Leveraging the Sentinel System for Signal Identification Among Infants Following Maternal Medication Use During Pregnancy

Sentinel Public Training

April 11, 2023

Sentinel Operations Center | Harvard Pilgrim Health Care Institute

Meet the Presenters

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Agenda

9:00 AM – Opening Remarks – Dr. Robert Ball, FDA

9:20 AM – Introduction to Sentinel

9:55 AM – Detecting Medication Adverse Effects

10:50 AM – Break

11:10 AM – Infant Outcomes Following Medication Exposures

11:50 AM – First Trimester Fluoroquinolones: A Case Study

12:35 PM – Closing Remarks – Dr. Judith Maro, Sentinel Operations Center

Session Logistics

Polling

Questions

Presentation availability

Pre-Training Poll

- All participants should see a poll appear on their personal screens
- Your answers help us improve our annual trainings; for each question, please select from the provided responses
- All responses are anonymous

Questions

1. What best describes your professional industry?
2. What is your role within your organization?
3. How did you learn about the training?
4. How well do you feel you understand the overall design of the Sentinel System?
5. How well do you feel you understand Sentinel's analytic capabilities?
6. Have you ever used Sentinel's analytic tools?

Sentinel

Introduction to the Sentinel System

2023 Sentinel Public Training

Session 1

11 April 2023

Agenda

1 **History and Purpose of Sentinel**

Objective: Provide background on the creation and purpose of the Sentinel System

2 **Data in Sentinel**

Objective: Explain the Sentinel Common Data Model and why it is crucial to Sentinel's distributed environment

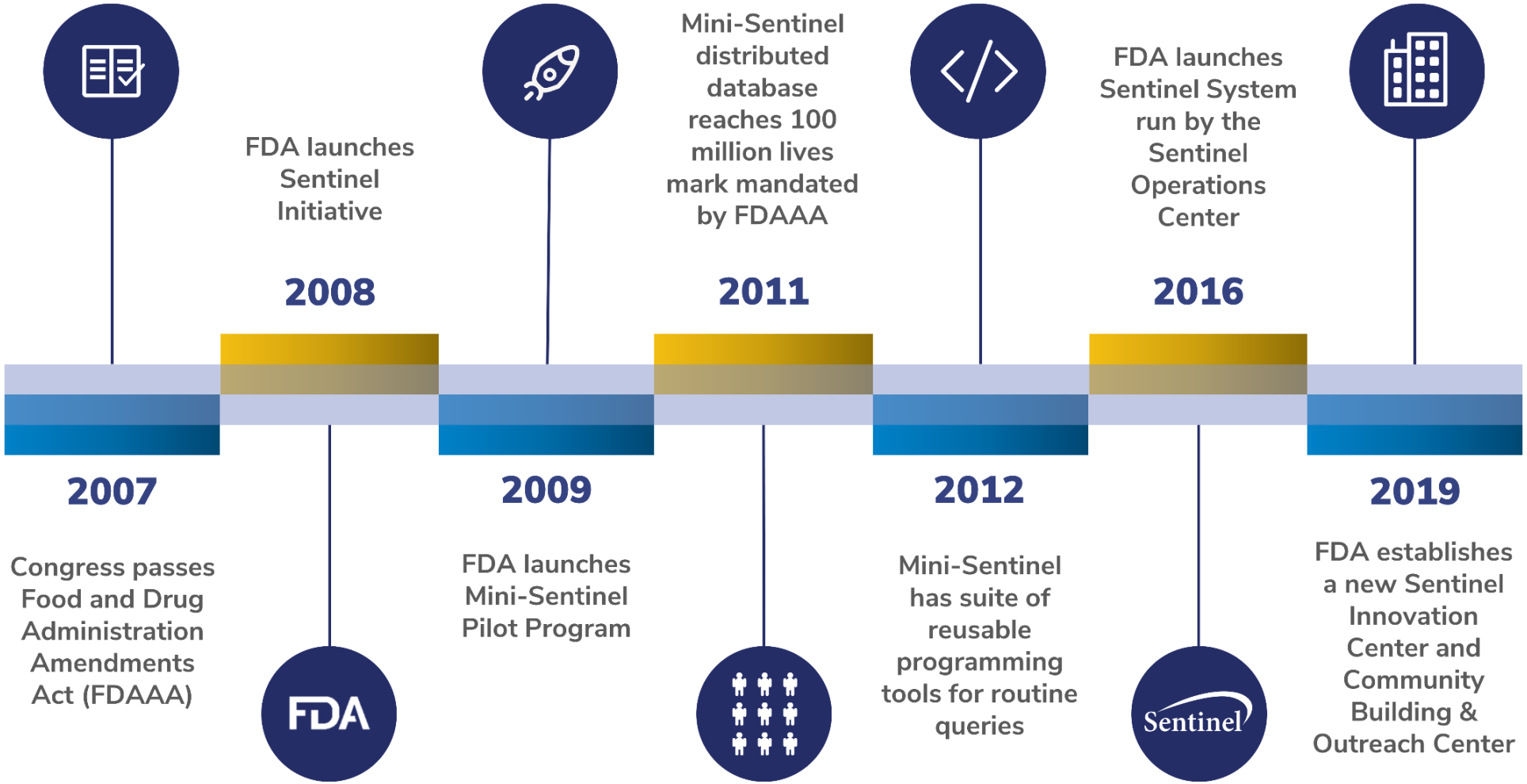
3 **Analyses in Sentinel**

Objective: Summarize analytical options in the Sentinel System, highlighting Signal Identification capabilities

4 **Sentinel and the Public**

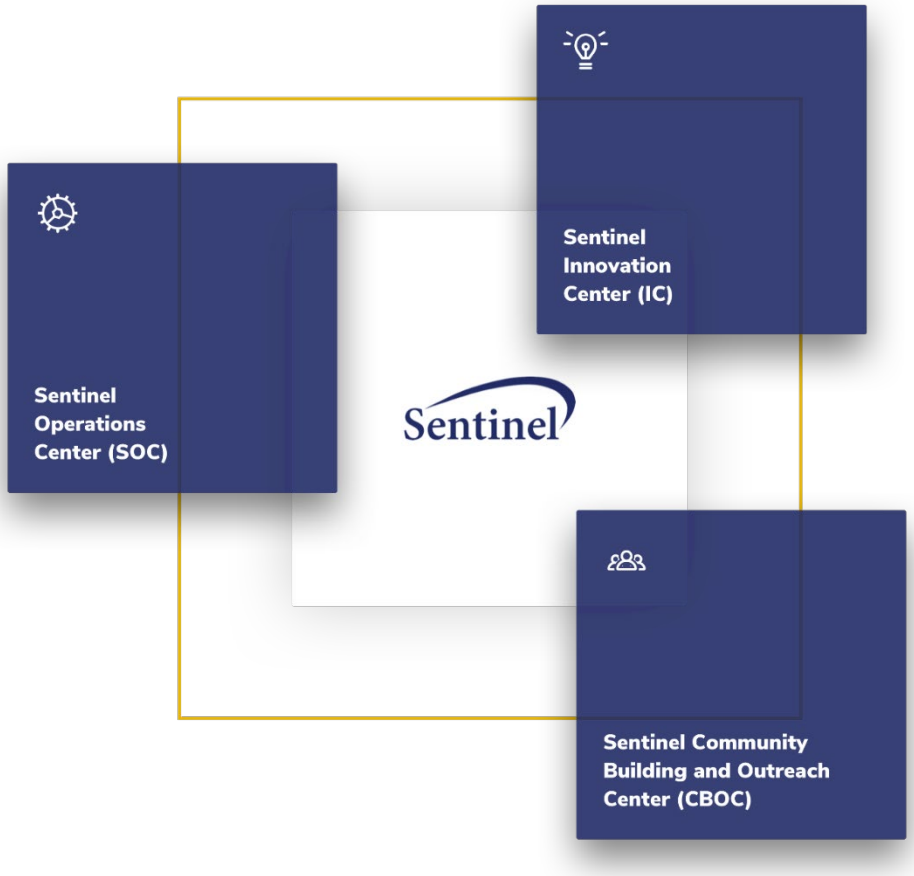
Objective: Review Sentinel's commitment to transparency and reproducibility in research and describe how members of the public can access analyses conducted in the Sentinel System

History of the Sentinel Initiative



https://sentinelinitiative.org/about

Sentinel System Structure



- Sentinel System created to meet 2007 Congressional mandate to "create an **active postmarket drug safety surveillance system**"
- Led by FDA's **Office of Surveillance and Epidemiology** in the **Center for Drug Evaluation and Research**
- Three centers collaborate to proactively assess safety of approved drugs under real-world conditions

https://www.sentinelinitiative.org/about/sentinel-structure

PDUFA VII and Sentinel

- FDA committed to optimize Sentinel System not only through maintenance but also through conducting demonstration projects to address gaps in knowledge about performance characteristics of different study designs, specifically with regards to pregnancy safety

> "The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner."
>
> *Prescription Drug User Fee Amendment VII: Fiscal Years 2023-2027 Commitment Letter (I)(M)(2)(b)(i)*

Center for Drug Evaluation and Research. PDUFA VII: Fiscal Years 2023 – 2027. Food and Drug Administration; 2023. Accessed March 1, 2023. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

The Sentinel Initiative and Real-World Data

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

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

How does Sentinel work?

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

What kinds of questions?

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

What about privacy?

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

What happens next?

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

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

Key Components in Sentinel

- Two main components are key to success in the Sentinel System
  - Administrative data generated from healthcare claims (some linked to electronic health records) in the **Sentinel Common Data Model** accessed through a **distributed data network**
  - State-of-the-art **analysis tools** to monitor the safety of medications
- These components allow for efficient multi-site safety analyses

Data in Sentinel

Key component of the Sentinel System:

A Distributed Database in the Sentinel Common Data Model

Operations Center Collaborations

Lead: Harvard Pilgrim - Health Care Institute

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL | Harvard Pilgrim Health Care Institute

a Point32Health company

TN Division of TennCare

carelon | Elevance Health

CVSHealth Clinical Trial Services

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TriNetX

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VANDERBILT UNIVERSITY MEDICAL CENTER

UF College of Pharmacy
Department of Pharmaceutical Outcomes and Policy
UNIVERSITY of FLORIDA

SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

UMass Chan MEDICAL SCHOOL

MHCI Meyers Health Care Institute

healthverity

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Department of Population Health Sciences
Duke University School of Medicine

Brigham and Women's Hospital
Founding Member, Mass General Brigham

CCEB

Perelman School of Medicine
University of Pennsylvania

Sentinel Data Philosophy

Sentinel Common Data Model (SCDM) is designed to meet FDA's needs for analytic flexibility, transparency, and control

Flexible: Adapts to ever-changing priorities

- Predominantly claim-based, but allows electronic health record (EHR), registry, survey, and free-text data

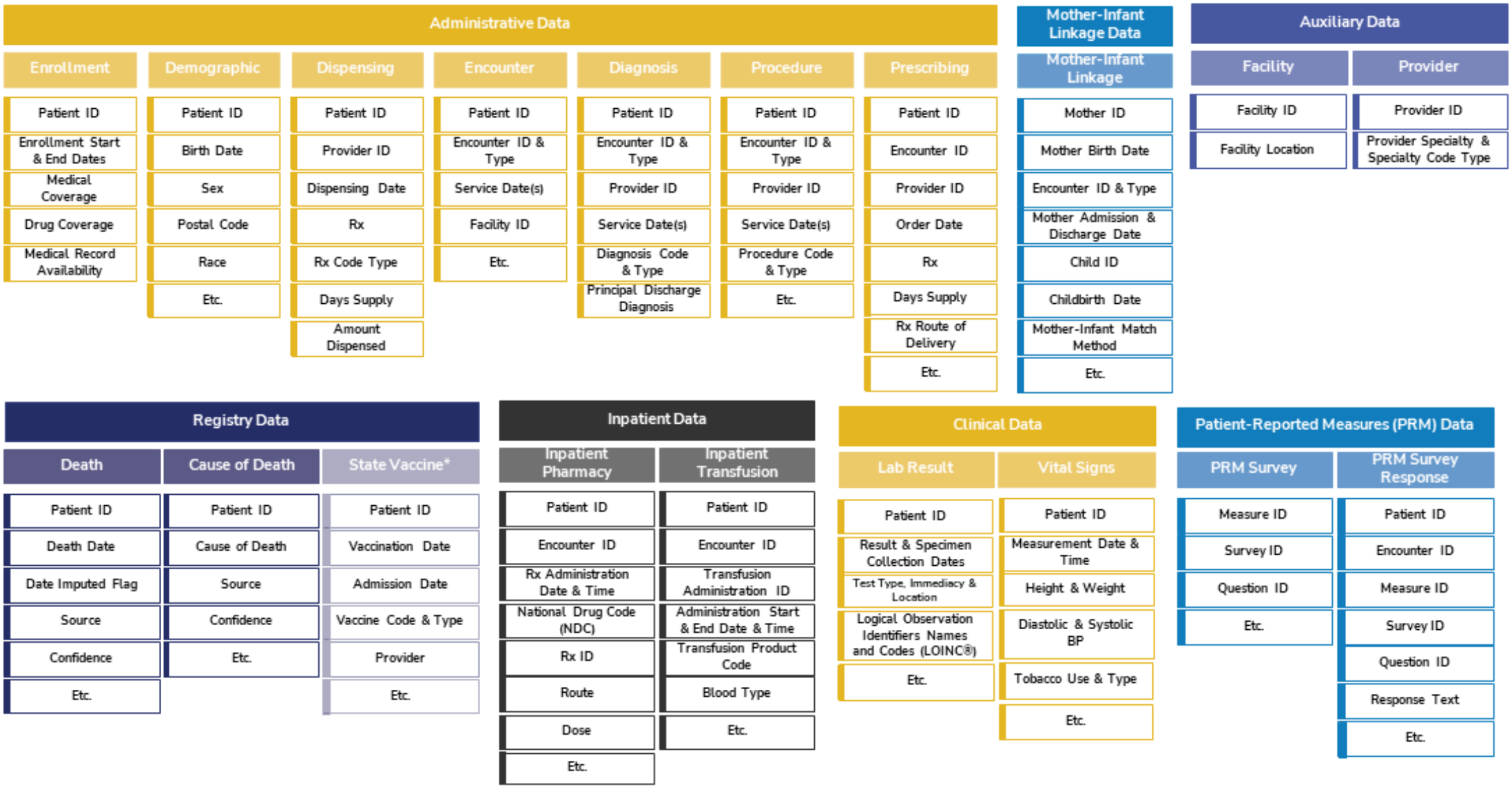
Transparent: Distinct data types kept separate with minimal mapping

- Construction of medical concepts (e.g., outcome algorithms) from these elemental data is a project-specific design choice

Control: Data Partners work closely with Sentinel Operations Center when populating tables

- Appropriate use and interpretation of local data requires the Data Partners' local knowledge and data expertise

Sentinel Common Data Model



*The State Vaccine table has not been used since SCDM v6.0.
https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Following a Patient in the Sentinel Common Data Model

DEMOGRAPHIC

PATID	BIRTH_DATE	SEX	HISPANIC	RACE	ZIP
PatID1	02/02/1984	F	N	5	32818
PatID2	05/02/2006	M	N	5	32818

ENROLLMENT

PATID	ENR_START	ENR_END	MEDCOV	DRUGCOV
PatID1	7/1/2004	12/31/2018	Y	Y
PatID2	6/1/2006	12/31/2018	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
PatID2	03/02/2016	54868056400	10	10

ENCOUNTER

PATID	ENCOUNTERID	ADATE	DDATE	ENCTYPE
PatID1	EncID1	10/18/2005	10/20/2005	IP
PatID1	EncID2	05/02/2006	05/03/2006	IP
PatID2	EncID1	03/02/2016	.	AV

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	EncID2	5/2/2006	Provider1	IP	V30.00	9	P
PatID2	EncID1	03/02/2016	Provider2	AV	H66.13	10	X

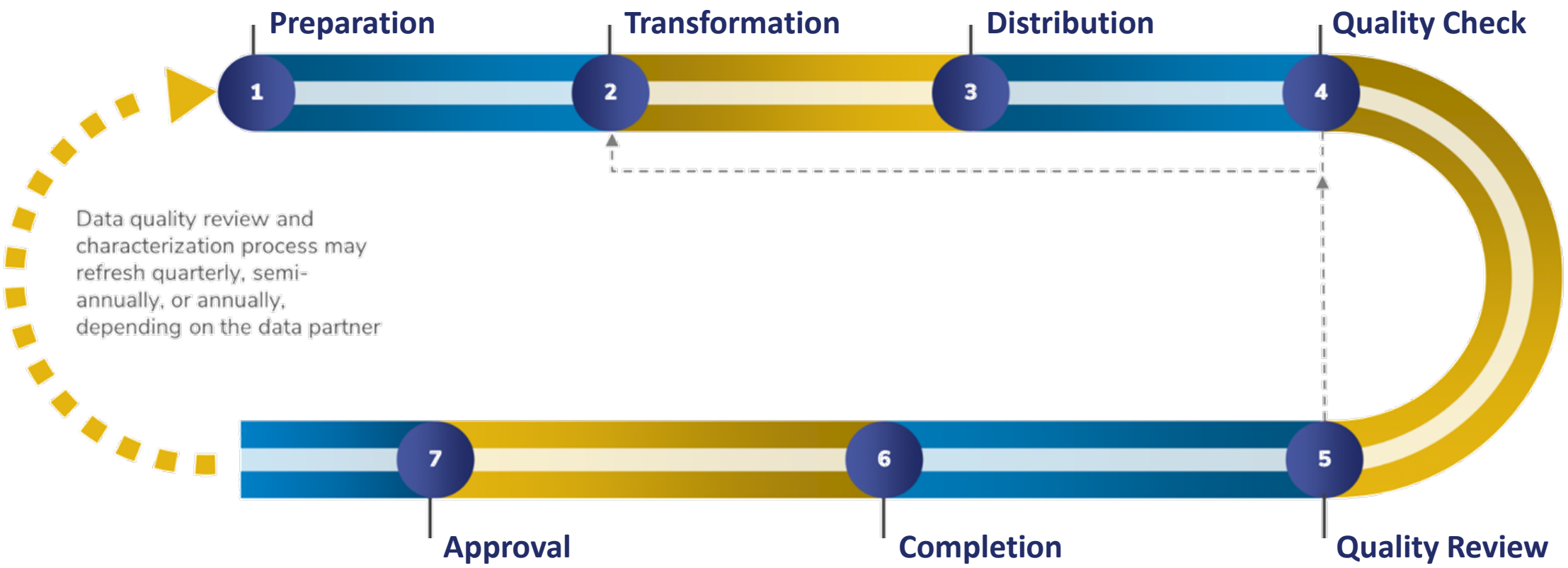
PROCEDURE

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4
PatID1	EncID2	05/02/2006	Provider1	IP	59400	C4
PatID2	EncID1	03/02/2016	Provider2	AV	99203	C4

MOTHER-INFANT LINKAGE

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

Data Quality Review and Characterization



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

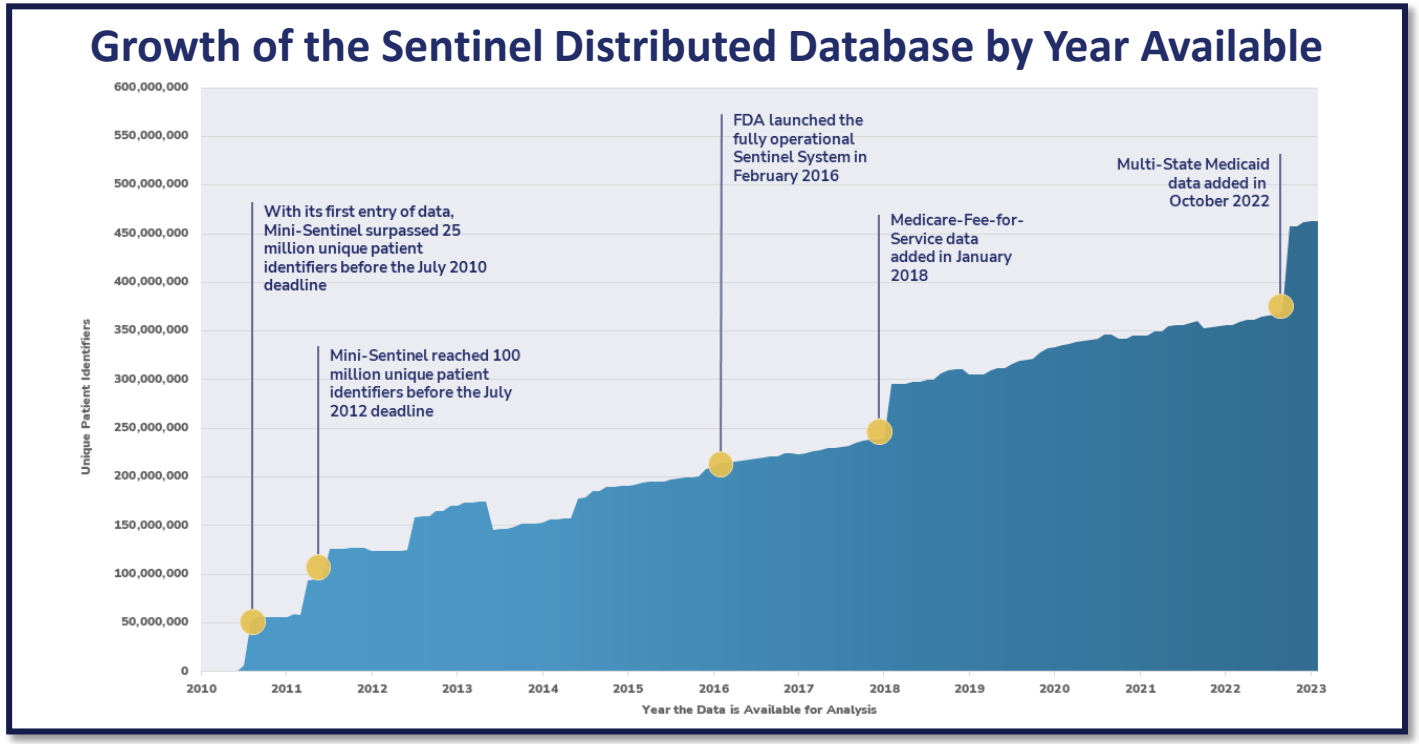
Types of Data Quality Checks

Single-table checks	✓ **Completeness** *Ex: Admission date is not missing value* ✓ **Validity** *Ex: Admission date is in the "date" format*
Cross-table checks	✓ **Accuracy** *Ex: Admission date in diagnosis table occurs before patient's discharge in encounter table* ✓ **Integrity** *Ex: Admission date occurs within the patient's active enrollment period*
Cross-time checks	✓ **Trend Consistency** *Ex: No sizable percent change in admission date record counts*

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

Sentinel Distributed Database Growth

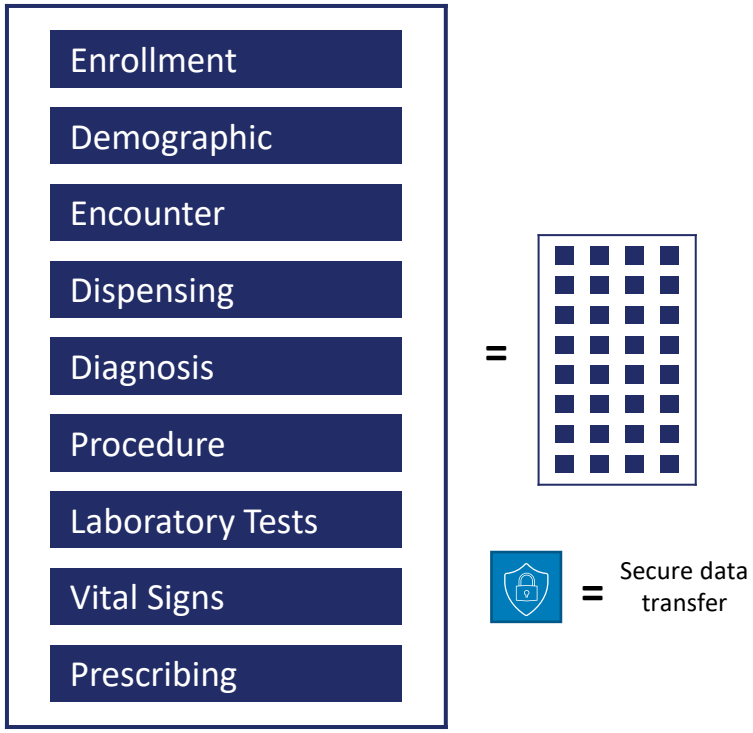
- Sentinel Distributed Database came online in 2010
- Now contains ~463 million unique patient IDs from enrolled 2000 – 2023
  - ~342 million have ≥1 day of medical and drug coverage
    - *~113 million currently accruing new data*
  - ~8 million live birth deliveries with a mother-infant linkage

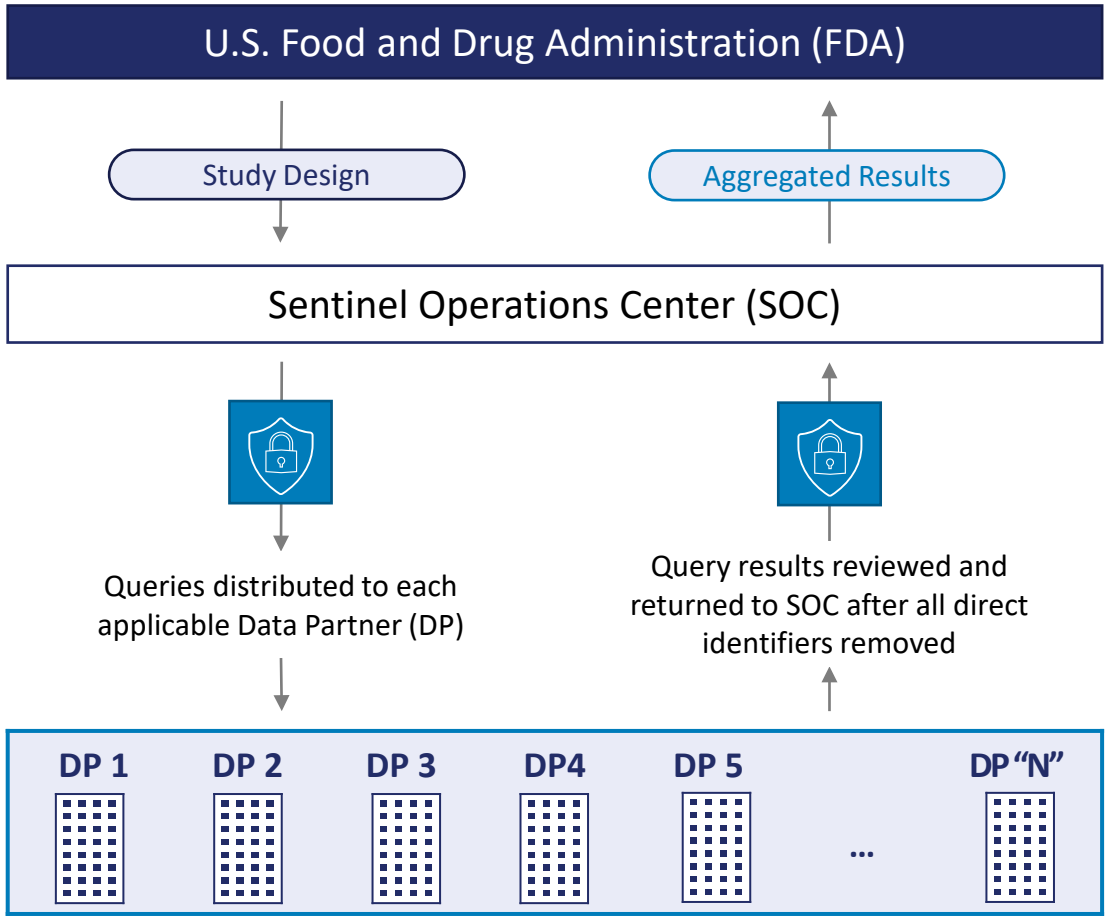


Current as of March 2023; https://sentinelinitiative.org/about/key-database-statistics

Sentinel Distributed Data Network

- Data Partners (DPs) hold data in the Sentinel Common Data Model format





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

Analyses in Sentinel

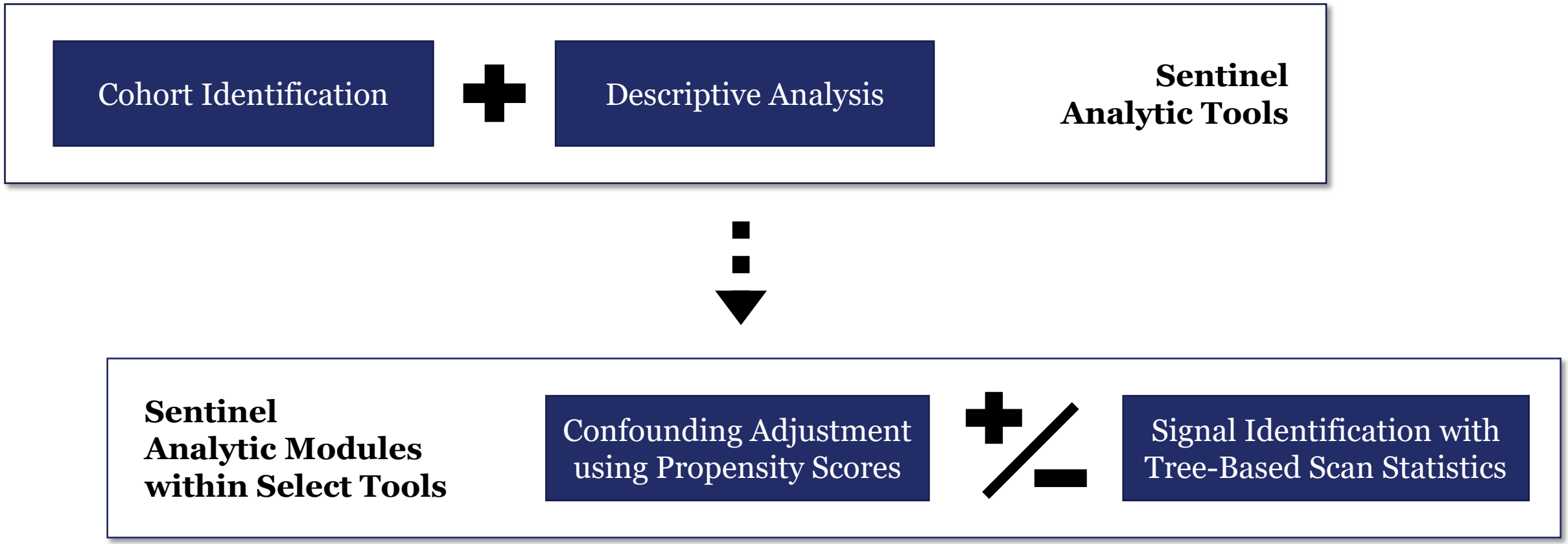
A key component of the Sentinel System:

Analytic Tools and Modules

Sentinel Analytic Tools

- SAS program templates designed to run against the Sentinel Common Data Model
  - Pre-tested and quality-checked
  - Output standardized (but customizable) reports
  - Parameterized for project-specific design elements at program execution
    - Choice of tool depends on question of interest

Conducting Analyses in Sentinel



Choosing an Analytic Tool

Exposure Only

- Calculate medical product* background rates
- Describe medical product utilization metrics
- Describe medical product switching

Exposure and Outcome

- Identify outcomes during follow-up
  - Outcomes may be health conditions, events (multiple or single), or overlap
- Identify health outcomes during risk and control windows within the same patient
- Identify pregnancy duration and pregnancy start in order to describe medical product utilization during pregnancy
  - May access Mother-Infant Linkage to identify health outcomes among linked infants

* Medical products are the most common exposure, but any concept defined using standardized medical terminologies can be used as an exposure
See https://sentinelinitiative.org/methods-data-tools/routine-querying-tools for more information

Using Optional Modules

- Tools that identify both exposures and outcomes contain additional modules to perform inferential analyses
- Modules are optional and may be used alone or with each other

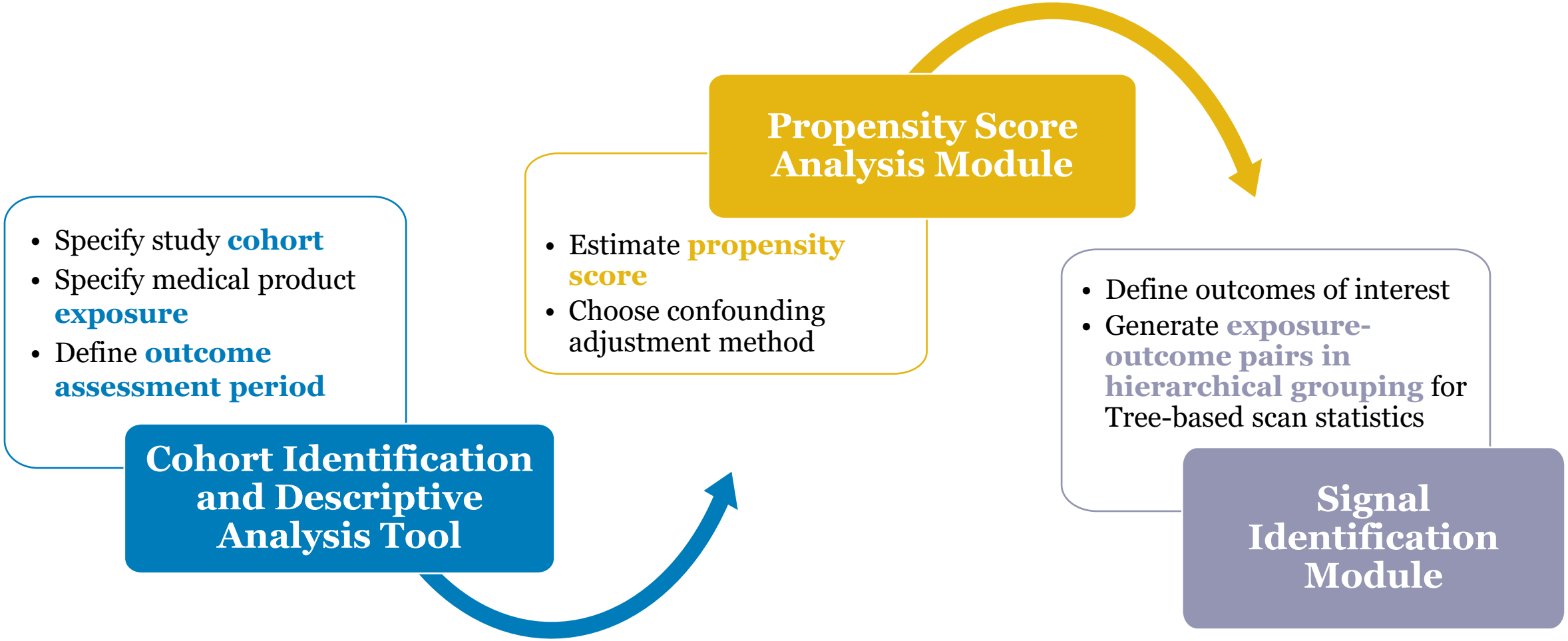
Propensity Score Module

- Estimates propensity scores (PS) with user-specified or empirically-defined model
- Uses propensity scores to adjust for confounding with matching, stratification, or weighting schemes
- Calculates adjusted effect estimates

Signal Identification Module

- Specifies simultaneous collection of many health outcomes of interest using tree-based structure
- Generates analytic datasets for use with TreeScan™ software (www.treescan.org)

Analysis Process for Signal Identification



Custom programming is needed to implement confounding adjustment methods other than PS matching and self-controlled designs with signal identification

Reporting Sentinel Analysis Findings

- After obtaining study results, Sentinel Operations Center aggregates across all contributing Data Partners

- A single report summarizes findings in tables and figures
  - Option to output to Excel Workbook or PDF
  - SAS code template with parameterizable customizations

Sentinel and the Public

Sentinel Common Data Model

- Current and past specifications for **Sentinel Common Data Model** maintained in Git repository
- Quality review and characterization specifications and code package, including for the Mother-Infant Linkage
- Specifications and code to transform certain data sources into Sentinel Common Data Model:
  - Merative™ Marketscan® Research Databases
  - CMS Medicaid/CHIP Research Identifiable Files
  - CMS Medicare Fee-for-Service Research Identifiable Files

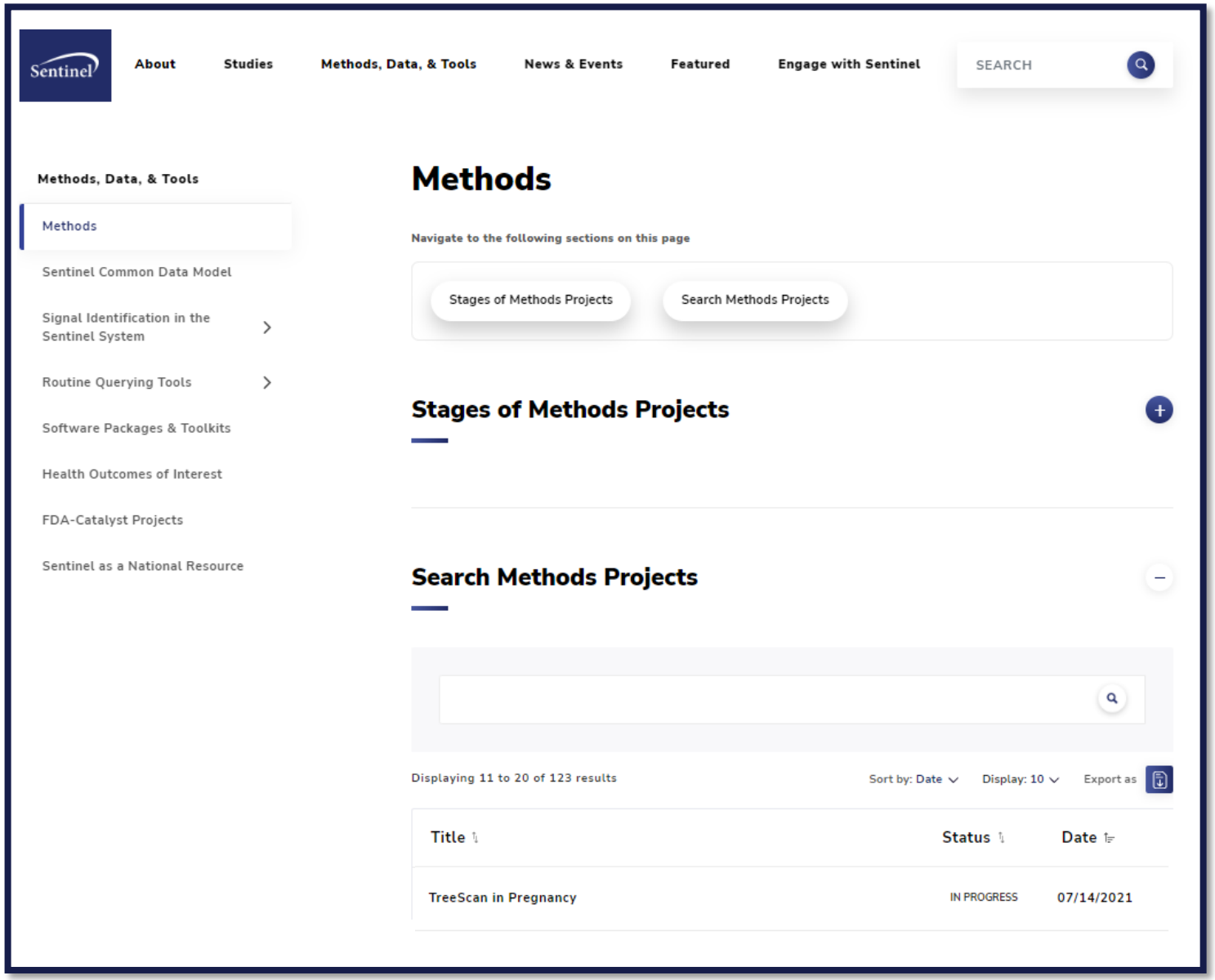
Analytic Tools

- Cohort Identification, Descriptive Analysis, and Associated Modules
  - SAS Code
  - Documentation

- Reporting Tool used after results generated
  - SAS Code
  - Documentation

Study Results

- All final findings posted on Sentinel website
- Analytic packages posted on individual drug analysis pages



https://www.sentinelinitiative.org/methods-data-tools/methods/treescan-pregnancy

Questions or Comments?

Sentinel

Detecting Medication Adverse Effects in Sentinel

2023 Sentinel Public Training

Session 2

11 April 2023

Agenda

1 **Background on Signal Identification**

Objective: Review the process of Signal Identification and highlight key methods to identify safety signals.

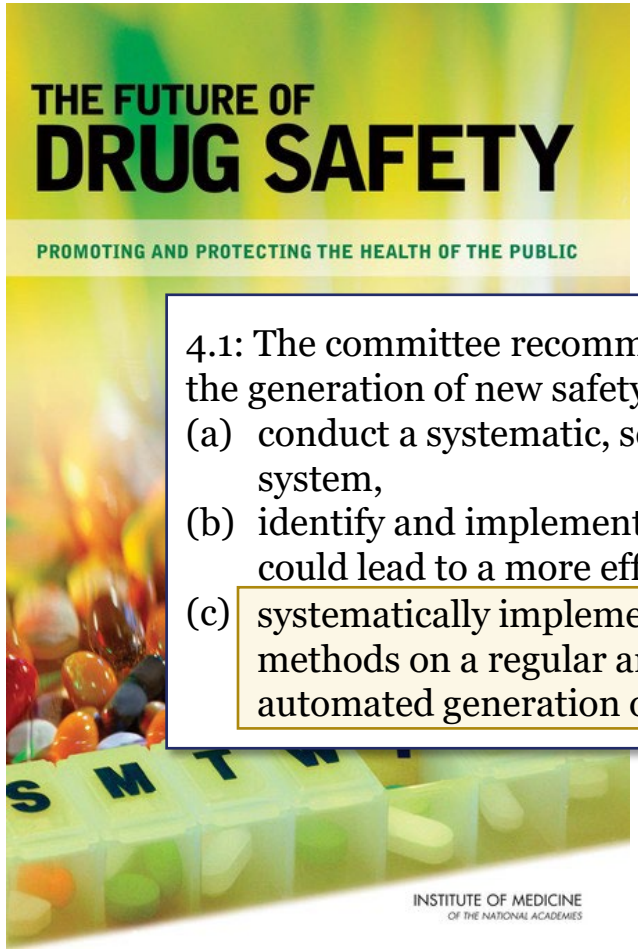
2 **Using TreeScan™ for Signal Identification**

Objective: Overview of the use of TreeScan™ to conduct Signal Identification in Sentinel.

Background on Signal Identification

Institute of Medicine Drug Safety System Assessment

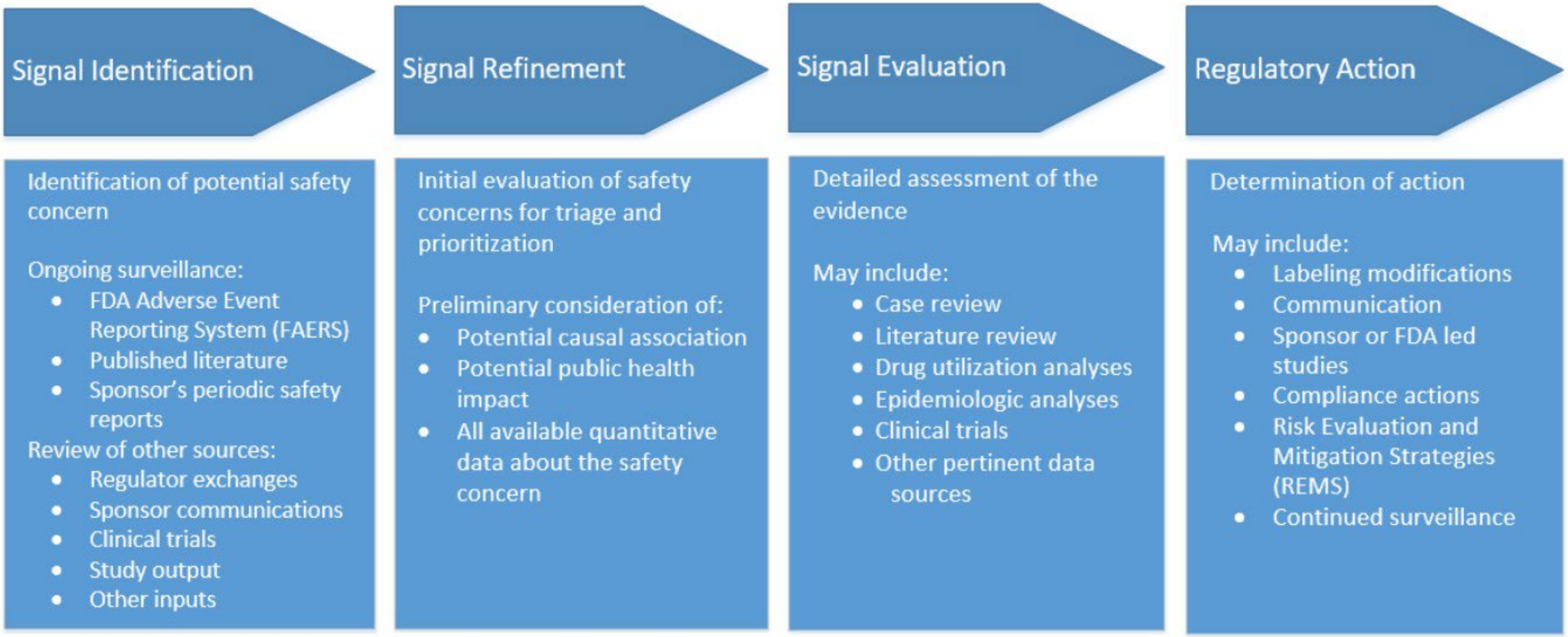
- In 2006, the FDA requested that the Institute of Medicine **examine the system of drug safety in the US**
- Institute of Medicine published "The Future of Drug Safety: Promoting and Protecting the Health of the Public" in 2007 calling for a comprehensive approach to drug safety



4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER
(a) conduct a systematic, scientific review of the AERS system,
(b) identify and implement changes in key factors that could lead to a more efficient system, and
(c) systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals

Committee on the Assessment of the US Drug Safety System; Board on Population Health and Public Health Practice; Institute of Medicine. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*; Stratton, K., Baciu, A., Burke, S. P., Eds.; National Academies Press: Washington, D.C., 2007. https://doi.org/10.17226/11750.

Signal Management at the FDA



Muñoz M (2018, December 3): Integrating Signal Identification with Sentinel into FDA's Pharmacovigilance Framework. Retrieved from: https://healthpolicy.duke.edu/sites/default/files/2020-02/sessions_1_2_sentinel_detection_master_slide_deck_final.pdf

Data Sources for Quantitative Signal Identification

	FDA Adverse Event Reporting System	Sentinel Distributed Database
Type of Surveillance	Passive	Active
Type of Database	Spontaneous Reporting	Longitudinal Database
Database Description	Collects adverse event reports* from healthcare providers and consumers	Standardized and quality-assured administrative claims and electronic healthcare record data for ~400 million members
Statistical Identification of Alerts	Disproportionality analysis	Estimation of relative risk

* In addition to adverse event reports, FDA Adverse Event Reporting System also contains medication error reports and product quality complaints resulting in adverse events

Considerations for Using FDA Adverse Event Reporting System for Signal Identification

- FAERS is a valuable source of safety information
  - Particularly good for detecting serious rare events (e.g., liver failure)
  - Captures all products and settings of use
  - Can provide a patient perspectives
- FAERS has important limitations
  - Denominator is unknown
  - Quantification of risks is not feasible

Considerations for Using Sentinel for Signal Identification

- Longitudinal databases may serve as complement to spontaneous adverse event reports
  - Estimates of population exposures are available
  - Quantification of confounding adjusted risks is feasible
- Sentinel also has important limitations
  - Secondary data lack granular clinical information
  - Capture is limited to billed, medically attended events
  - Limited generalizability

FDA Adverse Event Reporting System and Sentinel are Complementary Data Sources

- Active hypothesis-free signal identification in Sentinel can complement current surveillance tools that largely rely on passive data sources

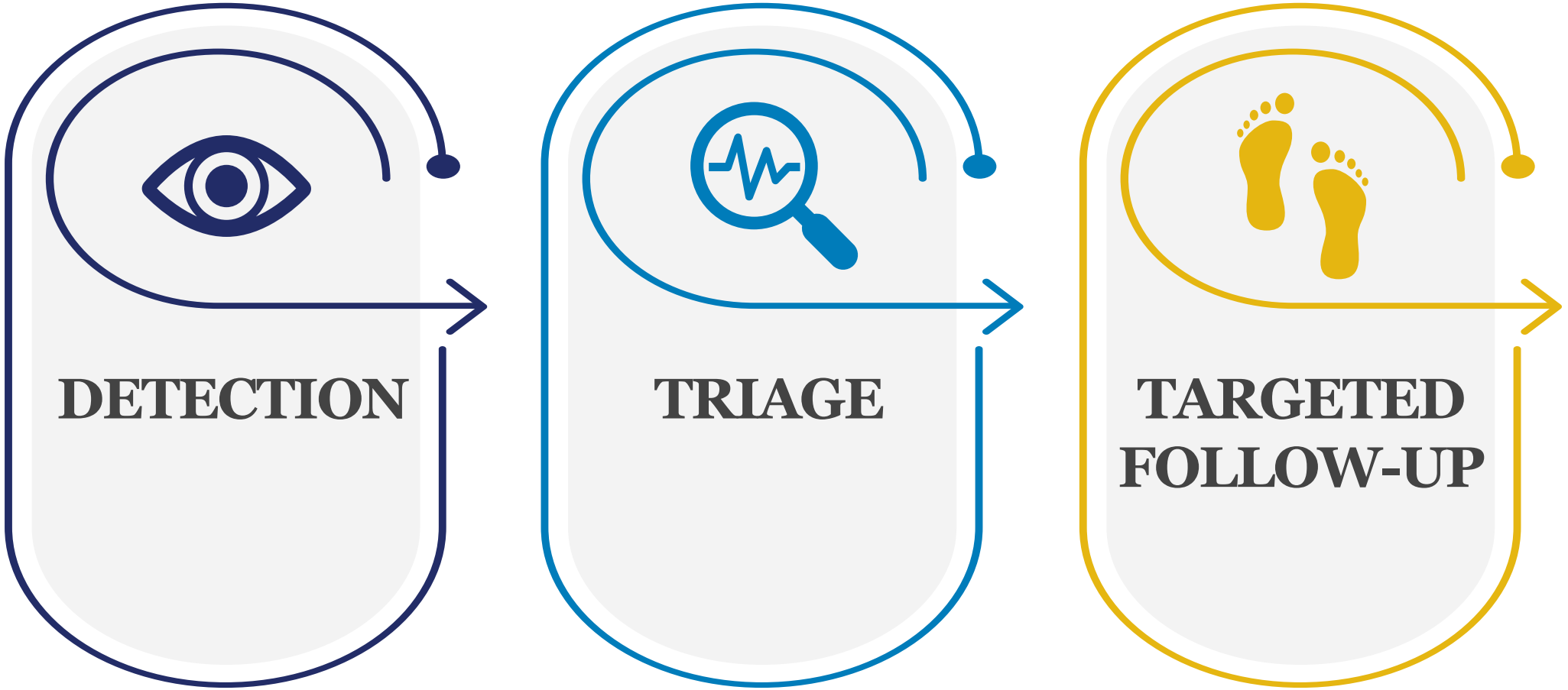
Muñoz M (2018, December 3): Integrating Signal Identification with Sentinel into FDA's Pharmacovigilance Framework. Retrieved from: https://healthpolicy.duke.edu/sites/default/files/2020-02/sessions_1_2_sentinel_detection_master_slide_deck_final.pdf

Signal Identification in Sentinel

- The signal identification process includes systematically evaluating potential adverse events related to the use of medical products without prespecifying an outcome of interest
  - Detect unexpected, higher numbers of health outcomes
  - Clinical review and/or epidemiology safety study follows signal identification

https://sentinelinitiative.org/methods-data-tools/signal-identification-sentinel-system

Steps in Sentinel Signal Identification



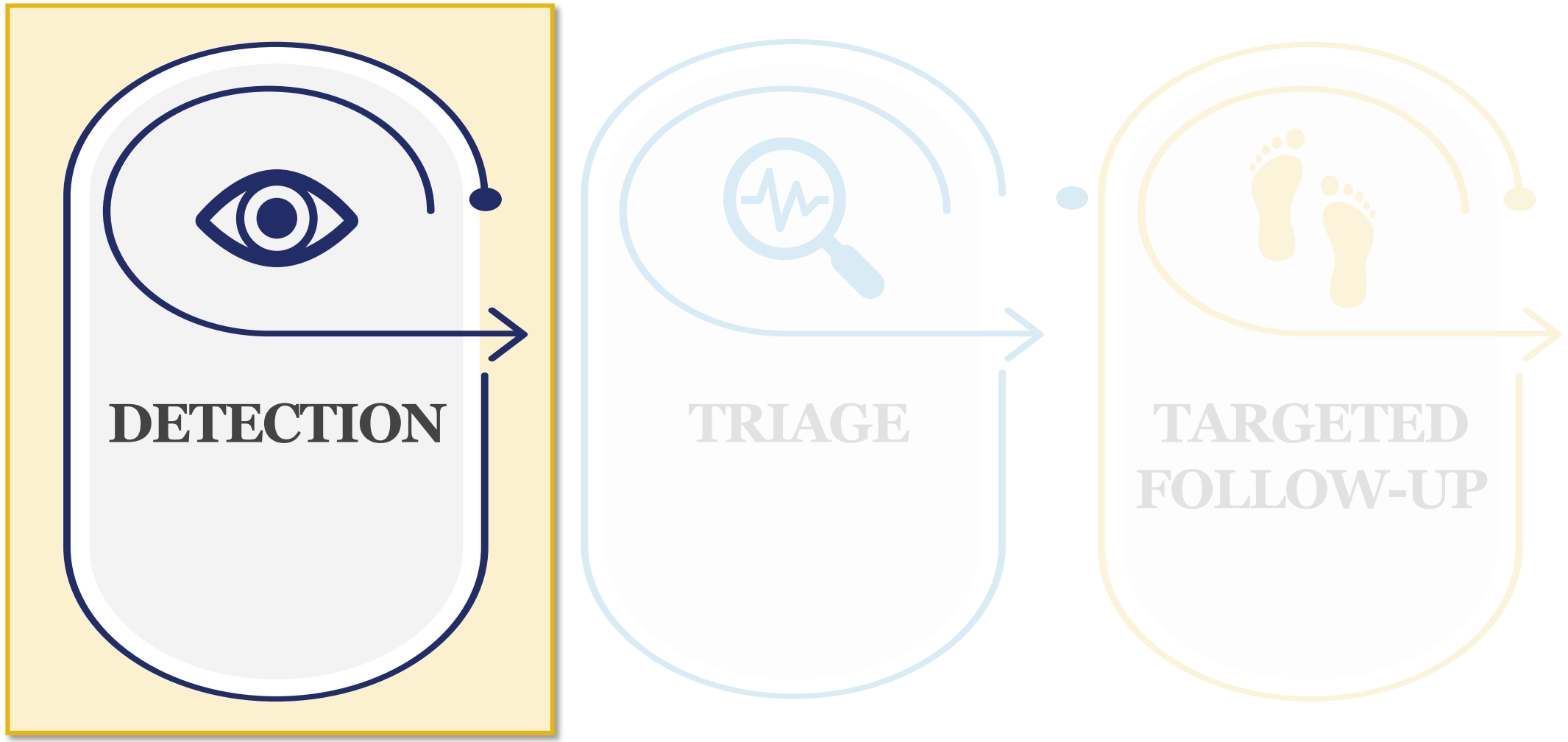
Overview of Signal Identification Techniques Utilized by the Sentinel System

Method	Study Design or Contrast	Test Statistic	Control for Multiple Testing	Adjustment for Trends in Healthcare Utilization
Information Component Temporal Pattern Discovery	Compares the rate of events in multiple pre-specified control and risk windows relative to the timing of a first dispensing using a self-controlled design, while adjusting for general dispensing patterns across the database	Ranks alerts based on the delta in Information Component between the risk and control windows	No, however, uses a shrinkage estimator to reduce false positives due to random variability or rare events	Yes
Propensity Score Based TreeScan	Compares the rate of events in a pre-specified risk window between persons newly exposed to a drug of interest who are matched by propensity score to a cohort of new users of a comparator drug	Ranks alerts based on the log-likelihood ration, a measure of observed versus expected counts, using a Bernoulli probability model	Yes, via Monte Carlo hypothesis testing	No
Self-Controlled TreeScan	Compares the rate of events in pre-specified control and risk windows within the same person			Optional
Sequence Symmetry Analysis	Compares whether an event occurs more frequently after exposure to a medication than before medication exposure using a self-controlled design	Ranks alerts based on magnitude of absolute difference in sequence orders and presented unadjusted p-values from chi-square tests	No	No
Tree-Temporal TreeScan	Compares the rate of events across multiple risk and control windows within the same person that do not require explicit pre-specification of the windows. Effectively combines the benefits of TreeScan with a temporal scan of many possible risk windows	Ranks alerts based on the log-likelihood ration, a measure of observed versus expected counts	Yes, via Monte Carlo hypothesis testing	Optional

https://sentinelinitiative.org/methods-data-tools/signal-identification-sentinel-system

Using TreeScan™ for Signal Identification

Steps in Sentinel Signal Identification



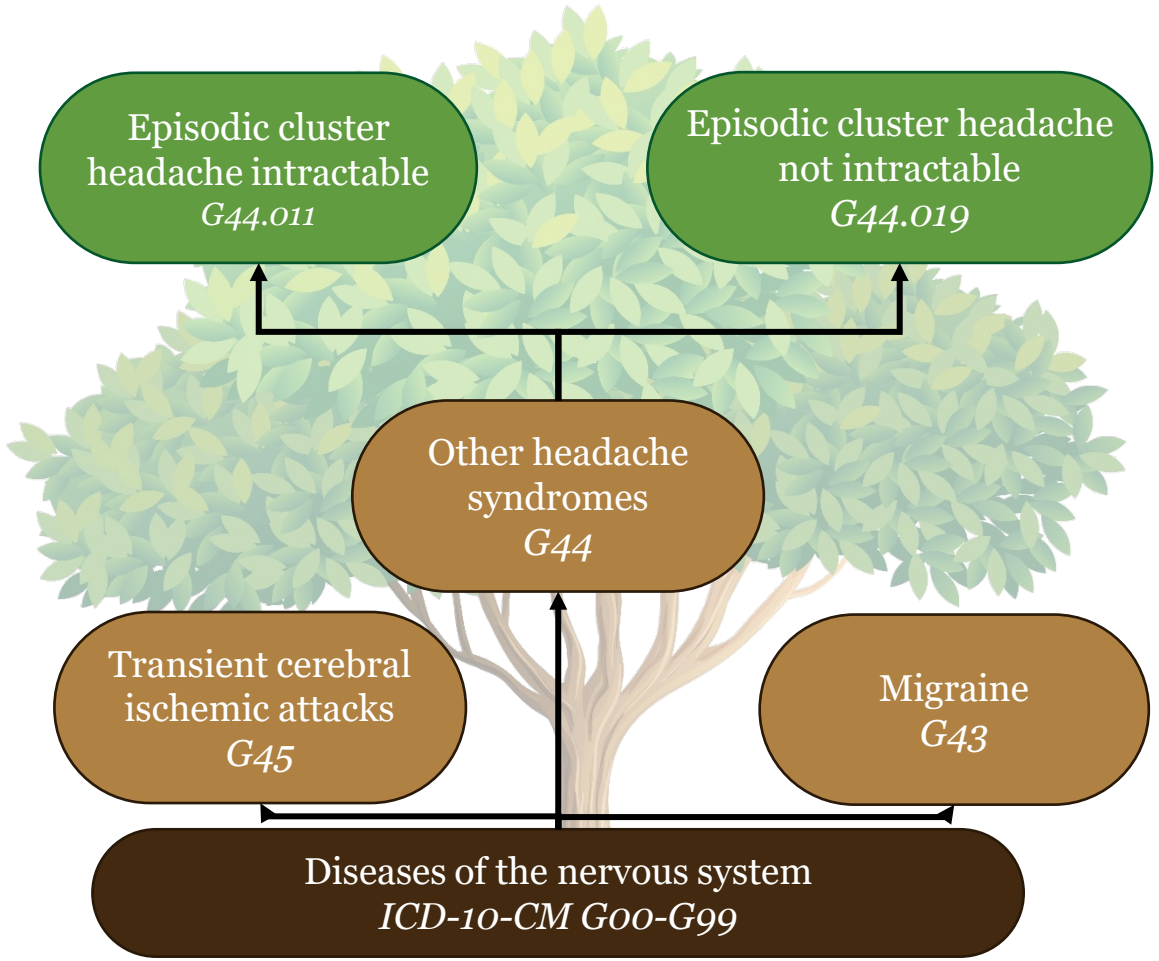
Overview of TreeScan™

- One of several signal identification methods
- Evaluates **thousands of outcomes** simultaneously to identify potential adverse events (AEs)
  - AEs can be very specific (e.g., atrial septal defect) or in groupings of concepts (e.g., congenital malformations of the circulatory system)
- Automatically **adjusts for multiple outcomes being scanned**
- Compatible with multiple epidemiologic study designs and methods for confounding control

https://www.treescan.org/

Kulldorff M et al. *Biometrics*, 2003,59:323-331
Kulldorff M et al. *Pharmacoepidemiology and Drug Safety*, 2013, 22:517-523.

Tree Structure



- Map a tree according to hierarchical structure of coding system
  - **Root:** broadest classification (body system)
  - **Leaves:** most specific classification (individual codes)
  - **Branches:** groupings of multiple codes
  - **Nodes:** any location on the tree (leaf or branch)

Scanning the Tree for Potential Signals

After building tree structure, scan tree to identify safety alerts (potential signals):

- Assume no increase in event risk for thousands of outcomes across the tree
- For each node on the tree, compute observed and expected numbers of events after adjusting for confounding
- Compare observed and expected events at each node
- Any unexpected findings?

TreeScan™ vs Traditional Studies

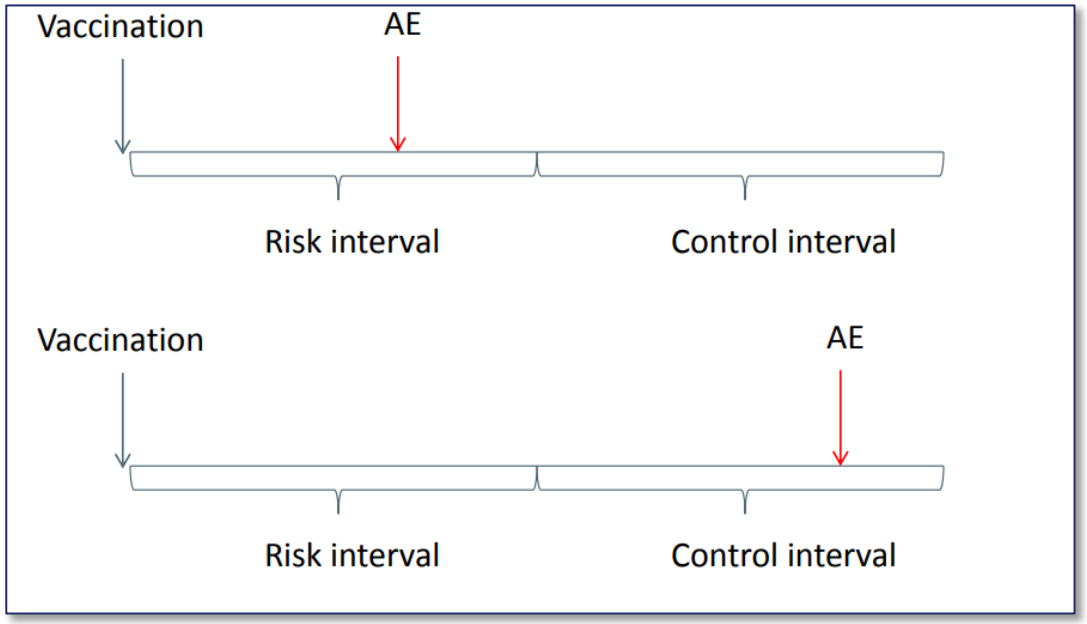
- Signal identification using a tree-based statistic assesses associations between a single exposure and several thousands of outcomes
- Traditional pharmacoepidemiologic studies are hypothesis driven assessments of the association between an exposure and a pre-specified outcome

Analytic Decisions for Signal Identification in Sentinel

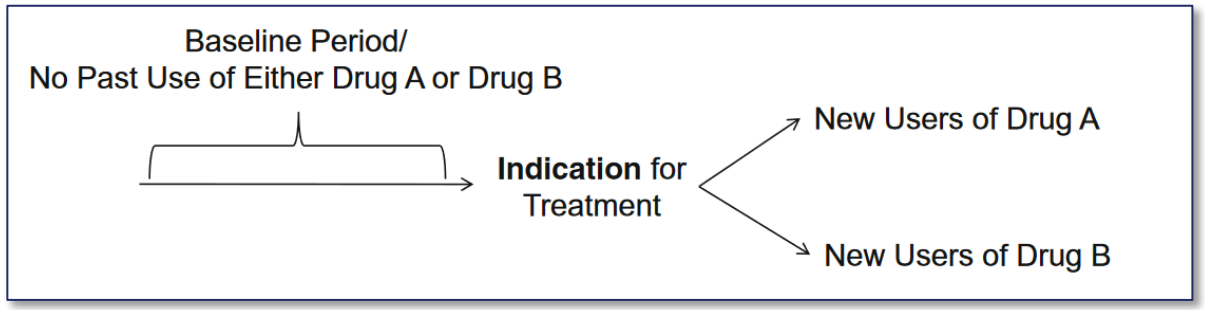
	Hypothesis Validation (Traditional)	Hypothesis Generation (Signal Identification)		
Choose Study Design	Cohort			
Identify Study Population	Specify study period, enrollment requirements, new use requirements, and inclusion/exclusion criteria for population of interest			
Identify Outcome(s)	Use validated algorithm to identify event following treatment initiation			
Confounding Control	Propensity score methods			
Statistical Analysis	Point estimate and confidence interval for exposure-outcome association (e.g., Hazard Ratio)			

Study Designs for Signal Identification in Sentinel

Self-Controlled Risk Interval



Cohort

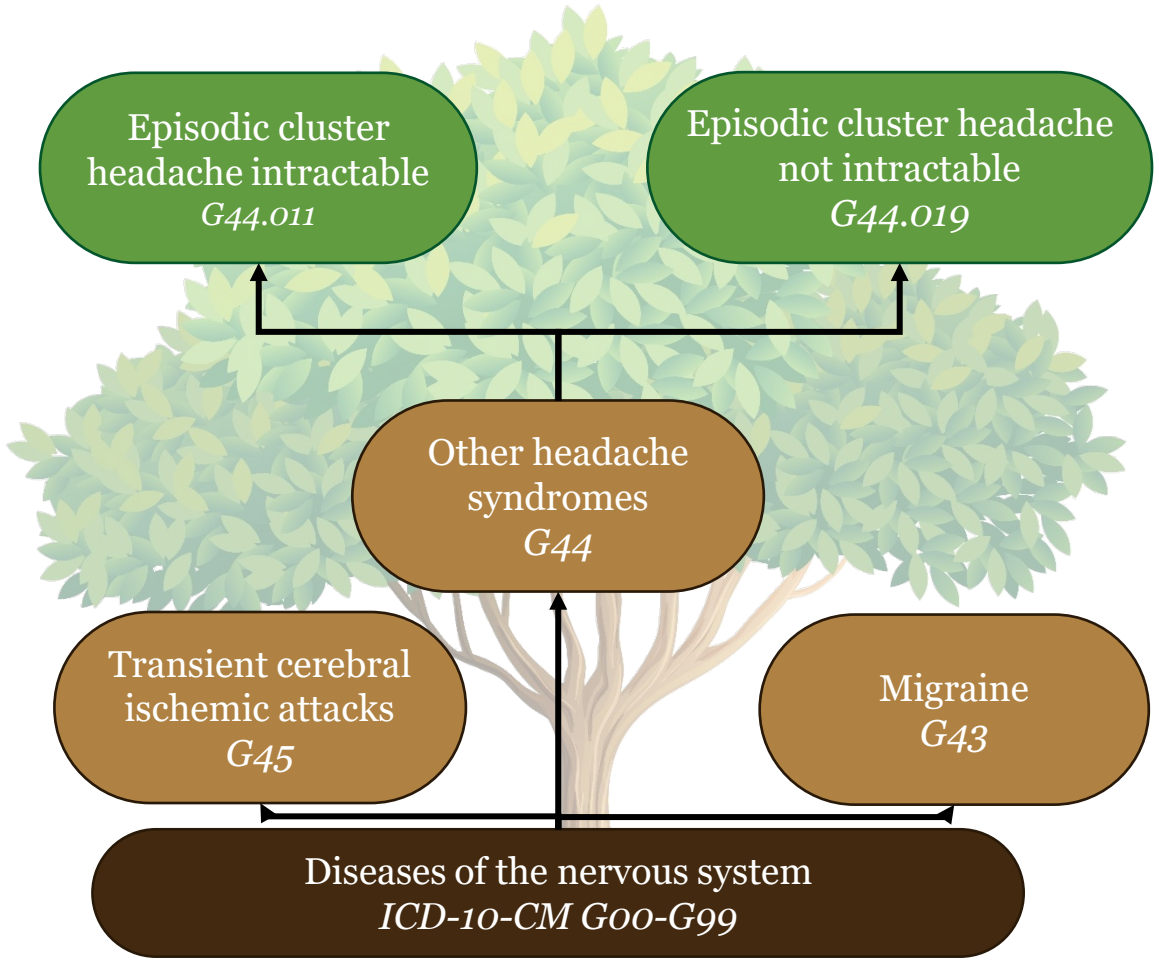


https://www.sentinelinitiative.org/sites/default/files/Sentinel-ICPE-2017-Course-PRISM-SCRI-Studies.pdf
Lund JL et al. *Current Epidemiology Reports*. 2015;2(4):221-228.

Analytic Decisions for Signal Identification in Sentinel

	Hypothesis Validation (Traditional)	Hypothesis Generation (Signal Identification)		
Choose Study Design	Cohort	Self-Controlled Risk Interval	Cohort	
Identify Study Population	Specify study period, enrollment requirements, new use requirements, and inclusion/exclusion criteria for population of interest			
Identify Outcome(s)	Use validated algorithm to identify event following treatment initiation	Create a hierarchical outcome tree		
Confounding Control	Propensity score methods			
Statistical Analysis	Point estimate and confidence interval for exposure-outcome association (e.g., Hazard Ratio)			

Tree Structure



- Tree can be pruned/curated

Analytic Decisions for Signal Identification in Sentinel

	Hypothesis Validation (Traditional)	Hypothesis Generation (Signal Identification)		
Choose Study Design	Cohort	Self-Controlled Risk Interval	Cohort	
Identify Study Population	Specify study period, enrollment requirements, new use requirements, and inclusion/exclusion criteria for population of interest			
Identify Outcome(s)	Use validated algorithm to identify event following treatment initiation	Create a hierarchical outcome tree		
Confounding Control	Propensity score methods	N/A	Fixed-ratio propensity score matching	Propensity score stratification
Statistical Analysis	Point estimate and confidence interval for exposure-outcome association (e.g., Hazard Ratio)			

Confounding Control for Signal Identification in Sentinel

- Self-controlled risk interval studies adjusts for time fixed confounding by design
  - Each patient serves as their own comparator

- Cohort studies require some form of control for confounding
  - Typically with the use of conventional or high dimensional propensity scores

Propensity Scores

- A propensity score is a patient-specific probability of treatment with the exposure of interest
- Propensity scores are estimated using logistic regression models predicting exposure which include **all relevant confounders**
- Patients with similar propensity scores have **similar distributions of the confounders used to estimate the propensity scores** (in expectation)

Propensity Score Estimation

- Traditional propensity score
  - Logistic regression specified with measured confounders identified based on subject matter expertise
- High dimensional propensity score
  - Logistic regression can be additionally specified with empirically selected covariates that can adjust for unmeasured confounders via proxies

Propensity Score Methods for Cohort Studies

Matching

- Match referent to exposed patients based on a pre-specified maximum distance in their propensity score
- Follow-up for outcomes within matched pairs, reducing power
- Allows for strict confounding control

Stratification

- Create percentiles of propensity score distribution and assign patients to strata accordingly
- Allows for use of the full exposed and referent population, increasing power
- Potentially not as strict confounding control as matching

Analytic Decisions for Signal Identification in Sentinel

	Hypothesis Validation (Traditional)	Hypothesis Generation (Signal Identification)		
Choose Study Design	Cohort	Self-Controlled Risk Interval	Cohort	
Identify Study Population	Specify study period, enrollment requirements, new use requirements, and inclusion/exclusion criteria for population of interest			
Identify Outcome(s)	Use validated algorithm to identify event following treatment initiation	Create a hierarchical outcome tree		
Confounding Control	Propensity score methods	N/A	Fixed-ratio propensity score matching	Propensity score stratification
Statistical Analysis	Point estimate and confidence interval for exposure-outcome association (e.g.,Hazard Ratio)	Unconditional/Conditional Bernoulli model	Unconditional Bernoulli model	Unconditional/Conditional Poisson model

Identifying and Assessing Potential Signals

After building tree structure, scan tree to identify safety alerts (potential signals):

- Assume no increase in event risk for thousands of outcomes across the tree
- For each node on the tree (individual outcome or groups of outcomes), compute observed and expected numbers of events after adjusting for confounding
  - Expected events under Bernoulli or Poisson distribution
- Compare observed and expected events according to statistical model
- Test statistic is the maximum log likelihood ratio
- Compute p-value for the test statistic using Monte Carlo simulations that formally adjust for simultaneous scanning of thousands of outcomes across the tree
  - Maintains overall type I error at user-specified threshold (e.g., $\alpha = 0.05$)
- Alert if p-value below signaling threshold

Log-Likelihood Ratio Estimation

Assumptions about Distribution of Expected Events

- Bernoulli distribution
  - Compatible with self-controlled or propensity score-matched cohorts
- Poisson distribution
  - Compatible with propensity score-stratified cohorts
- Poisson models demonstrate greater statistical power to detect signals than Bernoulli models

Conditioning on Background Event Rate

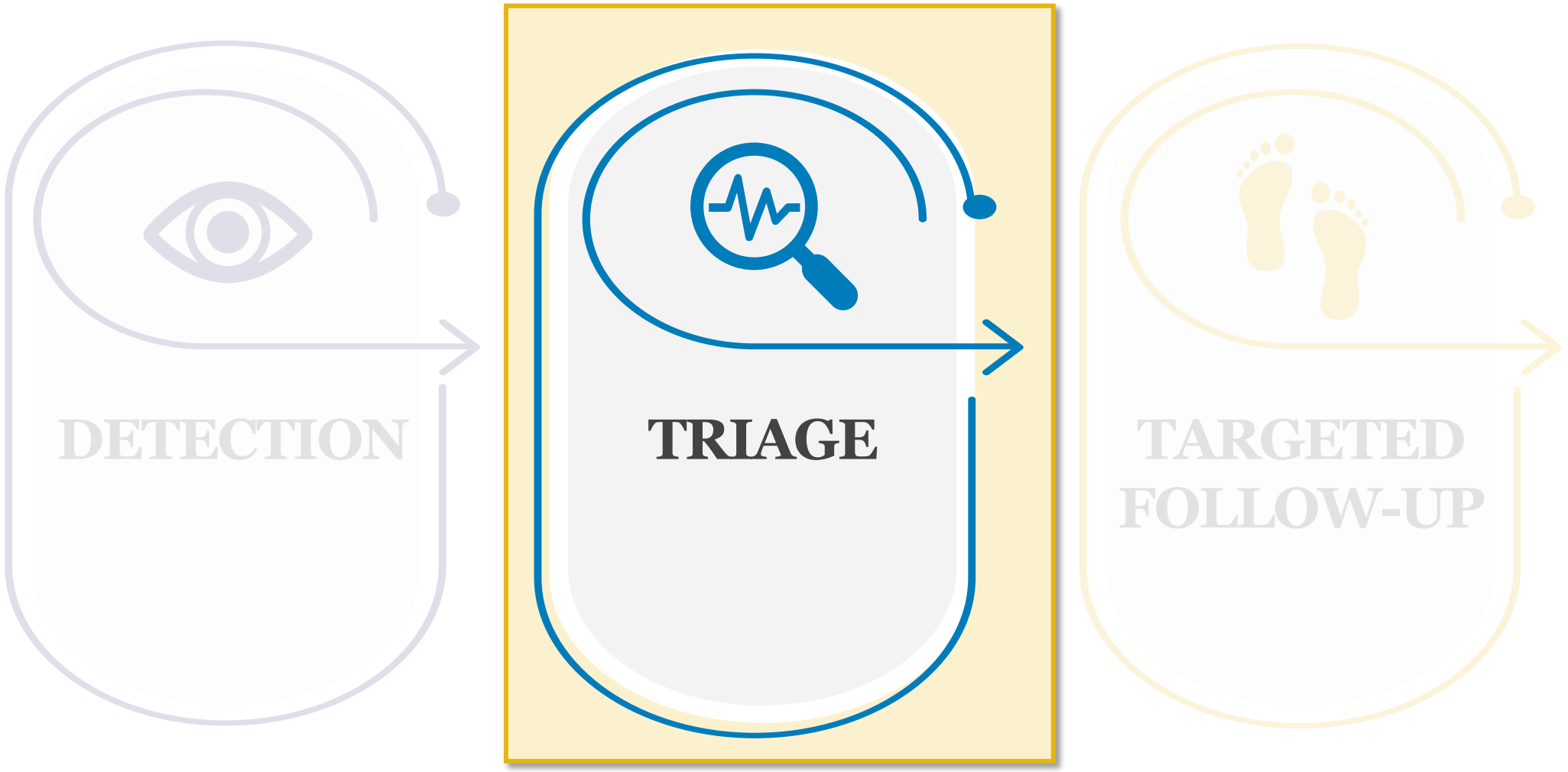
- Conditioning on total number of events **accounts for trends** in general healthcare utilization across the database
- In general, unconditional estimates tend to inflate type 1 error even in presence of low (2-3%) increase in utilization across the dataset

Maro JC et al. *EGEMS (Wash DC).* Jun 2017;5(1):6.
https://www.sentinelinitiative.org/sites/default/files/vaccines-blood-biologics/assessments/TreeScanPower_FinalReport.pdf
Suarez EA et al. *Epidemiology*. 2023;34(1):90-98

Statistical Alert

- Occurs when an outcome meets a pre-specified signaling threshold, i.e. log-likelihood ratio (LLR) indicates there is a departure from the expectation under the null hypothesis
  - LLRs are scaled differently for each analysis so this is plotted against a p-value (the percentile distribution against the test statistic)
  - Large LLRs = small test statistics
  - We typically use a conventional cutoff of p-value <=0.05.
  - LLR is driven by:
    - Distance between observed and expected values
    - Overall counts or sample information

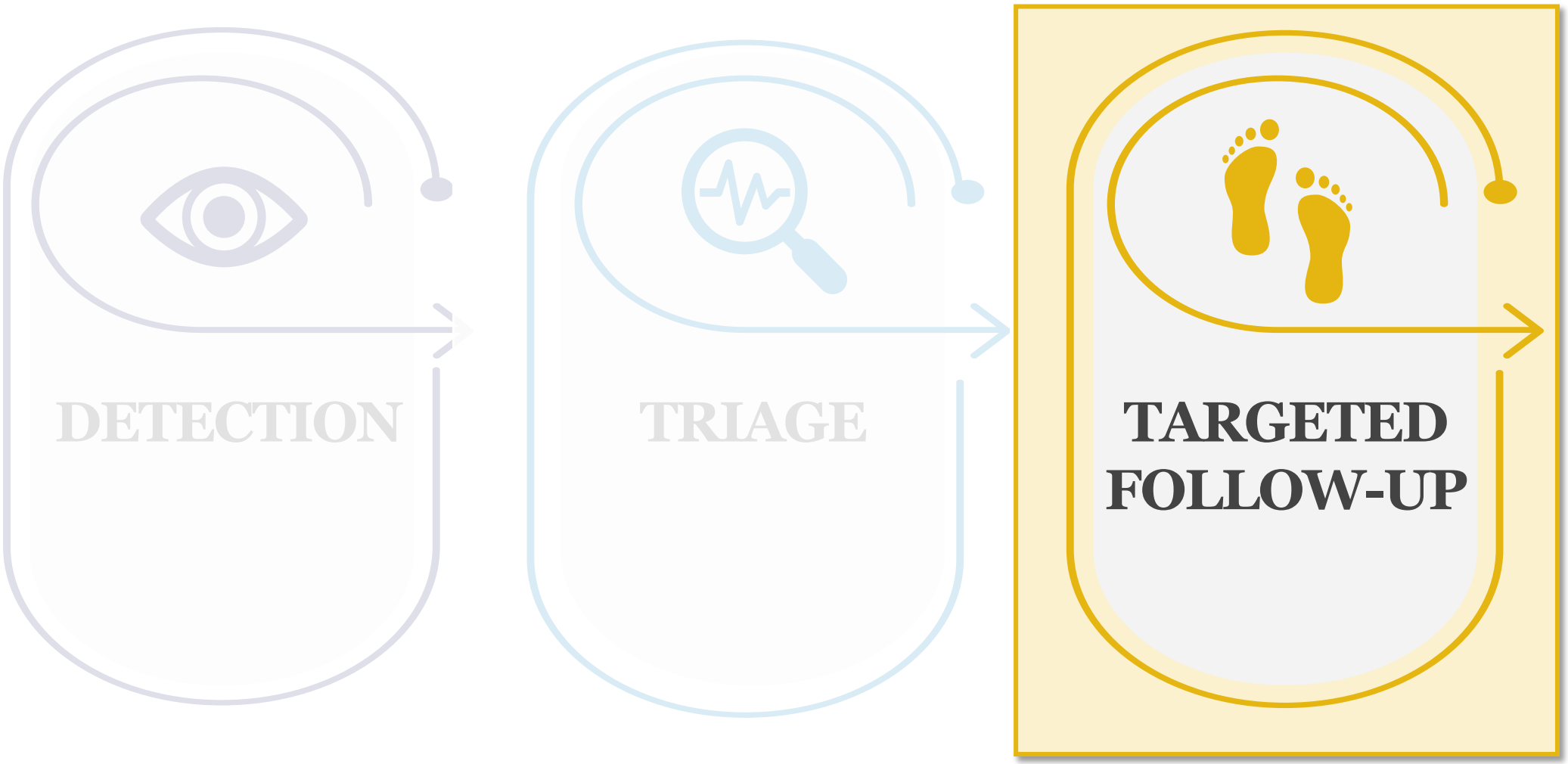
Steps in Sentinel Signal Identification



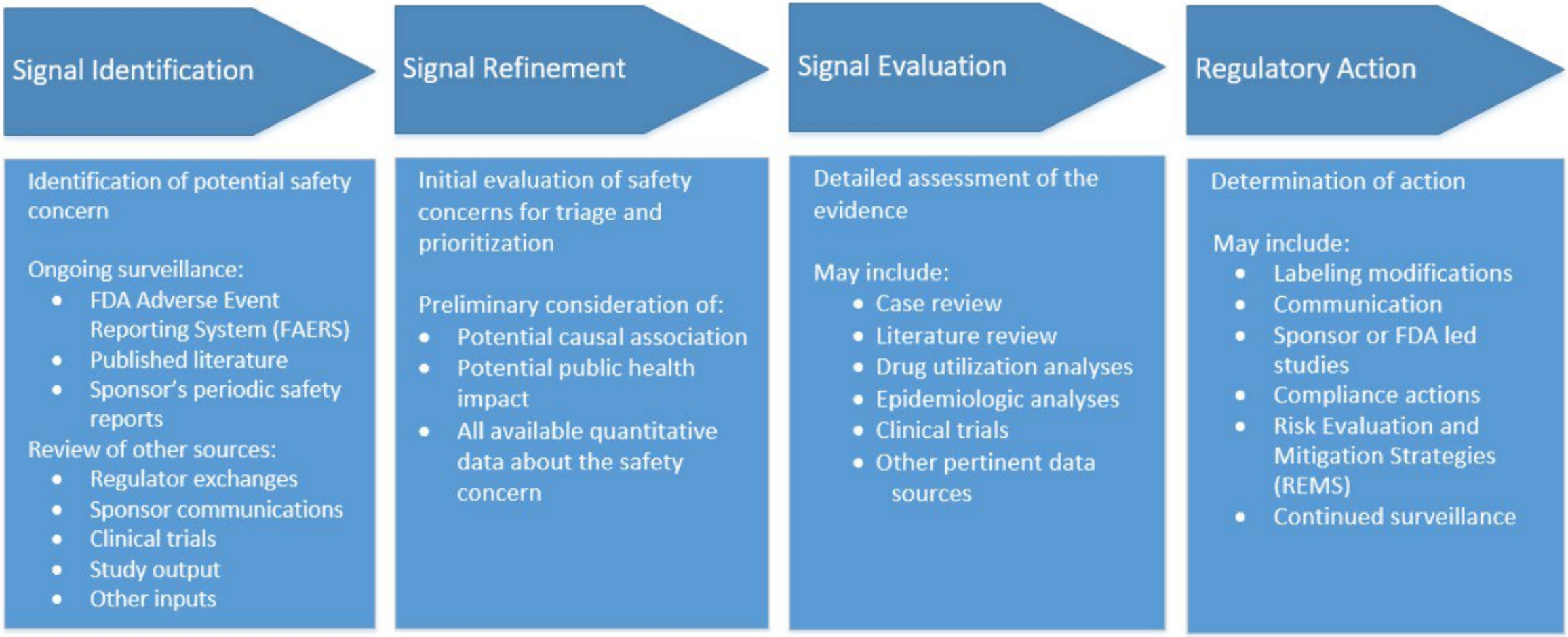
Alert Triage

- Review labeled conditions, commonly reported adverse reactions in the literature and in patient-facing medical materials (e.g., Cleveland Clinic, Mayo Clinic, etc..)
- Consider plausible explanations for observed alerts
- Review patient-level data around the time of treatment initiation and event occurrence

Steps in Sentinel Signal Identification



Monitoring Drug Safety Post-Signal Identification



Questions or Comments?

Sentinel

Break

Please return at 11:10AM

Agenda

9:00 AM – Opening Remarks – Dr. Robert Ball, FDA

9:20 AM – Introduction to Sentinel

9:55 AM – Detecting Medication Adverse Effects

10:50 AM – Break

11:10 AM – Infant Outcomes Following Medication Exposures

11:50 AM – First Trimester Fluoroquinolones: A Case Study

12:35 PM – Closing Remarks – Dr. Judith Maro, Sentinel Operations Center

Surveillance of Adverse Outcomes Following Gestational Medication Use

2023 Sentinel Public Training

Session 3

11 April 2023

Agenda

1 **Safety of Medication Use During Pregnancy**

Objective: Describe why medication use during pregnancy is a crucial area for signal identification and review available assessment methods.

2 **Sentinel's Unique Strengths to Identify Safety Signals Among Infants After Medication Use in Pregnancy**

Objective: Describe the three characteristics of the Sentinel Distributed Database that make it well-suited to identify safety signals among infants after maternal medication use in pregnancy:

1) Accurately identifying pregnancies,
2) Sufficiently capturing pregnancy medication exposures, and
3) Appropriately detecting infant outcomes.

Pharmacovigilance in Pregnancy

- FDA committed to optimize Sentinel System not only through maintenance but also through conducting demonstration projects to address gaps in knowledge about performance characteristics of different study designs, specifically with regards to pregnancy safety

> "The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner."
>
> *Prescription Drug User Fee Amendment VII: Fiscal Years 2023-2027 Commitment Letter (I)(M)(2)(b)(i)*

Center for Drug Evaluation and Research. PDUFA VII: Fiscal Years 2023 – 2027. Food and Drug Administration; 2023. Accessed March 1, 2023. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

In the United States, 9 in 10 women take medicine during pregnancy

"Should I keep taking my allergy medicine while pregnant?"

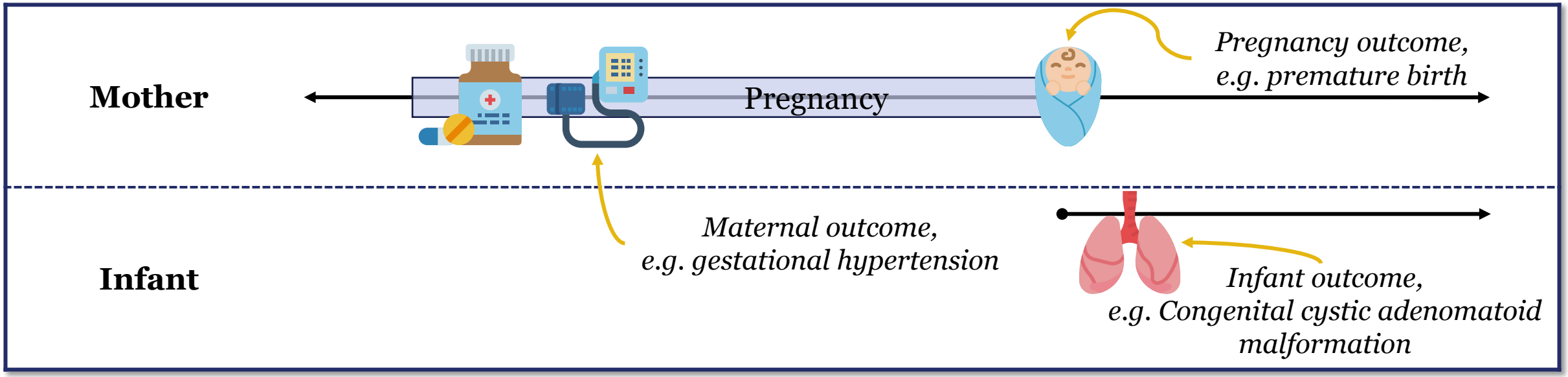
"What should I take to manage my pain while pregnant?"

"How should I change my pregnant patient's treatment plan?"

https://www.cdc.gov/pregnancy/meds/treatingfortwo/materials/providing-better-information.html

Safety Information is Lacking

- Certain medicines can cause adverse **pregnancy**, **maternal**, and/or **infant** outcomes when taken during pregnancy
  - Fewer than 10% of medicines approved since 1980 have enough information to determine their safety during pregnancy



Adam MP, Polifka JE, Friedman JM. Am J Med Genet C Semin Med Genet. 2011;157C(3):175-182

Safety Data Generation

- Pre-approval data exclude pregnant people for ethical reasons, leading most pregnancy safety data to be gathered post-approval
- However, most post-approval studies systematically exclude pregnant people
  - ≤5% of Phase IV clinical trials allow pregnant people to enroll[1]
- Other post-market data sources for medicine safety during pregnancy:
  - National Surveys
  - Adverse Event Reporting (e.g., FDA MedWatch program, data sent to FDA Adverse Event Reporting System)
  - Pregnancy Registries (FDA lists all required pregnancy registries online)

FAERS: FDA Adverse Event Reporting System; [1] Shields KE, Lyerly AD. *Orsett Gynecol.* 2013;122(5):1077-1081.

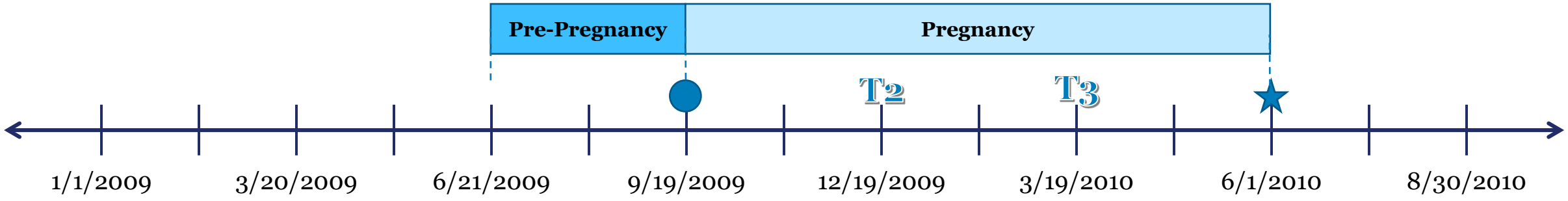
The Sentinel System: A National Resource

- Signal Identification for medications used during pregnancy within Sentinel enhances FDA's post-market surveillance system
- To be a successful signal identification platform for adverse outcomes after maternal gestational medication exposure, Sentinel should:
  - Consist of adequate numbers of pregnant people in which to identify medication use (**population**)
  - Accurately capture medication use during pregnancy periods (**exposure**)
  - Sufficiently capture adverse outcomes of interest: pregnancy, maternal, and/or infant (**outcome**)

Pregnant Populations in the Sentinel Distributed Database

Creating Pregnancy Episodes

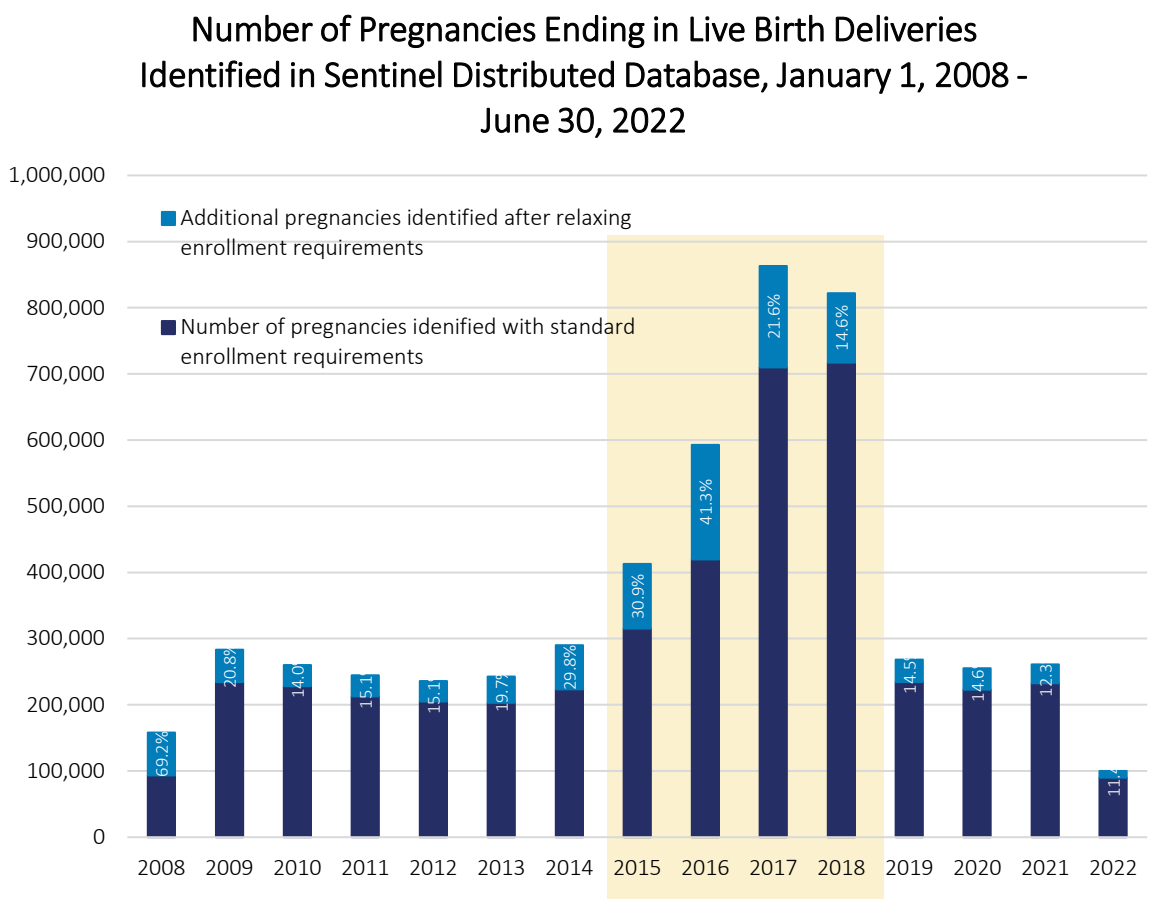
- Sentinel uses the validated Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) algorithm[1], adapted for ICD-10 era, to identify live birth deliveries and estimate pregnancy start date using gestational age codes
  - Example: live birth delivery on 6/1/2010 with **Z37.0** (Single Live Birth) & **Z3A.36** (36 wks gestation of pregnancy) ICD-10 codes, inpatient setting



[1] Li Q, Andrade SE, Cooper WO, et al. *Pharmacoepidemiol Drug Saf.* 2013;22(5):524-532. doi:10.1002/pds.3407

Pregnant People in Sentinel

- Identified ~9 million pregnancies with a live birth delivery, Jan 2008 – June 2022
  - **~4.3 million pregnancies included after applying standard enrollment requirements**
  - Relaxing enrollment requirements increased total included pregnancies to ~5.8 million



Data used represents Sentinel Distributed Database as of January 2023.

Medication Exposures During Pregnancy

FDA's Sentinel-Related Pregnancy Safety Commitments

- Current reauthorization of Prescription Drug User Fees Act (PDUFA) addresses enhancing Sentinel's ability to address product safety in pregnancy
- Demonstration projects to assess performance of Sentinel for signal identification when exposure is **common** and when exposure is **low**, compared to other data sources

Excerpt from PDUFA VII Commitment Letter (I)(M)(2)(b)(i)(2)

(2) Incorporating feedback from (1), conduct 5 demonstration projects to address gaps in knowledge about performance characteristics of different study designs. FDA will initiate the following demonstration projects which may be modified as needed, before September 30, 2024:

(a) Assess the performance of pregnancy registries versus electronic healthcare database studies to detect a signal when the exposure to medication in pregnancy is relatively common.

(b) Assess the performance of single arm safety studies versus signal identification methods using electronic healthcare data to detect a signal when the exposure to medication in pregnancy is anticipated to be low.

(c) Assess the performance of pregnancy registries versus electronic healthcare database studies to evaluate a signal when the exposure to medication in pregnancy is relatively common.

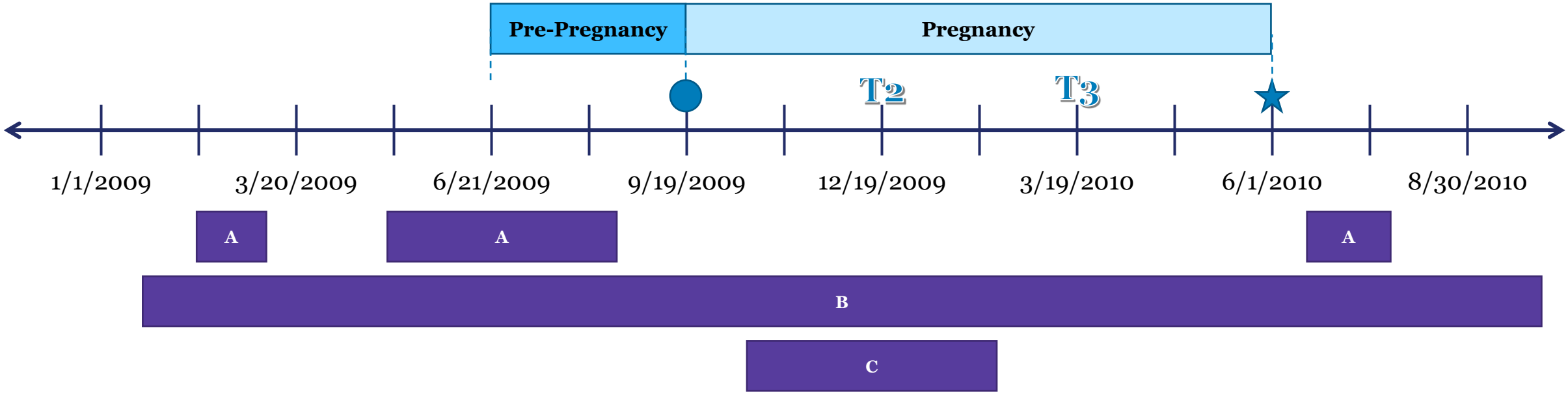
(d) Assess the performance of major congenital malformations (MCM) as a composite outcome in signal detection and evaluation when there is true risk for some but not all specific malformations.

(e) Assess the performance of an algorithm using electronic health record (EHR) and claims-linked healthcare data for a pregnancy-related outcome, or composite of outcomes (e.g., spontaneous abortion, stillbirth, congenital malformations), after use of vaccines in pregnant women. The parameters of the pregnancy-outcome algorithm will be developed to have general usability with therapeutic products.

"Commitment Letter," *PDUFA Reauthorization Performance Procedures Fiscal Years 2023 Through 2027*. Available at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

Identifying Medication Treatment Episodes

- Construct treatment episodes after adjusting for late/early refills
- Count medications that overlap each pregnancy period of interest

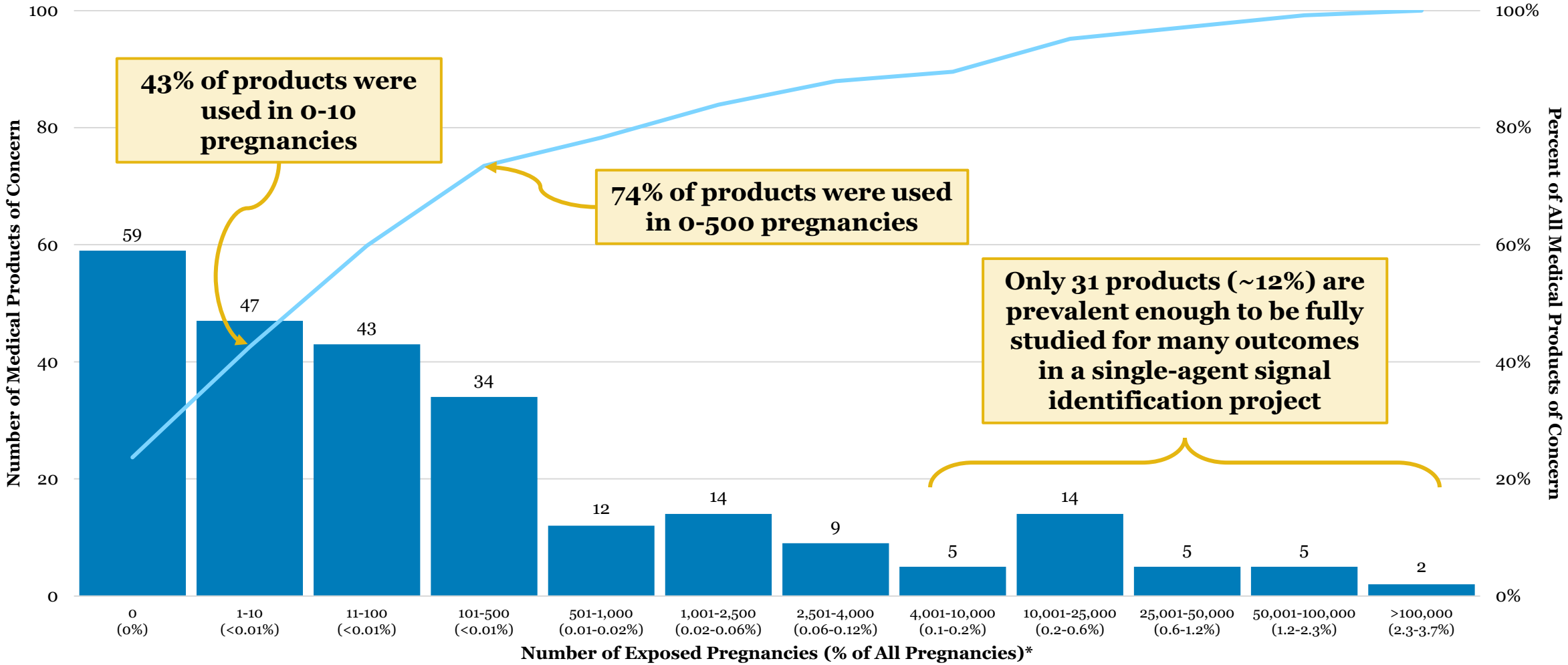


Medications of Concern in Pregnancy

- Drug sponsors can be required or can commit to post-marketing studies, clinical trials, or registries to gather additional information about a product's safety, efficacy, or optimal use
- Products with post-marketing requirements and/or commitments may be common (as in previous slide) or rare
- FDA recently compiled 249 medications with pregnancy-related postmarket requirements, commitments, registries, and/or clinical trials to understand their utilization in pregnancy

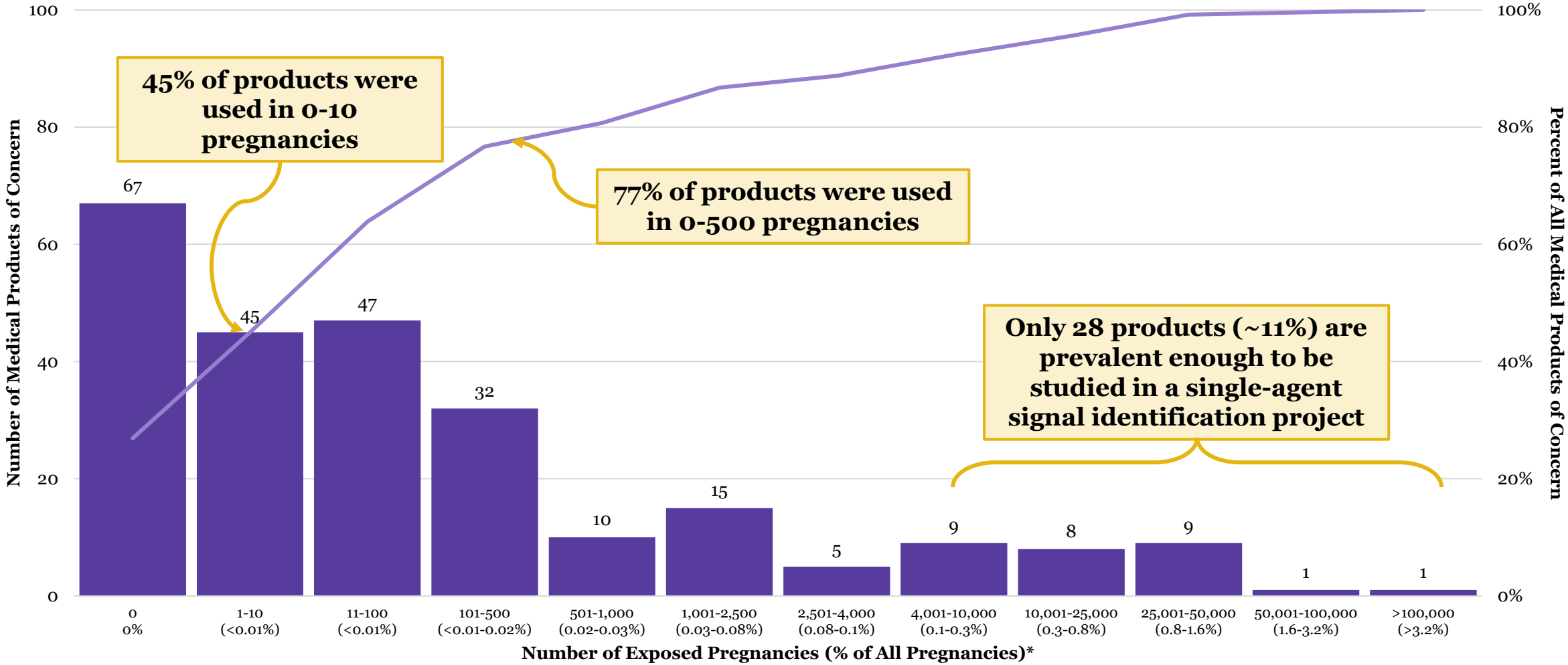
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments; www.clinicaltrials.gov; https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries

Prevalence of Medical Product Use During
All Pregnancies Ending in Live Birth Delivery



* N = 4,340,586 pregnancies ending in live birth delivery 2008-2022

Prevalence of Medical Product Use During All Pregnancies Ending in Live Birth Delivery Linked to an Infant



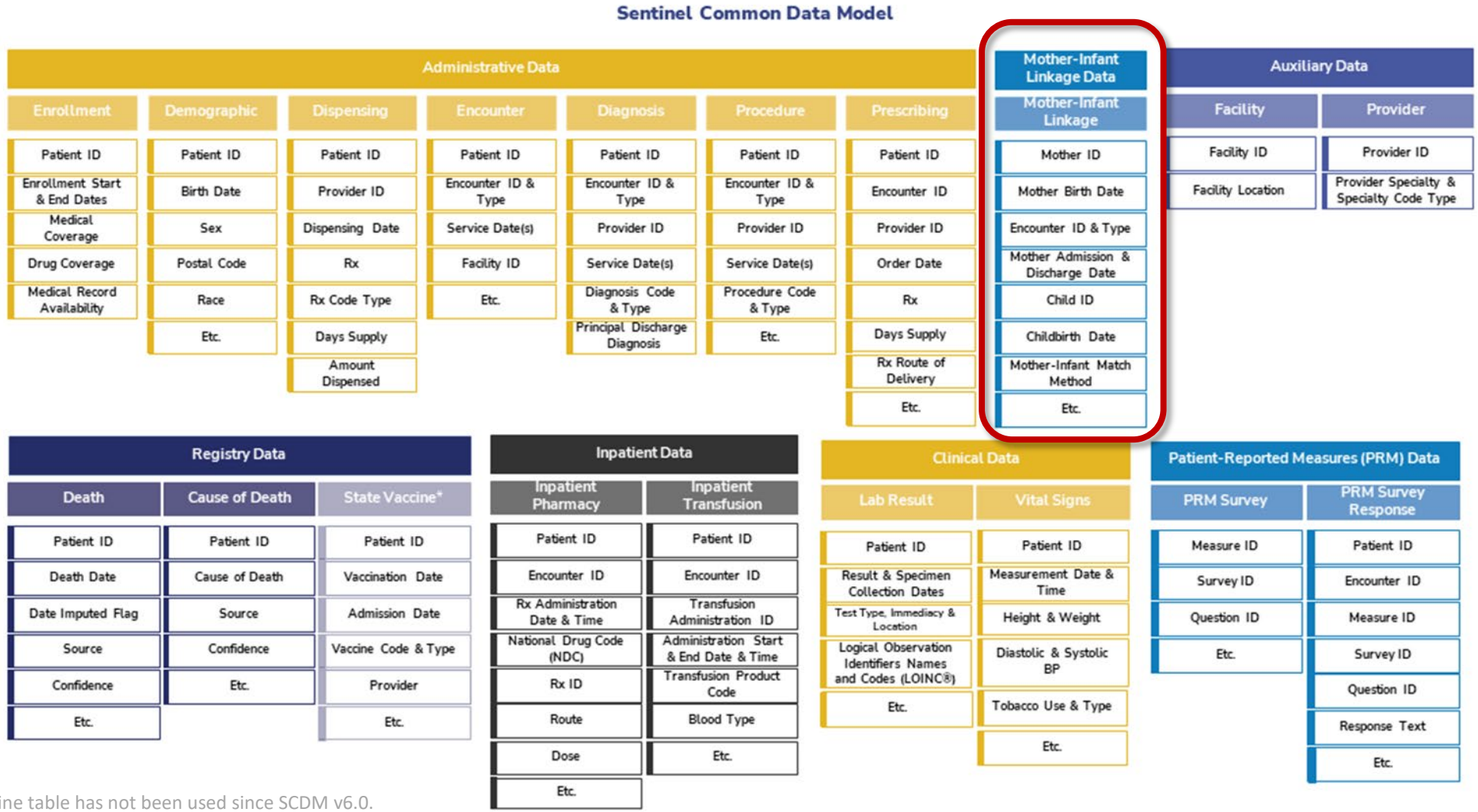
* N = 3,090,337 pregnancies ending in live birth delivery linked to a singleton infant 2008-2022

Adverse Outcomes after Medication Use in Pregnancy

Adverse Outcomes of Interest

- Outcomes of interest in a signal identification analysis will depend on the medication of concern
- Medications of concern may be associated with:
  - Pregnancy outcomes
  - Maternal outcomes during or post-pregnancy
  - Infant outcomes
- Population in which outcomes are identified influences study design choices
  - This presentation will focus on infant outcomes

Mother-Infant Linkage in Sentinel



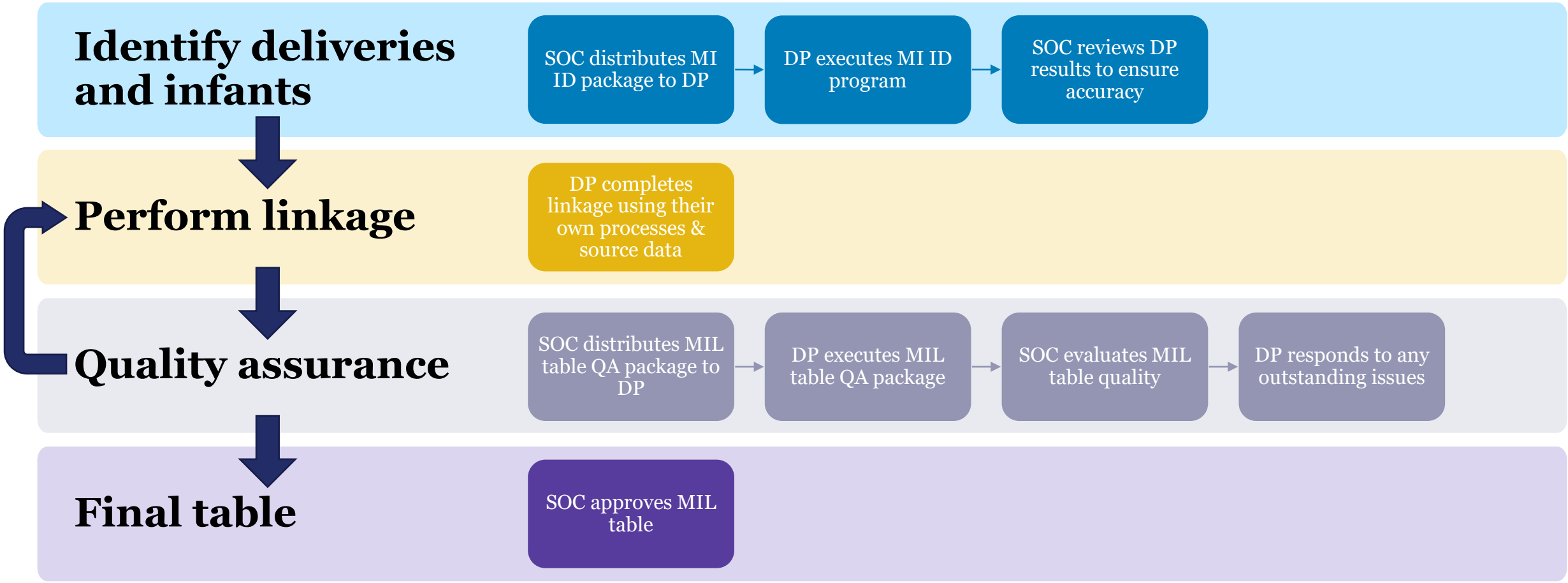
*The State Vaccine table has not been used since SCDM v6.0.
https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Mother-Infant Linkage Table

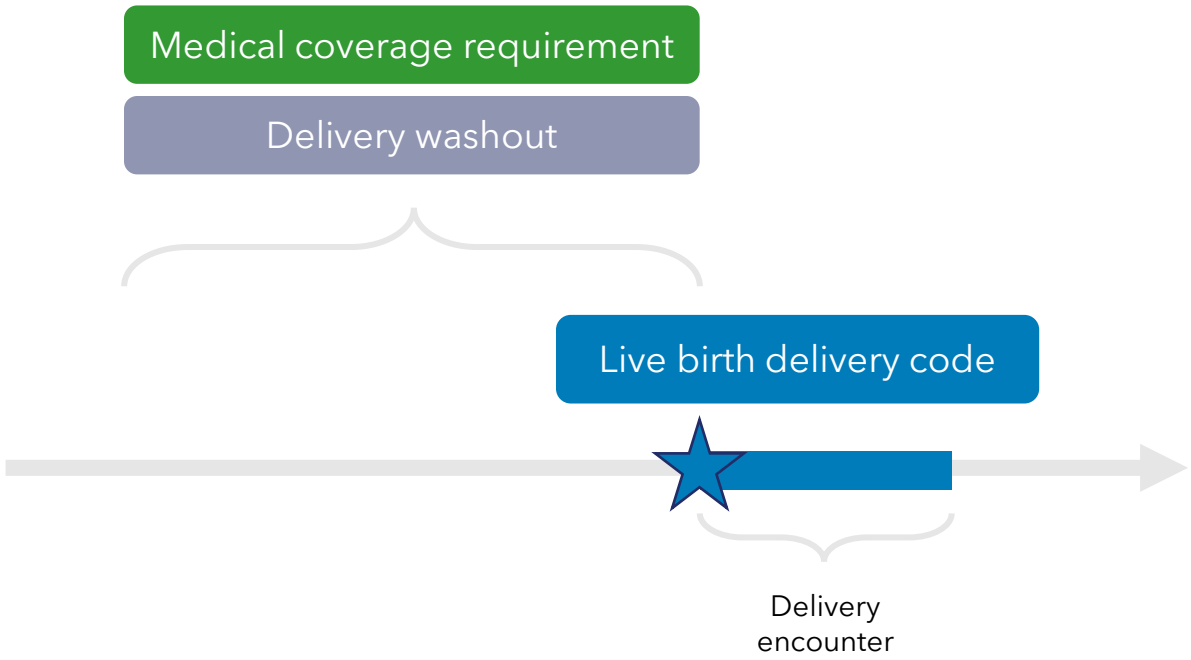
- Mother-Infant Linkage (MIL) Table is used to identify:
  - Deliveries that resulted in a live birth
  - Linked mother-infant pairs
  - Certain infant characteristics

- Analyses using the MIL table to identify deliveries can include all deliveries or restrict to only deliveries where the mother is linked to the infant

Creating the Mother-Infant Linkage Table



Identifying Deliveries

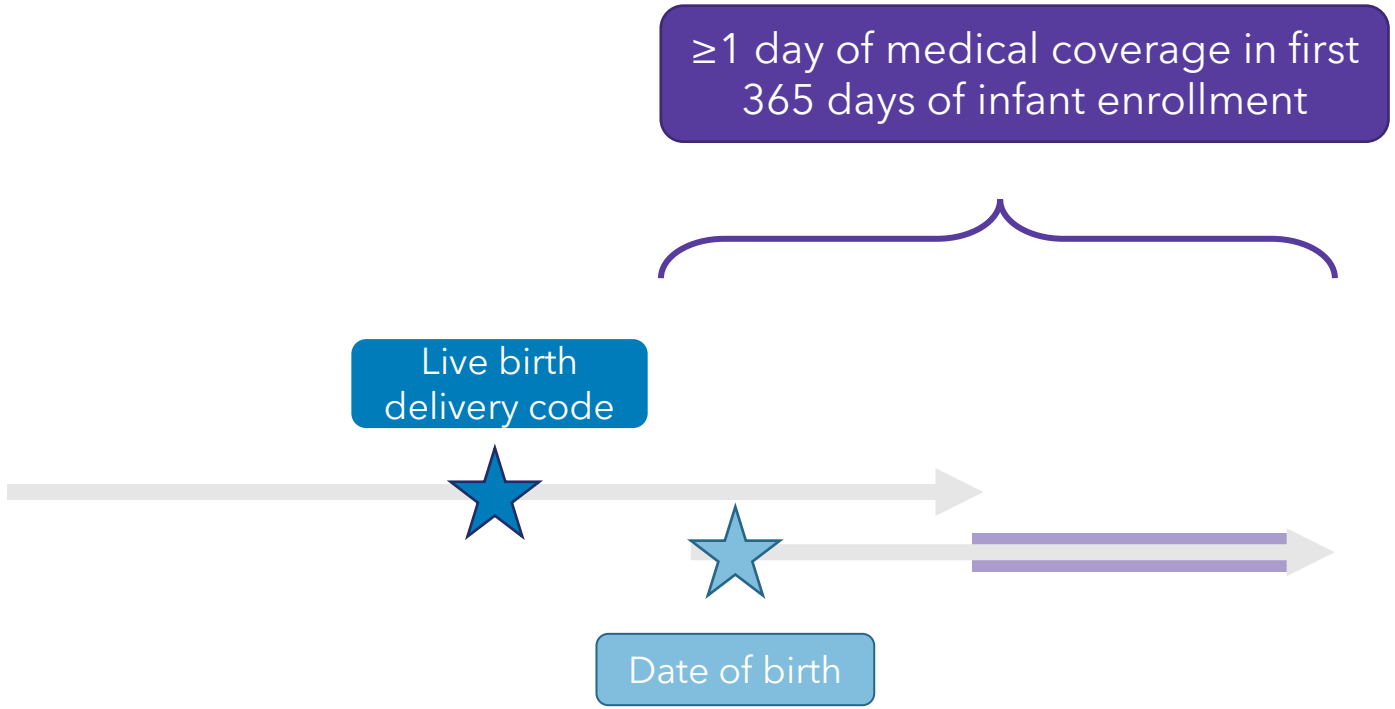


** Also required: female sex, aged 10-54 years at delivery admission*

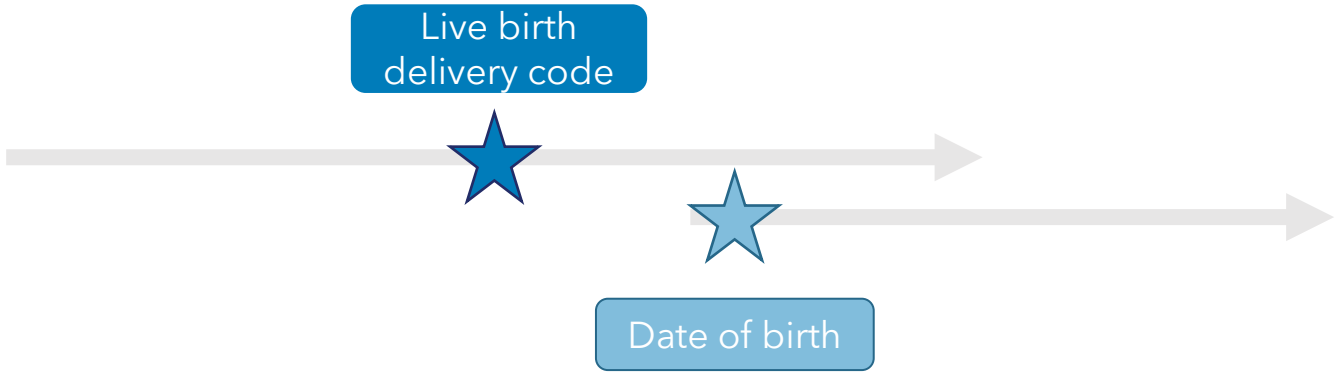
- Information recorded for mothers:
  - Patient ID
  - Birth date
  - Age
  - ID for delivery encounter
  - Delivery encounter type
  - Delivery encounter admission date
  - Delivery encounter discharge date
  - Singleton or multiple delivery
    - Codes from the delivery encounter

Identifying Infants

- Information recorded for infants:
  - Patient ID
  - Birth date
  - Sex
  - Date of first enrollment

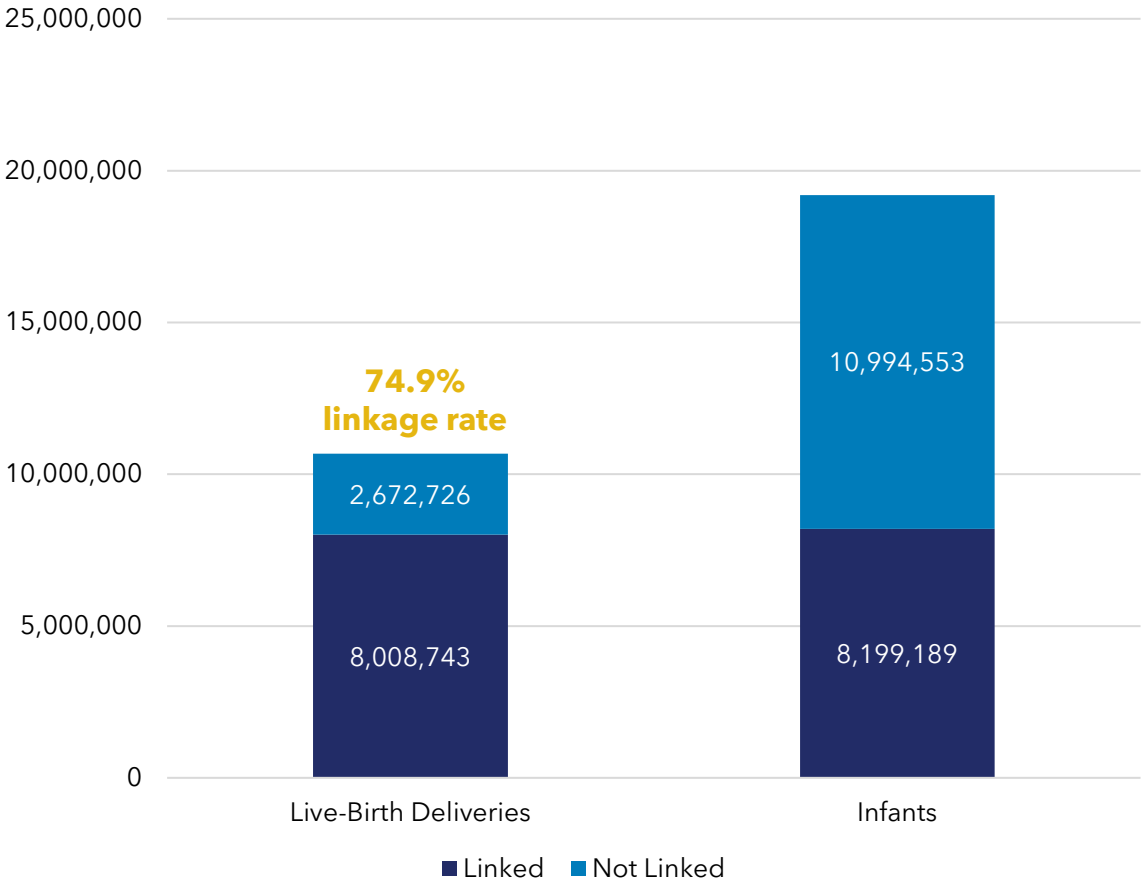


Linking Deliveries and Infants and Ensuring Quality



Successful Match Methods	Unsuccessful Match Reasons
Family subscriber number	No subscriber or family IDs available
Last name and address match	No name or address available
Birth certificate	Neither family IDs nor name/address available
DP-maintained birth registry	No linkage attempted
Other	

Final Mother-Infant Linkage Table



- **Factors impacting linkage rates**
  - Mother/infant on different insurance plans
  - Strict mother enrollment requirement
  - Low tolerance for potentially incorrect linkages

Stats current as of February 6, 2023

Conclusions

- Sentinel's linked mother-infant pairs can be used to identify safety signals in infants for medications used in pregnancy
  - This supplements existing use of registry data for monitoring medication safety in pregnancy
  - Enhancements include adding many states' *Medicaid data* (completed) and expanding algorithm to capture *non-live-birth deliveries* (ongoing)

- FDA (and others with data in the Sentinel Common Data Model) can conduct **inferential analyses** to examine **infant and maternal outcomes** following maternal exposures during pregnancy[1]

[1]Lyons JG, Suarez EA, Fazio-Eynullayeva E, et al. Pharmacoepidemiology and Drug Safety. 2022;n/a(n/a).

Questions or Comments?

First Trimester Exposure to Fluoroquinolones: A Case Study in Signal Identification

2023 Sentinel Public Training

Session 4

Suarez EA, Nguyen M, Zhang D, et al.
Novel methods for pregnancy drug safety surveillance in the FDA Sentinel System.
Pharmacoepidemiology and Drug Safety. 2023;32(2):126-136.

11 April 2023

Material Review

Today, we have covered:

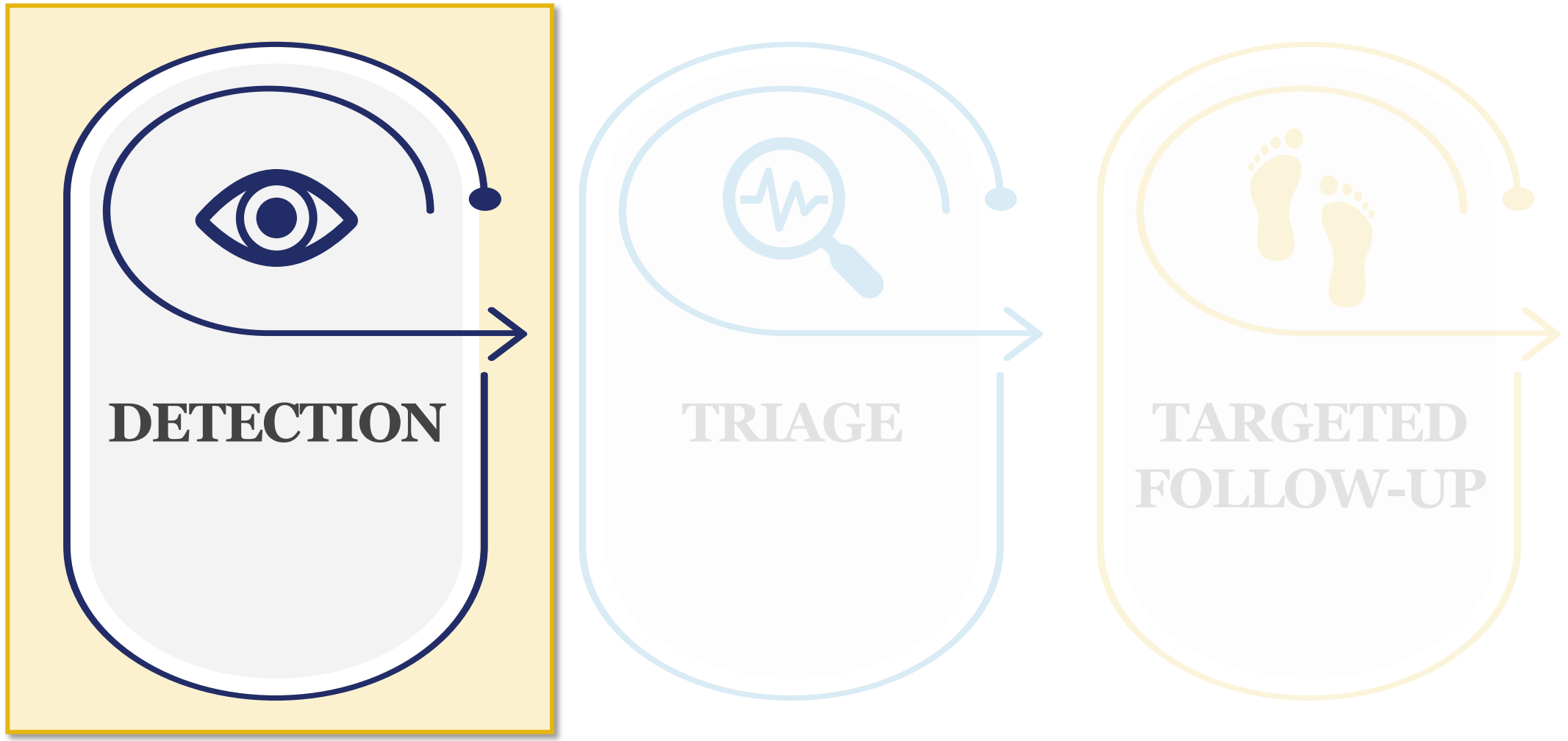
History and purpose of Sentinel	Data and analyses used in Sentinel	Using TreeScan™ for signal identification in Sentinel	Importance of signal identification following medication use in pregnancy

We will now review a case study to demonstrate application in the real-world

Purpose of Case Study

- Demonstrate the **capabilities** of TreeScan™ to identify potential **infant outcomes** following medication use during pregnancy
- Not designed to identify a new safety risk
  - Expected results: no new alerts
- Selected case study: **fluoroquinolone** exposure in first trimester compared to **cephalosporin** exposure in first trimester

Steps in Sentinel Signal Identification



Analytic Decisions for Signal Identification in Sentinel

	Hypothesis Validation (Traditional)	Hypothesis Generation (Signal Identification)		
Choose Study Design	Cohort	Self-Controlled Risk Interval	Cohort	
Identify Study Population	Specify study period, enrollment requirements, new use requirements, and inclusion/exclusion criteria for population of interest			
Identify Outcome(s)	Use validated algorithm to identify first event	Create a hierarchical outcome tree		
Confounding Control	Variety of propensity score adjustment methods	N/A	Fixed-ratio propensity score matching	Propensity score stratification
Statistical Analysis	Point estimate and confidence interval for exposure-outcome association (e.g.,Hazard Ratio)	Unconditional/Conditional Bernoulli model	Unconditional Bernoulli model	Unconditional/Conditional Poisson model

Medications of Interest

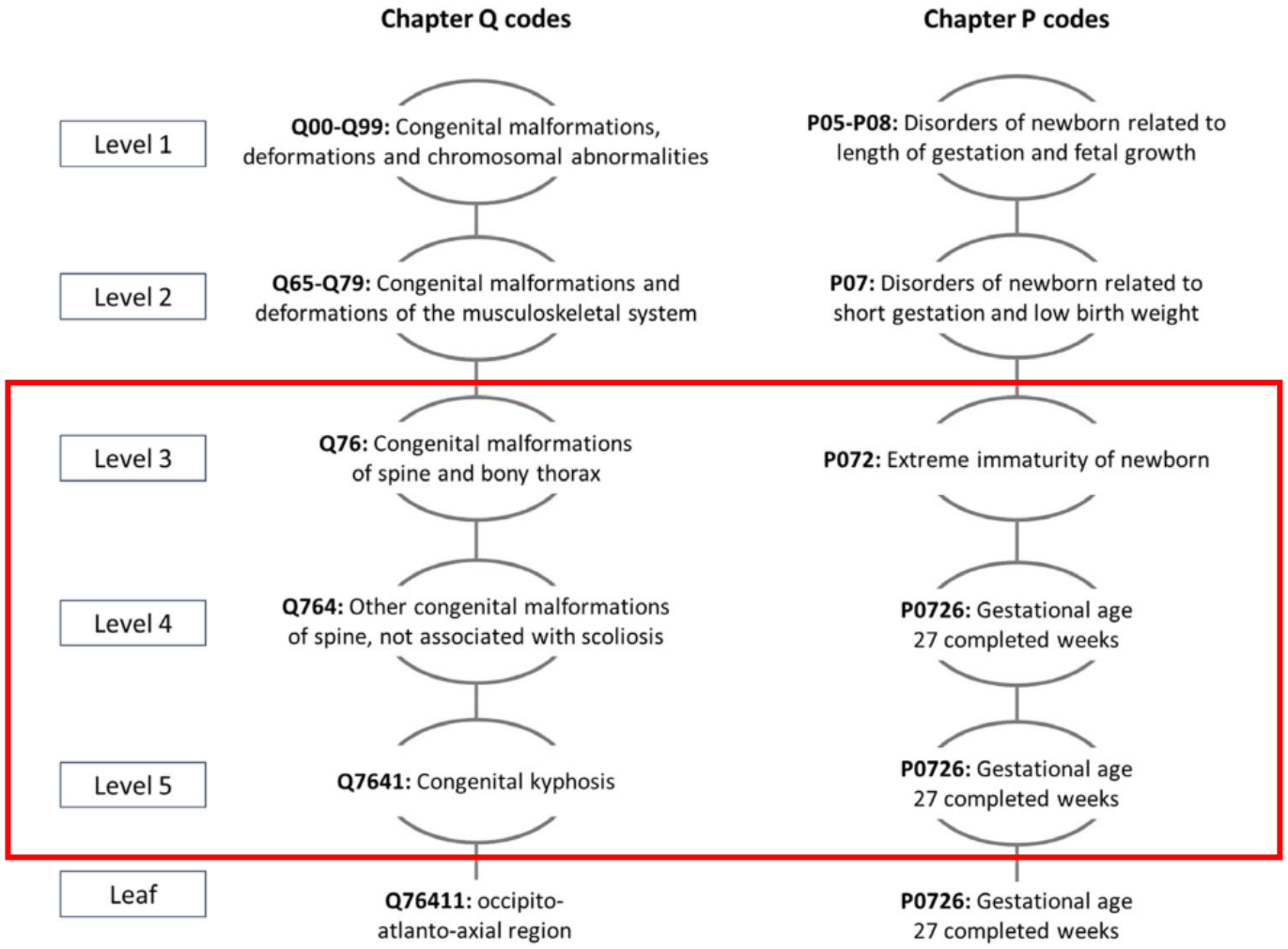
Fluoroquinolones (Exposure)

- Class of antibiotics used to treat a wide variety of infections
- Crosses the placenta
- Based on available data, no known risks following use during pregnancy
  - Available data relatively sparse
- Generally, only recommended in pregnancy for complicated and/or serious infections when no alternatives are appropriate

Cephalosporins (Comparator)

- Class of antibiotics used to treat a wide variety of infections
- Crosses the placenta
- Based on available data, no known risks following use during pregnancy
  - Available data relatively sparse
- Antibiotic class of choice in certain high-risk patients or for those with penicillin allergies

Sample Tree Structure for Infant Outcomes



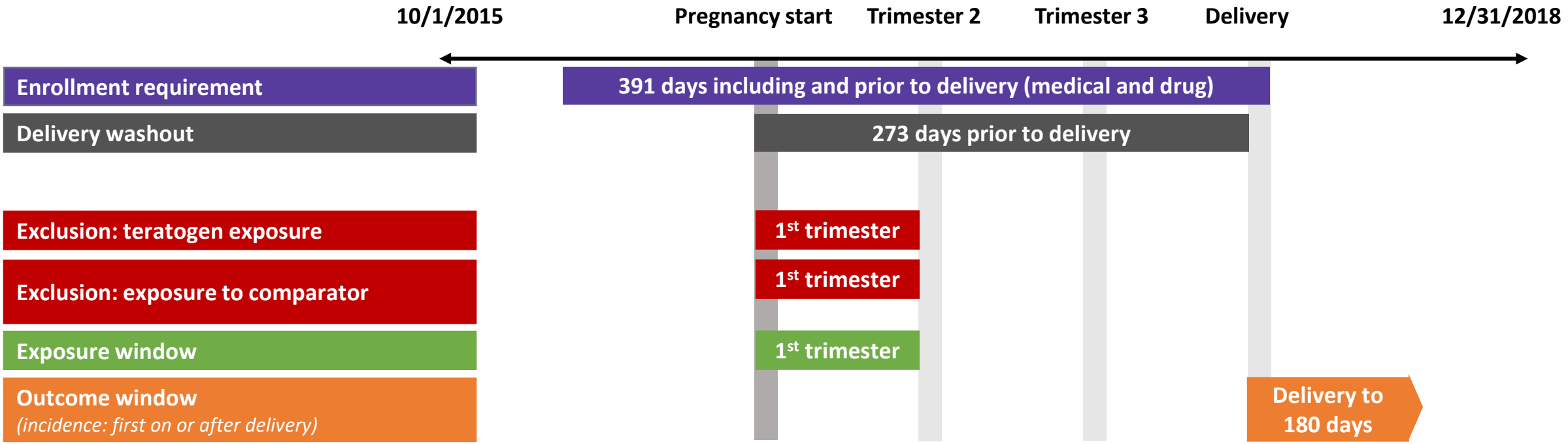
Suarez EA, Nguyen M, Zhang D, et al. Novel methods for pregnancy drug safety surveillance in the FDA Sentinel System. *Pharmacoepidemiology and Drug Safety*. 2023;32(2):126-136. doi:10.1002/pds.5512

Select Confounding Control

- Propensity score matched design
  - Main analysis: 1:1 matched
  - Sensitivity analyses: 1:2 matched, 1:3 matched
- Propensity score stratified design
  - Calculated expected counts within deciles of the propensity score

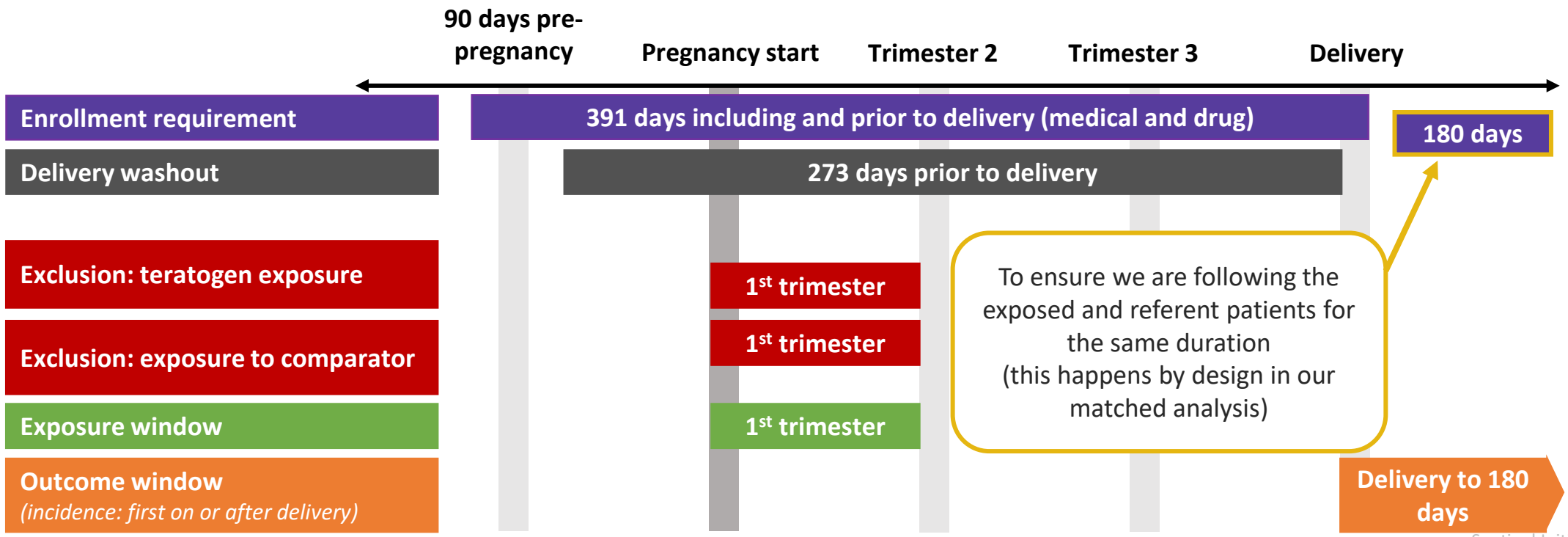
Study Design: Matched Cohort Study

Data Source	Merative MarketScan® Research Database
Eligible population	First live birth delivery linked to an infant between October 1, 2015, and December 31, 2018, aged 10-55 years at delivery



Study Design: Small Change for the Stratified Analysis

Data Source	Merative MarketScan® Research Database
Eligible population	Women with live birth deliveries Oct 2015 - Dec 2018, aged 10-55 years at delivery

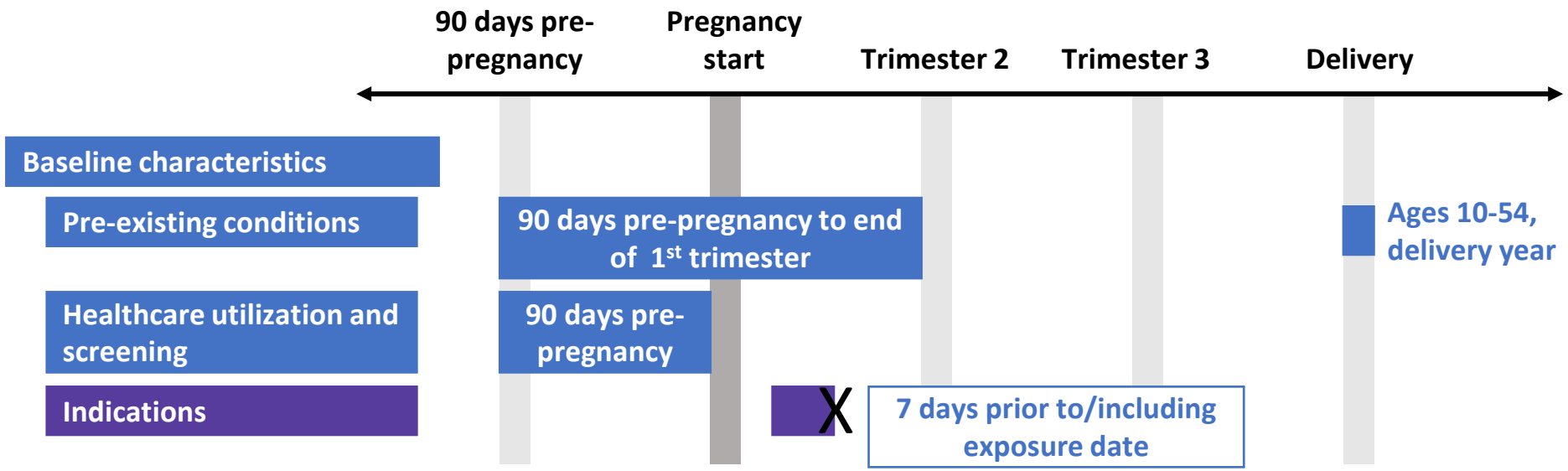


Propensity Score Models

1. **General model:** selected a general list of variables potentially related to increases in risk of adverse pregnancy outcomes that could be reused in future TreeScan™ evaluations
   - Demographics, pre-existing conditions, screening behaviors, health care utilization
2. **General model + indications:** added indications for fluoroquinolones and cephalosporins
   - Urinary tract and kidney infections, lower respiratory tract infections, ear, nose, and throat infections, gastrointestinal infections, and sexually transmitted infections
3. **High-dimensional propensity score:** used a data driven approach to select 200 variables that are associated with the exposure

Wang SV, Maro JC, Gagne JJ, Patorno E, Kattinakere S, Stojanovic D, et al. A General Propensity Score for Signal Identification Using Tree-Based Scan Statistics. Am J Epidemiol 2021 Feb 22

Assessment of Potential Confounders



Select Statistical Analysis

- Propensity score matched design
  - TreeScan™ Bernoulli model
- Propensity score stratified design
  - TreeScan™ Poisson model
- Alert threshold $p \leq 0.05$

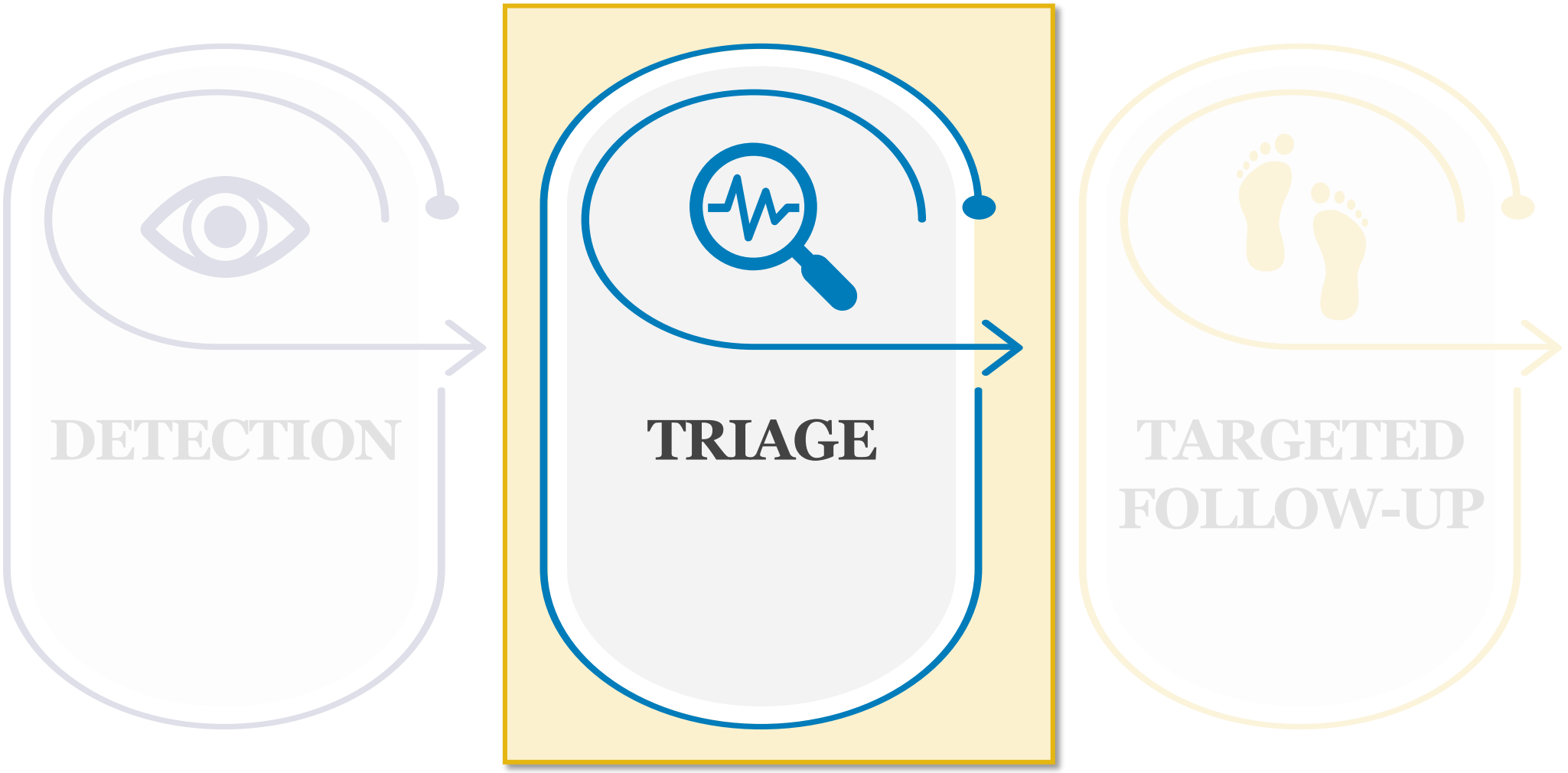
Results Using Propensity Score Matching and the Bernoulli Model

	Fluoroquinolones	Cephalosporins	
Analysis	**N**	**N**	**TreeScan™ Results**
TOTAL	1791	8739	
1:1 matched, general model	1791	1791	Q31grp (congenital malformations of larynx) was significant ($p<0.05$)
1:1 matched, general + indications model	1790	1790	No significant alerts
1:1 matched, HDPS model	1732	1732	No significant alerts
1:2 matched, general + indications model	1787	3574	No significant alerts
1:3 matched, general + indications model	1684	5052	No significant alerts

Results Using Propensity Score Stratification and Poisson Model

Analysis	Fluoroquinolones N	Cephalosporins N	TreeScan™ Results
Full cohort	1,509	7,165	
Stratified Poisson, general model	1,508	7,160	Q513grp (bicornate uterus) was significant (p=0.05)
Stratified Poisson, general + indications	1,507	7,155	Q513grp (bicornate uterus) was significant (p<0.05)
Stratified Poisson, HDPS	1,500	7,089	Q513grp (bicornate uterus) was significant (p<0.05)

Steps in Sentinel Signal Identification



Triaging the Observed Alert: is it Worth Investigating?

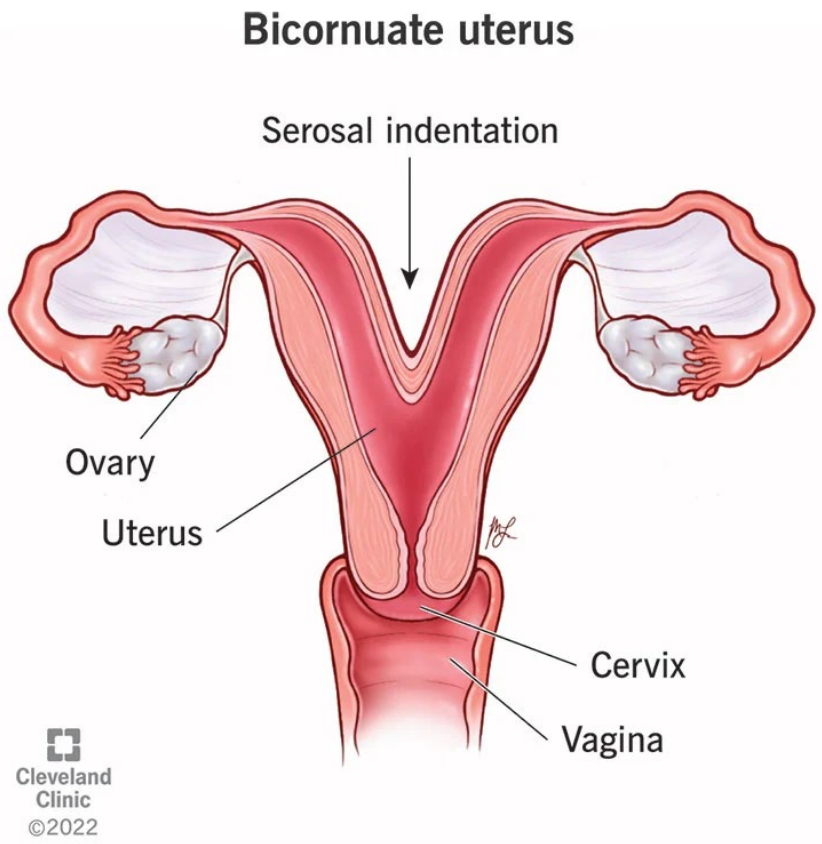
Observed vs expected cases in 1:1 matched analysis:

Code	Description	Total cases	Fluoroquinolones	Expected cases
Q31	Congenital malformations of larynx	34	27	17

- The observed alert was likely due to uncontrolled confounding, given that we did not observe it in analyses with theoretically better confounding control
- Conclusion: no need for additional follow-up

Triaging the Observed Alert: is it Worth Investigating?

- Q51.3: Bicornate uterus
  - A rare congenital malformation that is not generally detected until pregnancy
- Observed 6 cases in exposed group and expected <1 case, leading to a large relative risk
- Determined cases were with the mother's record
- Conclusion: no need for additional follow-up



Why Did We See Different Results by Method?

- The Poisson model has greater power than the Bernoulli model, therefore alerts observed with Poisson may not be able to be observed using Bernoulli
- Different propensity score methods result in slight changes to the referent population, resulting in different expected counts
  - The alert observed in the 1:1 matched analysis using the general propensity score model likely resulted in very tight control using a mis-specified model
  - Adding indications or using hdPS resulted in no alerts in the matched analysis

Summary of Study Results

- We did not observe evidence that fluoroquinolone use in first trimester increases risk of adverse infant outcomes when compared to cephalosporin use in first trimester
- Two alerts were observed that could be explained without targeted follow-up studies
- At 1791 fluoroquinolone exposed mother-infant pairs, we were underpowered to see smaller increases in risk
- Use of propensity score stratification did not result in many spurious alerts
  - In this active comparator setting, a slight decrease in confounding control is likely worth the increase in power attained by using Poisson vs Bernoulli

Conclusions

- TreeScan™ can be used for surveillance of potential adverse infant events following maternal medication exposure during pregnancy
- If <4,000 exposed pregnancies are available for study, the analysis may be underpowered to detect the rarest of congenital malformations
- Using TreeScan™ in Sentinel offers notable advantages:
  - Utilize large sample sizes available in administrative data
  - Leverage existing methods to identify pregnancies and mother-infant pairs
  - Scan for all types of malformations individually and in clinically relevant groupings

Questions or Comments?

Acknowledgments

Public Training Team

- Sentinel Operations Center
  - Judith Maro
  - Joy Kolonoski
  - Meighan Rogers-Driscoll
  - Carolyn Purington
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  - Monica Munoz
  - Jamila Mwidau
  - Yueqin Zhao

TreeScan™ in Pregnancy Query Team

- Elizabeth Suarez

Thank you to all FDA and Sentinel Operations Center colleagues and Data Partners who were involved in the development of the methods and data covered in this presentation.

Post-Training Poll

- All participants should see a poll appear on their personal screens
- Your answers help us improve our annual trainings; for each question, please select from the provided responses
- All responses are anonymous

Questions

1. Overall, how would you rate today's training?
2. Please describe the overall level of technical detail in the first session.
3. Please describe the overall level of technical detail in the second session.
4. Please describe the overall level of technical detail in the third session.
5. Please describe the overall level of technical detail in the fourth session.
6. Are you likely to attend this training next year?

Leveraging the Sentinel System for Signal Identification Among Infants Following Maternal Medication Use During Pregnancy

Closing Remarks

2023 Sentinel Public Training

April 11, 2023

Sentinel Operations Center | Harvard Pilgrim Health Care Institute

KEY TAKEAWAYS

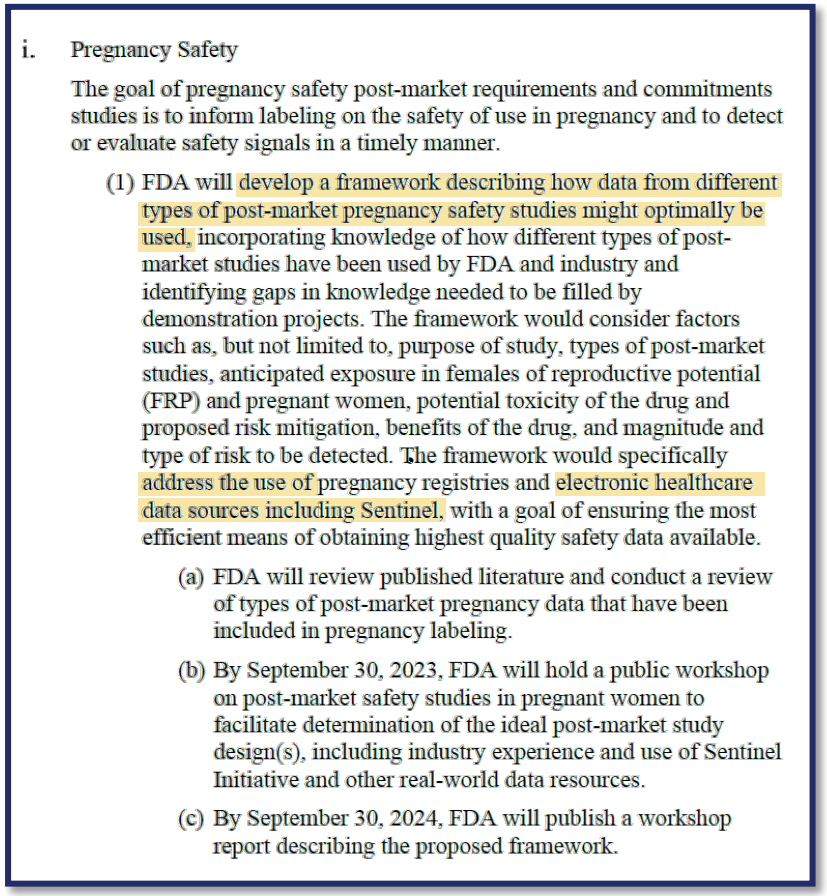
- FDA is committed to enhancing and modernizing their drug safety system
- The Sentinel System is one component of FDA's drug safety program well-suited to monitor medication use in pregnancy
- Enhancements in Sentinel have led to the ability to actively detect safety signals in large electronic healthcare databases

The Sentinel System signal identification for medication use in pregnancy enhances FDA's drug safety program.

Future exploration and maturation of Sentinel's signal identification capabilities are part of FDA's PDUFA VII commitments.

Upcoming Workshop: Pregnancy Safety

- **Pregnancy Safety Public Workshop**
  - Hosted by Duke-Margolis
    <u>September 19-20, 2023</u>
  - Aim: facilitate determination of ideal post-market study design(s), including industry experience & use of Sentinel System and other real-world data resources



i. Pregnancy Safety

The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner.

(1) FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of post-market studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects. The framework would consider factors such as, but not limited to, purpose of study, types of post-market studies, anticipated exposure in females of reproductive potential (FRP) and pregnant women, potential toxicity of the drug and proposed risk mitigation, benefits of the drug, and magnitude and type of risk to be detected. The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.

(a) FDA will review published literature and conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling.

(b) By September 30, 2023, FDA will hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s), including industry experience and use of Sentinel Initiative and other real-world data resources.

(c) By September 30, 2024, FDA will publish a workshop report describing the proposed framework.

Center for Drug Evaluation and Research. 2022. *PDUFA VII: Fiscal Years 2023 – 2027.* Silver Spring, MD: Food and Drug Administration