PRGLAC Taskforce

Experience from FDA CDER's Sentinel System:

Using electronic health record data to link mother and infant records

Nov 17, 2023

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Office of Surveillance & Epidemiology
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

Recommendation 12

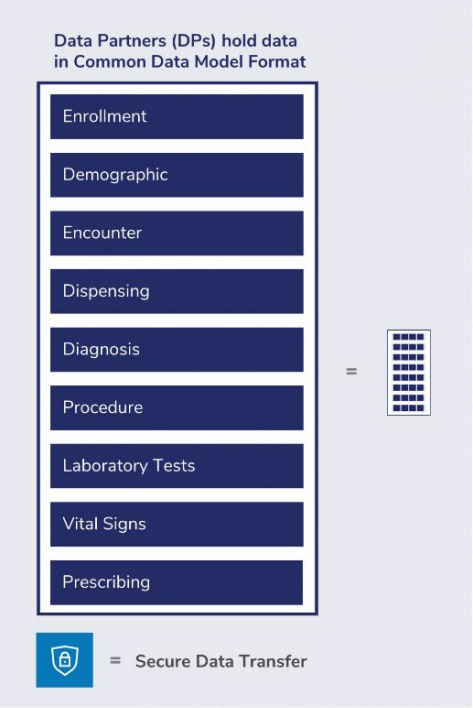
12A	Design health record systems to link mother and infant records.
12B	Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries.
12C	Use novel data resources. a. Support large post-marketing observational studies to evaluate the safety and effectiveness of medication classes during pregnancy and lactation b. Support studies across multiple drugs using the same infrastructure to conserve resources
12D	Use innovative methods of data analytics.
12E	Require common data elements (CDEs) to facilitate collaboration and use.

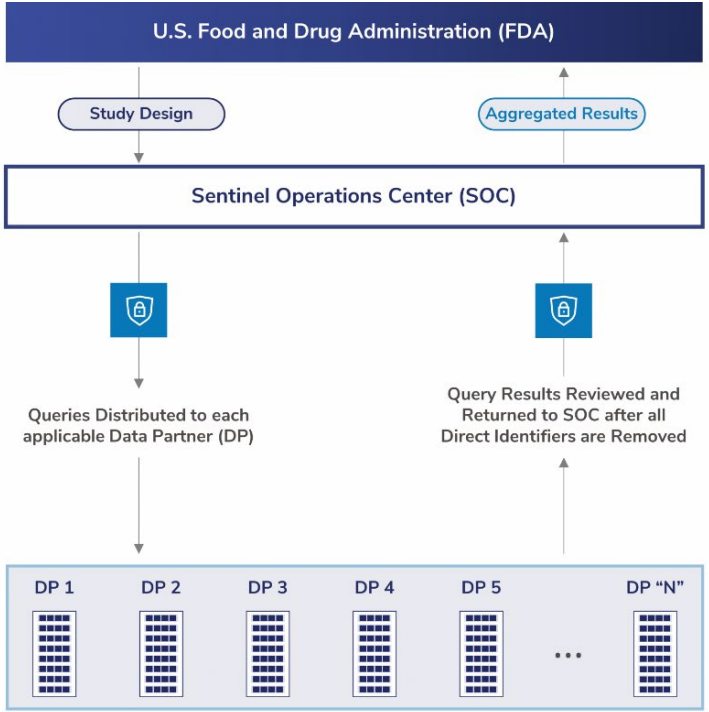
Key Elements of Sentinel's Active Risk Identification and Analysis (ARIA) System

1. Electronic healthcare data (typically insurance claims)
2. Common data model
3. Distributed network of Data Partners
4. Pre-defined, parameterized, reusable routine querying tools
5. Sophisticated quality assurance process

Sentinel's Distributed Database

- Data Partners maintain physical and operational control over their data
- Data partners execute standardized queries against their own data that is formatted into Sentinel's common data model and they return results to the Sentinel Operations Center
- Preserves patient privacy and institutional proprietary interests





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

Mother-Infant Linkage Table

Details | **Additional Information**

Date Posted: Thursday, January 31, 2019

Status: COMPLETE

Description:

The Mother-Infant Linkage (MIL) Table was added to the Sentinel Common Data Model (SCDM in October 2018.

This enhancement was added to enable routine evaluation of medical product exposures durin pregnancy on outcomes in infants.

The table contains one record per MPatID, CPatID, and ADate. This table is created following identification of mothers (via evidence of live delivery by women aged 10-54 inclusive) and infants (via date of birth) in the Sentinel Distributed Database (SDD). The file may include:

1. Live birth deliveries (with MPatID and ADate) that were linked to a child (CPatID);
2. Live birth deliveries (with MPatID and ADate) that were not linked to a child (CPatID, CBirth_Da Sex, and CEnr_Start will have missing values); and
3. Children (with CPatID) who were not linked to a mother (MPatID, MBirth_Date, Age, EncounterI EncType, ADate, DDate, Birth_Type, and Birth_Type_Primes will have missing values).

To facilitate linkage, Sentinel Operations Center has developed a reusable program package t identify mothers and infants in the SDD. The Quality Assurance program evaluates whether th data in the table conforms to SCDM specifications, and identifies anomalies that require furthe investigation or explanation (e.g., relatively high multiple-birth rate compared to national average).

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

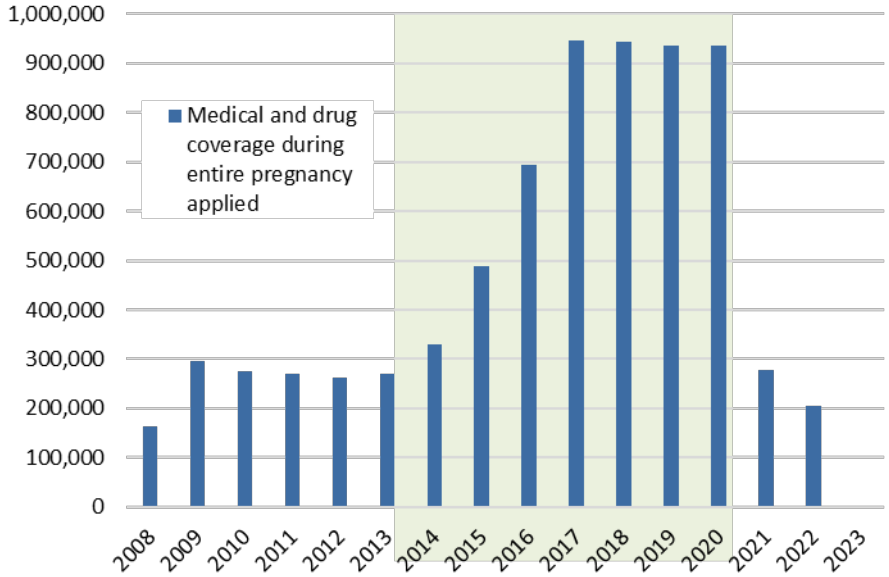
Deliverable(s) (6)

- Sentinel Common Data Model 7.0.0
- Mother-Infant Linkage Quality Assurance SAS Package
- Mother-Infant Linkage Quality Assurance Technical Specifications
- Mother-Infant Identification SAS Package
- Mother-Infant Identification Technical Programming Specifications
- Mother-Infant Linkage Frequently Asked Questions and Appendices

Live Birth Deliveries Available in Sentinel

There are currently 10.8 million linked deliveries, Jan 2008 –Jan 2023

Number of Pregnancies Ending in Live Birth Deliveries Identified in the Sentinel Distributed Database,
January 1, 2008 to January 31, 2023



This slide is an updated version of a slide previously shown here: https://www.sentinelinitiative.org/news-events/meetings-workshops-trainings/2023-sentinel-public-training-innovation-day-april-11-12. It is from a query executed in August 2023 to include Medicaid data from years 2014-2020

Public Training on Signal Identification Studies in Pregnancy

https://www.youtube.com/watch?v=A35DMjF4wms

12C	Use novel data resources. a. Support large post-marketing observational studies to evaluate the safety ~~and effectiveness~~ of medication classes during pregnancy ~~and lactation~~ b. Support studies across multiple drugs using the same infrastructure to conserve resources

Assessment of Heart Failure in Pregnancy to Support Pre-Market Review of Vericiguat

Background

U.S. FOOD & DRUG ADMINISTRATION

Vericiguat–Under Review

Indicated for heart failure (HF)

Embryo-fetal malformations in animal studies

Should a Risk Evaluation and Mitigation Strategy (REMS) program be required for vericiguat?

Analysis and Findings

Sentinel Distributed Database

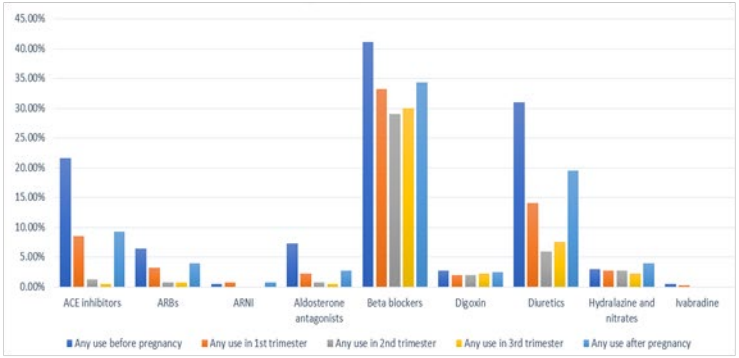
- Estimated prevalence of HF among reproductive age women
- Characterized medication use among pregnancies with HF

Jan. 2010 – Feb. 2020

Jan. 2010 – Mar. 2021

HF rare (0.5%) among women of reproductive age

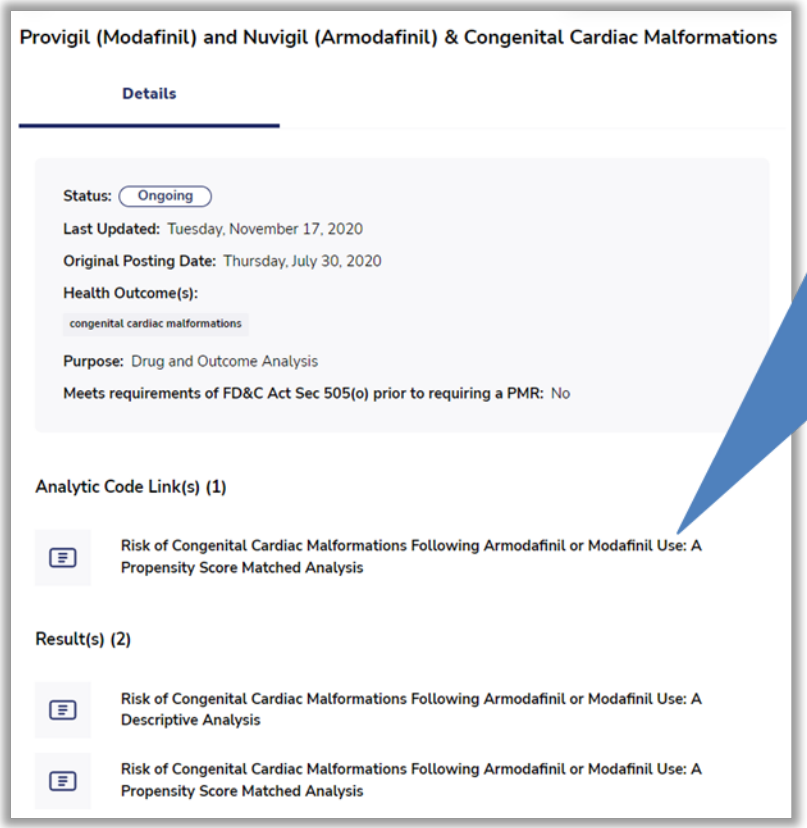
Potential embryo-toxic HF medication use during pregnancy was rare



Regulatory Recommendation: This information contributed to the FDA's determination that labeling would provide sufficient information to ensure the benefits of vericiguat outweigh its risks.

https://www.sentinelinitiative.org/studies/drugs/women-heart-failure

Publicly-Available Resources



https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/risk-congenital-cardiac-malformations-following-armodafinil

Six Years of the US Food and Drug Administration's Postmarket Active Risk Identification and Analysis System in the Sentinel Initiative: Implications for Real World Evidence Generation

Judith C. Maro, Michael D. Nguyen, Joy Kolonoski, Ryan Schoeplein, Ting-Ying Huang, Sarah K. Dutcher, Gerald J. Dal Pan, and Robert Ball. Clin Pharmacol Ther, 2023 Oct;114(4):815-824. doi: 10.1002/cpt.2979. Epub 2023 Jul 18

Table 3 Distribution of safety concerns insufficient for assessment in ARIA attributed to capture of health outcome, by regulatory approval stage (*N* =132 safety concerns)

Health outcome (MedDRA system organ class)	Safety concerns identified pre-approval	Safety concerns identified post-approval	Total
Pregnancy, puerperium and perinatal conditions	42	3	45
Neoplasms benign, malignant and unspecified (including cysts)	9	1	10
General disorders and administration site conditions	9	0	9
Cardiac disorders	6	0	6
Infections and infestations	4	2	6
Injury, poisoning and procedural complications	1	4	5
Nervous system disorders	4	1	5
Psychiatric disorders	4	1	5

Background: PDUFA VII Commitment Letter

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:

3) By September 30, 2027, based on the results of demonstration projects in (2) update the proposed framework and develop a guidance…

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.

3) By September 30, 2027, based on the results of demonstration projects in (2) 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.

Pregnancy Safety Demonstration Projects

	Study Designs Being Compared	Approach	Exposure
Project “a”	Pregnancy registries versus electronic healthcare database studies	Signal Detection	Common
Project “b”	Single arm safety study versus electronic healthcare database study	Signal Detection	Rare
Project “c”	Pregnancy registries versus electronic healthcare database studies	Signal Evaluation	Common

Optimizing the Use of Postapproval Pregnancy Safety Studies

September 18, 2023 10:00AM - September 19, 2023 2:30PM

Hybrid - National Press Club, Washington D.C.
529 14th St NW
Washington, DC 20045
United States

Contact Information
Luke Durocher

margolisevents@duke.edu

Materials

- Pregnancy Safety Study Workshop Agenda 9.15.23.pdf
- Postapproval Preg Safety Studies Attendee Know Before You Go.pdf
- Pregnancy Safety Study Workshop - Speaker Biosheet.pdf
- Preg Safety Study Master slide deck FINAL.pdf

https://healthpolicy.duke.edu/events/optimizing-use-postapproval-pregnancy-safety-studies

12C	Use novel data resources. b. Support studies across multiple drugs using the same infrastructure to conserve resources

Using common data model to study class effects

Eliquis (Apixaban), Pradaxa (Dabigatran), and Xarelto (Rivaroxaban) & Cutaneous Small-Vessel Vasculitis

- FDA also conducted a study on patients treated with direct oral anticoagulants versus warfarin and risk of cutaneous small vessel vasculitis (CSVV). The study did not find a statistically significant increase in CSVV risk among users of DOACs versus warfarin, or between different DOACs. The FDA determined that no regulatory action was needed.

https://www.sentinelinitiative.org/studies/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-1

Recent work with Medicaid data

- Within the U.S. FDA's Sentinel System, linkage of mother and infant data is **critical for the assessment of medication safety** during pregnancy.
- U.S. Medicaid/CHIP data in the new Transformed Medicaid Statistical Information System (T-MSIS) format were recently converted to the Sentinel Common Data Model and an initial mother-infant linkage was performed.

Rules for linking delivery records to infant records

Objective: Most accurate linkage

- Both delivery record and infant record must be associated with the ***same jurisdiction***
- Both delivery record and infant record must have the ***same case number identifier***
  - Case number is a state-assigned number that is often a proxy for a family identifier
- Infant's ***date of birth must be close to the admission/discharge dates*** on the delivery record. Specifically:
  - Infant's DOB must be within 3 days (±) of a delivery record's admission date, if discharge date is unknown, or
  - Infant's DOB must be between 3 days prior to the delivery record's admission date and the delivery record's discharge date

Linkage results

Overall

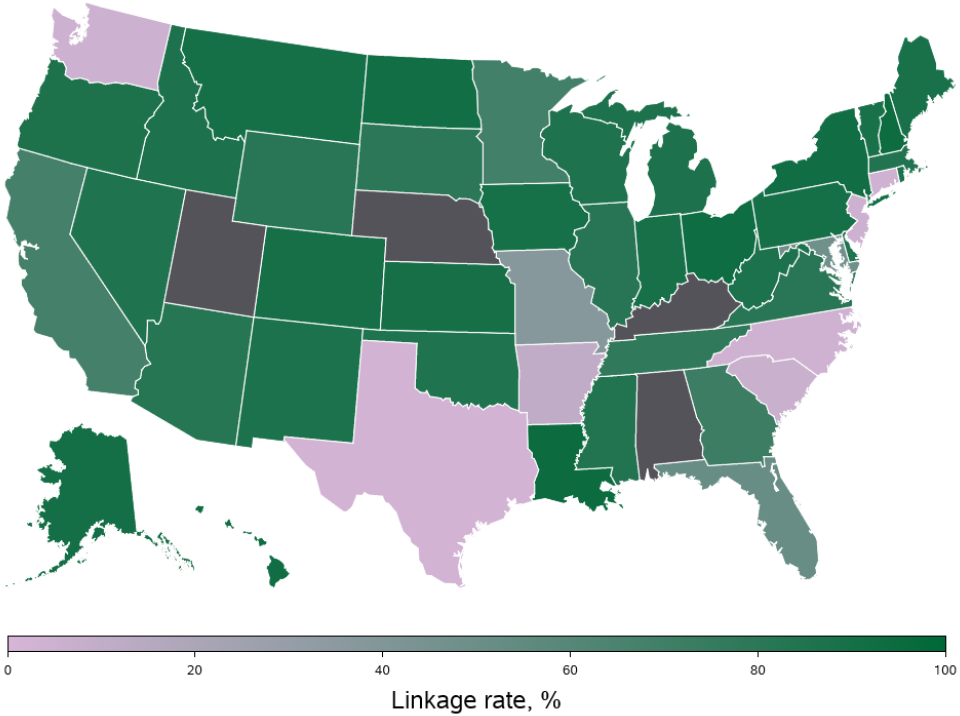
61% of mother's delivery records—**4.1 million of 6.7 million eligible** were linked to child records in the Medicaid/CHIP data

This statistic hides substantial variability

By jurisdiction

Among 49 jurisdictions (46 states, DC, PR, VI):

- 34 had linkage rates **over 75%**
- 7 had linkage rates **under 15%**



Not shown: Puerto Rico, 74% linkage; U.S. Virgin Islands, 79% linkage.

Continuity and Completeness of Data

Example Table of Years of Medicaid Data Contributed by State

FFS Plan

Jurisdiction	2014	2015	2016	2017	2018	2019	2020	Years Included
AK**	✓	✓	✓	✓	✓	✓	✓	7
AL***	a†	a†	a†	a†	a†	a†	a†	0
AR****	–	–	a†	✓	✓	✓	✓	4
AZ*****	–	✓	✓	✓	✓	✓	✓	6
CA*	–	–	✓	✓	✓	✓	✓	5
CO*	✓	✓	✓	✓	✓	✓	✓	7
CT*	–	–	✓	✓	✓	✓	✓	5
DC*	✓	c†	✓	✓	✓	✓	✓	6

CMC Plan

Jurisdiction	2014	2015	2016	2017	2018	2019	2020	Years Included
AK	✓	✓	✓	✓	✓	✓	✓	7
AL	a†	a†	a†	a†	a†	a†	a†	0
AR	–	–	a†	✓	✓	b: IP, LT, OT, RX†	✓	3
AZ	–	✓	✓	✓	✓	✓	✓	6
CA	–	–	✓	✓	✓	✓	✓	5
CO	b: LT, OT†	b: OT†	b: IP, OT†	✓	✓	✓	✓	4
CT	–	–	✓	✓	✓	✓	✓	5
DC	✓	c†	✓	✓	✓	✓	✓	6

ACA Status
*Adopted 2014
**Adopted 9/2015
***Not adopted
****Adopted 2014 with work reqs that were removed 2022
*****Adopted 2014 with work reqs

✓ data were included for a jurisdiction/year/plan.

Red† indicates data were excluded for a jurisdiction/year/plan.

Reasons data was deemed unusable, i.e., excluded:
-- Unavailable
a Dual Eligibility Code
b Comprehensive Managed Care Plan Encounters
c Number of Enrollment Spans

CMC = Comprehensive Managed Care,
FFS = Fee for Service
LT = Long-Term Care TAF File
OT = Other Services TAF File
IP = Inpatient TAF File
RX = Pharmacy File

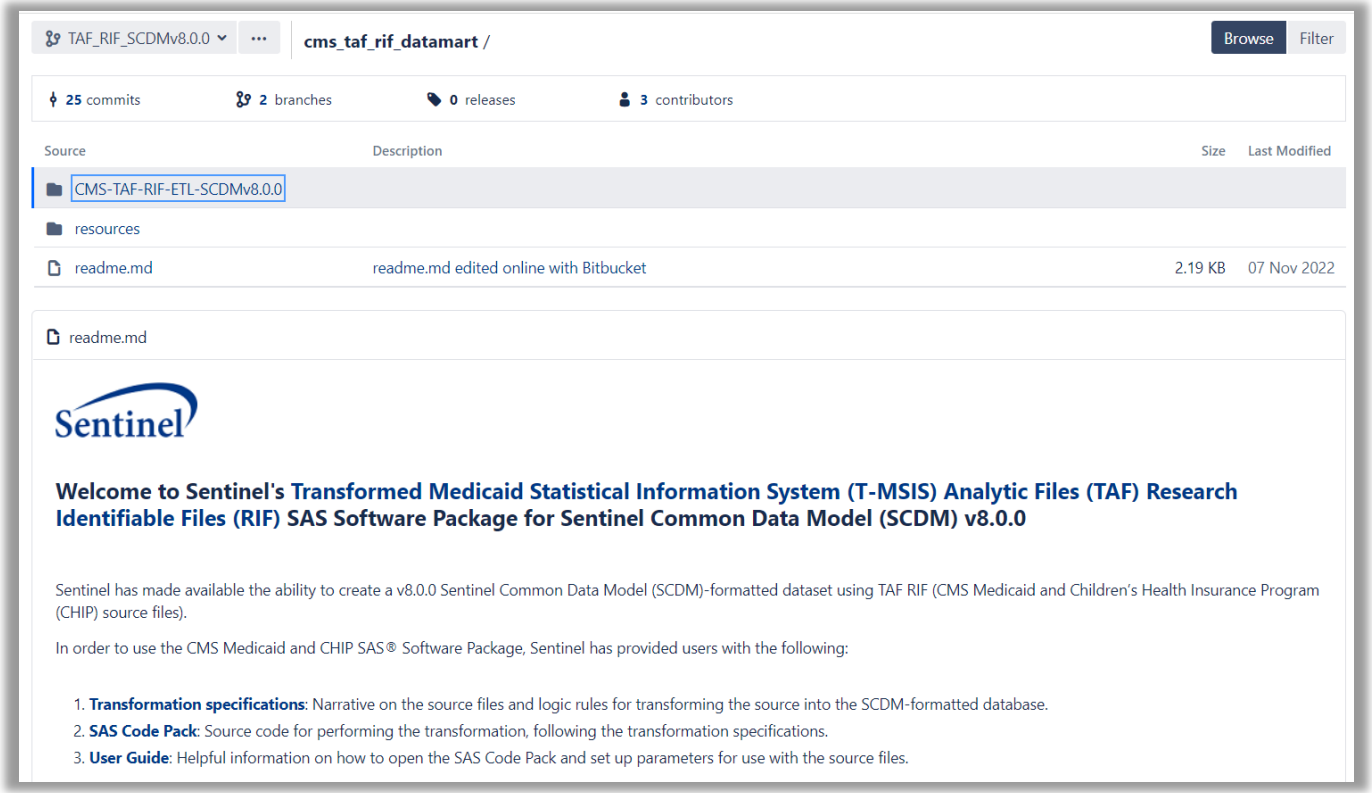
Continuity and Completeness of Data 2

Descriptions	Jurisdictions	Total
Jurisdictions with ≥5 Years of Inclusion*	AK, AZ, CA, CT, DC, DE, HI, IA, IL, IN, KS, LA, ME, MN, MO, MT, NC, NJ, NH, NM, NV, NY, OH, OR, PA, SD, TX, VA, VT, WA, WI, WV, WY	33
Jurisdictions with ≤4 Years of Inclusion	AR, CO, FL, GA, ID, MA, MD, MI, MS, ND, OK, PR, RI, SC, TN, VI	16
Jurisdictions without Any Inclusion	AL, KY, NE, UT	4

*An Included Year is counted only when both FFS and CMC are included.

Publicly-Available Resources

T-MSIS-to-SCDM Transformation Materials:



https://dev.sentinelsystem.org/projects/DCMS/repos/cms_taf_rif_datamart/browse/CMS-TAF-RIF-ETL-SCDMv8.0.0?at=TAF_RIF_SCDMv8.0.0

Conclusions

From FDA's Center for Drug Evaluation and Research (CDER)'s experience:

- What has been done in FDA's Sentinel System that might align with recommendation 12?
  - The Sentinel System currently has 10.8 million mother and infant linked deliveries.
- What barriers were encountered?
  - Lactation not addressed through the database studies
  - Still sorting through best practices for using complementary data sources for postmarket safety assessment and the programming tools are still being developed
  - Medicaid is a rich data source, but quality and capture differs by state
- What additional resources, policy change, regulations, etc., are needed to move forward?
  - See following link for current considerations: https://healthpolicy.duke.edu/events/optimizing-use-postapproval-pregnancy-safety-studies

Thank you for listening

Any questions?

MOTHER-INFANT LINKAGE

FREQUENTLY ASKED QUESTIONS & APPENDICES

Prepared by the Sentinel Operations Center
February 2019
Version: 1.0.0

Table of Contents

https://www.sentinelinitiative.org/sites/default/files/data/distributed-database/MIL_FAQs%26Appendices.pdf

Mother Infant Linkage Approaches

	Linkage Rates	Use of PHI?	Third Parties Required?	Logistic and Regulatory Burden	Sample Size
Birth Certificates	90-95%	Yes	Yes, State Vital Statistics Departments	High, (done state by state), Requires multiple data use agreements	Low because must be done state by state.
PHI Linkage within Data Source	70-85%	Yes	No	Low	Variable based on data source size.
Linkage within Data Source using Family/Subscriber ID without PHI	60-70%	No	No	Low	Variable based on data source size
Linkage with Privacy-Preserving Techniques	<50%	No	Yes	High	Very low because requires overlap with 2 sources.

PDS Pharmacoepidemiology & Drug Safety

ispe Official Journal of the International Society for Pharmacoepidemiology

ORIGINAL ARTICLE

Assessing medical product safety during pregnancy using parameterizable tools in the sentinel distributed database

Jennifer G. Lyons, Elizabeth A. Suarez, Elnara Fazio-Eynullayeva, Judith C. Maro, Catherine Corey, Jie Li, Sengwee Toh, Mayura U. Shinde

First published: 09 November 2022 | https://doi.org/10.1002/pds.5568

Disclaimer: The views expressed in this paper reflect those of the authors and should not be construed to represent U.S. Food and Drug Administration's views or policies.

Funding information: US Food and Drug Administration, Grant/Award Number: HHSF223201400030I

Read the full text >

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Validation of the Signal Tools

FDA

Mother-Infant Linked (MIL) data sources:

- Large insurance companies
- Data aggregator
- Academic center
- Medicaid

https://pubmed.ncbi.nlm.nih.gov/36351880/

Validation of Signal Identification in Pregnancy Using Empirical and Simulated Data

PDS Pharmacoepidemiology & Drug Safety — ispe Official Journal of the International Society for Pharmacoepidemiology

ORIGINAL ARTICLE

Novel methods for pregnancy drug safety surveillance in the FDA Sentinel System

Elizabeth A. Suarez, Michael Nguyen, Di Zhang, Yueqin Zhao, Danijela Stojanovic, Monica Munoz, Jane Liedtka, Abby Anderson, Wei Liu, Inna Dashevsky, David Cole, Sandra DeLuccia ... See all authors

First published: 24 July 2022 | https://doi.org/10.1002/pds.5512

This work was presented at the International Conference of Pharmacoepidemiology in August 2021 (virtual event).

Funding information: US Food and Drug Administration (FDA), Grant/Award Numbers: HHSF223201400030I, HHSF22301012T

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https://pubmed.ncbi.nlm.nih.gov/35871766/

EPIDEMIOLOGY

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PERINATAL EPIDEMIOLOGY

Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs

Suarez, Elizabeth A.[a]; Nguyen, Michael[b]; Zhang, Di[c]; Zhao, Yueqin[c]; Stojanovic, Danijela[b]; Munoz, Monica[b]; Liedtka, Jane[d]; Anderson, Abby[e]; Liu, Wei[b]; Dashevsky, Inna[a]; DeLuccia, Sandra[a]; Menzin, Talia[a]; Noble, Jennifer[a]; Maro, Judith C.[a]

Author Information

Epidemiology 34(1):p 90-98, January 2023. | *DOI:* 10.1097/EDE.0000000000001561

Cite Share Favorites Permissions BUY SDC Metrics

https://pubmed.ncbi.nlm.nih.gov/36252086/

Number of Contributing Jurisdictions

Plan	2014	2015	2016	2017	2018	2019	2020
FFS	16	25	41	44	43	44	46
CMC	12	21	38	41	40	41	45

Transition years

FFS = Fee-for-Service, CMC = Comprehensive Managed Care

Medicaid Data and the Sentinel System

- The CMS T-MSIS dataset is a valuable data source capturing key populations of public health interest, especially pregnant women and infants
- Sentinel's existing data infrastructure enables us to integrate Medicaid data with commercial claims data
  - Very large distributed database of linked mother-infant pairs
  - Necessary for studying rare drug-related adverse events to support FDAs mission to promote drug safety
- Commitment to transparency
  - All analytic tools and study materials are made publicly available
  - External researchers can leverage analytic code, transform their data into the SCDM, and replicate analyses or conduct new analyses


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ADMINISTRATION