women with live birth deliveries

Figure 1. Utilization of Phosphodiesterase Type 5 (PDE5) Inhibitors Among Women with Live Birth Deliveries in the Sentinel Distributed Database between January 1, 2001 and March 31, 2018, by Delivery Year

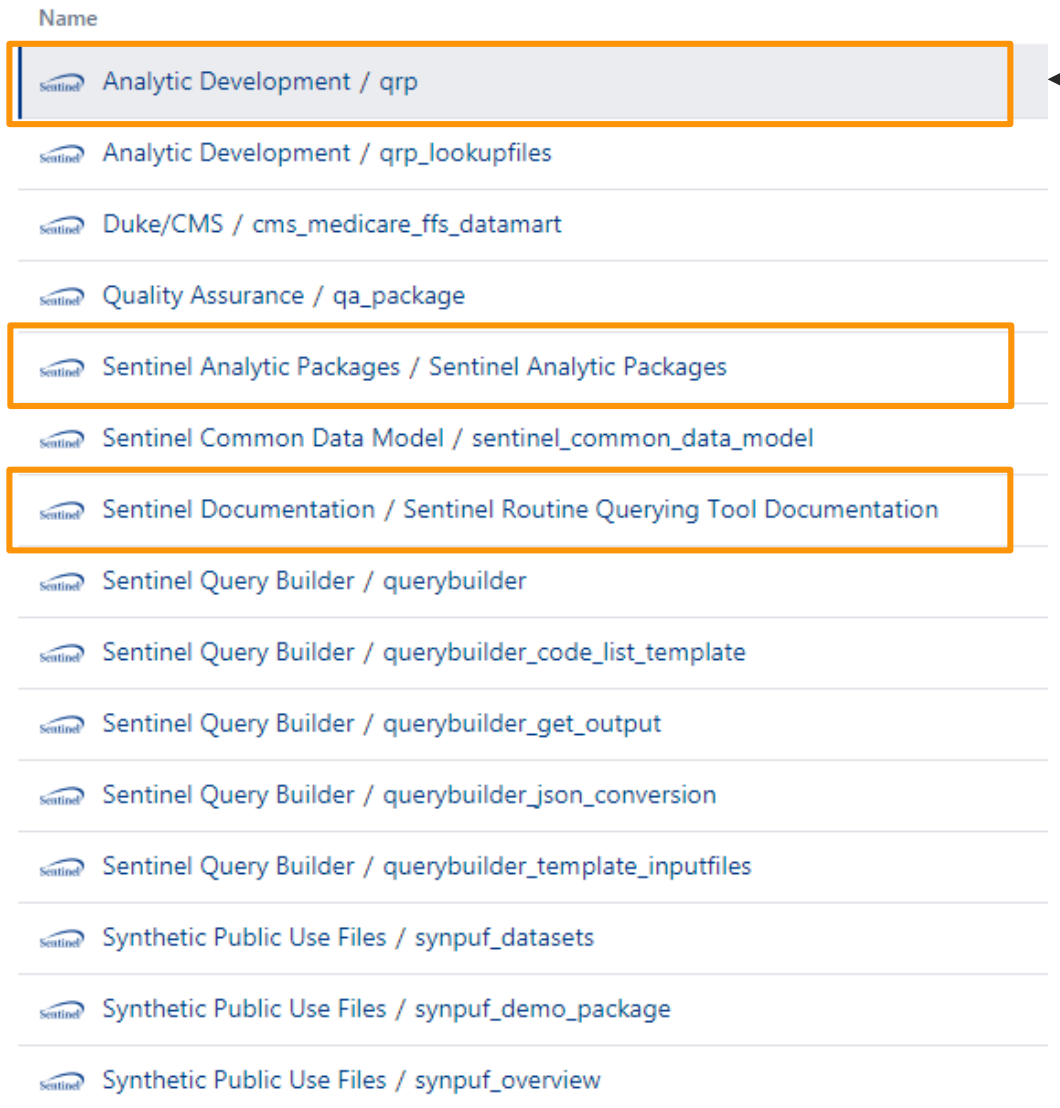


https://www.sentinelinitiative.org/drugs/assessments/phosphodiesterase-type-5-pde-5-inhibitor-utilization-among-women


What are you investigating?
Medical Products Only
Outcomes Only
Medical Products & Outcomes
How is the drug being utilized?
Utilization of individual drugs
Utilization patterns between multiple drugs
Utilization in pre
Background Rates
Type 1
L1
Incidence Rates
Type 2
L1
Medical Product Utilization
Type 5
L1
Medical Product Switching
Type 6
L1
Medical Product Use Overlap
Type 2
L1
Propensity Score Analysis
Type 2 or 4
SI L2 L3
Multiple Factor Matching
Type 2 or 4
SI L2 L3
Self-Controlled Risk Interval Design
Type 3
SI L2 L3
Interrupted Time Series
Type 2
L2
Evaluate maternal and infant outcomes in relation to medical product use during pregnancy
SI Signal Identification
L1 Level 1 Analysis
L2 Level 2 Analysis
L3 Level 3 Analysis

Sentinel's Public Documentation and SAS Program Depot

Public Repositories - https://dev.sentinelsystem.org/



Download a query request package

Download a package from a specific query

Read the documentation

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 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.

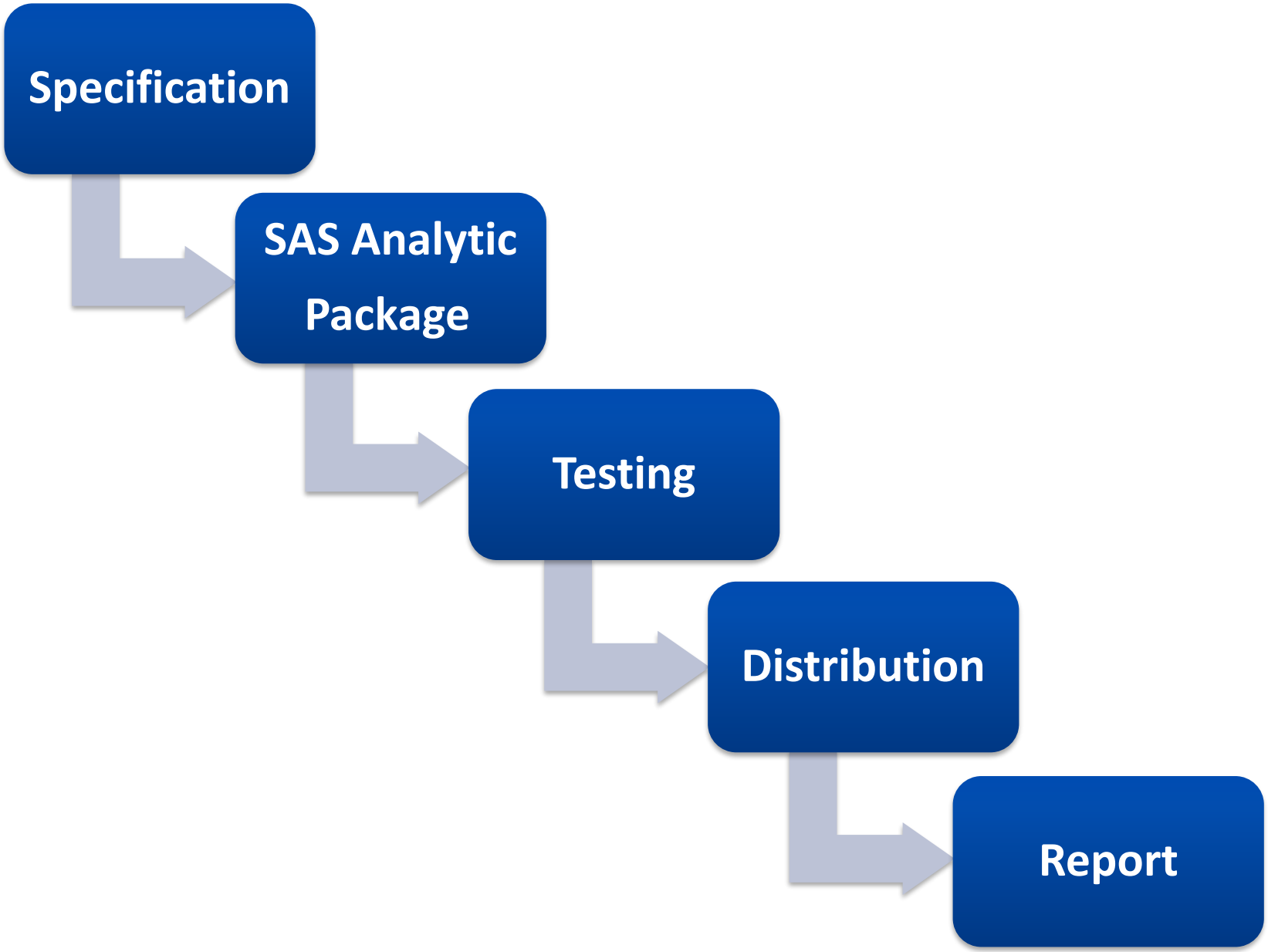
Analytic Request Packages Available for Download

Request ID	Summary
cder_mpl2p_wp011	Osteoporotic Fractures following Lupron Depot-PED Use: A Multiple Factor Matched Analysis
cder_mpl2p_wp016	Non-Melanoma Skin Cancer following Hydrochlorothiazide Use: A Propensity Score Matched Analysis
cder_mpl2p_wp007	Severe Uterine Bleed following Novel Oral Anticoagulants Use: A Propensity Score Matched Analysis
cder_mpl2r_wp008	Acute Myocardial Infarction and Hospitalized Heart Failure following Saxagliptin or Sitagliptin Use: A Propensity Score Matched Analysis
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

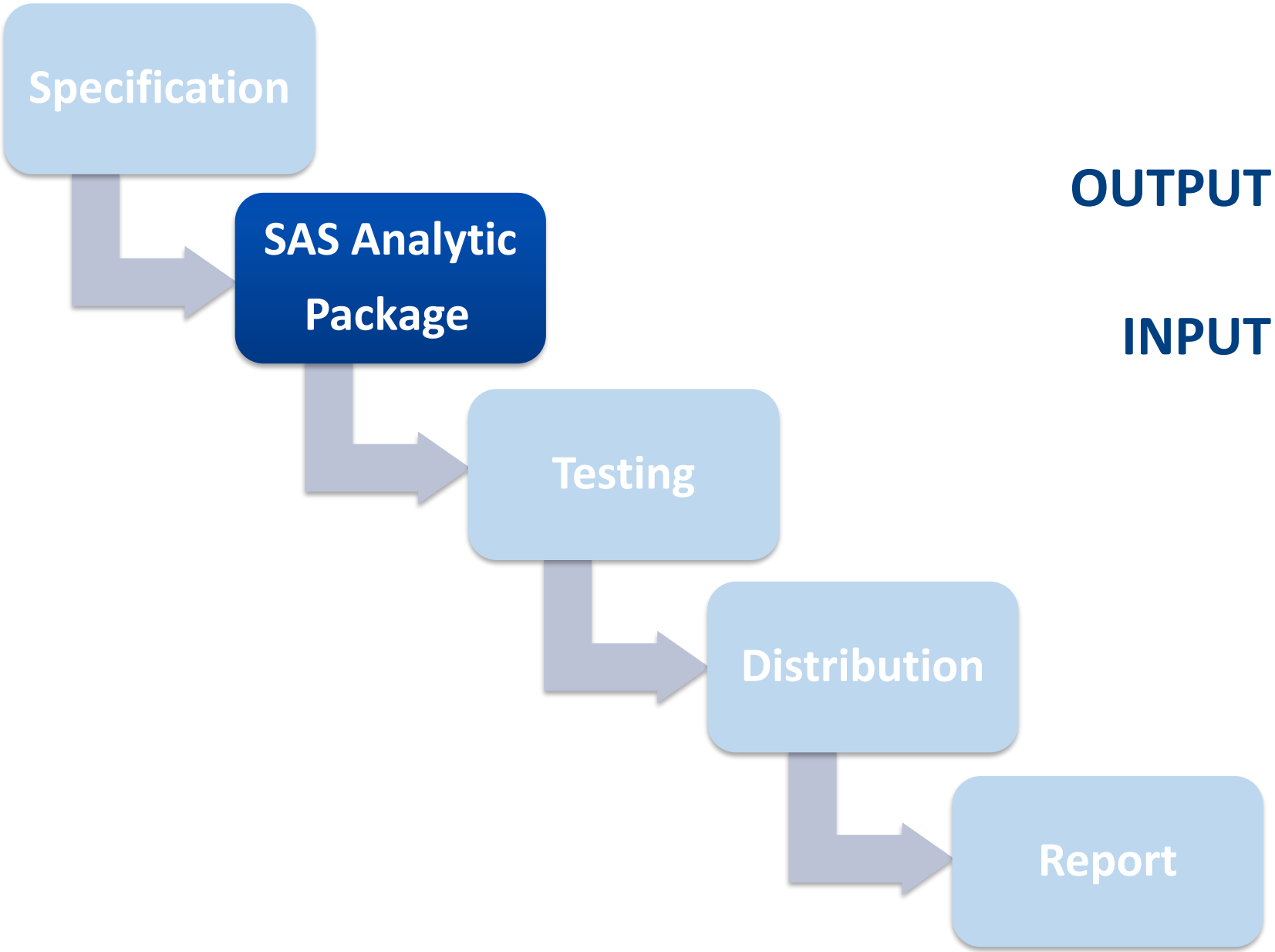
https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse

Query Request Package (QRP)

Operations Center Process Flow



Operations Center Process Flow



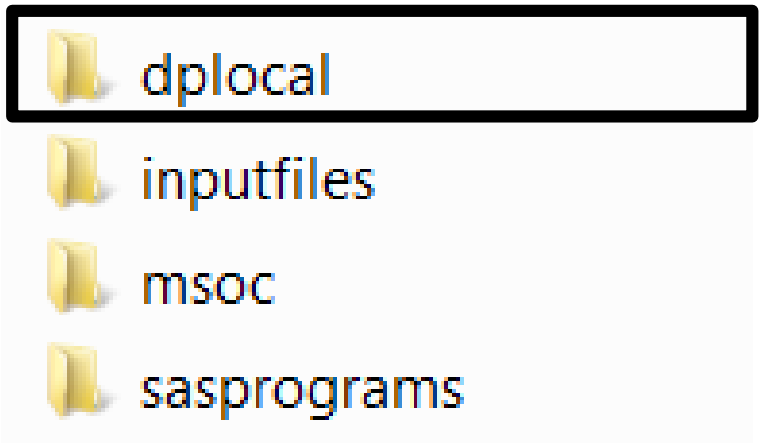
OUTPUT

- dplocal
- msoc

INPUT

- inputfiles
- sasprograms

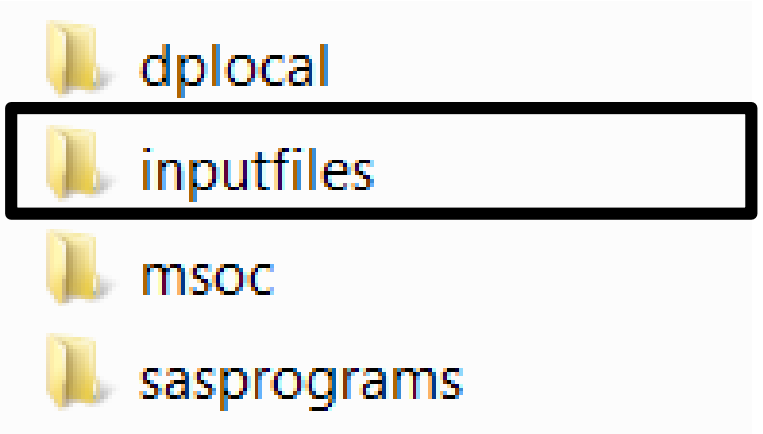
Query Request Package: folder structure



← **[empty before distribution]**

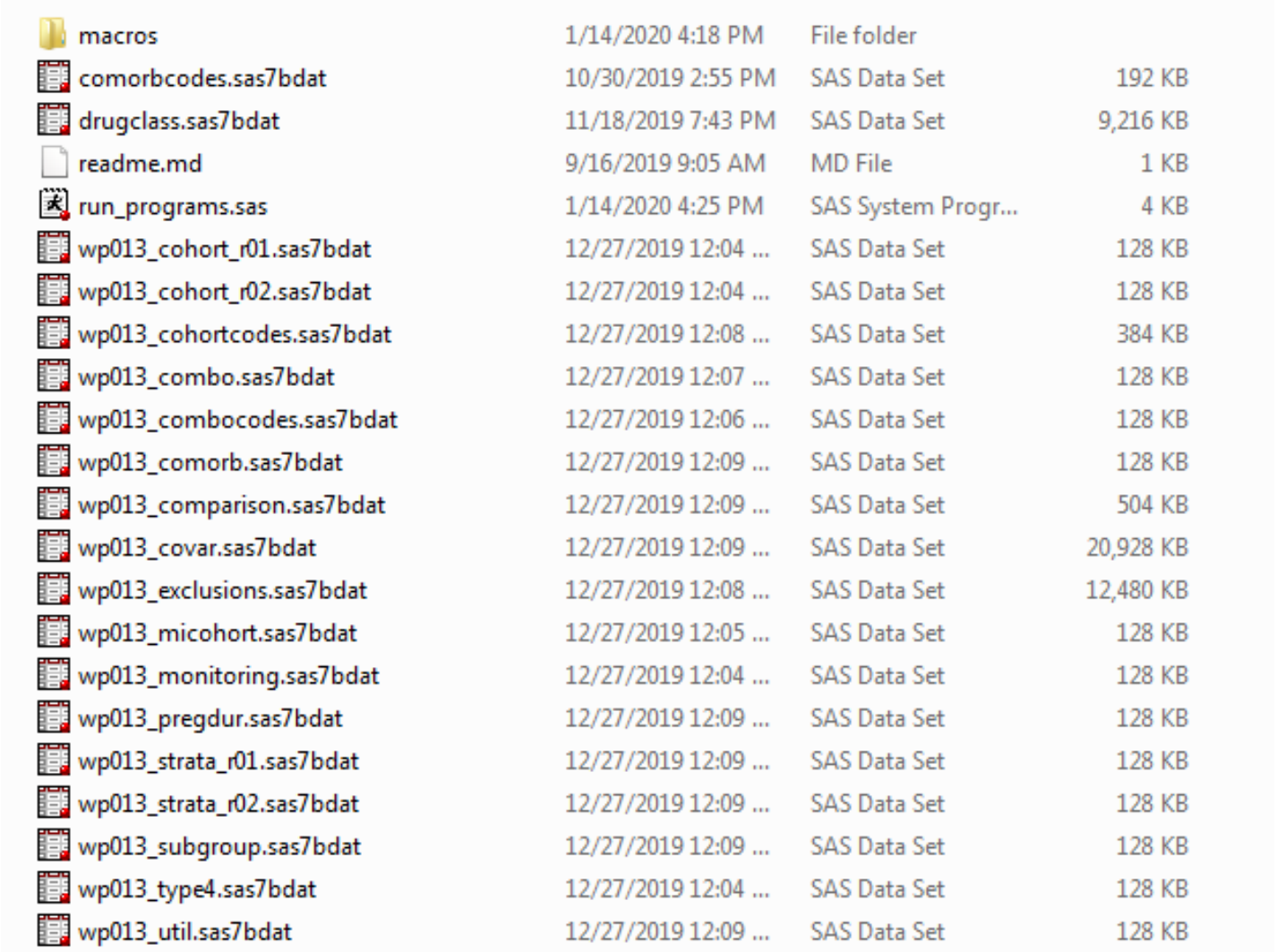
- Will contain patient-level data
- Will NOT be returned by DP

Query Request Package: folder structure



← **Macros for running standardized programs**
Parameterized files created specific to each request

Input Files: user-created with query parameters and codes

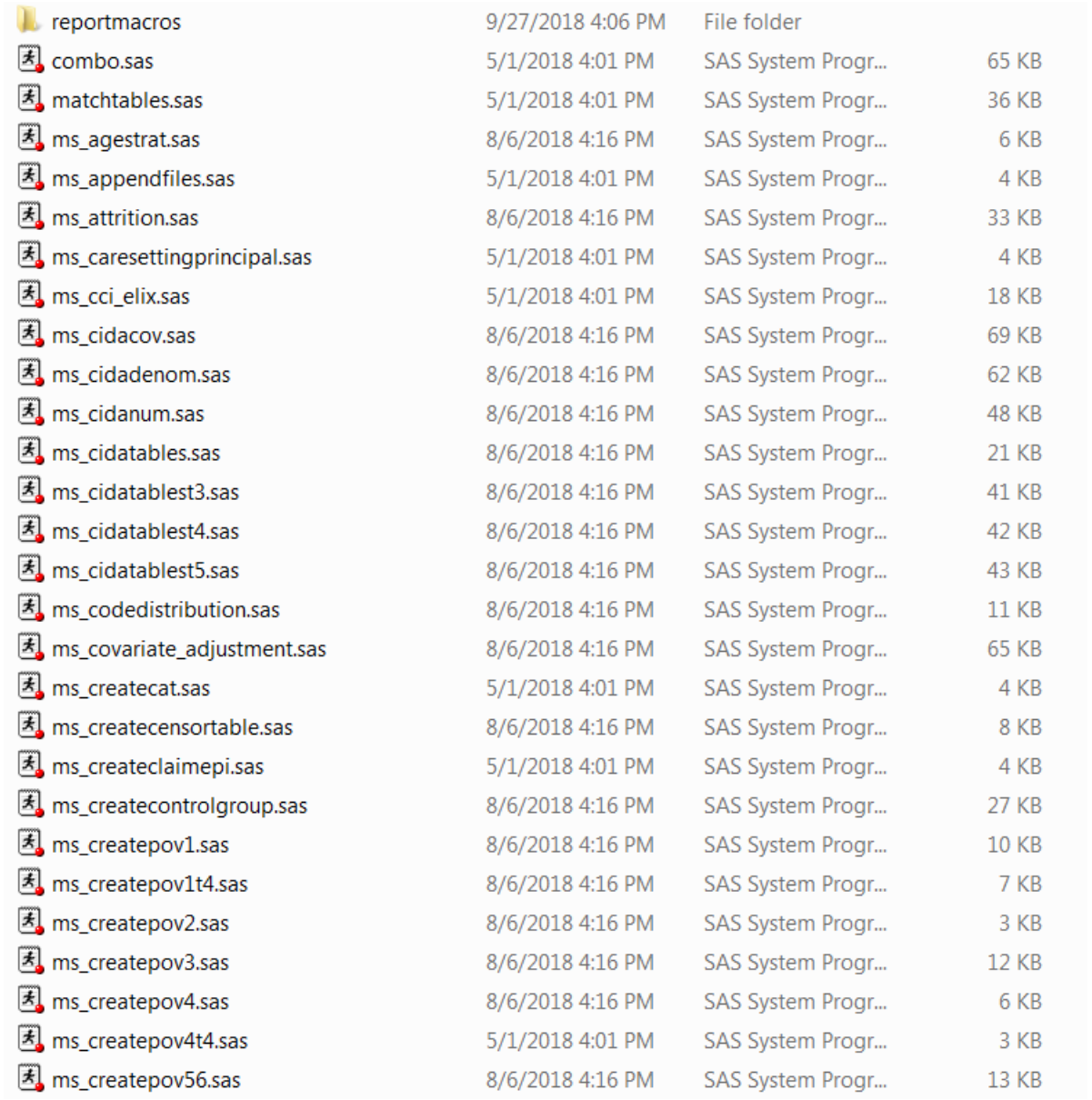


macros	1/14/2020 4:18 PM	File folder	
comorbcodes.sas7bdat	10/30/2019 2:55 PM	SAS Data Set	192 KB
drugclass.sas7bdat	11/18/2019 7:43 PM	SAS Data Set	9,216 KB
readme.md	9/16/2019 9:05 AM	MD File	1 KB
run_programs.sas	1/14/2020 4:25 PM	SAS System Progr...	4 KB
wp013_cohort_r01.sas7bdat	12/27/2019 12:04 ...	SAS Data Set	128 KB
wp013_cohort_r02.sas7bdat	12/27/2019 12:04 ...	SAS Data Set	128 KB
wp013_cohortcodes.sas7bdat	12/27/2019 12:08 ...	SAS Data Set	384 KB
wp013_combo.sas7bdat	12/27/2019 12:07 ...	SAS Data Set	128 KB
wp013_combocodes.sas7bdat	12/27/2019 12:06 ...	SAS Data Set	128 KB
wp013_comorb.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	128 KB
wp013_comparison.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	504 KB
wp013_covar.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	20,928 KB
wp013_exclusions.sas7bdat	12/27/2019 12:08 ...	SAS Data Set	12,480 KB
wp013_micohort.sas7bdat	12/27/2019 12:05 ...	SAS Data Set	128 KB
wp013_monitoring.sas7bdat	12/27/2019 12:04 ...	SAS Data Set	128 KB
wp013_pregdur.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	128 KB
wp013_strata_r01.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	128 KB
wp013_strata_r02.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	128 KB
wp013_subgroup.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	128 KB
wp013_type4.sas7bdat	12/27/2019 12:04 ...	SAS Data Set	128 KB
wp013_util.sas7bdat	12/27/2019 12:09 ...	SAS Data Set	128 KB

Input Files

- Varied from request to request / analyst to analyst
- Some are required
- Some are optional

Input Files: standard macros



reportmacros	9/27/2018 4:06 PM	File folder	
combo.sas	5/1/2018 4:01 PM	SAS System Progr...	65 KB
matchtables.sas	5/1/2018 4:01 PM	SAS System Progr...	36 KB
ms_agestrat.sas	8/6/2018 4:16 PM	SAS System Progr...	6 KB
ms_appendfiles.sas	5/1/2018 4:01 PM	SAS System Progr...	4 KB
ms_attrition.sas	8/6/2018 4:16 PM	SAS System Progr...	33 KB
ms_caresettingprincipal.sas	5/1/2018 4:01 PM	SAS System Progr...	4 KB
ms_cci_elix.sas	5/1/2018 4:01 PM	SAS System Progr...	18 KB
ms_cidacov.sas	8/6/2018 4:16 PM	SAS System Progr...	69 KB
ms_cidadenom.sas	8/6/2018 4:16 PM	SAS System Progr...	62 KB
ms_cidanum.sas	8/6/2018 4:16 PM	SAS System Progr...	48 KB
ms_cidatables.sas	8/6/2018 4:16 PM	SAS System Progr...	21 KB
ms_cidatablest3.sas	8/6/2018 4:16 PM	SAS System Progr...	41 KB
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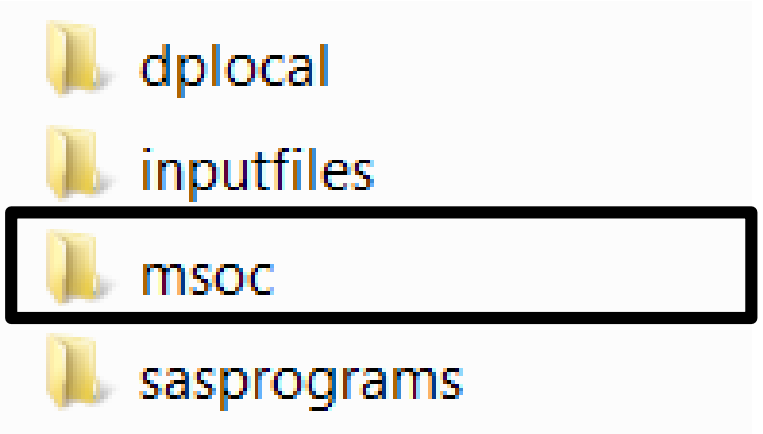
ms_createpov1t4.sas	8/6/2018 4:16 PM	SAS System Progr...	7 KB
ms_createpov2.sas	8/6/2018 4:16 PM	SAS System Progr...	3 KB
ms_createpov3.sas	8/6/2018 4:16 PM	SAS System Progr...	12 KB
ms_createpov4.sas	8/6/2018 4:16 PM	SAS System Progr...	6 KB
ms_createpov4t4.sas	5/1/2018 4:01 PM	SAS System Progr...	3 KB
ms_createpov56.sas	8/6/2018 4:16 PM	SAS System Progr...	13 KB

CIDA Macros

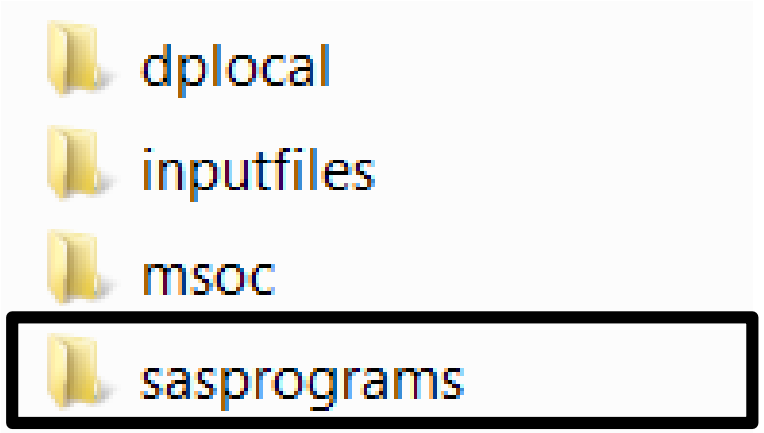
Query Request Package: folder structure



← **[empty before distribution]**

- Will contain aggregated DP-level data
- WILL be returned by DP

Query Request Package: folder structure

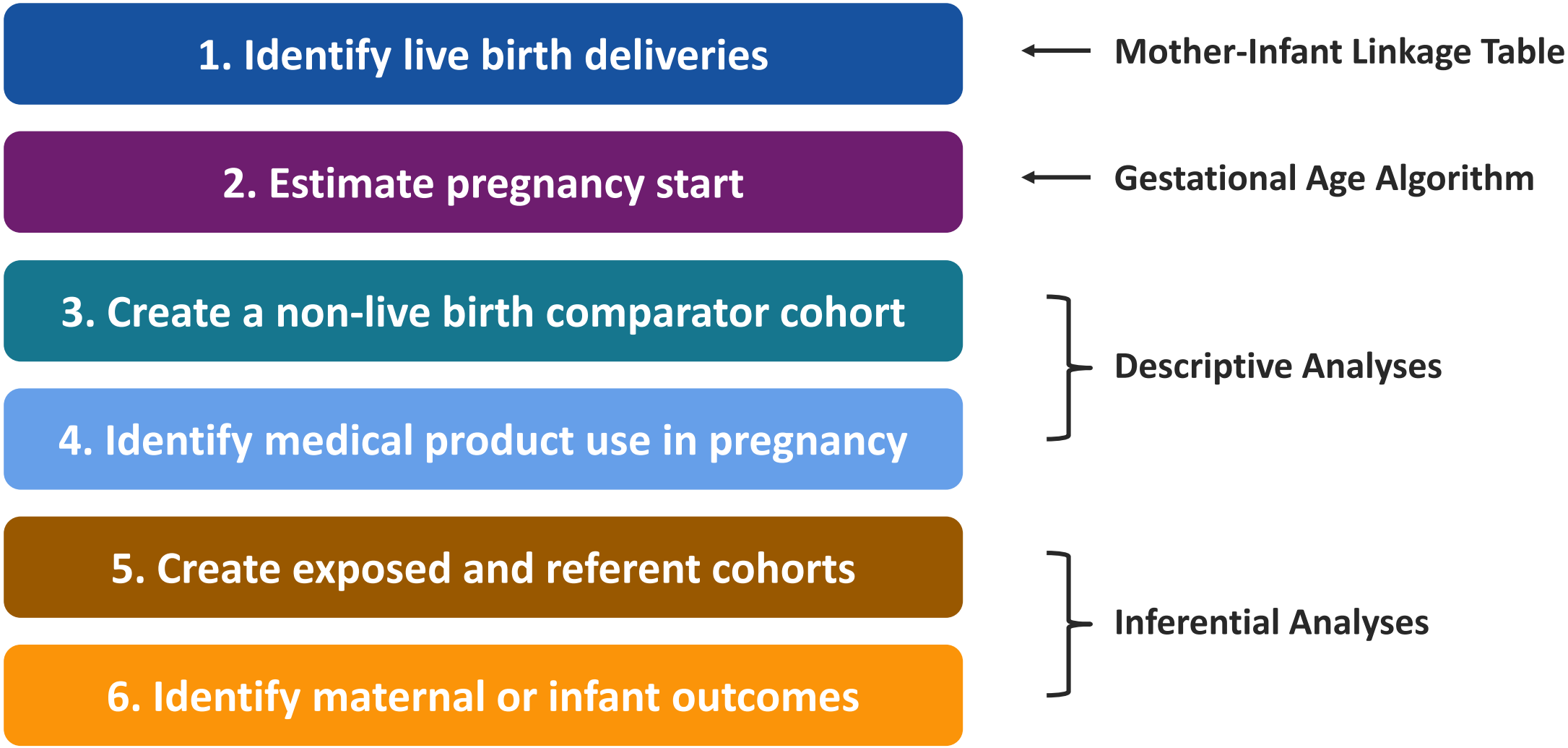


← **Contains header program "[request ID].sas"**

e.g. cber_mpl1r_wp023_nsdp_v01.sas

Conducting Pregnancy Analyses in Sentinel

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-live birth comparator cohort
4. Identify medical product use in pregnancy

} Descriptive Analyses

5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes

} Inferential Analyses

Identifying pregnancies in Sentinel Data

- Data available for identifying deliveries: insurance claims data
- This does NOT include: registry data, electronic health record data, birth certificate data, etc.

- **Live birth deliveries and pregnancy episodes are identified using validated algorithms**

- Currently, only live birth deliveries are identified
- Identification of non-live birth outcomes (miscarriage, stillbirth) is of interest, but is challenging in US insurance claims data
  - Accuracy of codes to identify non-live birth outcomes is questionable
  - Estimates of gestational age are uncertain

1. Identify live birth deliveries

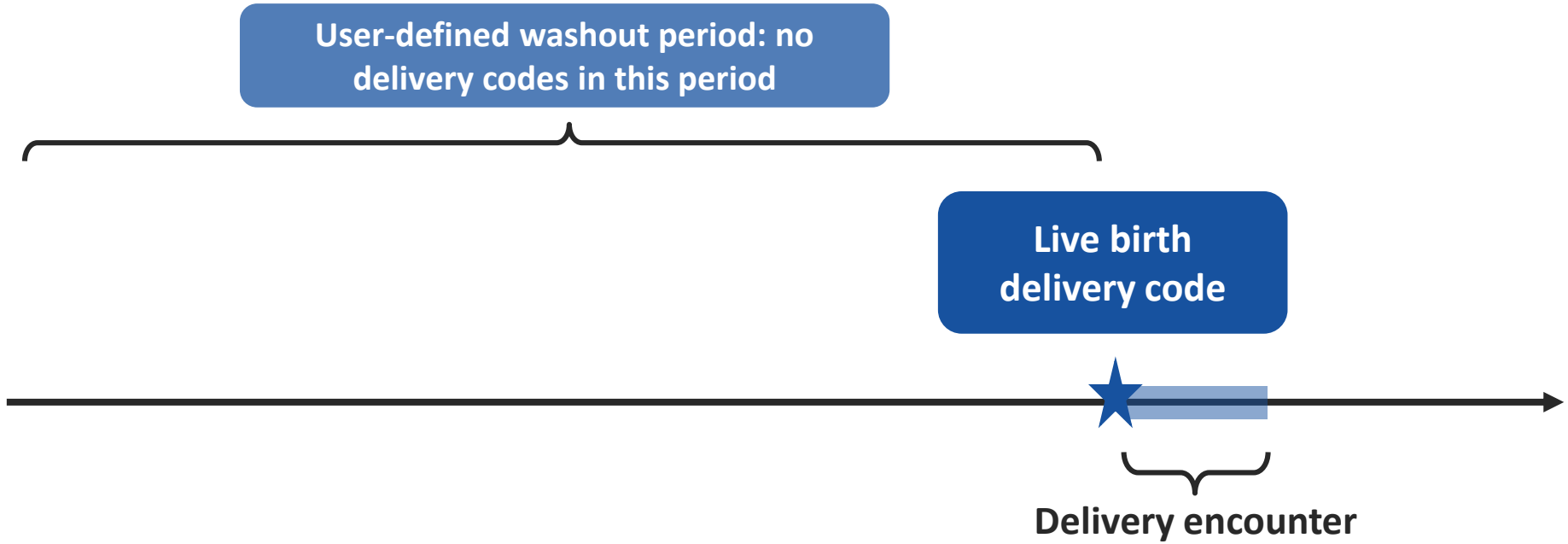
Methods for identifying a live birth cohort

Live birth deliveries and pregnancy episodes are identified using validated algorithms

Any live birth delivery	▪ Identified using ICD-9 and ICD-10 diagnosis and procedure codes ▪ Can be implemented at all Data Partners
Live birth delivery linked to an infant	▪ Identified using the Mother-Infant Linkage Table ▪ Can be implemented only at Data Partners that maintain a Mother-Infant Linkage Table (currently 6)

1. Identify live birth deliveries

Live birth deliveries: codes



User-specified: Live birth delivery encounter type

Live birth delivery date = admission date for delivery encounter

1. Identify live birth deliveries: codes

Live birth deliveries: codes

VIEWTABLE: TMP1.cohortcodes

	group	stockgroup	codecat	codetype	code	caresettingprincipal
1	base	delivery	PX	10	10D07Z3	IP*
2	base	delivery	PX	10	0W8NXZZ	IP*
3	base	delivery	PX	10	10D07Z4	IP*
4	base	delivery	PX	10	10D07Z5	IP*
5	base	delivery	PX	10	10S07ZZ	IP*
6	base	delivery	PX	10	10D07Z6	IP*
7	base	delivery	PX	10	10D07Z8	IP*
8	base	delivery	PX	10	10900ZC	IP*
9	base	delivery	PX	10	10908ZC	IP*
10	base	delivery	PX	10	10907ZC	IP*
11	base	delivery	PX	10	10904ZC	IP*
12	base	delivery	PX	10	10903ZC	IP*
13	base	delivery	PX	10	10D07Z7	IP*
14	base	delivery	PX	10	10E0XZZ	IP*
15	base	delivery	PX	10	10D00Z0	IP*
16	base	delivery	PX	10	10D00Z1	IP*
17	base	delivery	PX	10	10D00Z2	IP*
18	base	delivery	DX	10	O6012X0	IP*

This variable does two things:

1. Specifies encounter type
2. Specifies the position of discharge diagnosis codes

IP* = diagnosis code can be in the principle or secondary diagnosis position

Specifying IPP would result in:

- Including only delivery codes that occur in the inpatient setting
- Including only diagnosis codes that are the principle discharge codes

1. Identify live birth deliveries: codes

Mother-Infant Linkage Table

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.

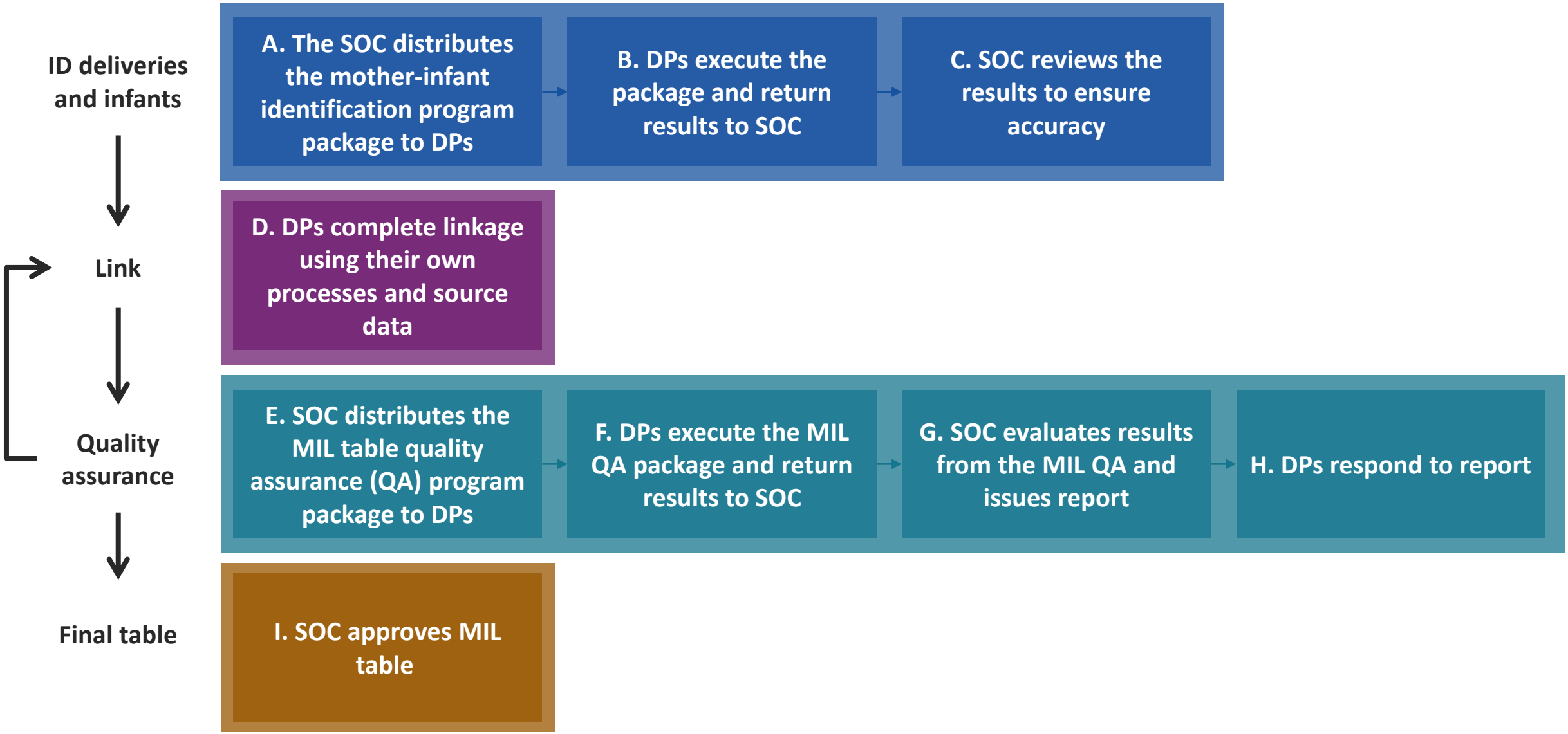
Table in the Sentinel Common Data Model, populated by six Data Partners

- 4 national claims insurers
- 1 Medicaid data source
- 1 regional claims insurer

Mother-Infant Linkage Table is used to identify linked mother-infant pairs for further analysis

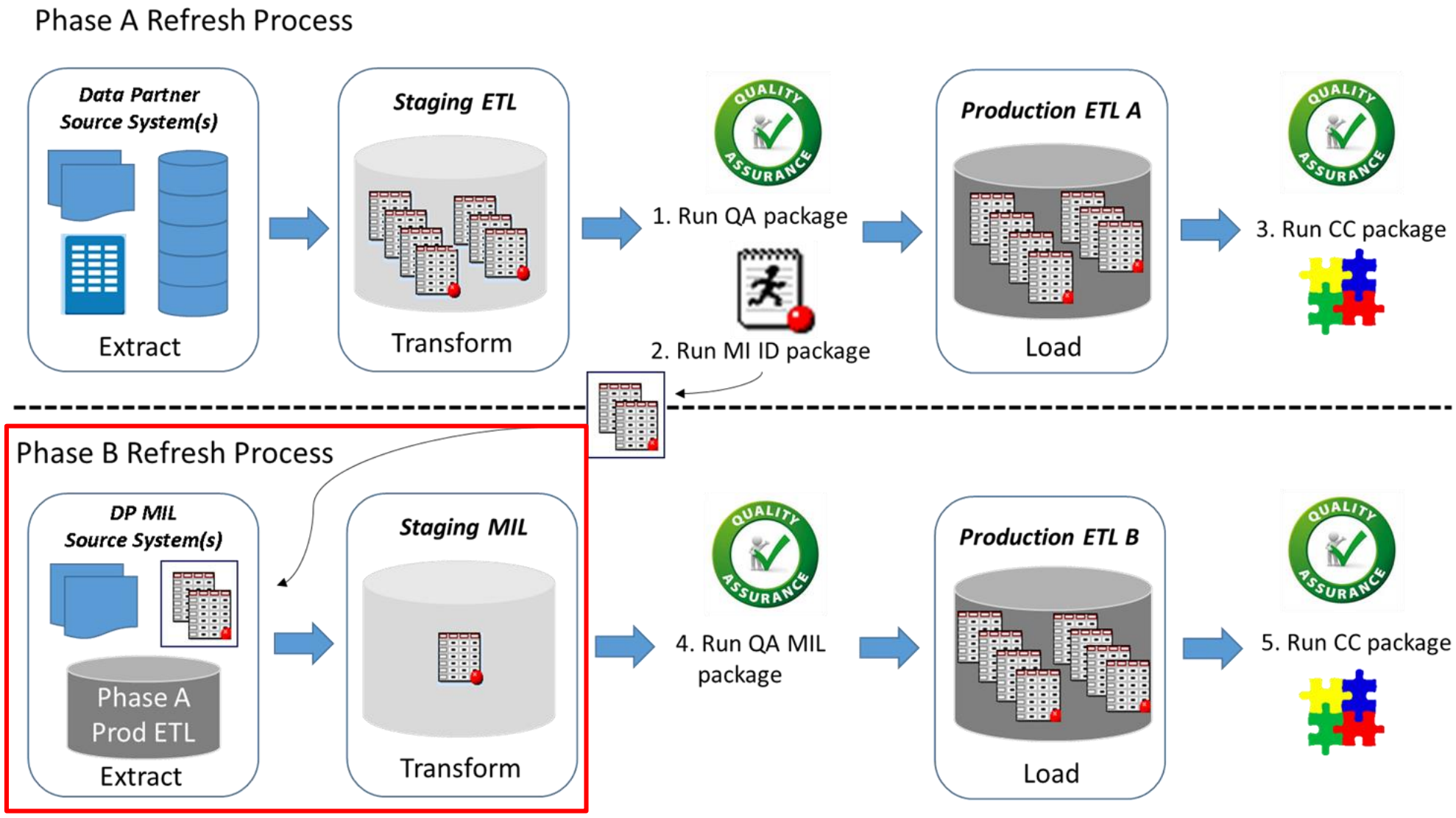
1. Identify live birth deliveries: MIL

Steps for creating the MIL table



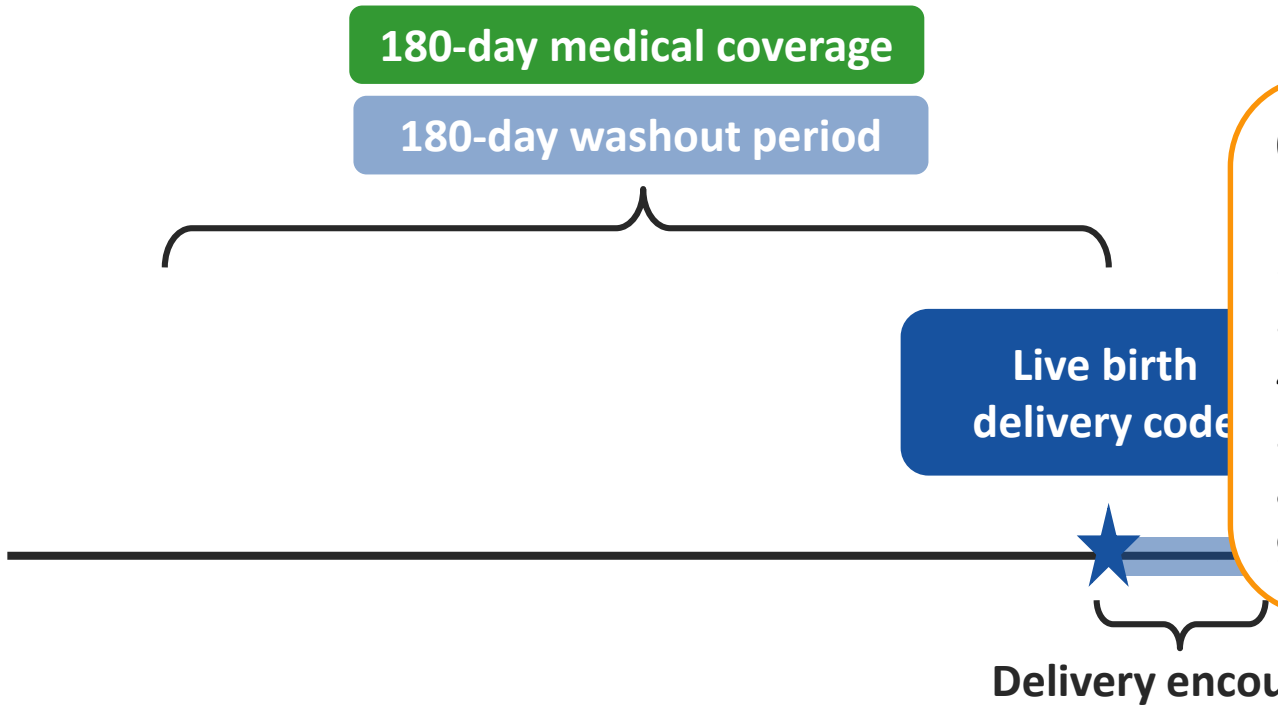
1. Identify live birth deliveries: MIL

Process of building MIL at each Data Partner



1. Identify live birth deliveries: MIL

Identifying deliveries for the MIL table



Information recorded for mothers:

- Patient ID

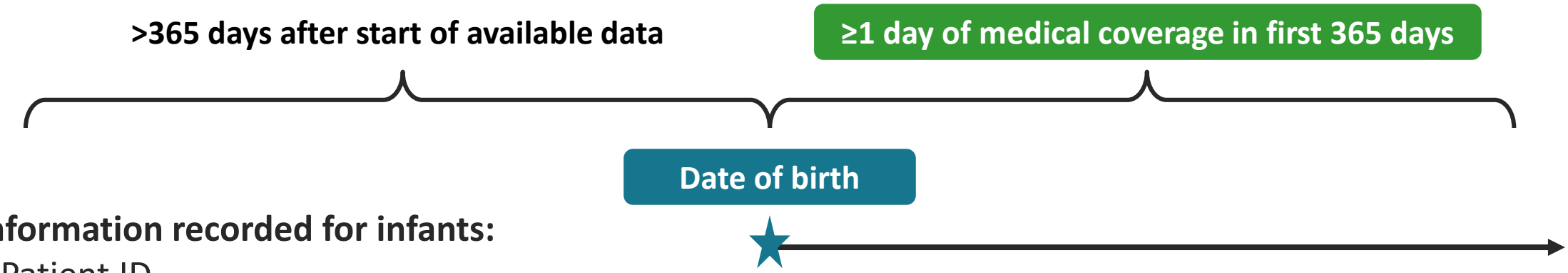
0 = Unspecified # of live births
1 = One live birth
2 = Two live births
3 = Three live births
4 = Four live births
5 = Five live births
8 = Multiple live births, unspecified number
9 = Conflicting code(s) for number of live births

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

Codes for singleton vs multiple are taken from the delivery encounter

1. Identify live birth deliveries: MIL

Identifying infants for the MIL table



Information recorded for infants:

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

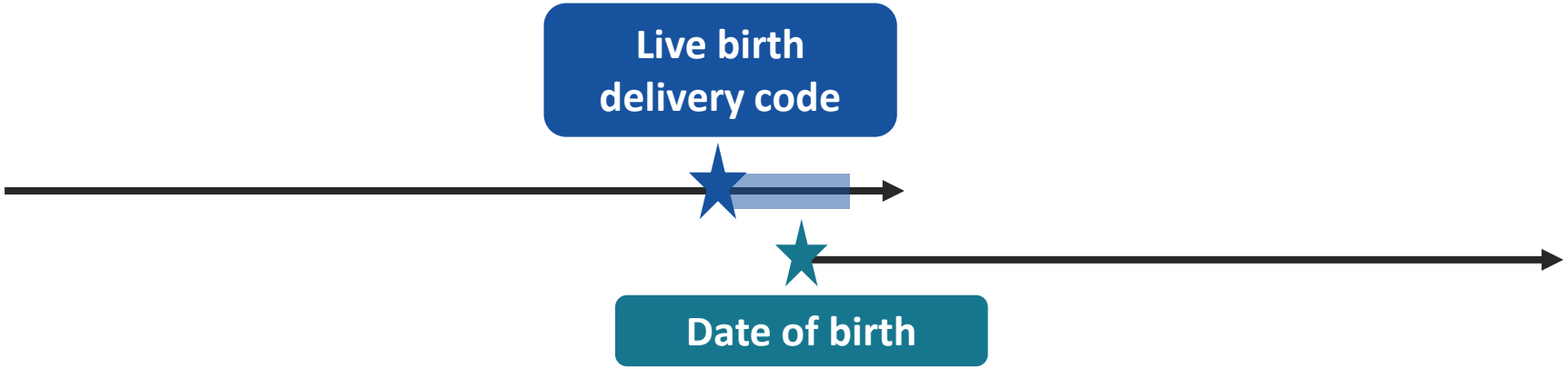
1. Identify live birth deliveries: MIL

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

1. Identify live birth deliveries: MIL

Linking mothers to infants

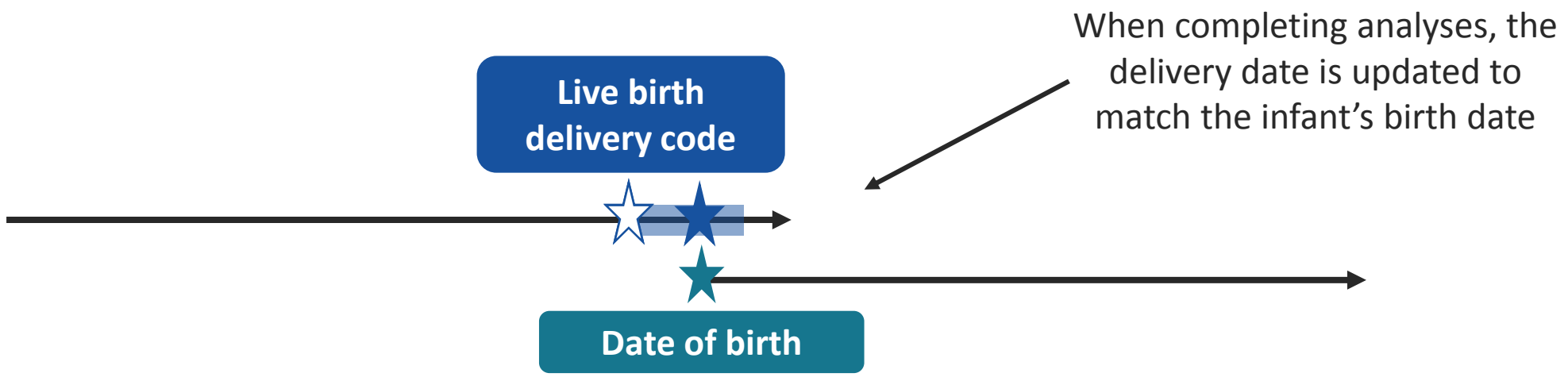


New variable for MatchMethod:
BC = Birth Certificate
RE = DP maintained birth registry
SI = health plan subscriber or family number
LA = exact or probabilistic last name and address match based upon health plan administrative data
OT = other

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

1. Identify live birth deliveries: MIL

Linking mothers to infants



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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

1. Identify live birth deliveries: MIL

Mother Infant Linkage – Latest Data

Approximately 4 million linked deliveries available in the SCDM currently – updated regularly

	Total
Deliveries	5,637,969
Infants	7,849,566
Linked deliveries	4,094,436
Linkage rate	72.62%

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

1. Identify live birth deliveries: MIL

Linkage Rates by Birth Types

	Birth type				
	No indicator of # of live births	One live birth	Two live births	Conflicting codes on # of live births	Total
Deliveries	492,437	5,021,394	101,266	17,462	5,637,969
Linked Deliveries	152,306	3,849,340	76,441	13,280	4,094,436
Linkage Rate	30.93%	76.66%	75.49%	76.05%	72.62%

1. Identify live birth deliveries: MIL

Linkage by age and encounter type

	Maternal age at delivery			
	10-19	20-44	45-54	Total
Deliveries	253,183	5,342,563	42,223	5,637,969
Linked Deliveries	116,419	3,966,493	11,524	4,094,436
Linkage Rate	45.98%	74.24%	27.29%	72.62%

	Encounter type of delivery					
	Inpatient Hospital Stay (IP)	Emergency Department (ED)	Non-Acute Institutional Stay (IS)	Ambulatory Visit (AV)	Other Ambulatory Visit (OV)	Total
Deliveries	5,312,558	8,215	4,457	219,646	93,093	5,637,969
Linked Deliveries	4,053,454	784	2,880	21,787	15,531	4,094,436
Linkage Rate	76.30%	9.54%	64.62%	9.92%	16.68%	72.62%

1. Identify live birth deliveries: MIL

Linkage Rates By Year

- Data are less complete in later years esp. for annual updaters
- Infants may not have yet acquired their own information (enrollment spans)

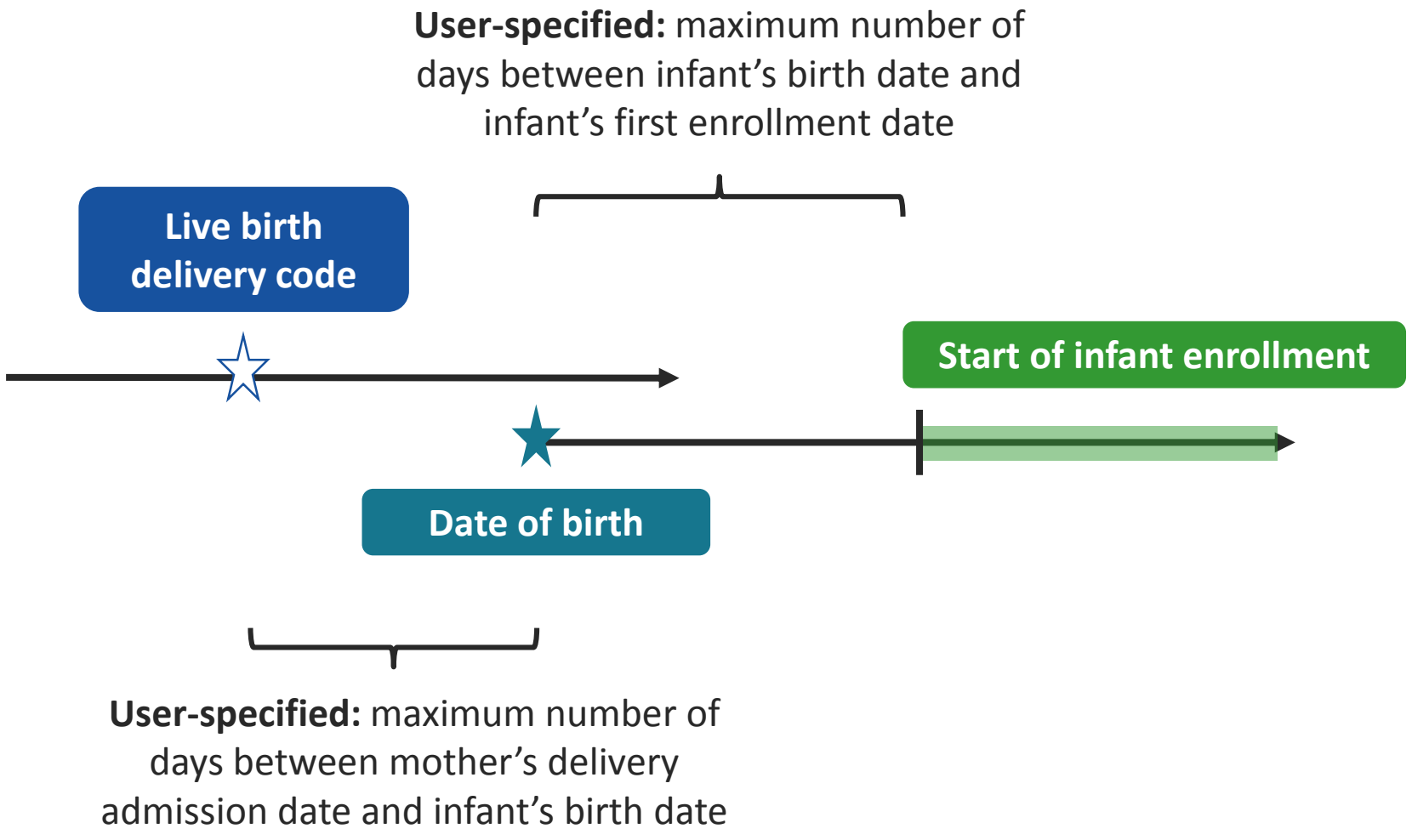
Year	Deliveries	Linked Deliveries	Linkage Rate
2007	210,411	163,324	77.6%
2008	230,638	180,807	78.4%
2009	574,267	466,248	81.2%
2010	552,878	451,358	81.6%
2011	561,007	449,315	80.1%
2012	563,277	428,430	76.1%
2013	570,823	431,943	75.7%
2014	569,901	439,447	77.1%
2015	572,415	439,543	76.8%
2016	570,223	412,536	72.3%
2017	417,434	18,314	4.4%
	5,637,969	**4,094,436**	**72.6%**

1. Identify live birth deliveries: MIL

Selecting 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



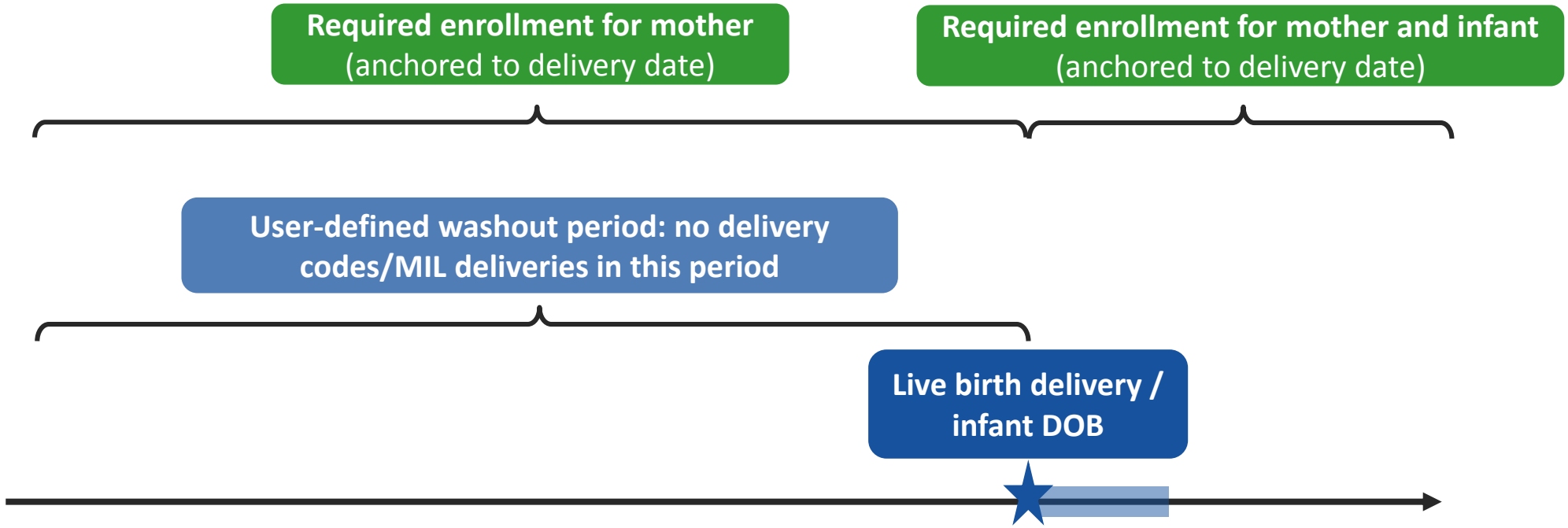
1. Identify live birth deliveries: MIL

Live birth deliveries: MIL table

	group	stockgroup	codecat	codetype	code
1	allpregnancies	delivery	MI	M	BC1
2	allpregnancies	delivery	MI	M	RE1
3	allpregnancies	delivery	MI	M	SI1
4	allpregnancies	delivery	MI	M	LA1
5	allpregnancies	delivery	MI	M	OT1

- Specifying the linkage types to include in the cohort
- Singleton infants only

Refining the cohort of deliveries



1. Identify live birth deliveries: MIL

Creating and analyzing a cohort of deliveries

1. Identify live birth deliveries

2. Estimate pregnancy start

3. Create a non-live birth comparator cohort

4. Identify medical product use in pregnancy

5. Create exposed and referent cohorts

6. Identify maternal or infant outcomes

← Mother-Infant Linkage Table

← **Gestational Age Algorithm**

} Descriptive Analyses

} Inferential Analyses

Gestational age algorithm

LMP is not available in US insurance claims data, therefore gestational age needs to be estimated

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 524–532
Published online 21 January 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3407

ORIGINAL REPORT

Validation of an algorithm to estimate gestational age in electronic health plan databases†

Qian Li[1,2], Susan E. Andrade[3], William O. Cooper[4], Robert L. Davis[5], Sascha Dublin[6], Tarek A. Hammad[7], Pamala A. Pawloski[8], Simone P. Pinheiro[7], Marsha A. Raebel[9], Pamela E. Scott[7], David H. Smith[10], Inna Dashevsky[2], Katherine Haffenreffer[2], Karin E. Johnson[6] and Sengwee Toh[2]*

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

2. Estimate pregnancy start

Gestational age algorithm: Li et al. results

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 524–532
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Underestimates the true prevalence of preterm birth

Using birth certificates as the gold-standard, classification of preterm birth (<259 days):

- Sensitivity: 45.5%
- Specificity: 98.3%
- PPV: 83.0%
- NPV: 90.9%

77% of estimated gestational durations were within ±14 days of the true duration

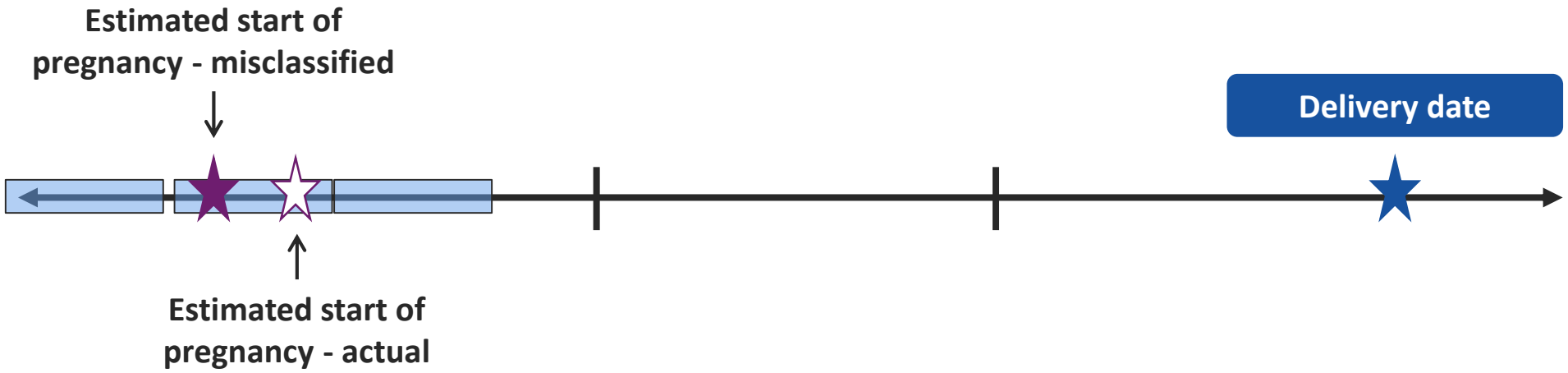
2. Estimate pregnancy start

Gestational age algorithm: Li et al. results

Classification of first trimester fluoxetine exposure status:

- Sensitivity: 96.9%
- Specificity: 99.9%
- PPV: 96.1%
- NPV: 99.9%

Accurately dates chronic medication exposure when classifying by overlapping day supply, despite misclassification in gestational age



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

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

Code	Description	Duration (weeks)	Duration (days)
765.24	27-28 completed weeks of gestation	28	196
Z3A.35	35 weeks gestation of pregnancy	35.5	249
644.21	Onset of delivery before 37 completed weeks of gestation	35	245
O60.12XX	Preterm labor 2nd trimester with preterm delivery 2nd trimester	24	168
645.10-645.13	Post-term pregnancy	41	287
O480	Post-term pregnancy	41	287

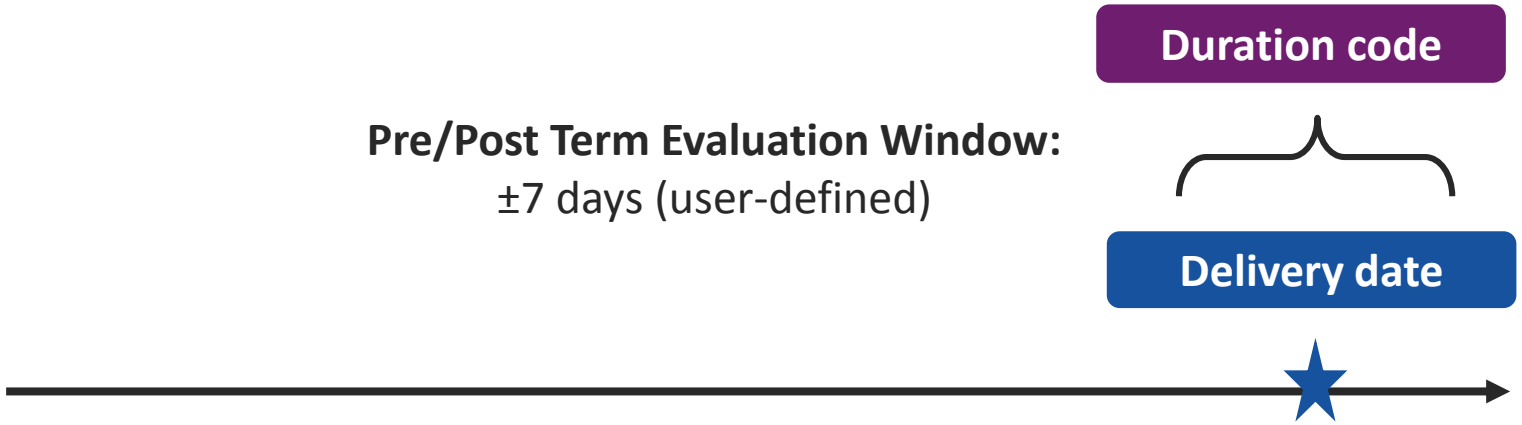
2. Estimate pregnancy start

Pregnancy duration input file

group	stockgroup	codecat	codetype	code	caresettingprincipal	PriorityGroup1	PriorityGroup2	priority	duration
allpregnancies	allpregnancies	DX	10	O481	'IP*'	0	1	1	294
allpregnancies	allpregnancies	DX	10	P0822	'IP*'	0	1	1	294
allpregnancies	allpregnancies	DX	10	Z3A49	'IP*'	1	0	1	301
allpregnancies	allpregnancies	DX	10	O480	'IP*'	0	1	2	287
allpregnancies	allpregnancies	DX	10	P0821	'IP*'	0	1	2	287
allpregnancies	allpregnancies	DX	10	Z3A42	'IP*'	1	0	2	298
allpregnancies	allpregnancies	DX	10	Z3A41	'IP*'	1	0	3	291
allpregnancies	allpregnancies	DX	10	Z3A40	'IP*'	1	0	4	284
allpregnancies	allpregnancies	DX	10	Z3A39	'IP*'	1	0	5	277
allpregnancies	allpregnancies	DX	10	Z3A38	'IP*'	1	0	6	270
allpregnancies	allpregnancies	DX	10	Z3A37	'IP*'	1	0	7	263
allpregnancies	allpregnancies	DX	10	P0739	'IP*'	1	0	8	256
allpregnancies	allpregnancies	DX	10	Z3A36	'IP*'	1	0	8	256
allpregnancies	allpregnancies	DX	10	P0738	'IP*'	1	0	9	249
allpregnancies	allpregnancies	DX	10	Z3A35	'IP*'	1	0	9	249
allpregnancies	allpregnancies	DX	10	P0737	'IP*'	1	0	10	242
allpregnancies	allpregnancies	DX	10	Z3A34	'IP*'	1	0	10	242
allpregnancies	allpregnancies	DX	10	P0736	'IP*'	1	0	11	235
allpregnancies	allpregnancies	DX	10	Z3A33	'IP*'	1	0	11	235
allpregnancies	allpregnancies	DX	10	P0735	'IP*'	1	0	12	228
allpregnancies	allpregnancies	DX	10	Z3A32	'IP*'	1	0	12	228

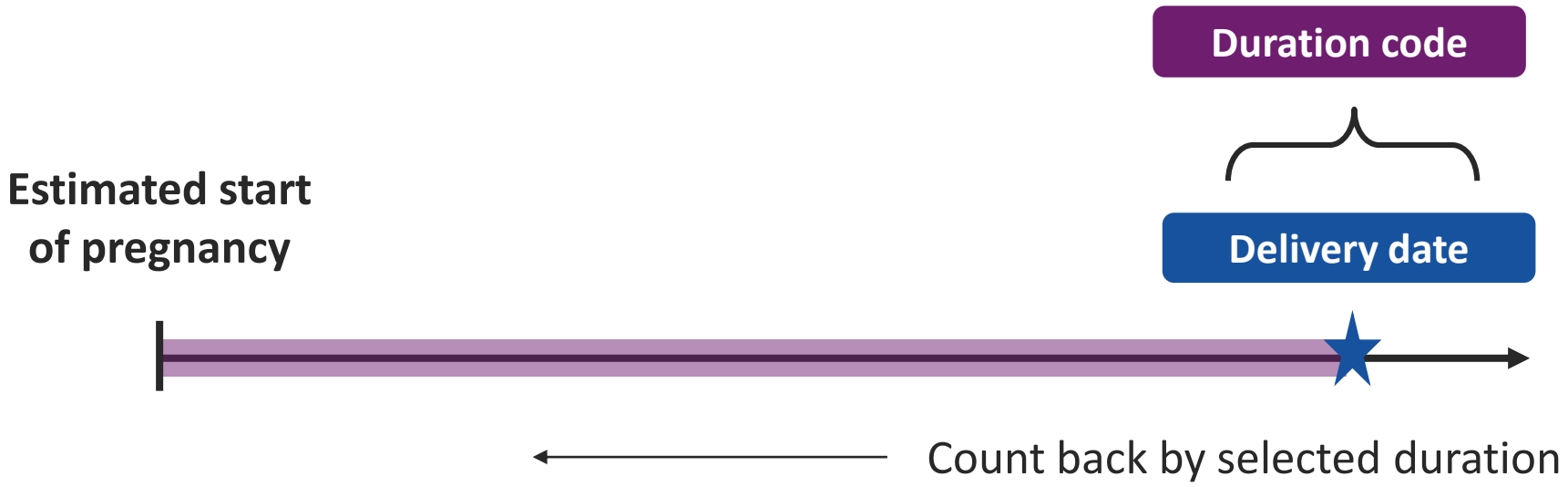
2. Estimate pregnancy start

Identifying duration codes



2. Estimate pregnancy start

Identifying duration codes

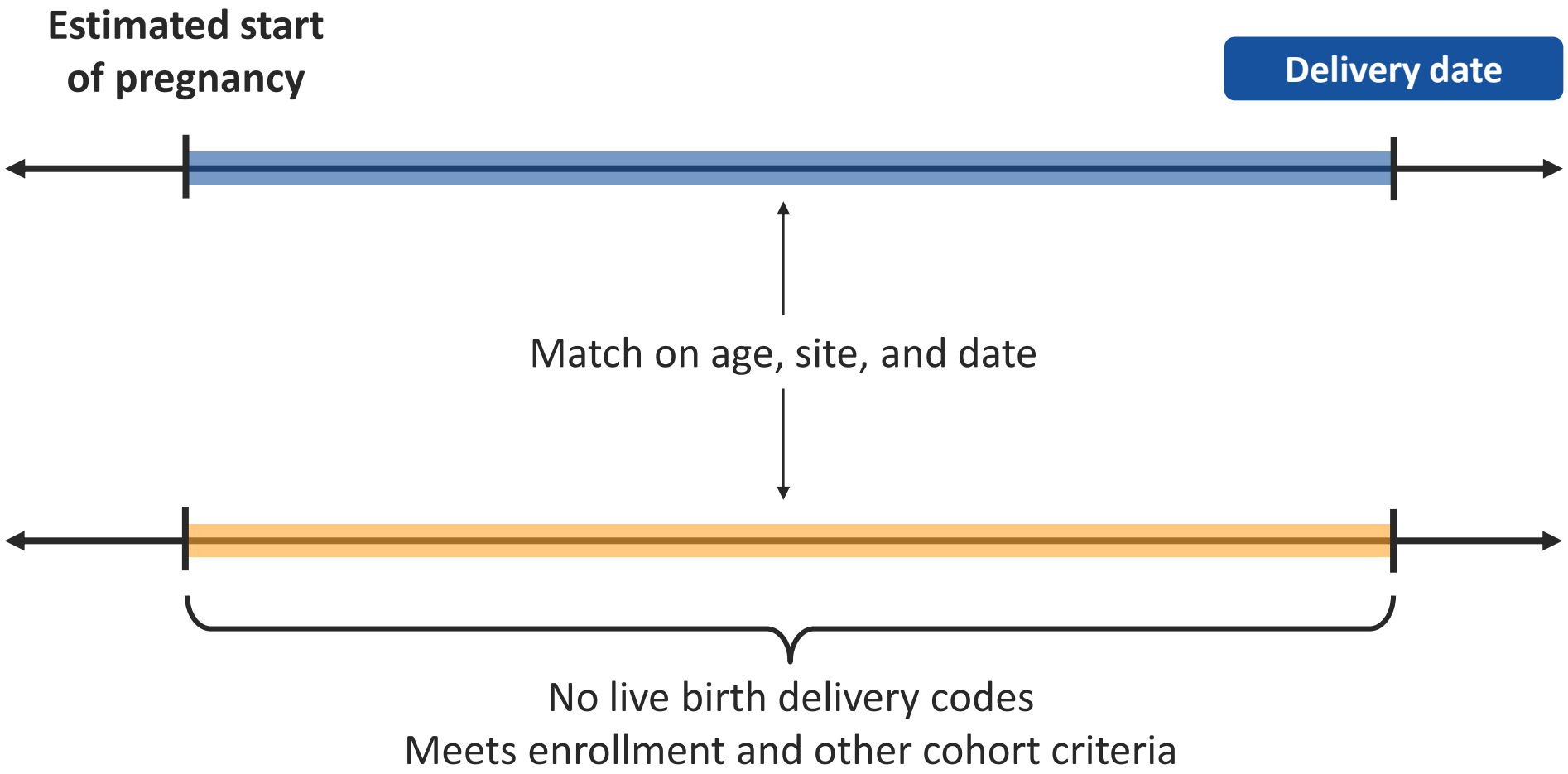


2. Estimate pregnancy start

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-live birth comparator cohort } Descriptive Analyses
4. Identify medical product use in pregnancy } Descriptive Analyses
5. Create exposed and referent cohorts } Inferential Analyses
6. Identify maternal or infant outcomes } Inferential Analyses

Create non-live birth comparator cohort



3. Create a non-live birth comparator cohort

Creating and analyzing a cohort of deliveries

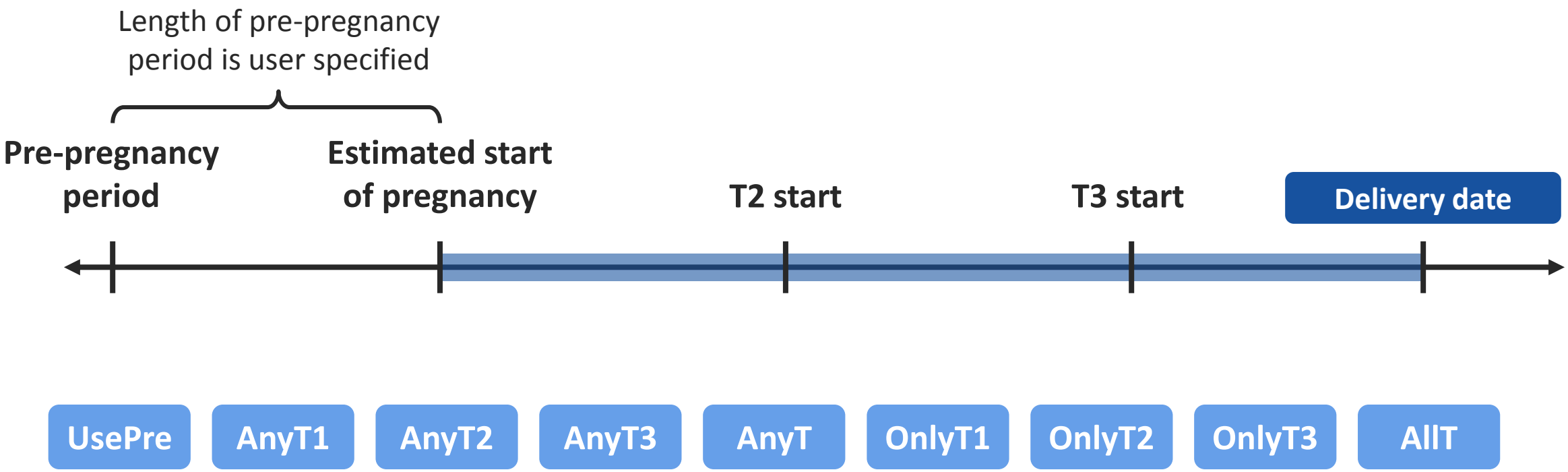
1. Identify live birth deliveries ← Mother-Infant Linkage Table
2. Estimate pregnancy start ← Gestational Age Algorithm
3. Create a non-live birth comparator cohort
4. Identify medical product use in pregnancy

} **Descriptive Analyses**

5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes

} Inferential Analyses

Classifying medical product use by timing during pregnancy



4. Identify medical product use in pregnancy

Defining medical product exposure episodes

Classified as first trimester exposure if using overlapping days supply:

Classified as first trimester exposure if using dispensing date:

4. Identify medical product use in pregnancy

Example – utilization in pregnant and non-pregnant cohorts

Submit Comment

Use of Multiple Sclerosis Drugs Among Pregnant Women

Project Title	**Use of Multiple Sclerosis Drugs Among Pregnant Women**
Date Posted	*Thursday, December 6, 2018*
Project ID	cder_mpl1p_wp009
Status	Complete
Deliverables	Sentinel Modular Program Report: Use of Multiple Sclerosis Drugs Among Pregnant Women
Related Links	2018 ICPE Presentation: Use of Multiple Sclerosis Drugs Among Live Birth Pregnancies in the United States
Description	This report contains estimates of multiple sclerosis (MS) drug use before, during, and after pregnancies resulting in a live-born delivery, among women in the Sentinel Distributed Database (SDD). Data from January 1, 2001 to August 31, 2017 from 16 Data Partners contributing to the SDD were included in this report. This request was distributed to Data Partners on November 20, 2017.

4. Identify medical product use in pregnancy

Prevalence of MS drugs among live birth deliveries

Table 1. Prevalence of Multiple Sclerosis (MS) Drug Use among Women with Live-Birth Deliveries in the Sentinel Distributed Database, by Trimester

Pregnant Cohort	Use in the 183 - 91 Days Pre-pregnancy	Use in the 90 Days Pre-pregnancy	Any Use During Pregnancy	Any Use, 1st Trimester	Any Use, 2nd Trimester	Any Use, 3rd Trimester	Use in the 90 Days Post-pregnancy	Use in the 91 - 183 Days Post-pregnancy
Total Pregnancies	2,205,383 (100.0%)	2,205,383 (100.0%)	2,205,383 (100.0%)	2,205,383 (100.0%)	2,205,383 (100.0%)	2,203,324 (100.0%%)	2,205,383 (100.0%)	2,205,383 (100.0%)
Drug of Interest								
Any multiple sclerosis drugs	1,407 (0.06%)	1,243 (0.06%)	1,011 (0.05%)	944 (0.04%)	269 (0.01%)	246 (0.01%%)	958 (0.04%)	1,330 (0.06%)
Dalfampridine	9 (0.00%)	10 (0.00%)	6 (0.00%)	6 (0.00%)	1 (0.00%)	0 (0.00%%)	7 (0.00%)	14 (0.00%)
Dimethyl fumarate	58 (0.00%)	54 (0.00%)	51 (0.00%)	45 (0.00%)	9 (0.00%)	11 (0.00%%)	63 (0.00%)	113 (0.01%)
Fingolimod	33 (0.00%)	26 (0.00%)	20 (0.00%)	20 (0.00%)	2 (0.00%)	2 (0.00%%)	30 (0.00%)	60 (0.00%)
Glatiramer acetate	602 (0.03%)	564 (0.03%)	501 (0.02%)	470 (0.02%)	171 (0.01%)	164 (0.01%%)	427 (0.02%)	538 (0.02%)
Interferon beta-1a with or without albumin	502 (0.02%)	421 (0.02%)	307 (0.01%)	283 (0.01%)	61 (0.00%)	51 (0.00%%)	302 (0.01%)	419 (0.02%)
Interferon beta-1b	126 (0.01%)	104 (0.00%)	78 (0.00%)	74 (0.00%)	10 (0.00%)	5 (0.00%%)	72 (0.00%)	104 (0.00%)
Peginterferon beta-1a	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%%)	2 (0.00%)	6 (0.00%)
Teriflunomide	2 (0.00%)	3 (0.00%)	2 (0.00%)	2 (0.00%)	2 (0.00%)	2 (0.00%%)	3 (0.00%)	7 (0.00%)
Alemtuzumab	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%%)	0 (0.00%)	1 (0.00%)
Natalizumab	99 (0.00%)	91 (0.00%)	61 (0.00%)	55 (0.00%)	14 (0.00%)	11 (0.00%%)	81 (0.00%)	120 (0.01%)
Daclizumab	1 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%%)	0 (0.00%)	0 (0.00%)
Mitoxantrone	3 (0.00%)	1 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%%)	1 (0.00%)	1 (0.00%)

4. Identify medical product use in pregnancy

Prevalence of MS drugs in non-pregnant comparator cohort

Table 2. Prevalence of Multiple Sclerosis (MS) Drug Use among Non-Pregnant Cohort in the Sentinel Distributed Database, by Matched Comparator's Trimester

Non-Pregnant Cohort[1,2]	Use in the 183 - 91 Days Pre-pregnancy	Use in the 90 Days Pre-pregnancy	Any Use During Pregnancy	Any Use, 1st Trimester	Any Use, 2nd Trimester	Any Use, 3rd Trimester	Use in the 90 Days Post-pregnancy	Use in the 91 - 183 Days Post-pregnancy
Total of Episodes	2,205,383 (100.0%)	2,205,383 (100.0%)	2,205,383 (100.0%)	2,205,383 (100.0%)	2,205,383 (100.0%)	2,203,324 (100.0%%)	2,205,383 (100.0%)	2,205,383 (100.0%)
Drug of Interest								
Any multiple sclerosis drugs	2,673 (0.12%)	2,772 (0.13%)	3,503 (0.16%)	3,000 (0.14%)	3,101 (0.14%)	3,188 (0.14%%)	3,226 (0.15%)	3,273 (0.15%)
Dalfampridine	31 (0.00%)	30 (0.00%)	59 (0.00%)	38 (0.00%)	50 (0.00%)	51 (0.00%%)	53 (0.00%)	60 (0.00%)
Dimethyl fumarate	135 (0.01%)	164 (0.01%)	298 (0.01%)	195 (0.01%)	227 (0.01%)	263 (0.01%%)	279 (0.01%)	296 (0.01%)
Fingolimod	122 (0.01%)	126 (0.01%)	212 (0.01%)	158 (0.01%)	175 (0.01%)	195 (0.01%%)	200 (0.01%)	224 (0.01%)
Glatiramer acetate	898 (0.04%)	931 (0.04%)	1,214 (0.06%)	979 (0.04%)	1,023 (0.05%)	1,038 (0.05%%)	1,050 (0.05%)	1,070 (0.05%)
Interferon beta-1a with or without albumin	1,086 (0.05%)	1,089 (0.05%)	1,349 (0.06%)	1,171 (0.05%)	1,175 (0.05%)	1,158 (0.05%%)	1,144 (0.05%)	1,135 (0.05%)
Interferon beta-1b	260 (0.01%)	272 (0.01%)	353 (0.02%)	289 (0.01%)	294 (0.01%)	296 (0.01%%)	278 (0.01%)	267 (0.01%)
Peginterferon beta-1a	0 (0.00%)	0 (0.00%)	7 (0.00%)	0 (0.00%)	4 (0.00%)	7 (0.00%%)	10 (0.00%)	13 (0.00%)
Teriflunomide	7 (0.00%)	12 (0.00%)	30 (0.00%)	18 (0.00%)	21 (0.00%)	27 (0.00%%)	28 (0.00%)	33 (0.00%)
Alemtuzumab	0 (0.00%)	0 (0.00%)	2 (0.00%)	1 (0.00%)	1 (0.00%)	0 (0.00%%)	3 (0.00%)	2 (0.00%)
Natalizumab	217 (0.01%)	237 (0.01%)	331 (0.02%)	256 (0.01%)	254 (0.01%)	278 (0.01%%)	293 (0.01%)	304 (0.01%)
Daclizumab	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%%)	0 (0.00%)	0 (0.00%)
Mitoxantrone	13 (0.00%)	15 (0.00%)	23 (0.00%)	17 (0.00%)	17 (0.00%)	10 (0.00%%)	10 (0.00%)	9 (0.00%)

4. Identify medical product use in pregnancy

Comparing utilization between pregnant and non-pregnant women

	Live birth delivery	Non-live birth delivery
Total of Episodes	(100.0%)	(100.0%)
Drug of Interest		
Any multiple sclerosis drugs	1,011 (0.05%)	3,503 (0.16%)
Dalfampridine	6 (0.00%)	59 (0.00%)
Dimethyl fumarate	51 (0.00%)	298 (0.01%)
Fingolimod	20 (0.00%)	212 (0.01%)
Glatiramer acetate	501 (0.02%)	1,214 (0.06%)
Interferon beta-1a with or without albumin	307 (0.01%)	1,349 (0.06%)
Interferon beta-1b	78 (0.00%)	353 (0.02%)
Peginterferon beta-1a	0 (0.00%)	7 (0.00%)
Teriflunomide	2 (0.00%)	30 (0.00%)
Alemtuzumab	0 (0.00%)	2 (0.00%)
Natalizumab	61 (0.00%)	331 (0.02%)
Daclizumab	0 (0.00%)	0 (0.00%)
Mitoxantrone	0 (0.00%)	23 (0.00%)

4. Identify medical product use in pregnancy

Creating and analyzing a cohort of deliveries

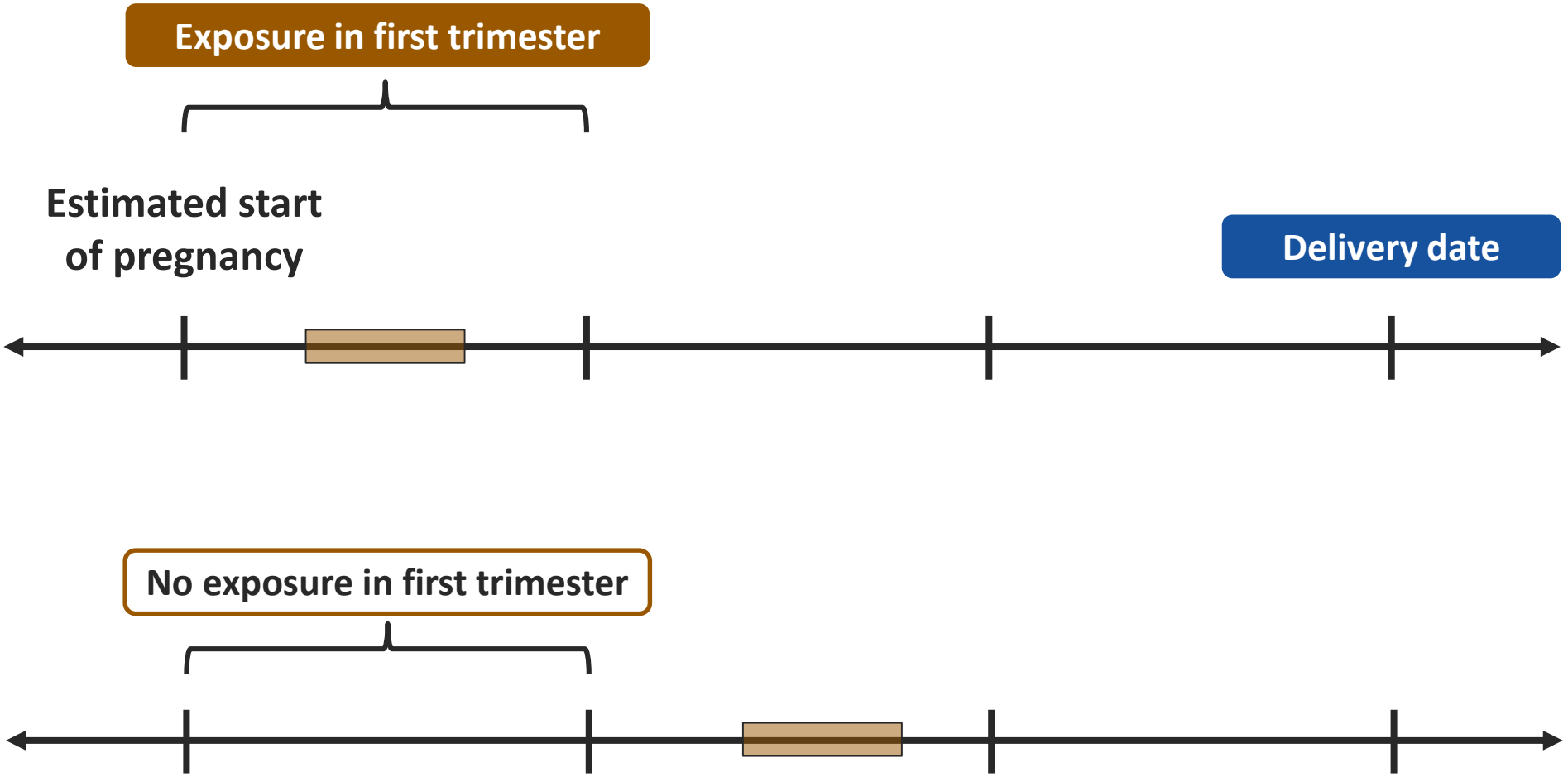
1. Identify live birth deliveries ← Mother-Infant Linkage Table
2. Estimate pregnancy start ← Gestational Age Algorithm
3. Create a non-live birth comparator cohort } Descriptive Analyses
4. Identify medical product use in pregnancy
5. Create exposed and referent cohorts } **Inferential Analyses**
6. Identify maternal or infant outcomes

Defining the Exposed and Referent Cohorts

- The exposure window can be specified in trimesters or gestational weeks anchored to the start of pregnancy
  - E.g. first trimester, or gestational weeks 6-12
- If an unexposed referent is used, pregnancy episodes without evidence of the exposure during the entire exposure period will be included
- If an active comparator is used, pregnancy episodes with evidence of the comparator drug during the exposure period will be included
  - Pregnancy episodes with evidence of the exposure drug and the referent drug during the exposure period will be excluded

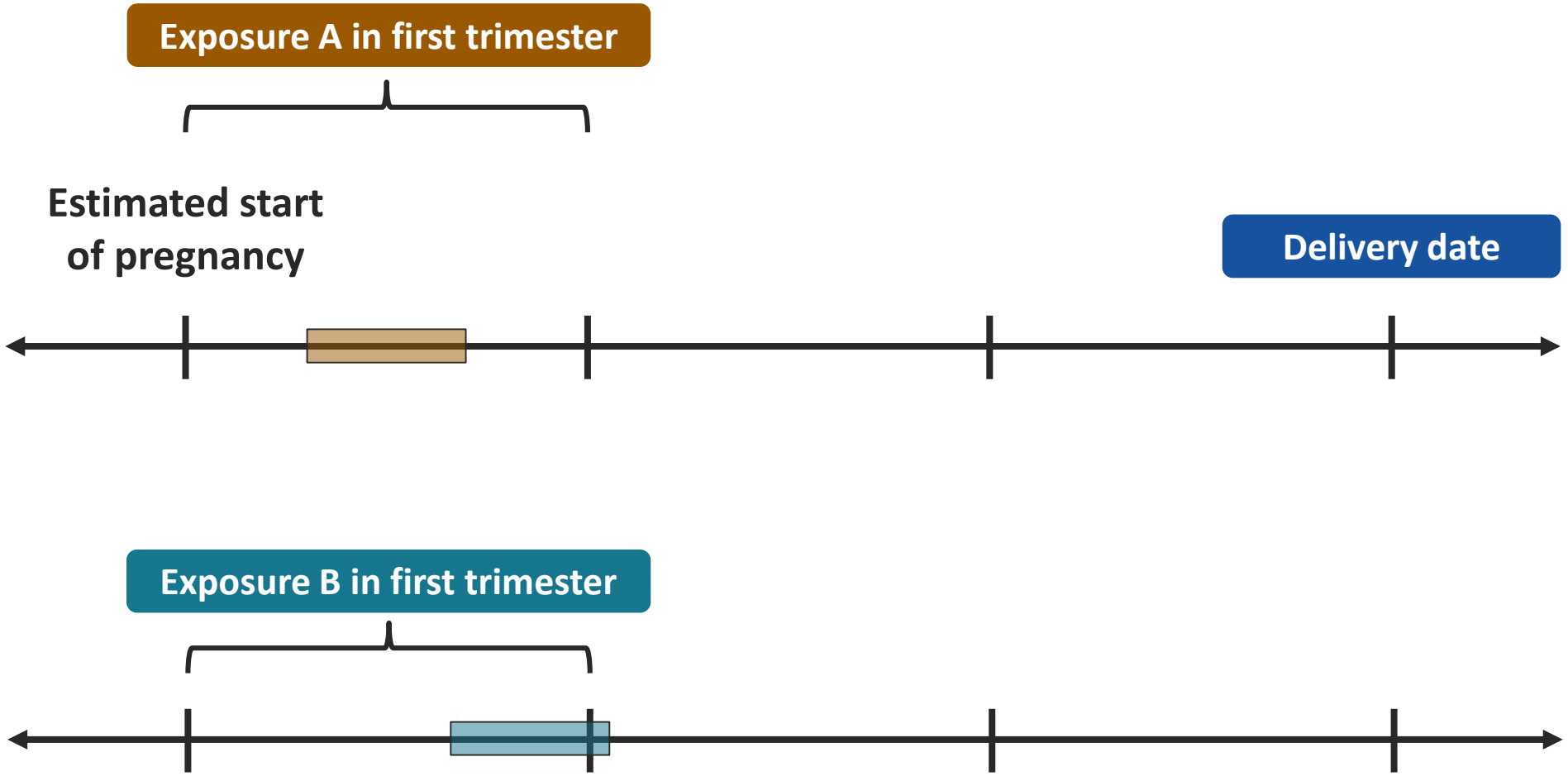
5. Create exposed and referent cohorts

Defining exposed and unexposed referent groups



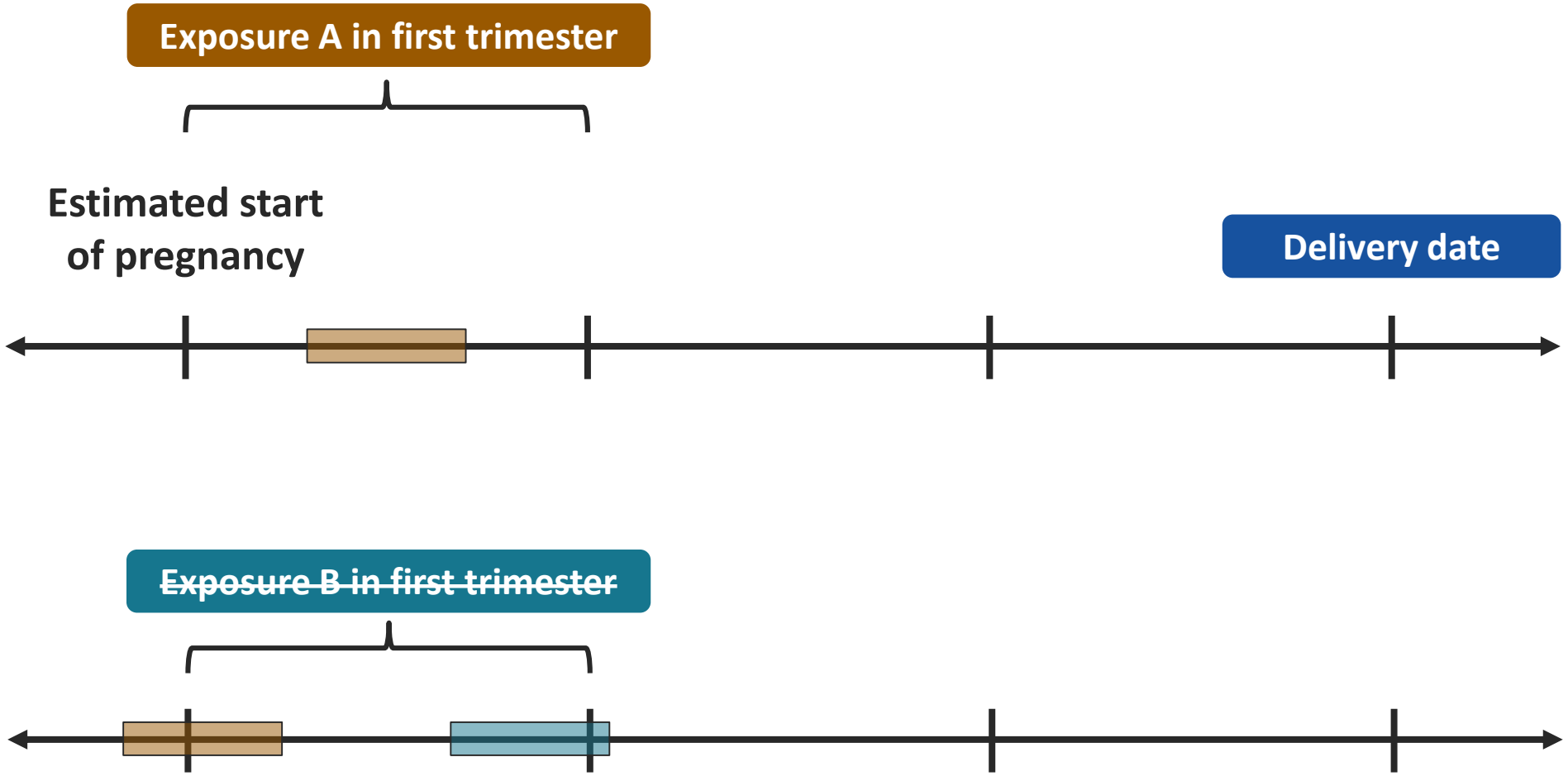
5. Create exposed and referent cohorts

Defining exposed and comparator exposed referent groups



5. Create exposed and referent cohorts

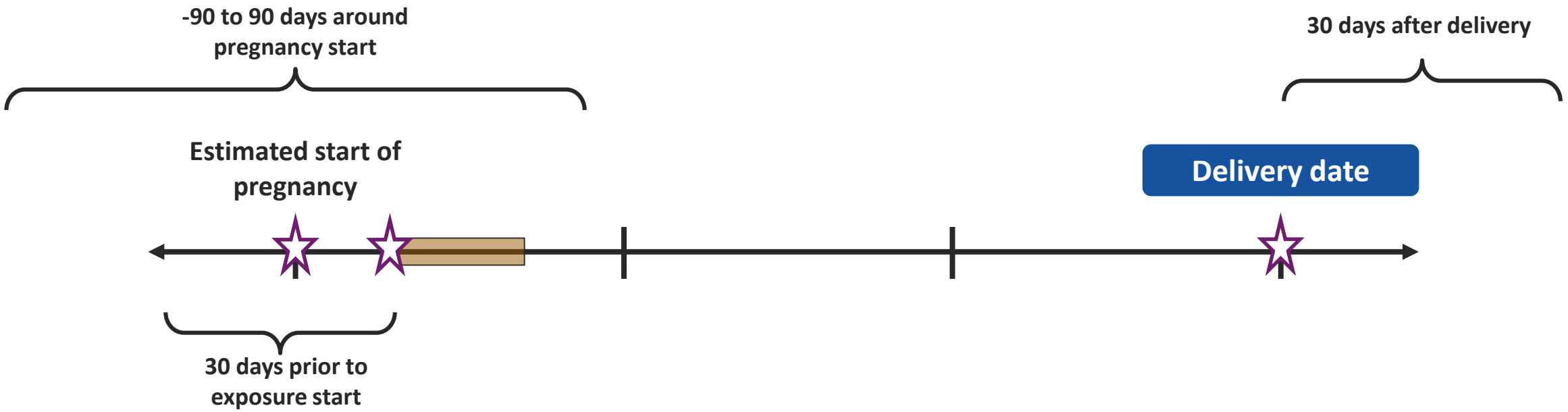
Defining exposed and comparator exposed referent groups



5. Create exposed and referent cohorts

Refine Exposed and Referent Cohorts

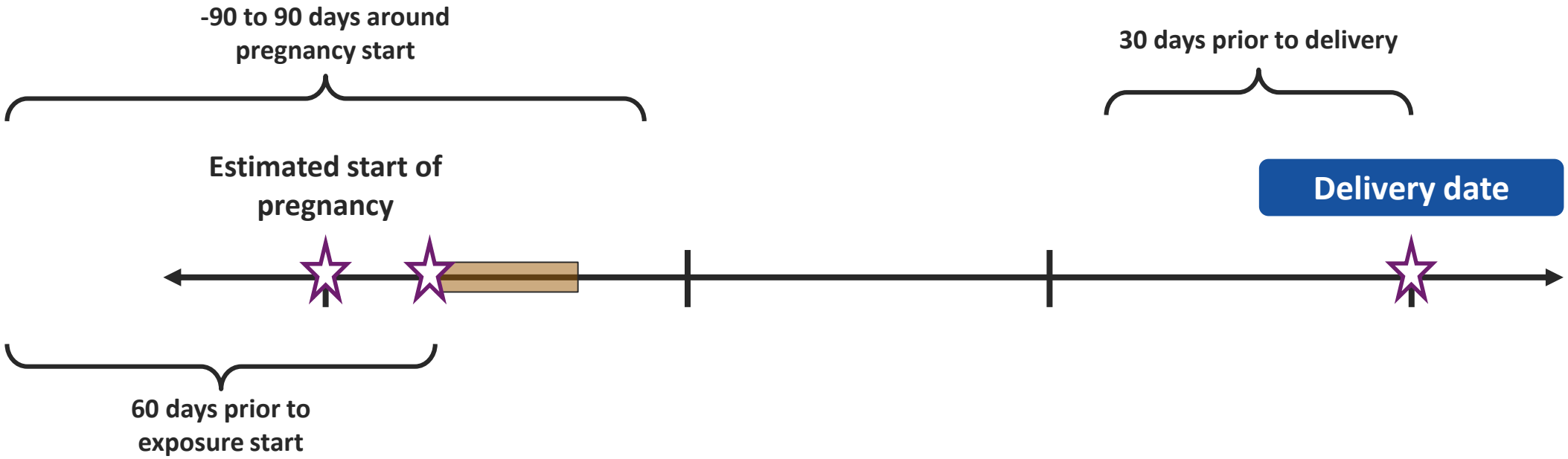
- Add Additional Exclusions or Inclusions using 3 potential anchor dates:
  - Estimated Pregnancy Start, Medication Exposure Start (when exposed), Delivery Date
  - Additional enrollment may be enforced for exclusion criteria



5. Create exposed and referent cohorts

Refine Exposed and Referent Cohorts

- Define window for covariate assessment
  - Estimated Pregnancy Start, Medication Exposure Start (when exposed), Delivery Date
  - Additional enrollment may be enforced for covariate assessment



5. Create exposed and referent cohorts

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-live birth comparator cohort
4. Identify medical product use in pregnancy

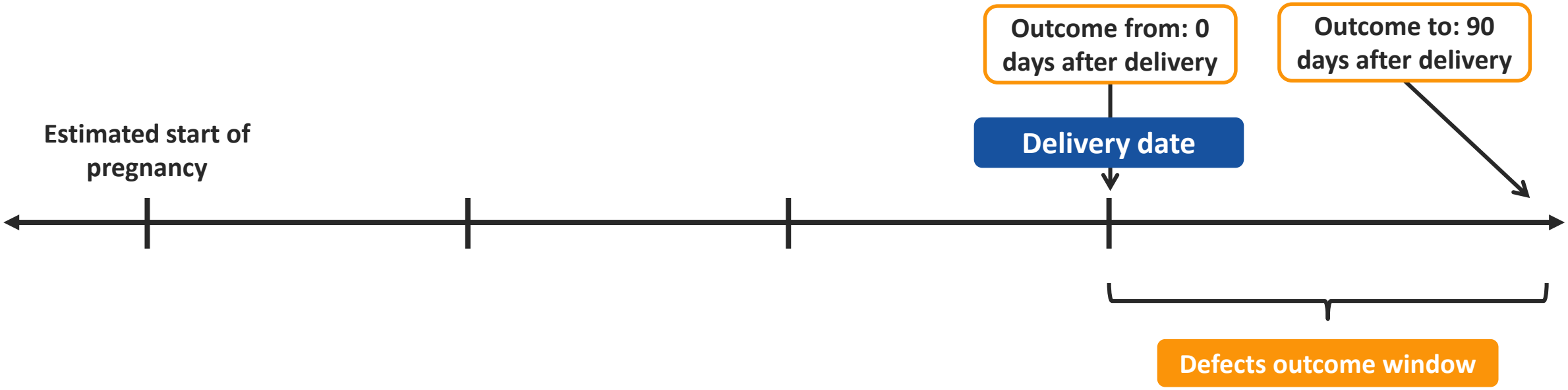
} Descriptive Analyses

5. Create exposed and referent cohorts
6. Identify maternal or infant outcomes

} **Inferential Analyses**

Defining infant outcomes

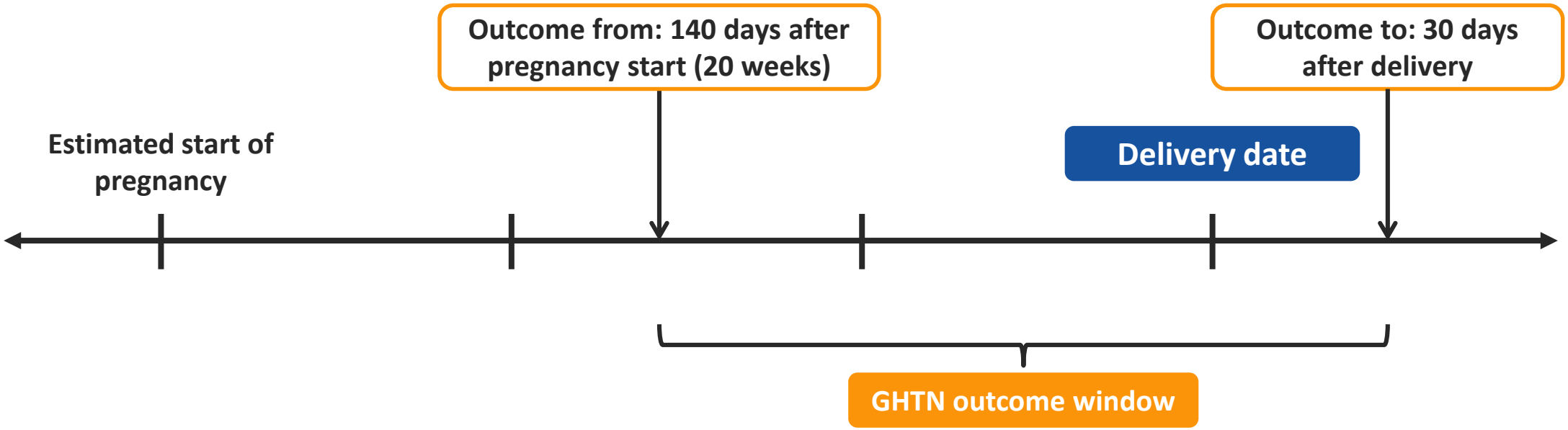
Outcomes are typically assessed after delivery – for example, cardiac defects



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

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 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

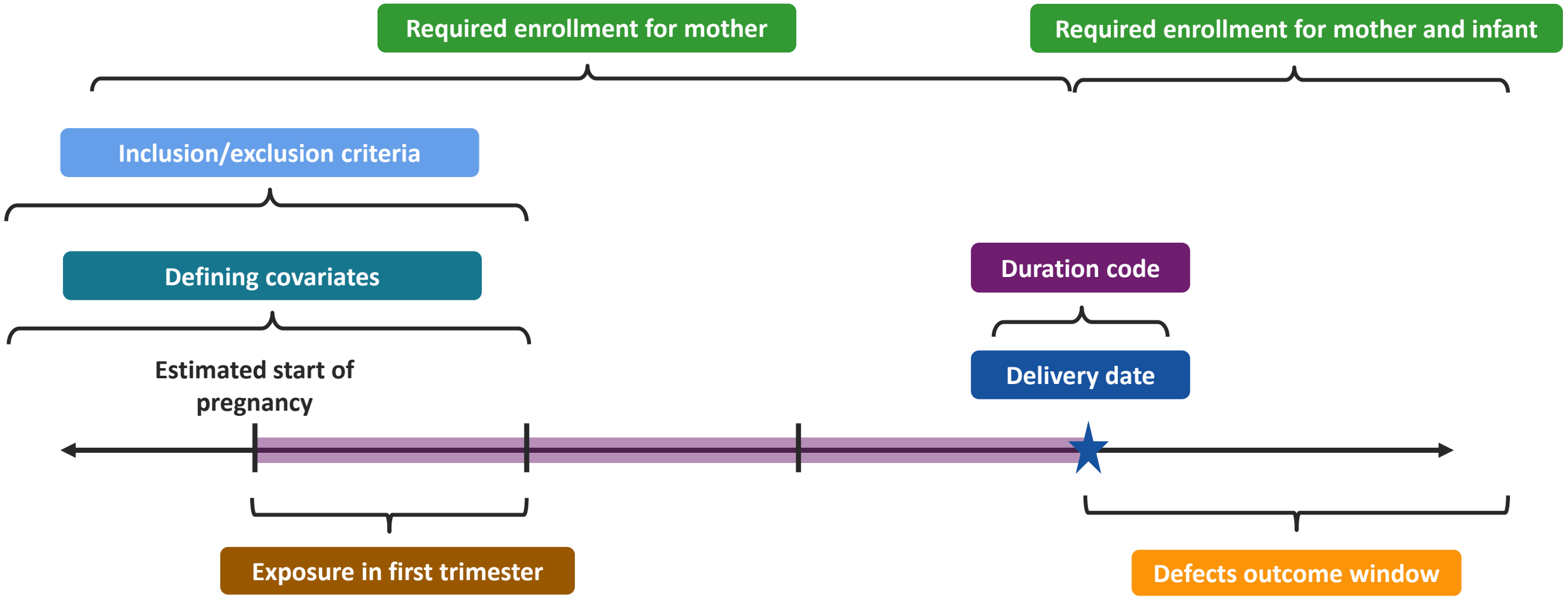
Analyzing maternal and infant outcomes

- Sentinel currently utilizes the following methods:
  - Propensity score matched or multifactor matched logistic regression
  - Propensity score matched or multifactor matched TreeScan for signal detection

6. Identify maternal or infant outcomes

Putting it all together

Example: Design for assessing infant birth defects in relation to first trimester exposure



Questions?