Sentinel Distributed Database: Use of Real-World Data for Surveillance of Medications in Pregnancy

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Disclaimer

The views expressed are my own and are not necessarily those of the U.S. Food and Drug Administration

I have no conflicts of interest to disclose

Overview

- Background and database statistics
- Pregnancy activities
- Sentinel's PDUFA VII pregnancy commitments

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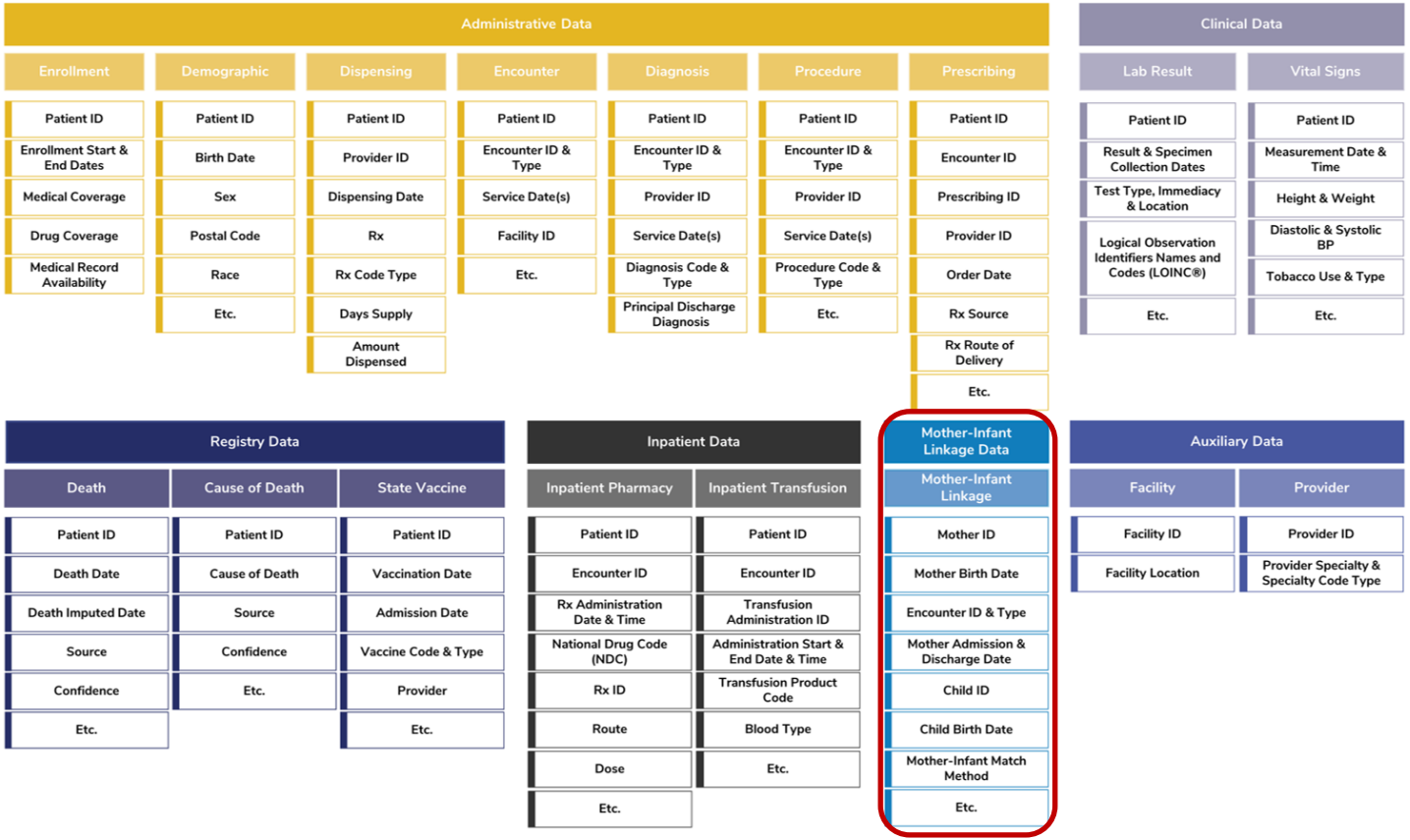
Background

- FDA's medical product active safety surveillance system
  - To assess the use and safety of regulated medical products and to inform FDA's understanding of how real-world data can generate real-world evidence for medical product effectiveness
  - To develop data, informatics, and methodologic capabilities to support these activities
  - Created in response to a U.S. Congressional mandate
- Key components:
  - Electronic healthcare data
  - Common Data Model
  - Distributed network of Data Partners
  - Pre-defined, parameterized, reusable routine querying tools
  - Sophisticated quality assurance process

https://sentinelinitiative.org

Sentinel Common Data Model



Sentinel's Data Partners

1. Aetna, a CVS Health company
2. Duke University School of Medicine: Department of Population Health Sciences (Medicare Fee-for-Service data)
3. HealthCore/Anthem
4. HealthPartners Institute
5. Humana, Inc.
6. Kaiser Permanente Colorado Institute for Health Research
7. Kaiser Permanente Hawai'i, Center for Integrated Health Care Research
8. Kaiser Foundation Health Plan of the Mid-Atlantic States, Inc.
9. Kaiser Permanente Northwest Center for Health Research
10. Kaiser Permanente Washington Health Research Institute
11. Marshfield Clinic Research Institute
12. Optum (OptumInsight Life Sciences Inc. and Optum Labs®)
13. Vanderbilt University Medical Center, Department of Health Policy (Tennessee Medicaid data)

* As of April 2022

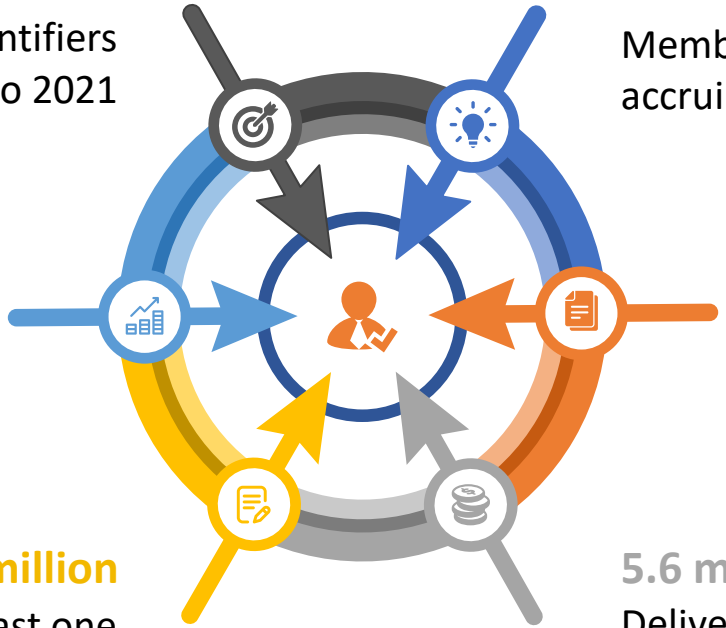
https://www.sentinelinitiative.org/about/who-involved#sentinel-data-partners

Key Database Statistics

360.2 million
Unique patient identifiers from 2000 to 2021

64.3 million
Members currently accruing new data

14.3 billion
Unique medical encounters



15.5 billion
Pharmacy dispensings

40.9 million
Members with at least one laboratory test result

5.6 million
Deliveries with a mother-infant linkage

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

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Mother-Infant Linkage

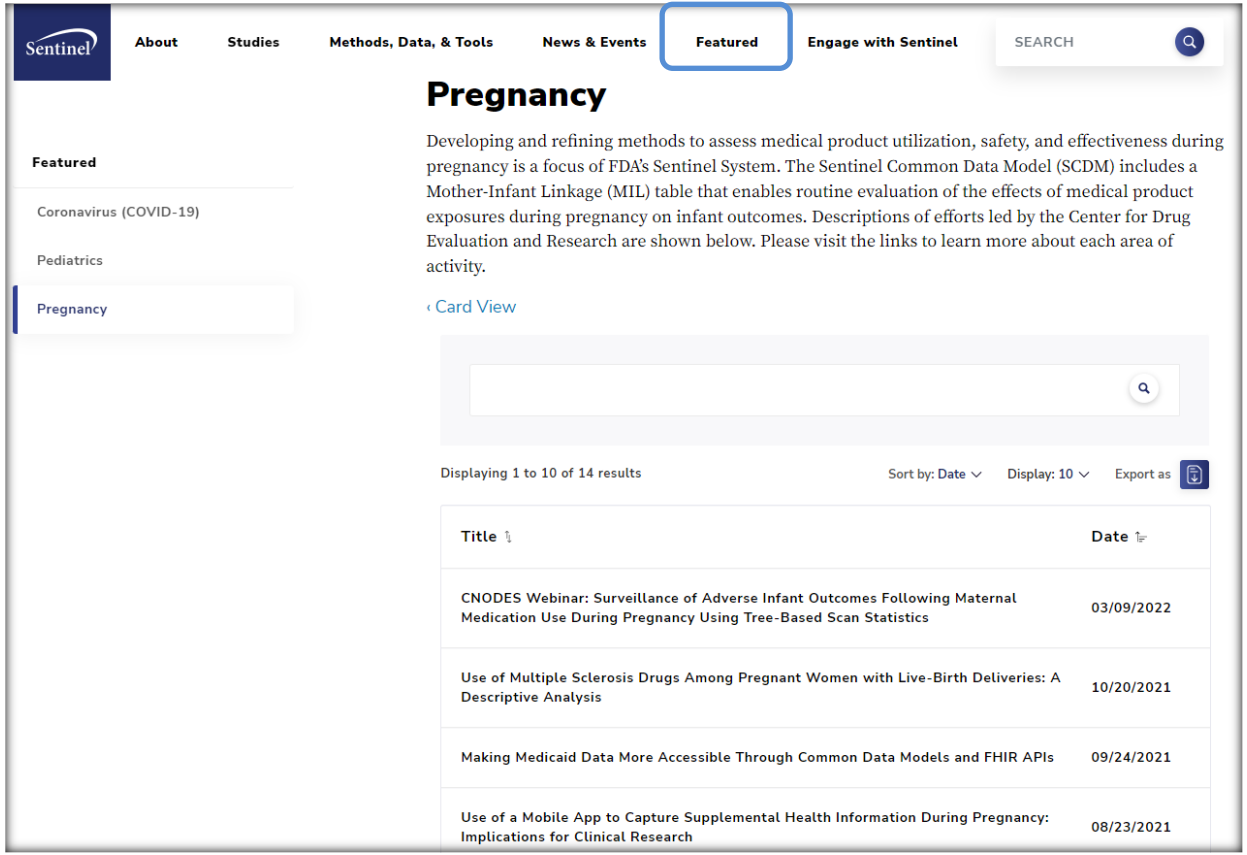
- Established in 2018 and routinely refreshed (four data partners)
- 79.1% linkage rate
- Mostly deterministic linkage approach
- Used to identify:
  - Deliveries that resulted in a live birth
  - Mother-infant pairs
  - Certain infant characteristics
- Pregnancies can be selected from linked mother-infant pairs
- All deliveries or only linked deliveries

https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model/mother-infant-linkage-table

Pregnancy-related Sentinel Analyses

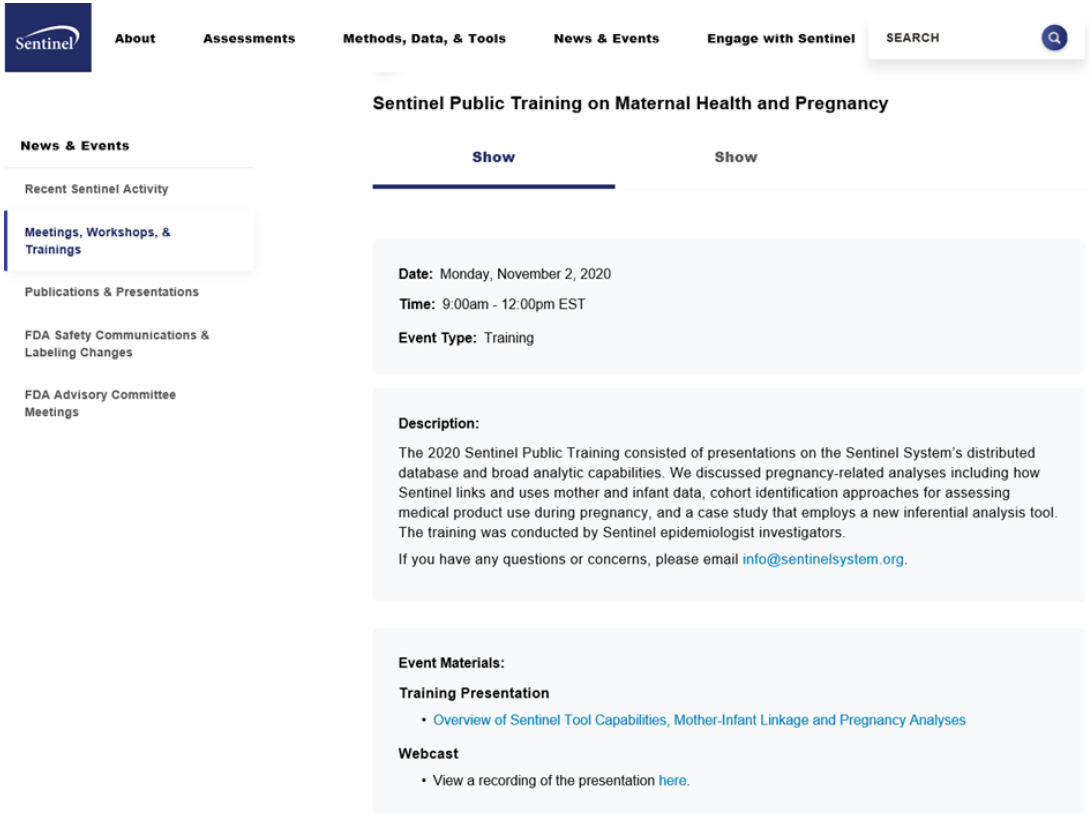
Descriptive Analyses	Medical product use among pregnancies with live-birth deliveries
Inferential Analyses	Association between exposure to a certain medical product in pregnancy and a prespecified outcome of interest among infants
Signal Identification	Identification of potential adverse events related to the use of medical products in pregnancy without prespecifying an outcome of interest

Pregnancy Activities in Sentinel



https://sentinelinitiative.org/featured-topics/pregnancy#

Pregnancy Activities in Sentinel



https://sentinelinitiative.org/news-events/meetings-workshops-trainings/sentinel-public-training-maternal-health-and-pregnancy

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Sentinel's PDUFA VII Commitments

M. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

FDA will continue to use user fees to enhance the drug safety system, including adopting new scientific approaches, improving the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events, modernizing REMS assessments, and coordinating regulatory activity in the pre-market and post-market settings. Enhancements to the drug safety system will improve public health by increasing patient protection while continuing to en access to needed medical products.

User fees will provide support for 1) modernization and improvement of REMS assessm 2) optimization of the Sentinel Initiative through a) maintenance of Sentinel Initiative capabilities and continued integration into FDA drug safety activities and b) enhanceme analytic capabilities of the Sentinel Initiative to address questions of product safety and the understanding of how real-world evidence can be used for studying effectiveness.

1. **Modernization and Improvement of REMS Assessments**

   FDA will use user fee funds to modernize and improve REMS assessments by incorporating REMS assessment planning into the design of REMS, clarifyi it

PDUFA VII: FY 2023-2027

2. **Optimization of the Sentinel Initiative**

The user fee funds initially provided in PDUFA VI to expand the Sentinel program will continue to systematically implement and integrate Sentinel and BEST (Biologics Effectiveness and Safety) Systems in FDA drug safety activities by sustaining the high quality and large quantity of data available, allowing continued application of advanced methods for determining when and how those data are utilized, and ensuring comprehensive training of review staff on the use of Sentinel and BEST. These capabilities will support the use of the Sentinel Initiative for regulatory decision making to address questions of product safety and advance our understanding of how real-world evidence can be used for studying effectiveness.

a. Maintenance of the Sentinel Initiative Capabilities and Continued Integration into FDA Drug Safety Activities

   FDA will use user fee funds to maintain the quality and quantity of data available through the Sentinel Initiative (Sentinel and BEST), to maintain the processes and tools for determining when and how those data are utilized, and to support comprehensive training of review staff on the use of Sentinel.

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https://www.fda.gov/media/151712/download

Sentinel's PDUFA VII Commitments

M. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

1. Modernization and Improvement of REMS Assessments
2. Optimization of the Sentinel Initiative
   a. Maintenance of the Sentinel Initiative Capabilities and Continued Integration into FDA Drug Safety Activities
   b. Enhancement of the Analytic Capabilities of the Sentinel Initiative to Address Questions of Product Safety and Advance the Understanding of How Real-World Evidence Can Be Used for Studying Effectiveness
      i. Pregnancy Safety
      ii. Use of Real-World Evidence – Negative Controls

Sentinel's PDUFA VII Commitments Pregnancy Safety

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.

- By Sep 30, 2023:
  - Hold a public workshop on post-marketing safety studies in pregnant women
- By Sep 30, 2024:
  - Publish a workshop report describing the proposed framework

Sentinel's PDUFA VII Commitments Pregnancy Safety

(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:

(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.

- By Sep 30, 2027:
  - Update the proposed framework and develop a guidance or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs

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