Medical Product Safety: Ten Years of the U.S. Sentinel System

May 23, 2019

Sarah Dutcher, PhD
U.S. Food and Drug Administration

Judith C. Maro, PhD
Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

David Martin, MD, MPH
U.S. Food and Drug Administration

Required Disclosures

- Funding sources:
  - U.S. Food and Drug Administration, FDA HHSF223201400030I, Task Order: HHSF22301003T

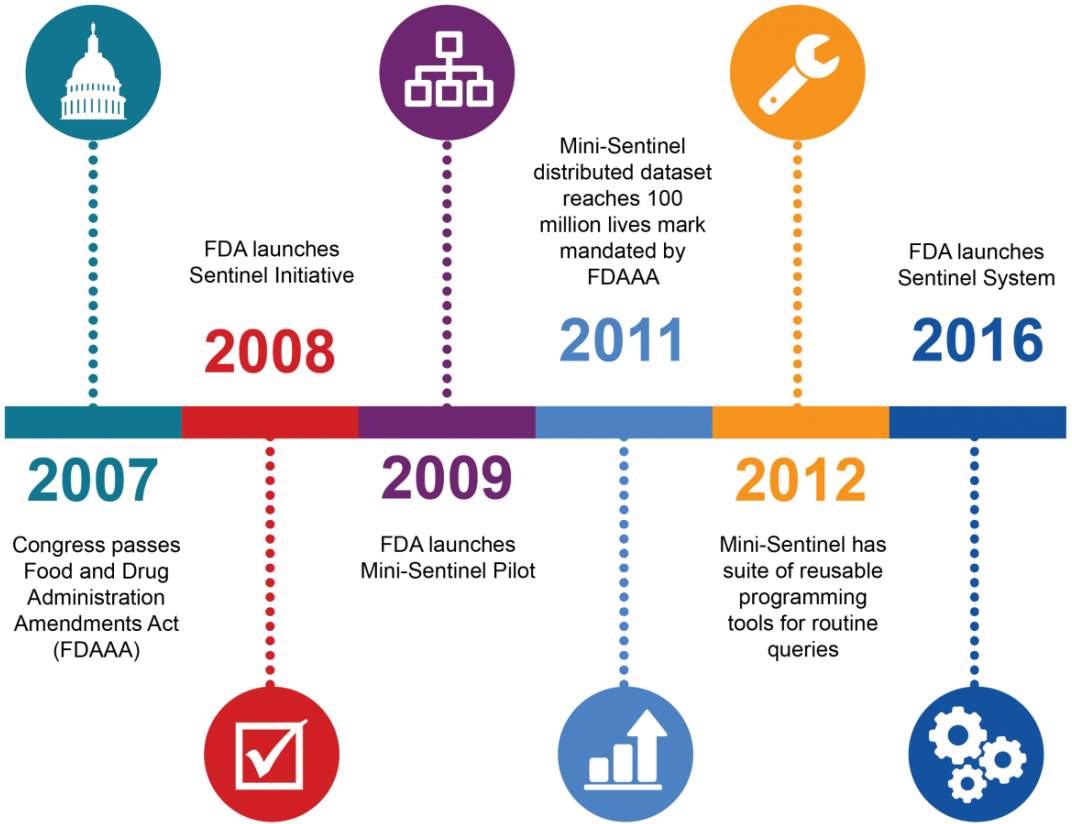
- No relationships to disclose
- The views expressed are the authors' and not necessarily those of the Food and Drug Administration, or the Department of Health and Human Services

What is Sentinel?

- FDA's medical product active safety surveillance system
  - To assess the use, safety, and effectiveness of regulated medical products
  - To develop data, informatics, and methodologic capabilities to support these activities
- Key components:
  - Distributed data network of 18 Data Partners
  - Electronic healthcare data
  - Common data model
  - Sophisticated quality assurance process
- Created in response to a U.S. Congressional mandate

https://www.sentinelinitiative.org/

History of the Sentinel Initiative



FDA Amendments Act of 2007

Sec. 905. Active Postmarket Risk Identification and Analysis

(B) DEVELOPMENT OF POSTMARKET RISK IDENTIFICATION AND ANALYSIS METHODS.

The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities—

(i) develop methods to **obtain access to disparate data sources** including the data sources specified in subparagraph (C);

(ii) develop validated methods for the **establishment of a postmarket risk identification and analysis system** to link and analyze safety data from multiple sources, with the goals of including, in aggregate—

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012

FDA Amendments Act of 2007

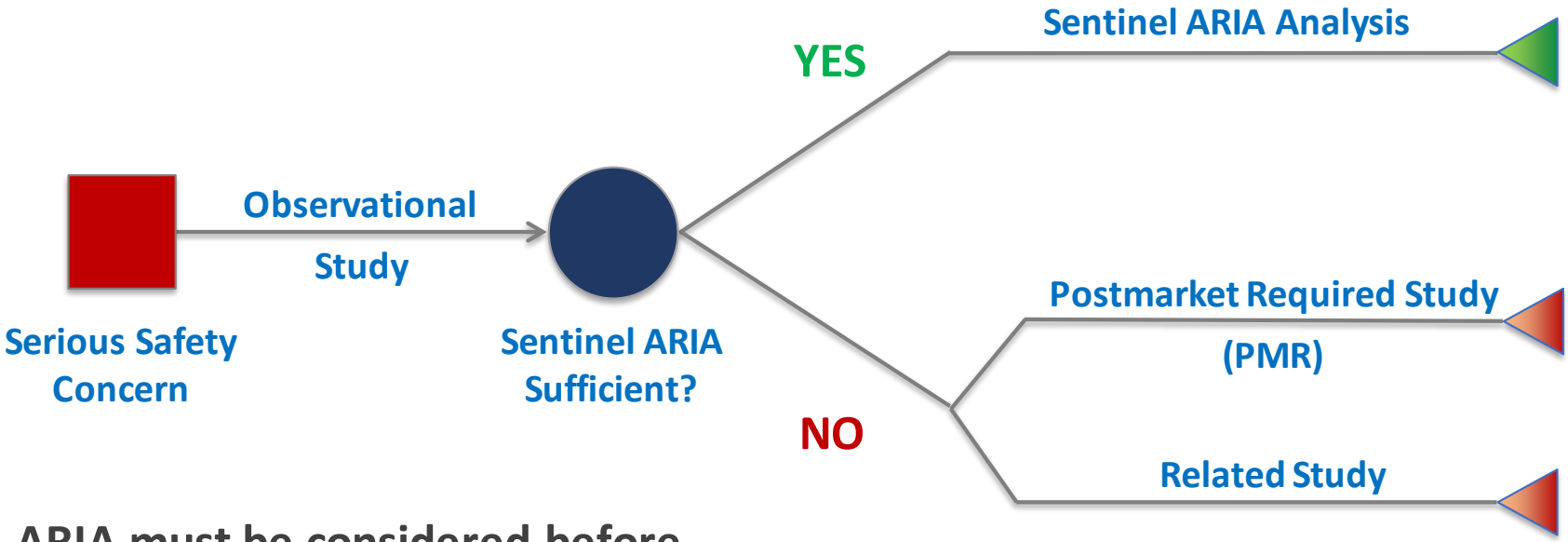
Section 905
Mandates creation of Sentinel

Section 901
New FDAAA PMR authority

SEC. 901. POSTMARKET STUDIES AND CLINICAL TRIALS REGARDING HUMAN DRUGS; RISK EVALUATION AND MITIGATION STRATEGIES.

"The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the **active postmarket risk identification and analysis system** as available under subsection (k)(3) will not be **sufficient** to meet the purposes set forth in subparagraph (B)."

Sentinel's Active Risk Identification and Analysis (ARIA)



ARIA must be considered before a sponsor PMR can be issued

What is ARIA?

- Electronic claims data, without manual medical record review
- Pre-defined, parameterized, and re-usable to enable faster safety surveillance (vs. protocol based assessments with fully customized programming)

Determining ARIA Sufficiency

- What is the purpose of the analysis?
  - Signal detection, signal refinement, or signal evaluation?
- What is the desired study population?
- What are the treatment and comparator exposures?
- What are the outcome(s) of interest?
- What are relevant and important covariates for the analysis?
- What is the desired analytic approach?

Signal Identification

- FDAAA of 2007: "…create a robust system to identify adverse events and potential drug safety signals"
- Purpose: To detect new and unsuspected potential drug-related safety concerns
  - Hypothesis generation
  - Will be followed by clinical review and/or well-designed safety studies
- TreeScan is currently available in Sentinel
  - Multiple projects are ongoing to support and enhance signal identification methods

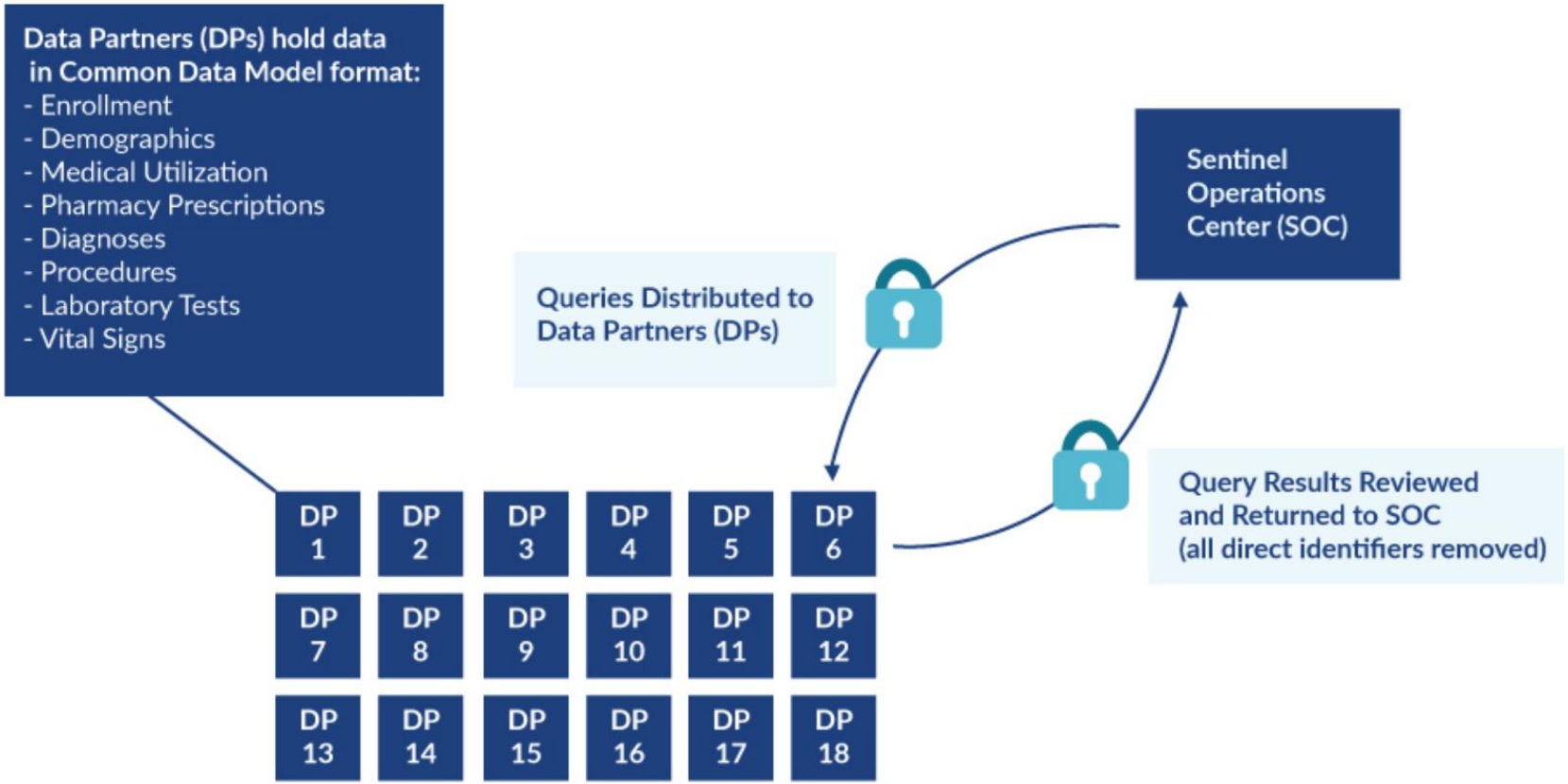
http://sentinelinitiative.org/sentinel/surveillance-tools/signal-identification-sentinel-system

Sentinel System:
Data, Tools, Methods

Sentinel Design Requirements

- Electronic health data for >100M persons
  - Include special populations (pregnant women, elderly)
  - Ability to link to external sources, e.g., National Death Index
  - Ability to access full text medical records
- Expertise in the way health care delivery and payment influence electronic healthcare data
- Rapid answers to many FDA safety questions
- Accuracy sufficient to support regulatory decision making
- Federal Information Security Management Act (FISMA)-compliant data security
- Ability to protect non-public information and to keep records on all data requests for public record-keeping

Sentinel Distributed Database



https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model

Collaborating Organizations

Sentinel

Lead – HPHC Institute

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

Data & Scientific Partners

MASSACHUSETTS
HealthCore Anthem
HCA Healthcare
health care systems research network
Department of Population Health Sciences
Duke University School of Medicine
VANDERBILT SCHOOL OF MEDICINE
OPTUM
HUMANA
KAISER PERMANENTE
aetna

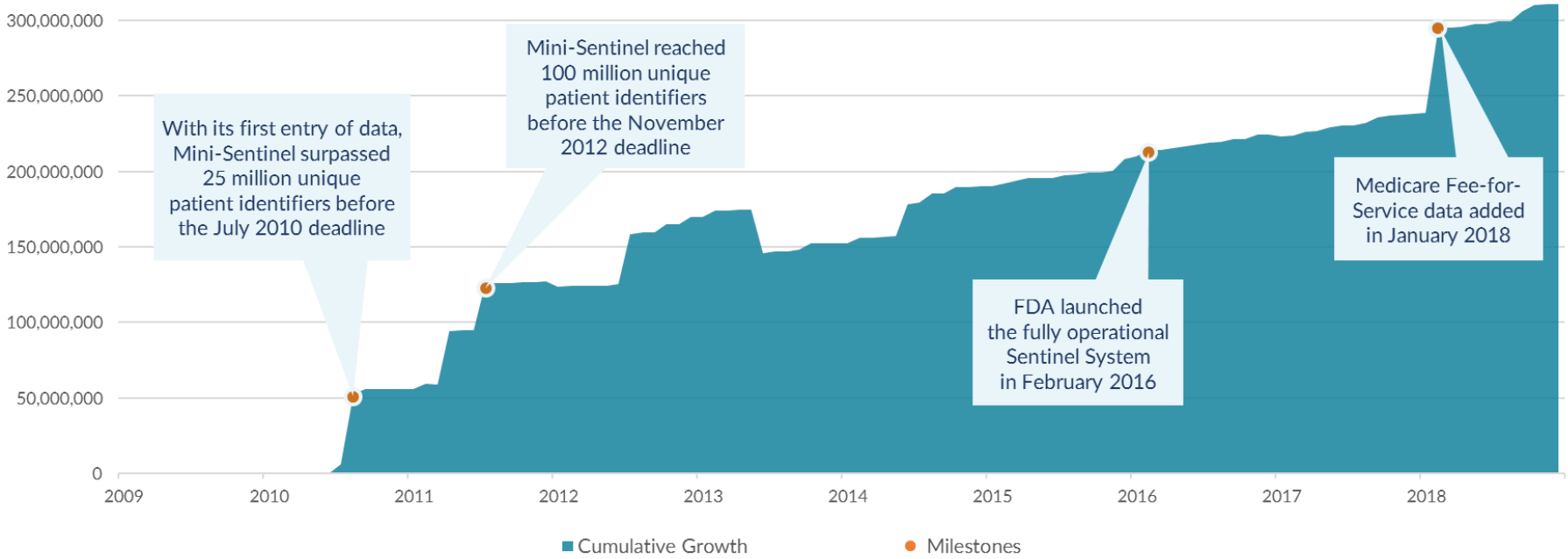
Scientific Partners

Penn Medicine
IQVIA
Cincinnati Children's change the outcome
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF MEDICINE BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL
AHIP America's Health Insurance Plans
UF College of Pharmacy UNIVERSITY of FLORIDA
UAB
UIC
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
RUTGERS

https://www.sentinelinitiative.org/collaborators

Growth of the Sentinel Distributed Database

- 70 million members currently accruing new data



The area above depicts the cumulative number of unique patient identifiers in the Sentinel Distributed Database from 2010 to present. If patients move health plans, they may have more than one patient identifier.

http://www.sentinelinitiative.org/sentinel/data/snapshot-database-statistics

Sentinel Common Data Model Guiding Principles

- Includes claims, electronic health record (EHR), and registry data and flexible enough to accommodate new data domains (e.g., free text).
  - Typically, we do not include empty tables – we expand as needed when fit for purpose.
- Data are stored at most **granular/raw level possible** with minimal mapping.
  - Distinct data types should be kept separate (e.g., prescriptions, dispensings)
  - Construction of medical concepts (e.g., outcome algorithms) from these elemental data is a **project-specific** design choice.
  - Sentinel stores these algorithms in a library for future use.
- Appropriate use and interpretation of local data requires the Data Partners' local knowledge and data expertise.
  - Not all tables are populated by all Data Partners → site-specificity is allowed.
- Designed to meet FDA needs for analytic flexibility, transparency, and control.

Available Data Elements

Administrative Data

Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID
Enrollment Start & End Dates	Birth date	Dispensing Date	Service Date(s)	Service date(s)	Service Date(s)
Drug Coverage	Sex	National Drug Code (NDC)	Encounter ID	Encounter ID	Encounter ID
Medical Coverage	Zip code	Days Supply	Encounter Type and Provider	Encounter Type and Provider	Encounter Type and Provider
Medical Record Availability	Etc.	Amount Dispensed	Facility	Diagnosis Code & Type	Procedure Code & Type
			Etc.	Principle Discharge Diagnosis	Etc.

Clinical Data

Lab Result	Vital Signs
Patient ID	Patient ID
Result & Specimen Collection Dates	Measurement Date & Time
Test Type, Immediacy & Location	Height & Weight
Logical Observation Identifiers Names and Codes (LOINC®)	Diastolic & Systolic BP
Etc.	Tobacco Use & Type
	Etc.

Registry Data

Death	Cause of Death	State Vaccine
Patient ID	Patient ID	Patient ID
Death Date	Cause of Death	Vaccination Date
Source	Source	Admission Date
Confidence	Confidence	Vaccine Code & Type
Etc.	Etc.	Provider
		Etc.

Inpatient Data

Inpatient Pharmacy	Inpatient Transfusion
Patient ID	Patient ID
Administration Date & Time	Administration Start & End Date & Time
Encounter ID	Encounter ID
National Drug Code (NDC)	Transfusion Administration ID
Route	Transfusion Product Code
Dose	Blood Type
Etc.	Etc.

Mother-Infant Linkage Data

Mother-Infant Linkage
Mother ID
Mother Birth Date
Encounter ID & Type
Admission & Discharge Date
Child ID
Child Birth Date
Mother-Infant Match Method
Etc.

https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model

Single Patient Example Data in Model

DEMOGRAPHIC

PATID	BIRTH_DATE	SEX	HISPANIC	RACE	zip
PatID1	2/2/1964	F	N	5	32818

DISPENSING

PATID	RXDATE	NDC	RXSUP	RXAMT
PatID1	10/14/2005	00006074031	30	30
PatID1	10/14/2005	00185094098	30	30
PatID1	10/17/2005	00378015210	30	45
PatID1	10/17/2005	54092039101	30	30
PatID1	10/21/2005	00173073001	30	30
PatID1	10/21/2005	49884074311	30	30
PatID1	10/21/2005	58177026408	30	60
PatID1	10/22/2005	00093720656	30	30
PatID1	10/23/2005	00310027510	30	15

ENROLLMENT

PATID	ENR_START	ENR_END	MEDCOV	DRUGCOV
PatID1	7/1/2004	12/31/2004	Y	N
PatID1	1/1/2005	12/31/2005	Y	Y

DEATH

PATID	DEATHDT	DTIMPUTE	SOURCE	CONFIDENCE
PatID1	12/27/2005	N	S	E

ENCOUNTER

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

DIAGNOSIS

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	DX	DX_CODETYPE	PDX
PatID1	EncID1	10/18/2005	Provider1	IP	296.2	9	P
PatID1	EncID1	10/18/2005	Provider1	IP	300.02	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	305.6	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	311	9	P
PatID1	EncID1	10/18/2005	Provider1	IP	401.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	493.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	715.9	9	S

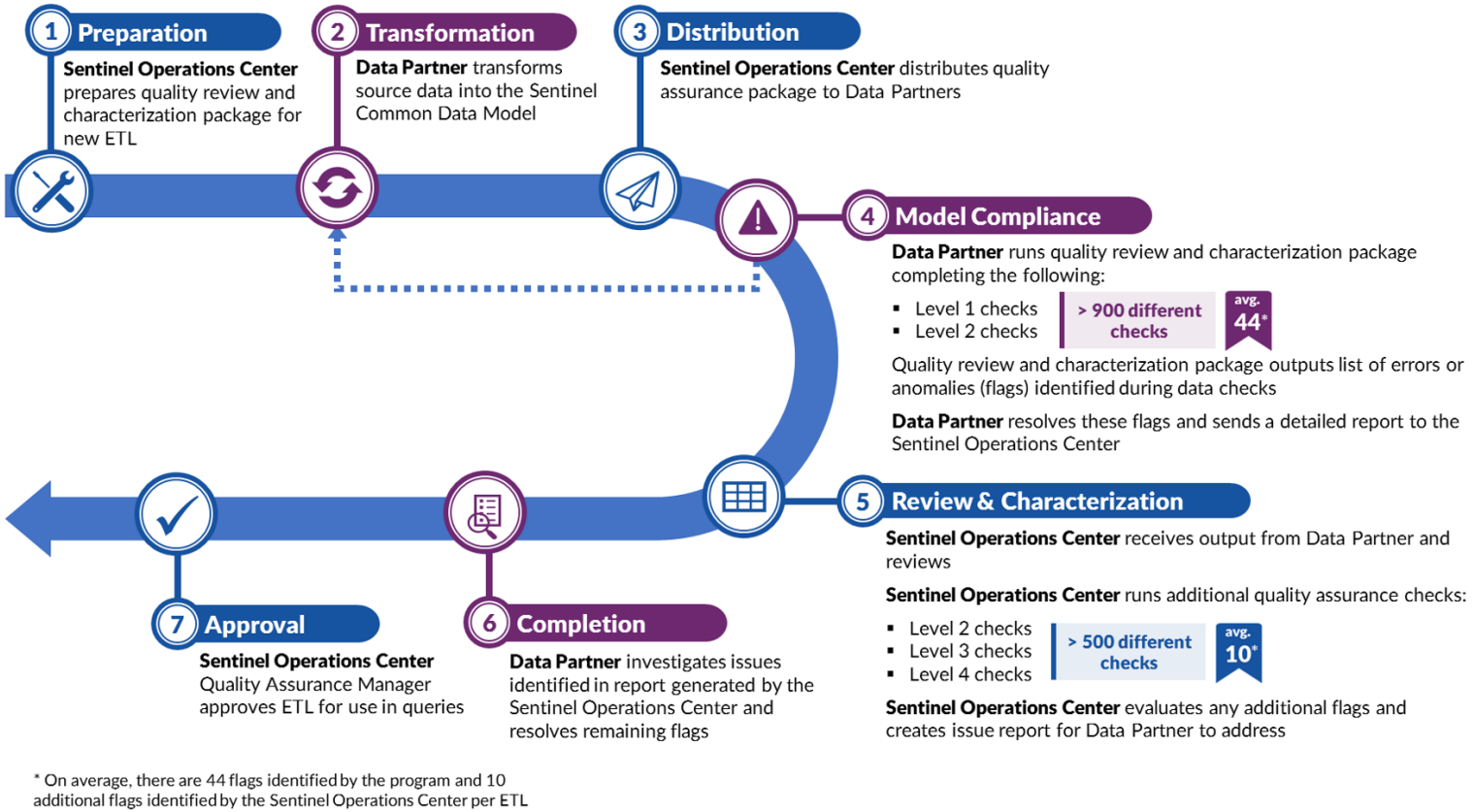
PROCEDURE

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99222	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99238	C4
PatID1	EncID1	10/18/2005	Provider2	IP	27445	C4

CAUSE OF DEATH

PATID	COD	CODETYPE	CAUSETYPE	SOURCE	CONFIDENCE
PatID1	J18.0	10	U	S	E

Data Quality Review and Characterization Process



* On average, there are 44 flags identified by the program and 10 additional flags identified by the Sentinel Operations Center per ETL

https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization

Data Quality Checks and Examples

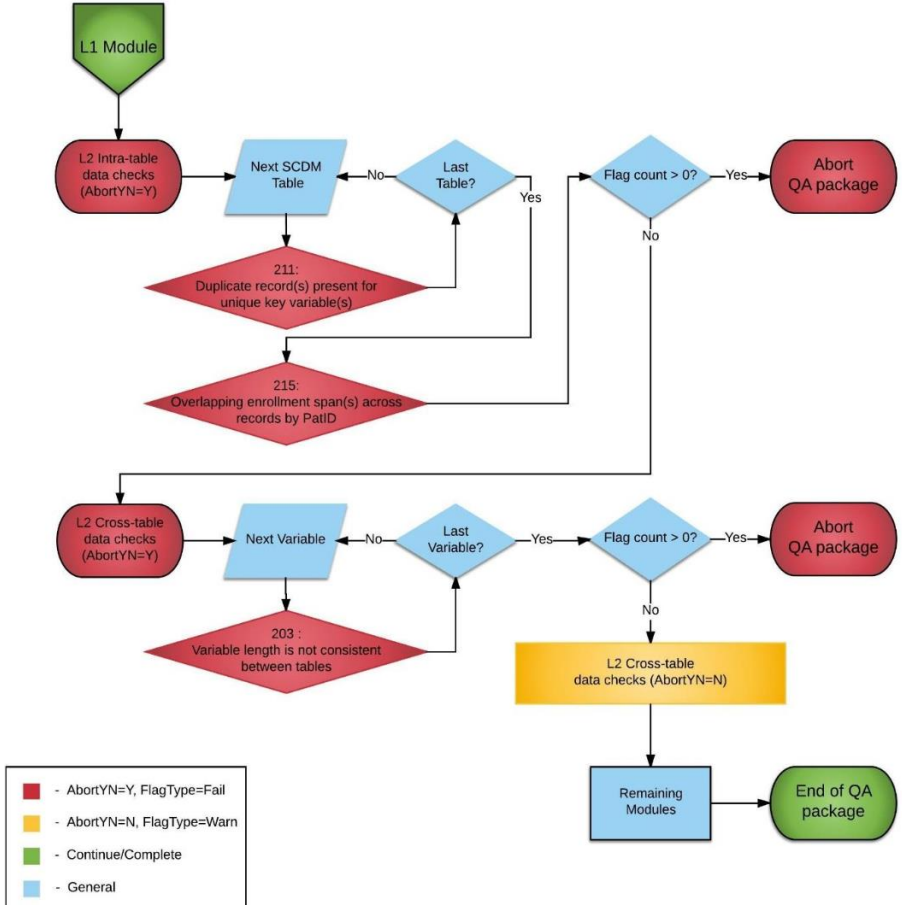
Level 1 Checks	**Completeness** ✓ Admission date is not missing value **Validity** ✓ Admission date is in date format	Sentinel Common Data Model Compliance
Level 2 Checks	**Accuracy** ✓ Admission date occurs before the patient's discharge date **Integrity** ✓ Admission date occurs within the patient's active enrollment period	Cross-Variable and Cross-Tabular
Level 3 Checks	**Consistency of Trends** ✓ There is no sizable percent change in admission date record counts by month-year	Cross-ETLs
Level 4 Checks	**Plausibility** ✓ There is no sizable percent change in the number of prostate cancer encounters by sex*	Cross-ETLs

**Under development*

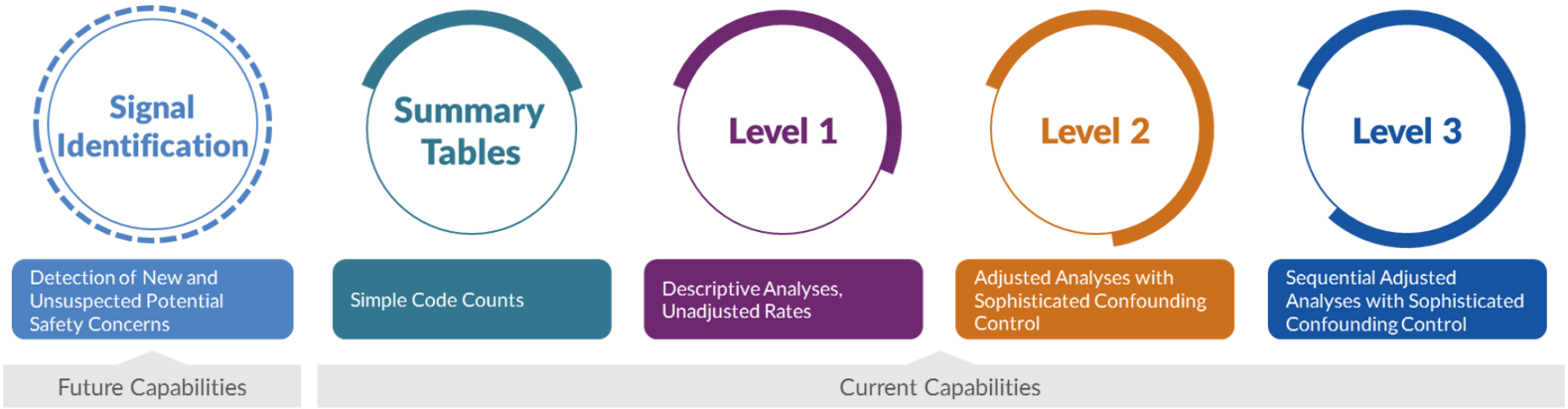
https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization

Quality Review and Characterization Program Logic

- Compliance checks for all tables are mandatory.
- Quality Review and Characterization Program will abort after it runs through all compliance checks, producing an automatically created report on failures.



Active Risk Identification and Analysis (ARIA)



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

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

Cohort Identification and Descriptive Analysis (CIDA)

OVERVIEW

The purpose of this repository is to document version 7.3.0 of the Sentinel Routine Querying System. Functional documentation sections describe the capabilities of the tools in the system. Technical documentation sections specify the tools' inputs and outputs and provide the information required to build analytic packages to address research questions of interest.

SENTINEL ROUTINE QUERYING SYSTEM TOOLS

Sentinel's Routine Querying System includes three tools:

The **COHORT IDENTIFICATION AND DESCRIPTIVE ANALYSIS (CIDA) TOOL** identifies and extracts cohorts of interest from the Sentinel Distributed Database based on requester-defined options (e.g., exposures, outcomes, continuous enrollment requirements, incidence criteria, inclusion/exclusion criteria, relevant age groups, demographics).

The CIDA tool calculates descriptive statistics for the cohort(s) of interest and outputs datasets that may be useful for additional analyses. The CIDA tool may be used alone or in conjunction with the Propensity Score Analysis Tool or the Multiple Factor Matching Tool.

There are six cohort identification strategies available:

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

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

Downloading Sentinel Analytic Packages

Sentinel Analytic Packages

Overview

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

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

Analytic Request Packages Available for Download

Request ID	Summary
cder_mpl2p_wp009	Stroke, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Apixaban or Warfarin Use in Patients with Non-Valvular Atrial Fibrillation: a Propensity Score Matched Analysis
cder_mpl2p_wp006	Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis (an update to cder_mpl2p_wp002)
cder_mpl2p_wp005	Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a Propensity Score Matched Analysis
cder_mpl2p_wp001	Venous Thromboembolism following Continuous or Extended Cycle Contraceptive Use: a Propensity Score Matched Analysis
cder_mpl2p_wp004	Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis
cder_mpl2p_wp002	Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis

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

Methods Development: Summary Scores

Sentinel

Extension of Disease Risk Score–Based Confounding Adjustments for Multiple Outcomes of Interest: An Empirical Evaluation

FREE

Rishi J Desai

Austin Cosgr

Rita Ouellet-

American Jo

/aje/kwy130

Published:

ORIGINAL REPORT

Evaluating the use of bootstrapping in cohort studies conducted with 1:1 propensity score matching—A plasmode simulation study

Rishi J. Desai, Richard Wyss, Younathan Abdia, Sengwee Toh, Margaret Johnson, Hana Lee, Sara Karami, Jacqueline M. Major, Michael Nguyen, Shirley V. Wang, Jessica M. Franklin, Joshua J. Gagne

First published: 24 April 2019 | https://doi.org/10.1002/pds.4784

Methods Development: Privacy Preserving Regression

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

ORIGINAL REPORT

Comparison of privacy-protecting analytic and data-sharing methods: A simulation study

Kazuki Yoshida, Susan Gruber, Bruce H. Fireman, Sengwee Toh

First published: 18 July 2018 | https://doi.org/10.1002/pds.4615

Methods Development: Signal Detection

Epidemiology. 29(6):895–903, NOV 2018
DOI: 10.1097/EDE.0000000000000907, PMID: 30074538
Issn Print: 1044-3983
Publication Date: 2018/11/01

Print

Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic

Shirley V. Wang; Judith C. Maro; Elande Baro; Rima Izem; Inna Dashevsky; James R. Rogers; Michael Nguyen; Joshua J. Gagne; Elisabetta Patorno; Krista F. Huybrechts; Jacqueline M. Major; Esther Zhou; Megan Reidy; Austin Cosgrove; Sebastian Schneeweiss; Martin Kulldorff

+ Author Information

Methods Development in Sentinel: Machine Learning

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

ORIGINAL REPORT

Evaluating automated approaches to anaphylaxis case classification using unstructured data from the FDA Sentinel System

Robert Ball ✉, Sengwee Toh, Jamie Nolan, Kevin Haynes, Richard Forshee, Taxiarchis Botsis

First published: 28 August 2018 | https://doi.org/10.1002/pds.4645

FDA'S USE OF THE SENTINEL SYSTEM TO ADDRESS REGULATORY QUESTIONS

How is Sentinel Used?

- To evaluate safety signals identified during the pre-market review of new drug applications
- To evaluate safety signals identified during the post-market period
- To identify new potential safety signals during the post-market period

How is Sentinel Used?

Update the benefit risk for a product	Support population-level data questions	Assist with public-facing decision making	Establish system capabilities	Information dissemination

• Drug Safety Communication
• Label change
• Modification of patient medication guide
• Downgrade of TE rating for a generic drug
• Product or packaging redesign
	• Address questions on real-world population exposure
	• Provide context for other safety data
	  • Enrollment in pregnancy registries
	  • Comparison with clinical trial data
		• Support an Advisory Committee (AC)
		• Response to a Citizen Petition
		• Response to a Congressional inquiry
			• Assess feasibility of potential inferential analysis
			  • Conducted by sponsor (e.g., PMR, PASS)
			  • Conducted by regulatory agency
				• International scientific conference
				• Publication
				• Sentinel website

• Determine that no action is needed				

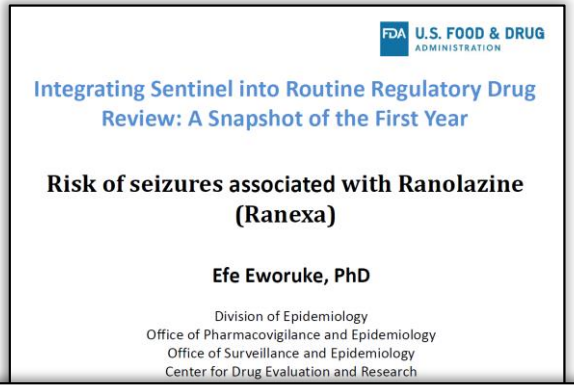
Real-World Example: Ranolazine

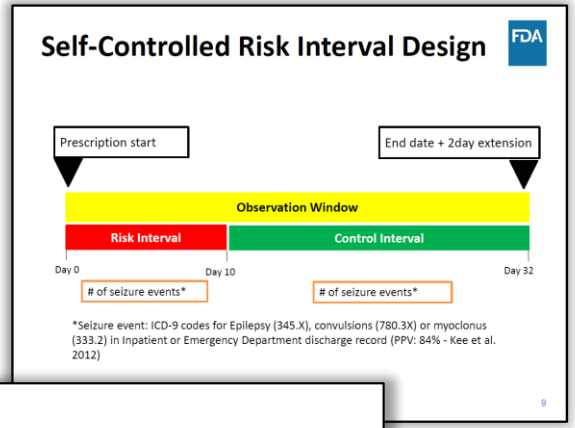
- Exposure: Ranolazine (Ranexa)
  - Indicated for the treatment of chronic angina
- Outcome: Seizure
- Analysis: Self-controlled risk interval design
- Regulatory determination: FDA decided that no action is necessary at this time, based on available information
  - Combined with evidence from a study done in the U.S. Medicare population, risk of seizure was determined to be driven primarily by underlying comorbidities

http://sentinelinitiative.org/drugs/assessments/ranexa-ranolazine-and-seizures

Real-World Example: Ranolazine

ICPE Symposium, August 2017





Drug Safety
https://doi.org/10.1007/s40264-019-00798-2

ORIGINAL RESEARCH ARTICLE

Use of FDA's Sentinel System to Quantify Seizure Risk Immediately Following New Ranolazine Exposure

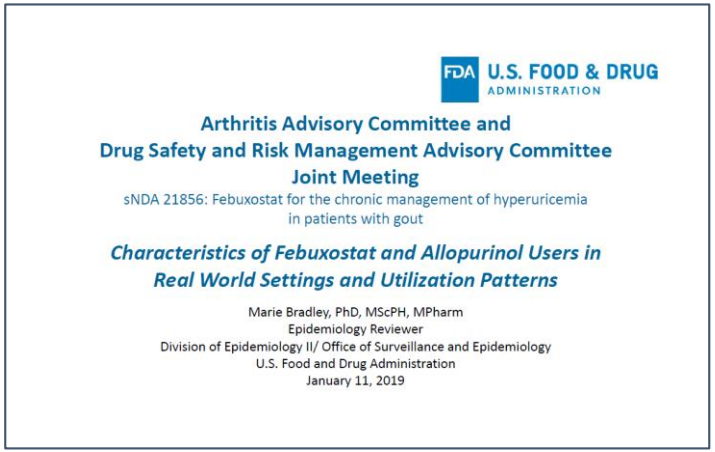
Efe Eworuke[1] · Emily C. Welch[2] · Anne Tobenkin[3] · Judith C. Maro[2]

Real-World Example: Febuxostat

- Exposure: febuxostat (Uloric)
  - Indicated for the chronic management of hyperuricemia in adult patients with gout
- Outcomes: User characteristics, duration of use, switching between urate-lowering therapies
- Analysis: Level 1, Level 1
- Regulatory Use: Presented at an Advisory Committee meeting

http://sentinelinitiative.org/drugs/assessments/characteristics-gout-patients-and-use-urate-lowering-therapies

AC Presentation on Febuxostat



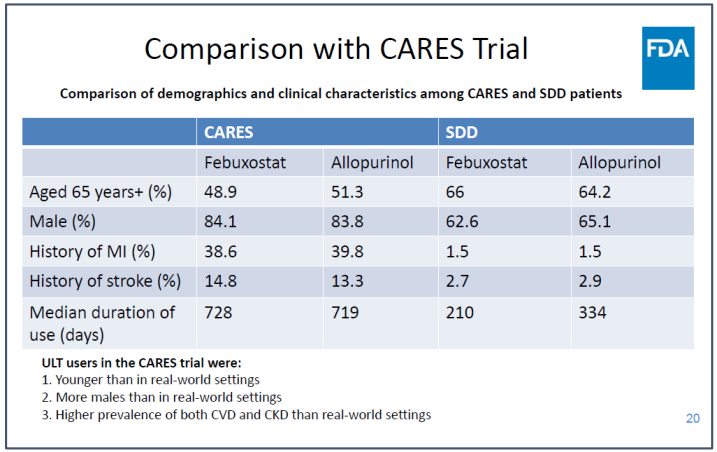
U.S. FOOD & DRUG ADMINISTRATION

Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Joint Meeting

sNDA 21856: Febuxostat for the chronic management of hyperuricemia in patients with gout

Characteristics of Febuxostat and Allopurinol Users in Real World Settings and Utilization Patterns

Marie Bradley, PhD, MScPH, MPharm
Epidemiology Reviewer
Division of Epidemiology II/ Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
January 11, 2019



Comparison with CARES Trial

Comparison of demographics and clinical characteristics among CARES and SDD patients

	CARES		SDD	
	Febuxostat	Allopurinol	Febuxostat	Allopurinol
Aged 65 years+ (%)	48.9	51.3	66	64.2
Male (%)	84.1	83.8	62.6	65.1
History of MI (%)	38.6	39.8	1.5	1.5
History of stroke (%)	14.8	13.3	2.7	2.9
Median duration of use (days)	728	719	210	334

ULT users in the CARES trial were:
1. Younger than in real-world settings
2. More males than in real-world settings
3. Higher prevalence of both CVD and CKD than real-world settings

20

- In light of a post-market clinical trial that identified an elevated risk of CV events, Sentinel analyses described real-world use of urate-lowering therapies
- Results informed the Advisory Committee's determination that a population exists for whom the benefit-risk is favorable

Additional Real-World Examples

Journal of Clinical Psychopharmacology. 38(5):505–508, OCT 2018
DOI: 10.1097/JCP.0000000000000939, PMID: 30102629
Issn Print: 0271-0749
Publication Date: 2018/10/01

Print

Incidence of Heart Failure and Cardiomyopathy Following Initiation of Medications for Attention-Deficit/Hyperactivity Disorder: A Descriptive Study

Andrew D. Mosholder; Lockwood Taylor; Glenn Mannheim; Lisa Ortendahl; Tiffany S. Woodworth; Sengwee Toh

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

ORIGINAL REPORT

Use of tumor necrosis factor-alpha inhibitors during pregnancy among women who delivered live born infants

Efe Eworuke, Genna Panucci, Margie Goulding, Rosemarie Neuner, Sengwee Toh

First published: 14 November 2018 | https://doi.org/10.1002/pds.4695

This project was presented at the 33rd Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management.

Original Investigation ONLINE FIRST

October 1, 2018

Association of Risk for Venous Thromboembolism With Use of Low-Dose Extended- and Continuous-Cycle Combined Oral Contraceptives

A Safety Study Using the Sentinel Distributed Database

Jie Li, PhD[1]; Genna Panucci, SM[2]; David Moeny, RPh[1]; et al

Author Affiliations

JAMA Intern Med. Published online October 1, 2018. doi:10.1001/jamainternmed.2018.4251

Regulatory Uses of Sentinel Analyses

How ARIA Analyses Have Been Used by FDA

Drug Name	Outcome Assessed	ARIA Analysis	Regulatory Determination / Use	Date Posted
Non-insulin antidiabetics	• Duration of follow-up • Duration of use	Level 1	Feasibility assessment that supported an ARIA sufficiency determination to replace a sponsor postmarketing requirement (PMR) safety study for canagliflozin and renal cell carcinoma. • Results • Efficacy Supplement Approval Letter	04/02/2019
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	• Use in type 1 diabetes mellitus (T1DM) • Diabetic ketoacidosis (DKA)	Level 1	In response to clinical trials showing an increased risk of DKA with sotagliflozin in T1DM, FDA assessed off-label use of SGLT2 inhibitors (approved for use in T2DM) and real-world rates of DKA when used in patients with T1DM. Elevated rates of DKA with off label SGLT2 inhibitor use among patients with T1DM were seen compared to clinical trials. These findings were presented at the Advisory Committee meeting for sotagliflozin, and this helped inform the committee member discussion on the benefit-risk assessment. • Results • Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Materials	04/01/2019
Dolutegravir (Tivicay and combination products Juluca, Triumeq)	• Exposure in pregnancy	Level 1	FDA assessed the feasibility of conducting a postmarket study in Sentinel to further investigate preliminary results from an observational study suggesting a higher risk of neural tube defects among offspring of pregnant women using	03/28/2019

https://www.sentinelinitiative.org/drugs/how-aria-analyses-have-been-used-fda

Sentinel Analyses are Publicly Available

Assessments

This webpage provides access to Sentinel assessments that have been conducted by U.S. FDA's Center for Drug Evaluation and Research (CDER). The search options below can be used to find materials based on medical product, safety outcome, and the following study types:

- **Exploratory Analyses** characterize the rates of health outcomes, examine medical product use, and explore the feasibility of more detailed evaluations.
- **Safety Analyses** build on exploratory work and formally evaluate medical product-outcome associations using more advanced study designs and statistical methods to control for confounding.

Disclaimer

The information contained on this website is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Please read the disclaimer.

Product Name

Safety Outcome

Assessment Type

Any

Submit | Show All

Most Recent Drug Assessments

Title	Date Posted
Sentinel Modular Program Report: Use of Multiple Sclerosis Drugs Among Pregnant Women	12/06/2018
Sentinel Modular Program Report: Pulmonary Arterial Hypertension and Interstitial Lung Disease Events Among AOSD and SJIA Cohorts, Report 1	12/03/2018
Sentinel Modular Program Report: Pulmonary Arterial Hypertension and Interstitial Lung Disease Events Among Interleukin Inhibitor Users, Report 2	12/03/2018

Overview for Request cder_mpl1p_wp009_nsdp_v01

Request ID: cder_mpl1p_wp009_nsdp_v01

Request Description: This report contains estimates of multiple sclerosis (MS) drug use before, during, and after pregnancies resulting in a live-born delivery, among women in the Sentinel Distributed Database (SDD).

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 5.0.5, with additional ad hoc programming.

Data Source: Data from January 1, 2001 to August 31, 2017 from 16 Data Partners contributing to the SDD were included in this report. See Appendix A for a list of the dates of available data for each Data Partner. This request was distributed to Data Partners on November 20, 2017.

Study Design: The total number of pregnancies and the number and percentage of pregnancies with multiple sclerosis drug exposure were assessed among women of reproductive age. Results were stratified by exposure during the 183 to 91 and 90 to 1 days prior to pregnancy start, pregnancy trimester, and during the 90 and 91 to 183 days after delivery. Additionally, the results were stratified by maternal age at delivery, and by calendar year of delivery. An age-matched cohort of non-pregnant women was used as a comparator during the same time period in which pregnancy episodes were assessed.

Cohort Eligibility Criteria: Women members in the following age groups were included in the cohort: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, and 45-49 years. Eligible women were required to be enrolled in plans with medical and drug coverage for 274

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

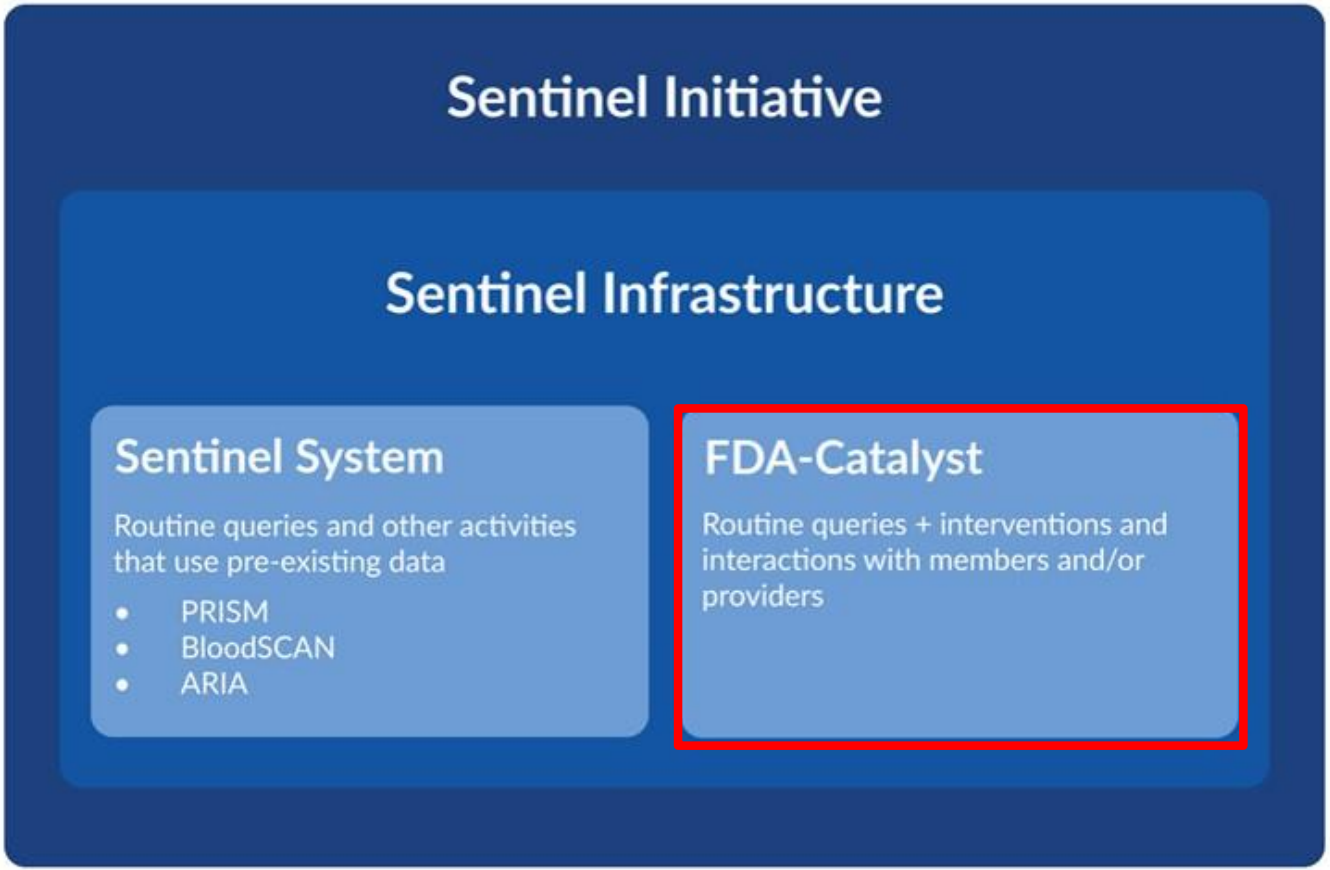
Pregnant Cohort	Use in the 183 - 91 Days Pre-pregnancy	Use in the 90 Days Pre-pregnancy	Any Use During Pregnancy	Any Use, 1st Trimester	Any Use, 2nd Trimester	Any Use, 3rd Trimester	Use in the 90 Days Post-pregnancy	Use in the 91 - 183 Days Post-pregnancy
Total Pregnancies	2,205,383 (100.0%)	2,205,383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

https://www.sentinelinitiative.org/drugs/assessments

FDA-CATALYST

The 21st Century Cures Act

- FDA shall establish a program *to evaluate the potential use* of real world evidence (RWE) to support:
  - Approval of new indication for a drug approved under section 505(c)
  - Satisfy post-approval study requirements
- Program will be based on a framework that:
  - Categorizes sources of RWE and gaps in data collection activities
  - Identifies standards and methodologies for collection and analysis
  - Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address
- Draft Guidance to be issued by 2021
- PDUFA commitments aligned with 21st Century Cures Act



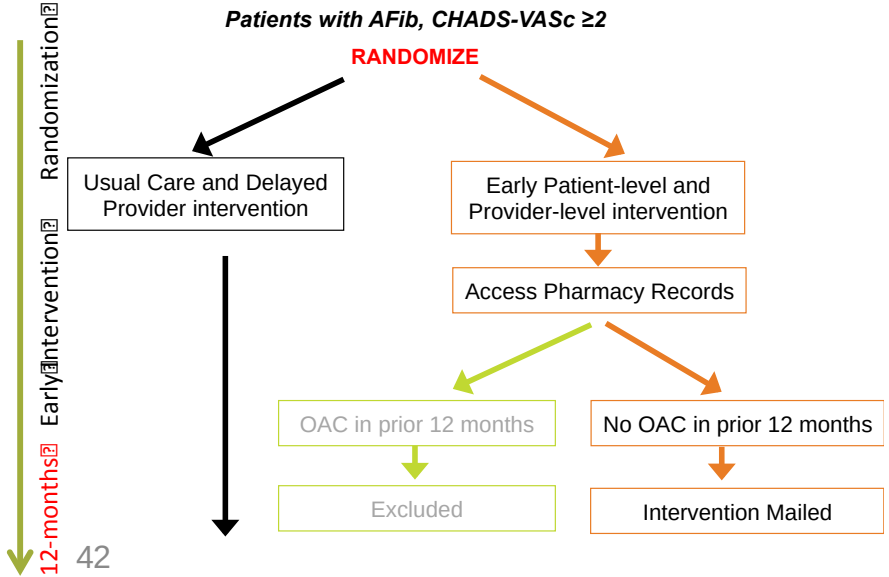
https://www.sentinelinitiative.org/sentinel/about

IMPACT Afib Trial

IMplementation of a randomized controlled trial to im**P**rove treatment with oral **A**nti**C**oagulan**T**s in patients with **A**trial **Fib**rillation

Test the ability of an education intervention to increase the appropriate use of oral anticoagulants in a patient population with atrial fibrillation (afib) at high risk of stroke

Enrollment of approximately 80,000 individuals in the early and late intervention arms

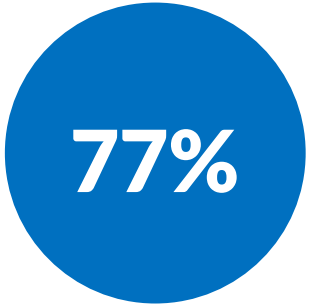


42

FDA MyStudies

- **Mobile App**
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)
- **Web-based Configuration Portal (WCP)**
  - Enables support of multiple types of medical product effectiveness and safety studies with minimal software development
- **Secure Storage Environment**
  - Generates secure tokens
  - Separates registration information and responses
  - Partitioned for multisite, decentralized, or distributed models

Smartphone use among U.S. adults is increasing[1]



now own Smartphones (35% in 2011)

Fewer (73%) own a laptop or desktop

Growth of "smartphone only" internet use[2]

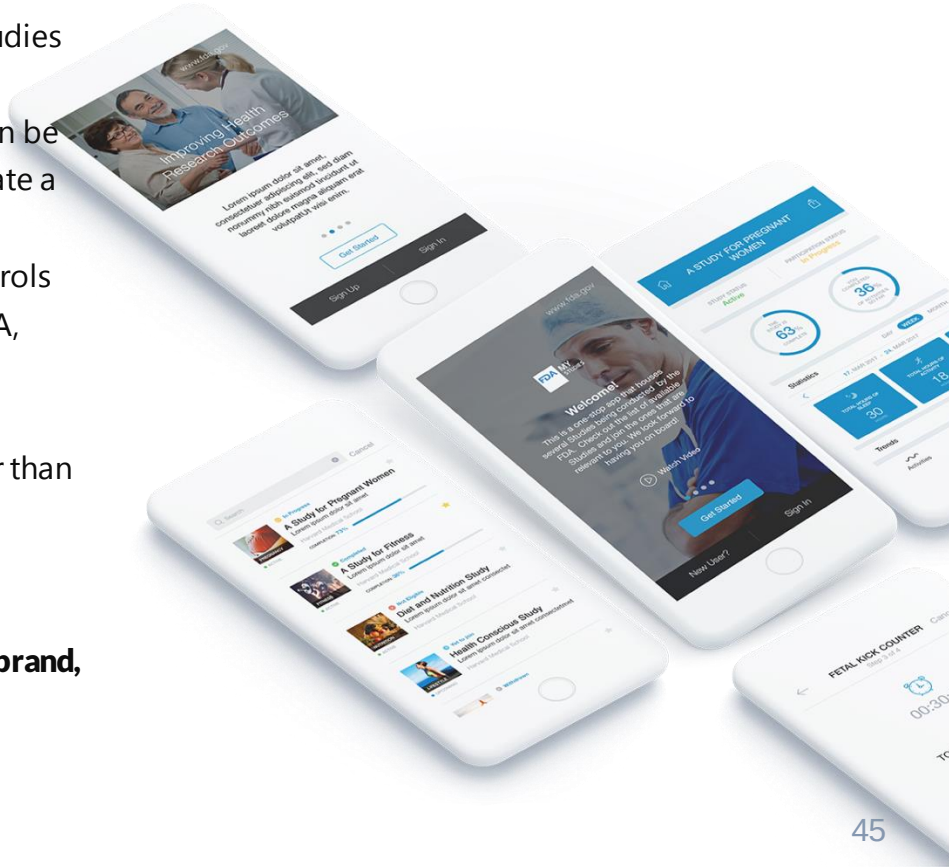
of US adults do not rely on traditional home internet service for access

Variation in "smartphone only" internet use[3]

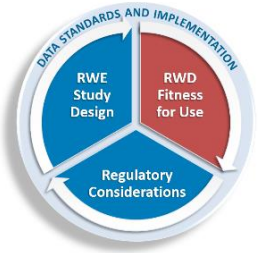
Reliance on smartphones for online access is especially common among younger adults (<50), non-whites and lower-income Americans.

Key System Attributes

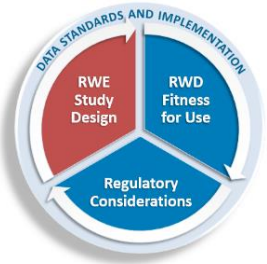
- **Scalable:** Capability to simultaneously support multiple studies for a research organization
- **Modular:** Various modular components of the platform can be integrated with external/3rd party system of choice to create a tailored solution for your organization.
- **Secure:** Partitions all data and provides robust access controls
- **Compliant**: Can be deployed to comply with HIPAA, FISMA, and 21 CFR Part 11
- **Customizable:** All study content as seen in the app can be authored and updated via the WCP web application rather than through new software development per study or app
- **Tested:** FDA and PCORI sponsored clinical research demonstration projects
- **Open-source and ready for research organizations to re-brand, publish, and use!**



RELIANCE Trial

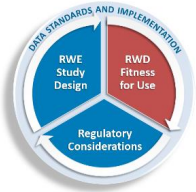


- RofLumilast or Azithromycin to prevent COPD Exacerbations
  - Randomized “real world” trial; 1,600 adults in each arm
  - Azithromycin - macrolide with anti-inflammatory properties
  - Roflumilast - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor
- Primary outcomes
  - All cause hospitalization
  - All cause mortality
- Follow-up
  - 6-36 months, no visits, call center, Patient Portal, Site EMR
  - CMS linkage through FDA-Catalyst for outcomes and exposures
    - Enrollment files: all cause mortality
    - Inpatient claims files: all cause hospitalization for fee for service
    - Part C (Medicare Managed Care): new data source – will request if feasible
    - Part D: medication dispensing



Limit JIA trial

- **Randomized real world trial in patients with Limited Juvenile Idiopathic Arthritis** (<=4 joints affected and no uveitis)
  - **Six month course of subcutaneous Abatacept** (T cell co-stimulation inhibitor) **plus usual care** with NSAIDs and intra-articular glucocorticoids **vs. usual care alone**
  - **Outcome:** extension to more than 4 joints, new uveitis, and/or need for treatment with systemic medication at 18 months



- **FDA-Catalyst is aligning with the trial by providing support from the MyStudies App**
  - First use of FDA-Catalyst to support a pediatric trial
  - Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry
  - Collection of primary outcome (uveitis) from ophthalmology appointments - Configured
  - Collection of adherence information/adverse events for study drug with “drug diary” – Configuration stage

SPARC registry

- **SPARC Inflammatory Bowel Disease cohort within the IBD Plexus research exchange platform**
  - Provider based recruitment of individuals >18 years of age with a confirmed IBD diagnosis from academic and community sites

- **FDA-Catalyst is aligning registry by providing support from the My Studies App**
  - Configuration stage
- Registry responses will be included in the **PCORI Comparative Effectiveness of Biologic or Small Molecule Therapies in Inflammatory Bowel Disease study** (prospective cohort for patient reported outcomes)

Discussion


FDA
U.S. FOOD & DRUG
ADMINISTRATION