The FDA Sentinel System

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Sentinel

- What Sentinel is
- How Sentinel gets, standardizes, and checks its data
- How Sentinel supports post-market surveillance
- How Sentinel builds trust through transparency
- Discussion

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Public Law 110–85
110th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Sept. 27, 2007
[H.R. 3580]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

Food and Drug Administration Amendments Act of 2007.
21 USC 301 note.

This Act may be cited as the "Food and Drug Administration Amendments Act of 2007".

SEC. 905. ACTIVE POSTMARKET RISK IDENTIFICATION AND ANALYSIS.

(a) IN GENERAL.—Subsection (k) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended by adding at the end the following:

"(3) ACTIVE POSTMARKET RISK IDENTIFICATION.—

"(A) DEFINITION.—In this paragraph, the term 'data' refers to information with respect to a drug approved under this section or under section 351 of the Public Health Service Act, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

"(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

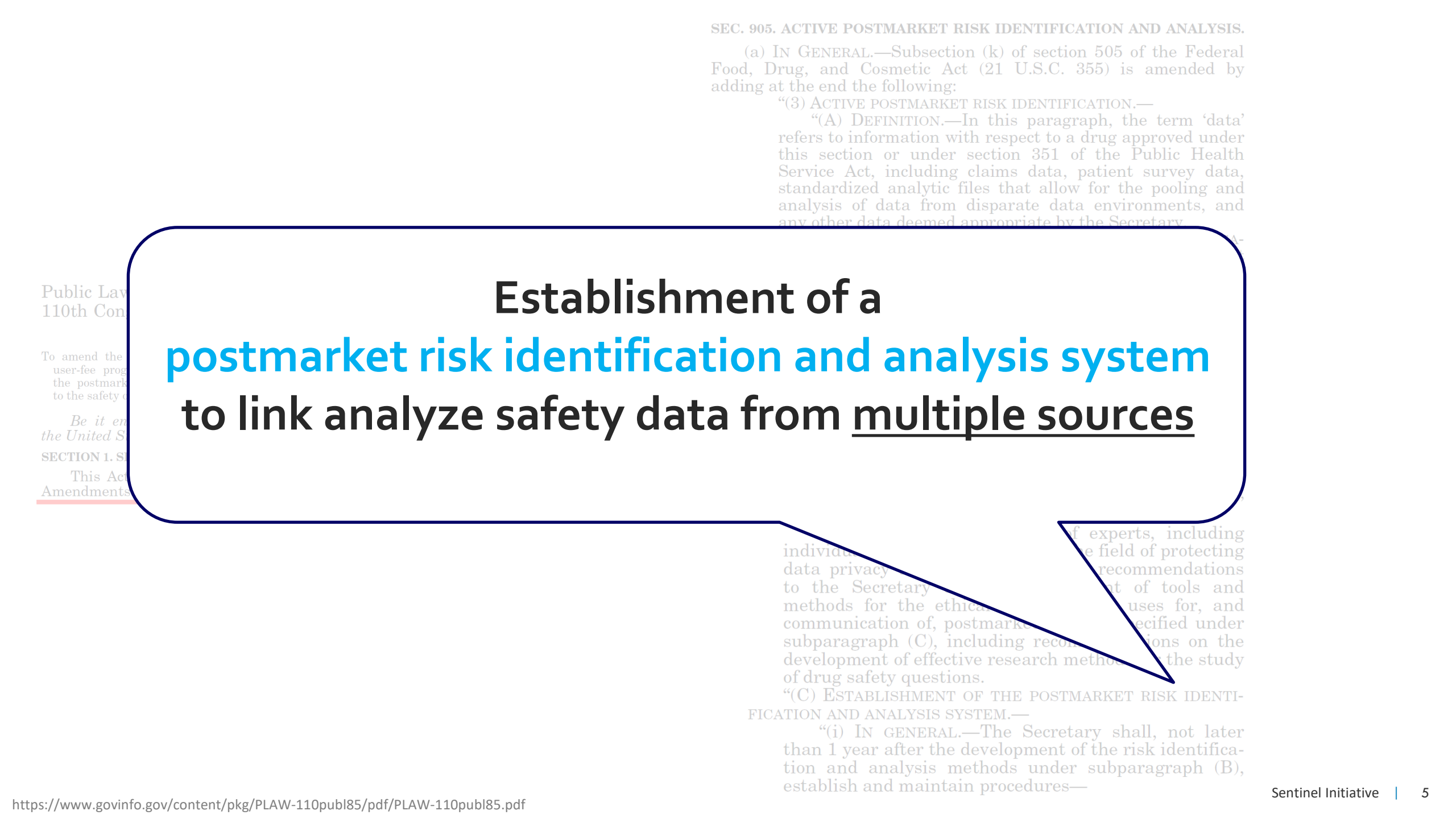
"(II) at least 100,000,000 patients by July 1, 2012; and

"(iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.

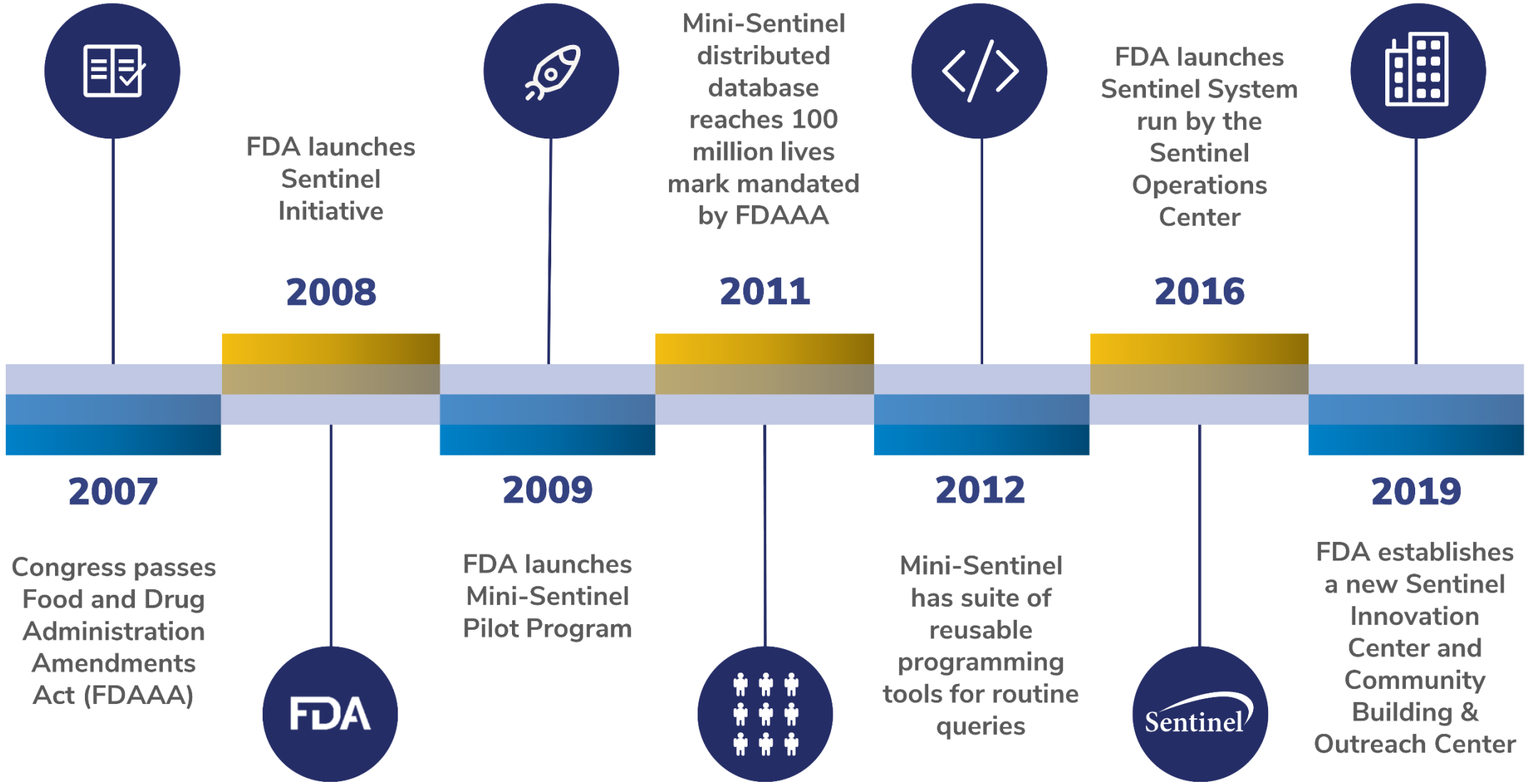
"(C) ESTABLISHMENT OF THE POSTMARKET RISK IDENTIFICATION AND ANALYSIS SYSTEM.—

"(i) IN GENERAL.—The Secretary shall, not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), establish and maintain procedures—

https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf



https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf



https://www.sentinelinitiative.org/about

Sentinel

- What Sentinel is
- **How Sentinel gets, standardizes, and checks its data**
- How Sentinel supports post-market surveillance
- How Sentinel builds trust through transparency
- Discussion

Collaborating Institutions

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

Harvard Pilgrim Health Care Institute

CVS Health

aetna™

Aetna, part of the CVS Health Family of companies.

carelon

Elevance Health

Optum

HealthPartners® Institute

Humana Healthcare Research

TN Division of TennCare

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

KAISER PERMANENTE®
Colorado
Hawaii
Mid-Atlantic
Northwest
Washington

TriNetX

Marshfield Clinic Research Institute

HCA Healthcare℠

merative

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

Male, 55 Years Old, From Boston

Has Appendectomy

Diagnosed with Hypertension

Routine Office Visit

2017 | 2018 | 2019 | 2020

1/1/2017

Encounter

Office Visit Diagnosis:
Influenza with pneumonia

Dispensings

Prescription:
Antibiotic

3/15/2018

Encounters

Emergency Department Procedure:
Appendectomy

3/15/2018 - 3/18/2018

Hospital:
Inpatient Stay

12/11/2018

Encounter

Office Visit Diagnosis:
Hypertension

Dispensings

Prescription:
Anti-hypertensive

10/31/2019

Encounter

Office Visit Diagnosis:
Hypertension

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

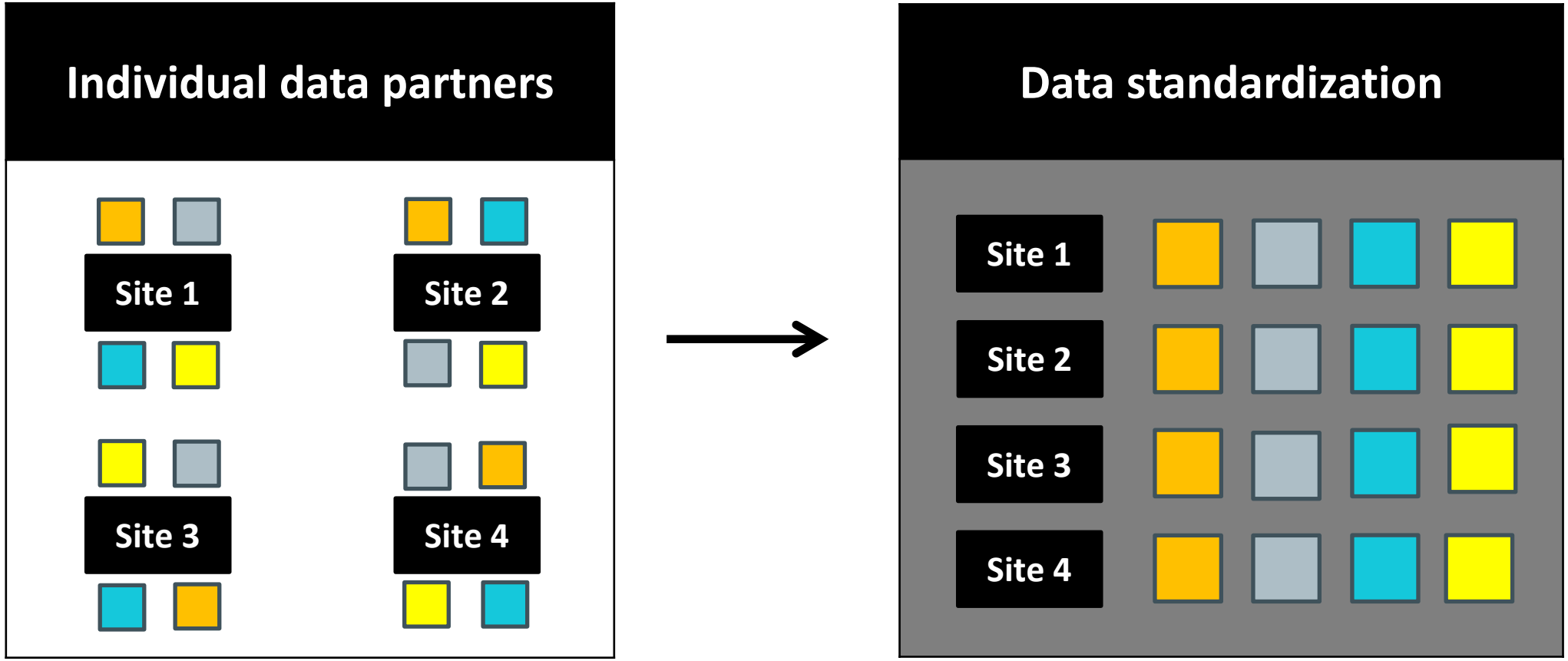
PROCEDURE

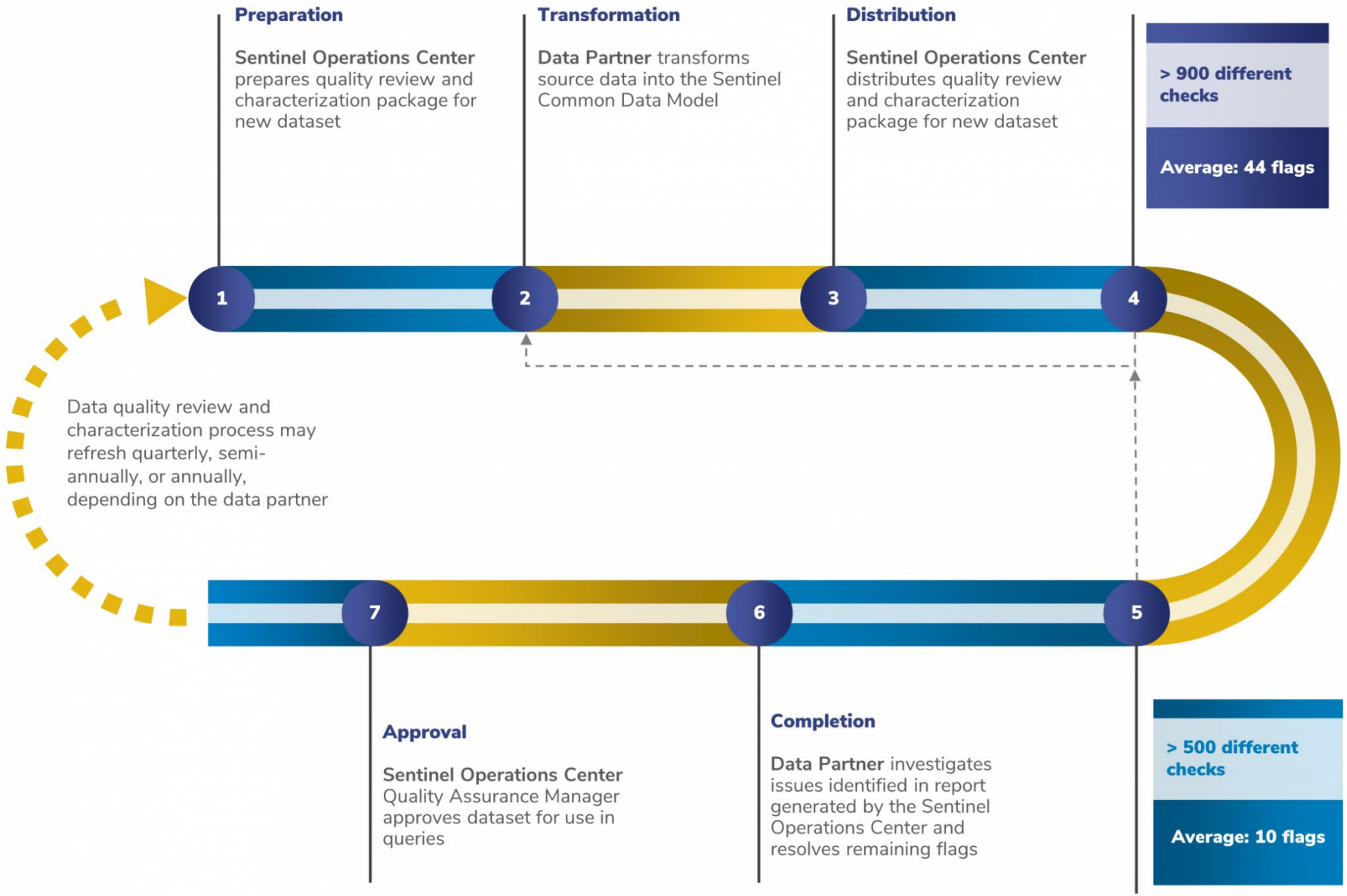
PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99222	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99238	C4
PatID1	EncID1	10/18/2005	Provider2	IP	27445	C4

CAUSE OF DEATH

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

Hypothetical numbers; for illustrative purposes only


Individual data partners
Site 1
Site 2
Site 3
Site 4
Data standardization
Site 1
Site 2
Site 3
Site 4



Quality Assurance Checks & Model Compliance

Data Partner runs quality review and characterization package completing the following:

-Level 1 checks: single table checks
-Level 2 checks: cross-table checks

Quality reviews and characterization package outputs lists of errors or anomalies (flags) identified during data checks

Data Partner resolves these flags and sends a detailed response to the Sentinel Operations Center

Quality Assurance Review

Sentinel Operations Center receives output from Data Partner and reviews

Sentinel Operations Center runs additional quality assurance checks:

-Level 3 checks: cross-time checks

Sentinel Operations Center evaluates any additional flags and creates issue report for Data Partner to address

Types of Data Quality Checks and Examples

Level 1 Checks:
Single table checks

- **Completeness**
  Admission date is not missing value
- **Validity**
  Admission date is in date format

Level 2 Checks:
Cross-table checks

- **Accuracy**
  Admission date occurs before the patient's discharge
- **Integrity**
  Admission date occurs within the patient's active enrollment period

Level 3 Checks:
Cross-time checks

- **Consistency of Trends**
  There is no sizable percent change in admission date record counts by month-year

Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

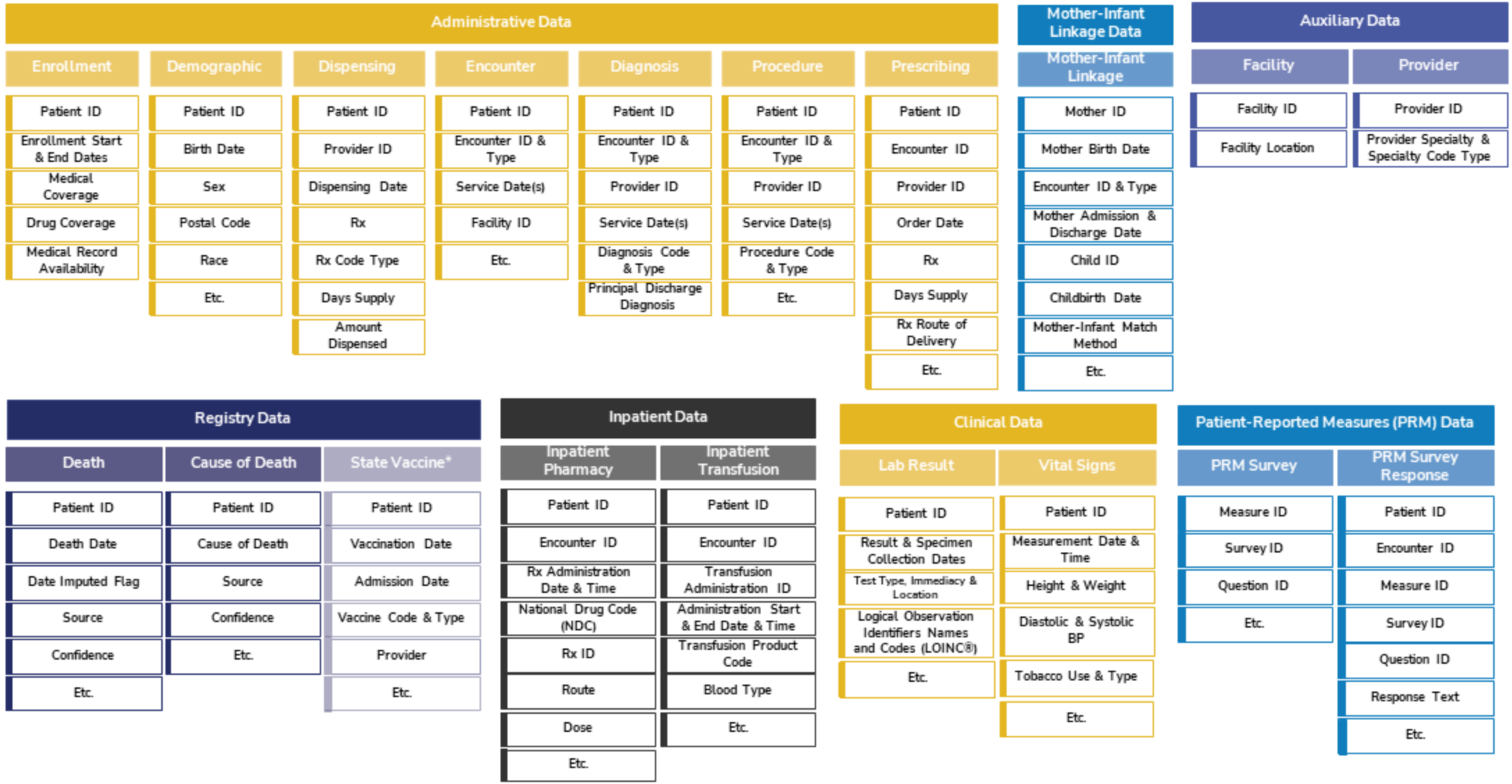
Sentinel

SENTINEL DATA QUALITY ASSURANCE PRACTICES

COMPLIANCE WITH "GUIDANCE FOR INDUSTRY AND FDA STAFF: BEST PRACTICES FOR CONDUCTING AND REPORTING PHARMACOEPIDEMIOLOGIC SAFETY STUDIES USING ELECTRONIC HEALTHCARE DATA"

https://www.fda.gov/downloads/drugs/guidances/ucm243537.pdf
https://www.fda.gov/media/152503/download
https://www.sentinelinitiative.org/sites/default/files/data/distributed-database/Sentinel_DataQAPractices_Memo.pdf

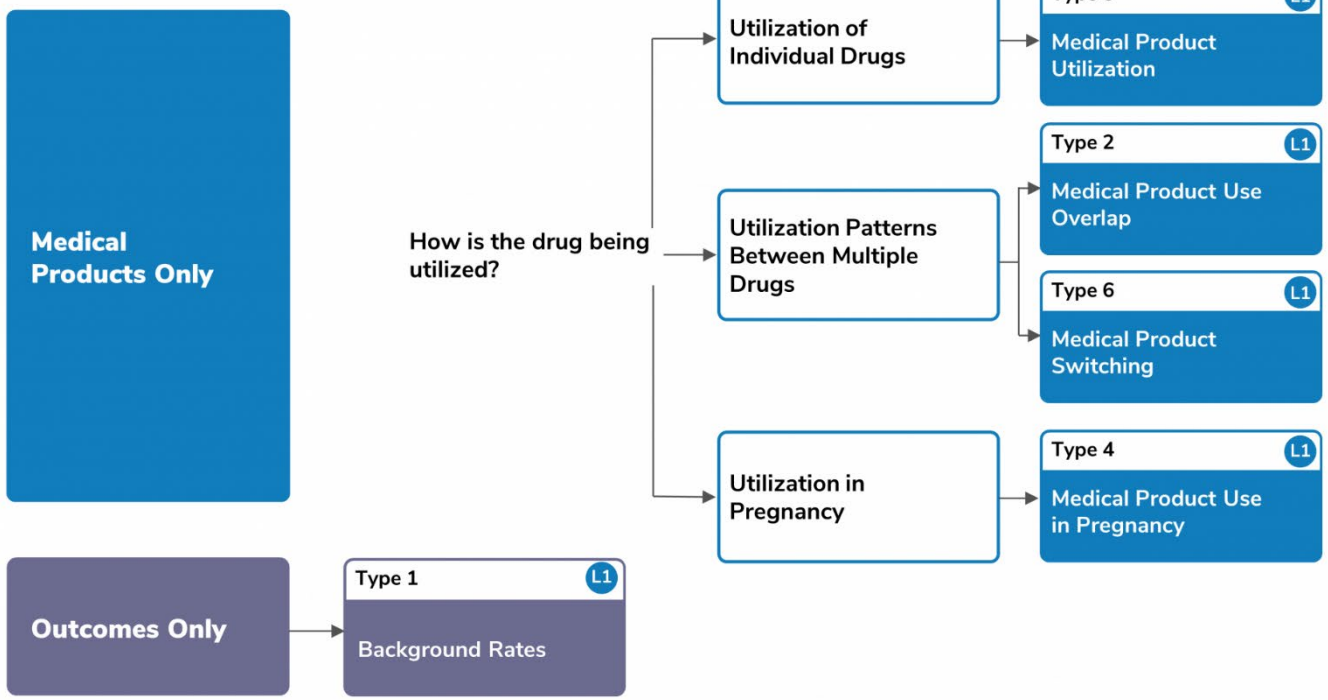
Sentinel Common Data Model



*The State Vaccine table has not been in use since SCDM v6.0.

What are you investigating?

SI Signal Identification | L1 Level 1 Analysis | L2 Level 2 Analysis | L3 Level 3 Analysis



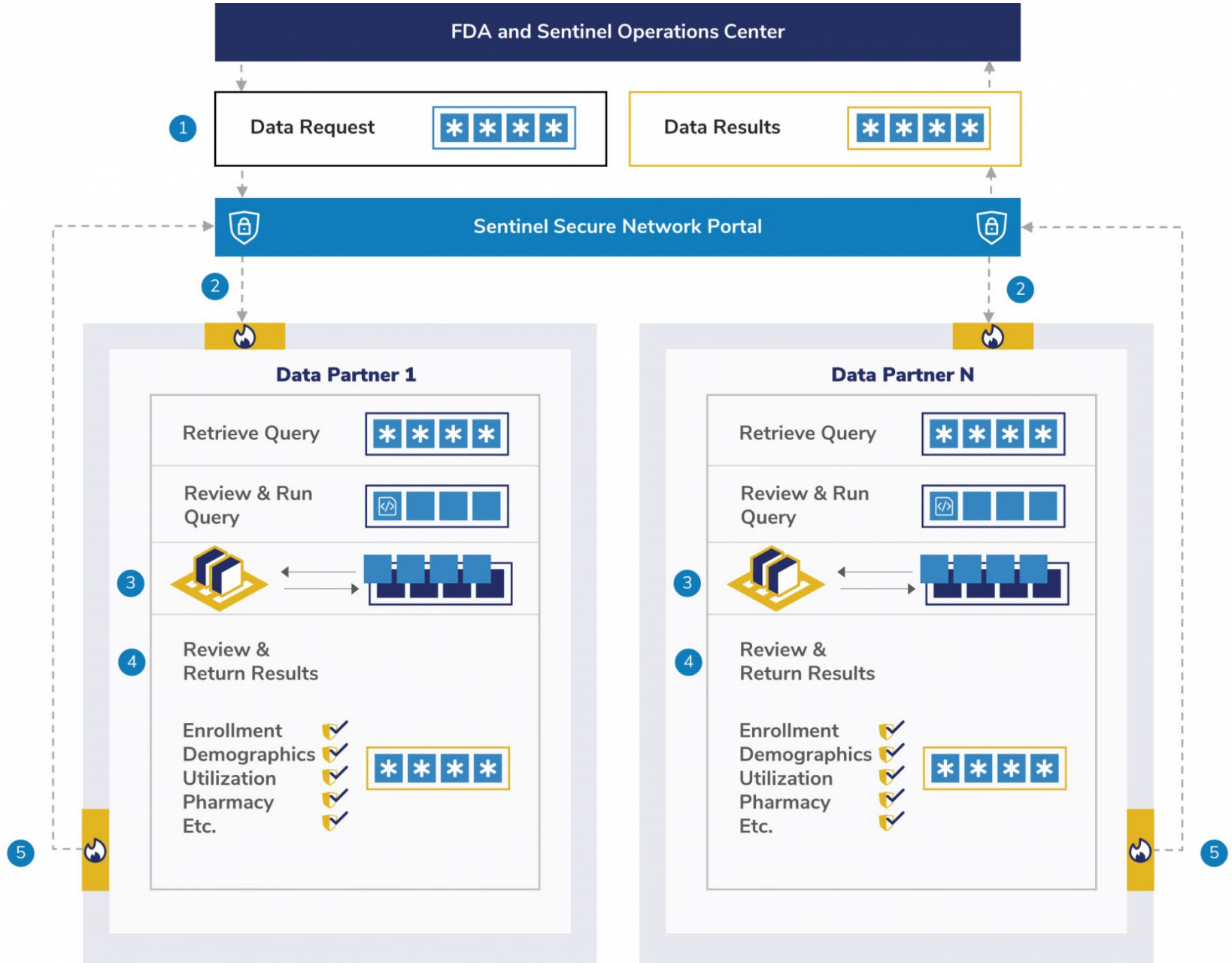
Medical Products & Outcomes						
Type 2 L1	Type 2 or 4 SI L2 L3	Type 2 or 4 L2 L3	Type 3 SI L2 L3	Type 2 L2	Type 2 L1
Incidence Rates	Propensity Score Analysis	Covariate Stratification	Self-Controlled Risk Interval Design	Interrupted Time Series	Multiple Events Tool

1. FDA data request sent to Data Partners via FISMA-compliant secure network portal
2. Data Partners retrieve query
3. Data Partners review and run query against their local data behind their firewalls
4. Data Partners review results for accuracy and privacy compliance
5. Data Partners return de-identified results to SOC via secure portal

Firewall

Local Data

Privacy Compliance



463 million
unique patient identifiers (2000-2023)

1.1 billion
person-years of data*

113 million
members currently accruing data*

20 billion
pharmacy dispensing*

20 billion
medical encounters*

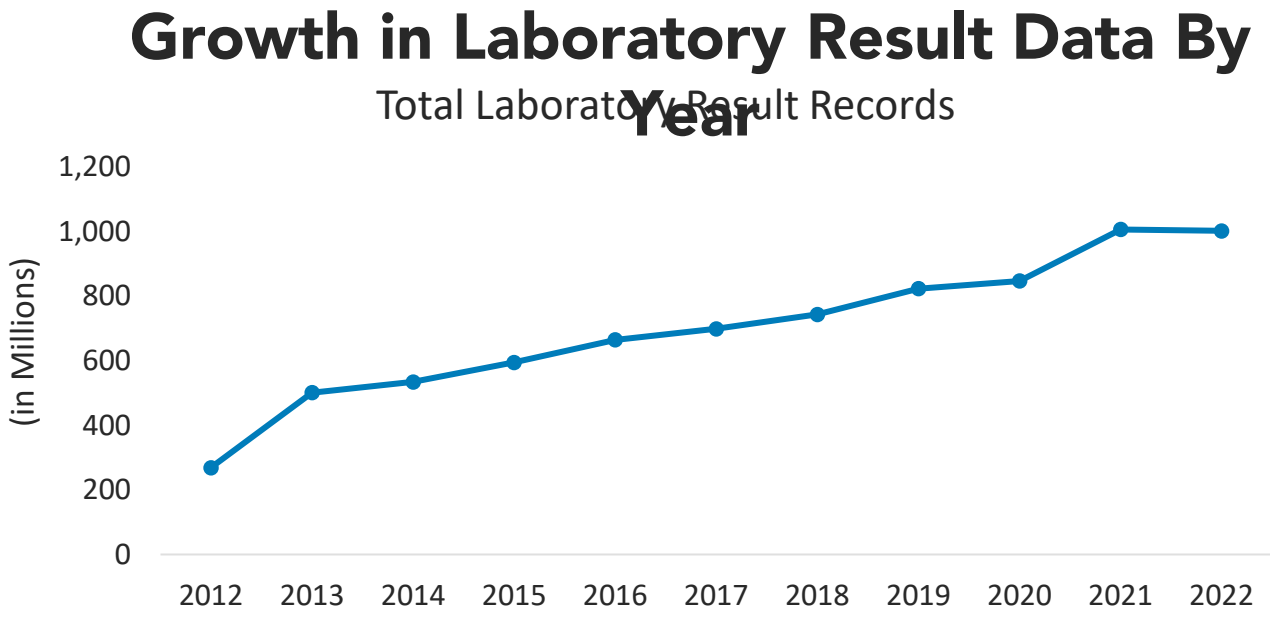
8 million
deliveries with mom-baby linkage

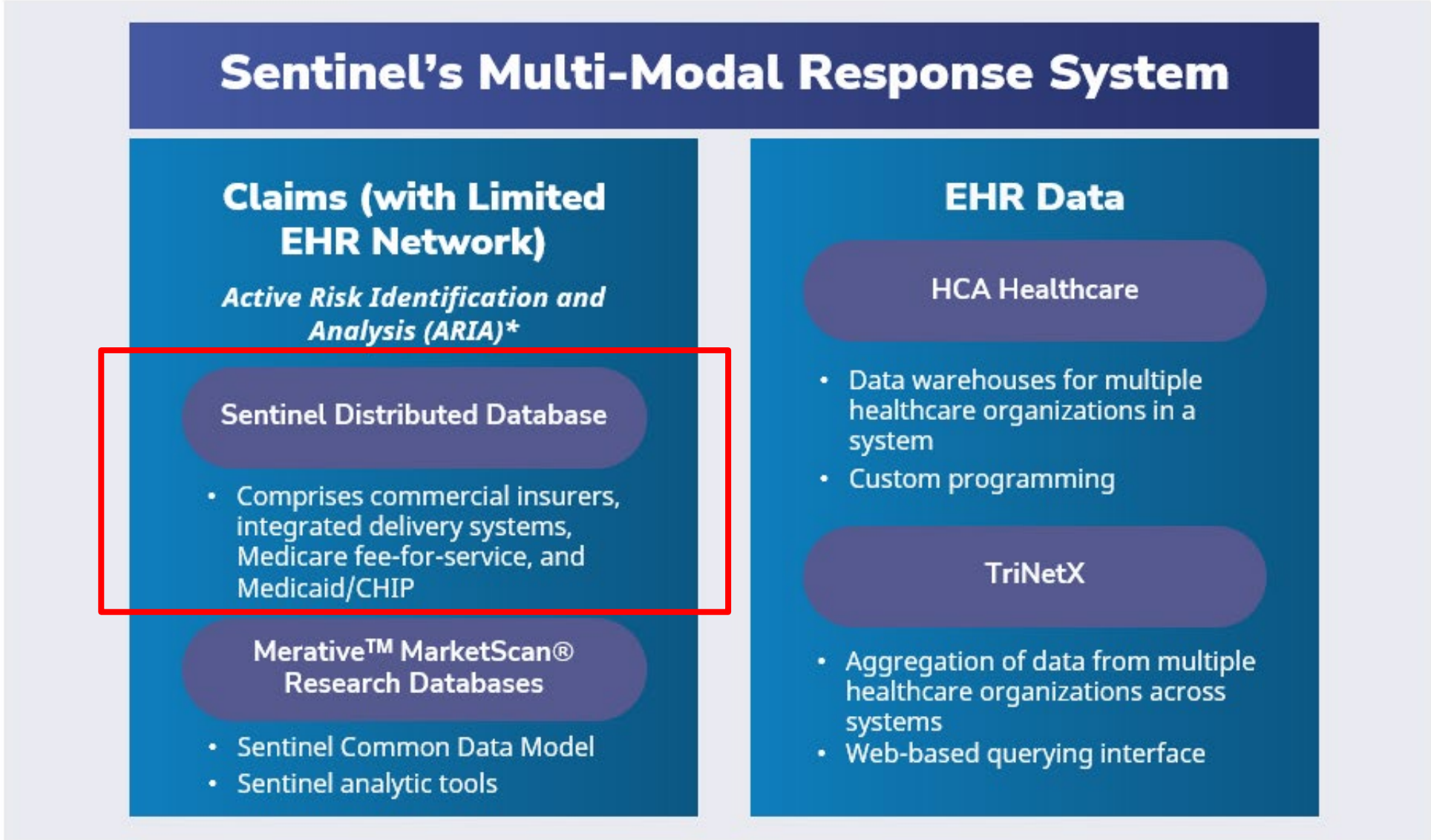
* Among individuals with both medical and drug coverage

Table	DP Count	Member Count	Record Count
Laboratory Results	11	99,358,668	8,857,509,772
Vital Signs	7	10,636,075	368,812,494
Prescribing	3	3,271,299	162,101,760

Members with Medical and Drug Coverage who Have at least One Vital Sign Measurement, by Vital Sign Measure

Vital Sign	Member Count
Diastolic Blood Pressure	6,253,679
Systolic Blood Pressure	6,254,628
Weight	6,416,934
Height	5,942,271





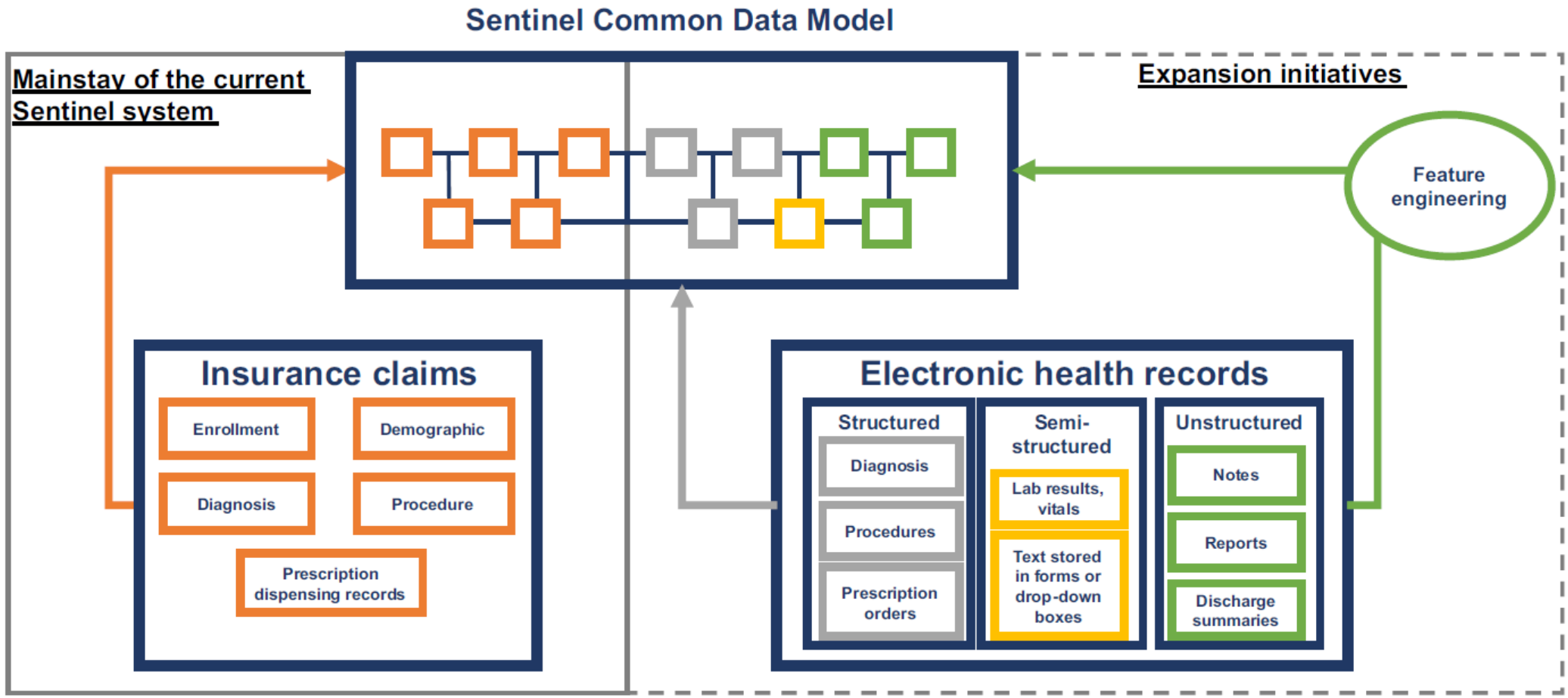
**Note: The Active Risk Identification and Analysis (ARIA) System is comprised of the Sentinel Distributed Database, the Sentinel Common Data Model, and Sentinel analytic tools.*

PERSPECTIVE OPEN

Broadening the reach of the FDA Sentinel system: A roadmap for integrating electronic health record data in a causal analysis framework

Rishi J. Desai[1✉], Michael E. Matheny[2], Kevin Johnson[2], Keith Marsolo[3], Lesley H. Curtis[3], Jennifer C. Nelson[4], Patrick J. Heagerty[5], Judith Maro[6], Jeffery Brown[6], Sengwee Toh[6], Michael Nguyen[7], Robert Ball[7], Gerald Dal Pan[7], Shirley V. Wang[1], Joshua J. Gagne[1,8] and Sebastian Schneeweiss[1]

npj Digital Medicine (2021) 170



PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**(S1): 100–128
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2312

ORIGINAL REPORT

A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data

Susan E. Andrade*, Leslie R. Harrold, Jennifer Tjia, Sarah L. Cutrona, Jane S. Saczynski, Katherine S. Dodd, Robert J. Goldberg and Jerry H. Gurwitz

Meyers Primary Care Institute (Reliant Medical Group, Fallon Community Health Plan, and University of Massachusetts Medical School), Worcester, MA, USA

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**(S1): 129–140
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2313

ORIGINAL REPORT

A systematic review of validated methods for identifying heart failure using administrative data

Jane S. Saczynski*, Susan E. Andrade, Leslie R. Harrold, Jennifer Tjia, Sarah L. Cutrona, Katherine S. Dodd, Robert J. Goldberg and Jerry H. Gurwitz

Division of Geriatric Medicine and Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester, MA, USA

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**(S1): 174–182
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2335

ORIGINAL REPORT

A systematic review of validated methods for identifying suicide or suicidal ideation using administrative or claims data

James T. Walkup[1]*, Lisa Townsend[2], Stephen Crystal[2,3] and Mark Olfson[4]

[1] *Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA*
[2] *School of Social Work, Rutgers University, New Brunswick, NJ, USA*
[3] *Chronic Disease Management and Outcomes, Center for Health Services Research on Pharmacotherapy, New Brunswick, NJ, USA*
[4] *Department of Psychiatry, Columbia University, New York, New York, USA*

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**(S1): 194–202
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2334

ORIGINAL REPORT

A systematic review of validated methods for identifying pancreatitis using administrative data

Kevin Moores[1,2]*, Bradley Gilchrist[1,2], Ryan Carnahan[3] and Thad Abrams[4,5]

[1] *Division of Drug Information Service, The University of Iowa College of Pharmacy, Iowa City, IA, USA*
[2] *Iowa Drug Information Service, The University of Iowa College of Pharmacy, Iowa City, IA, USA*
[3] *Department of Epidemiology, University of Iowa College of Public Health, Iowa City, IA, USA*
[4] *Department of Internal Medicine, Division of General Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA*
[5] *Center for Implementation of Innovative Strategies in Practice, Iowa City Veterans Affairs Medical Center, Iowa City, IA, USA*

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 40–54
Published online 29 June 2012 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3310

ORIGINAL REPORT

Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program

Sarah L. Cutrona[1]*, Sengwee Toh[2], Aarthi Iyer[2], Sarah Foy[1], Gregory W. Daniel[5], Vinit P. Nair[6], Daniel Ng[7], Melissa G. Butler[8], Denise Boudreau[9], Susan Forrow[2], Robert Goldberg[1], Joel Gore[3], David McManus[3], Judith A. Racoosin[4] and Jerry H. Gurwitz[1]

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 861–872
Published online 25 June 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3470

ORIGINAL REPORT

Validity of diagnostic codes to identify cases of severe acute liver injury in the U.S. Food and Drug Administration's Mini-Sentinel Distributed Database

Vincent Lo Re III[1,2]*, Kevin Haynes[2], David Goldberg[2,3], Kimberly A. Forde[2,3], Dena M. Carbonari[2], Kimberly B. F. Leidl[2], Sean Hennessy[2], K. Rajender Reddy[3], Pamala A. Pawloski[4], Gregory W. Daniel[5,6], T. Craig Cheetham[7], Aarthi Iyer[8], Kara O. Coughlin[8], Sengwee Toh[8], Denise M. Boudreau[9], Nandini Selvam[5], William O. Cooper[10], Mano S. Selvan[11], Jeffrey J. VanWormer[12], Mark I. Avigan[13], Monika Houstoun[13], Gwen L. Zornberg[13], Judith A. Racoosin[13] and Azadeh Shoaibi[13]

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 1205–1213
Published online 5 September 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3505

ORIGINAL REPORT

Validation of anaphylaxis in the Food and Drug Administration's Mini-Sentinel

Kathleen E. Walsh[1]*, Sarah L. Cutrona[1,2], Sarah Foy[1], Meghan A. Baker[3,4], Susan Forrow[4], Azadeh Shoaibi[5], Pamala A. Pawloski[6], Michelle Conroy[7], Andrew M. Fine[8], Lise E. Nigrovic[8], Nandini Selvam[9], Mano S. Selvan[10], William O. Cooper[11] and Susan Andrade[1]

Mini-Sentinel

VALIDATION OF ACUTE KIDNEY INJURY CASES IN THE MINI-SENTINEL DISTRIBUTED DATABASE

Prepared by: Uptal D. Patel, MD,[1,2] N. Chantelle Hardy, MPH,[2] David H. Smith, RPh, PhD,[3] Jerry H. Gurwitz, MD,[4] Chi-yuan Hsu, MD, MSc,[5] Chirag R. Parikh, MD, PhD,[6] Steven M. Brunelli, MD, MSCE,[7] Meghan Baker, MD,ScD[8] Susan Forrow, BA,[8] Carly Comins, BS,[8] Denise M. Boudreau, PhD, RPh,[9] Chunfu Liu, ScD,[10] Pamala A. Pawloski, PharmD,[11] Nandini Selvam, PhD, MPH,[10] Mano S. Selvan, PhD,[12] Shannon Stratton, BS,[13] Jeffrey J. VanWormer, PhD,[14] George Aggrey, MD, MPH,[15] Melanie Blank, MD,[15] Patrick Archdeacon, MD[15]

Received: 11 August 2020 | Revised: 1 April 2021 | Accepted: 20 April 2021
DOI: 10.1002/pds.5256

ORIGINAL ARTICLE

WILEY

Validation of an electronic algorithm for Hodgkin and non-Hodgkin lymphoma in ICD-10-CM

Mara M. Epstein[1,2] | Sarah K. Dutcher[3] | Judith C. Maro[4] | Cassandra Saphirak[1,2] | Sandra DeLuccia[4] | Muthalagu Ramanathan[5] | Tejaswini Dhawale[6] | Sonali Harchandani[5] | Christopher Delude[2] | Laura Hou[4] | Autumn Gertz[4] | Nina DiNunzio[4] | Cheryl N. McMahill-Walraven[7] | Mano S. Selvan[8] | Justin Vigeant[4] | David V. Cole[4] | Kira Leishear[3] | Jerry H. Gurwitz[1,2] | Susan Andrade[1,2] | Noelle M. Cocoros[4]

Received: 5 February 2021 | Revised: 24 May 2021 | Accepted: 1 June 2021
DOI: 10.1002/pds.5300

ORIGINAL ARTICLE

WILEY

Validation of an ICD-10-based algorithm to identify stillbirth in the Sentinel System

Susan E. Andrade[1] | Mayura Shinde[2] | Tiffany A. Moore Simas[3] | Steven T. Bird[4] | Justin Bohn[2] | Kevin Haynes[5] | Lockwood G. Taylor[4] | Julianne R. Lauring[3] | Erin Longley[6] | Cheryl N. McMahill-Walraven[7] | Connie M. Trinacty[8] | Cassandra Saphirak[1] | Christopher Delude[1] | Sandra DeLuccia[2] | Tancy Zhang[2] | David V. Cole[2] | Nina DiNunzio[2] | Autumn Gertz[2] | Elnara Fazio-Eynullayeva[2] | Danijela Stojanovic[4]

Received: 1 February 2021 | Accepted: 11 April 2021
DOI: 10.1002/pds.5253

ORIGINAL ARTICLE

WILEY

Validity of ICD-10-CM diagnoses to identify hospitalizations for serious infections among patients treated with biologic therapies

Vincent Lo Re III[1,2] | Dena M. Carbonari[2] | Jerry Jacob[1] | William R. Short[1] | Charles E. Leonard[2] | Jennifer G. Lyons[3] | Adee Kennedy[3] | Jolene Damon[3] | Nicole Haug[3] | Esther H. Zhou[4] | David J. Graham[4] | Cheryl N. McMahill-Walraven[5] | Lauren E. Parlett[6] | Vinit Nair[7] | Mano Selvan[7] | Yunping Zhou[7] | Gaia Pocobelli[8] | Judith C. Maro[3] | Michael D. Nguyen[4]

Received: 19 May 2021 | Revised: 5 November 2021 | Accepted: 9 December 2021
DOI: 10.1002/pds.5401

BRIEF REPORT

WILEY

Validation of diagnosis codes to identify hospitalized COVID-19 patients in health care claims data

Sheryl A. Kluberg[1] | Laura Hou[1] | Sarah K. Dutcher[2] | Monisha Billings[2] | Brian Kit[2] | Sengwee Toh[1] | Sascha Dublin[3] | Kevin Haynes[4] | Annemarie Kline[5] | Mahesh Maiyani[6] | Pamala A. Pawloski[7] | Eric S. Watson[8] | Noelle M. Cocoros[1]

Received: 31 December 2017 | Revised: 3 July 2018 | Accepted: 1 August 2018
DOI: 10.1002/pds.4645

ORIGINAL REPORT

WILEY

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

Robert Ball[1] | Sengwee Toh[2] | Jamie Nolan[2] | Kevin Haynes[3] | Richard Forshee[4] | Taxiarchis Botsis[4]

Pharmacoepidemiol Drug Saf. 2018;**27**:1077–1084.

Journal of the American Medical Informatics Association, 28(7), 2021, 1507–1517
doi: 10.1093/jamia/ocab036
Advance Access Publication Date: 13 March 2021
Research and Applications

Research and Applications

Electronic phenotyping of health outcomes of interest using a linked claims-electronic health record database: Findings from a machine learning pilot project

Teresa B. Gibson,[1]* Michael D. Nguyen,[2] Timothy Burrell,[1] Frank Yoon,[1] Jenna Wong,[3] Sai Dharmarajan,[4] Rita Ouellet-Hellstrom,[5] Wei Hua,[2] Yong Ma,[6] Elande Baro,[7] Sarah Bloemers,[1] Cory Pack,[1] Adee Kennedy,[3] Sengwee Toh,[3] and Robert Ball[8]

ARTICLES

Successful Comparison of US Food and Drug Administration Sentinel Analysis Tools to Traditional Approaches in Quantifying a Known Drug-Adverse Event Association

JJ Gagne[1], X Han[2], S Hennessy[2], CE Leonard[2], EA Chrischilles[3], RM Carnahan[3], SV Wang[1], C Fuller[4], A Iyer[4], H Katcoff[4], TS Woodworth[4], P Archdeacon[5], TE Meyer[6], S Schneeweiss[1] and S Toh[4]

VOLUME 100 NUMBER 5 | NOVEMBER 2016:558-564

ORIGINAL ARTICLE

Sentinel Modular Program for Propensity Score–Matched Cohort Analyses

Application to Glyburide, Glipizide, and Serious Hypoglycemia

Meijia Zhou,[a] Shirley V. Wang,[b] Charles E. Leonard,[a] Joshua J. Gagne,[b] Candace Fuller,[c] Christian Hampp,[d] Patrick Archdeacon,[d] Sengwee Toh,[c] Aarthi Iyer,[c] Tiffany Siu Woodworth,[c] Elizabeth Cavagnaro,[c] Catherine A. Panozzo,[c] Sophia Axtman,[c] Ryan M. Carnahan,[e] Elizabeth A. Chrischilles,[e] and Sean Hennessy[a]

Epidemiology 2017;28: 838–846

Received: 18 September 2017 | Revised: 19 January 2018 | Accepted: 8 February 2018

DOI: 10.1002/pds.4420

ORIGINAL REPORT

WILEY

Evaluation of the US Food and Drug Administration sentinel analysis tools in confirming previously observed drug-outcome associations: The case of clindamycin and *Clostridium difficile* infection

Ryan M. Carnahan[1] | Jennifer L. Kuntz[2] | Shirley V. Wang[3] | Candace Fuller[4] | Joshua J. Gagne[3] | Charles E. Leonard[5] | Sean Hennessy[5] | Tamra Meyer[6] | Patrick Archdeacon[6] | Chih-Ying Chen[6] | Catherine A. Panozzo[4] | Sengwee Toh[4] | Hannah Katcoff[4] | Tiffany Woodworth[4] | Aarthi Iyer[4] | Sophia Axtman[4] | Elizabeth A. Chrischilles[1]

Pharmaceutical Medicine (2019) 33:29–43
https://doi.org/10.1007/s40290-018-00265-w

ORIGINAL RESEARCH ARTICLE

CrossMark

Evaluation of the US Food and Drug Administration Sentinel Analysis Tools Using a Comparator with a Different Indication: Comparing the Rates of Gastrointestinal Bleeding in Warfarin and Statin Users

Ryan M. Carnahan[1] · Joshua J. Gagne[2] · Christian Hampp[3] · Charles E. Leonard[4] · Sengwee Toh[5] · Candace C. Fuller[5] · Sean Hennessy[4] · Laura Hou[5] · Noelle M. Cocoros[5] · Genna Panucci[5] · Tiffany Woodworth[5] · Austin Cosgrove[5] · Aarthi Iyer[5] · Elizabeth A. Chrischilles[1]

Sentinel

- What Sentinel is
- How Sentinel gets, standardizes, and checks its data
- How Sentinel supports post-market surveillance
- How Sentinel builds trust through transparency
- Discussion

Conduct drug safety studies for safety concerns that arise during the review of an application for a new drug or biologic

NDA 211801

NDA APPROVAL

Ardelyx, Inc.
Attention: Robert C. Blanks, M.S., RAC
Senior Vice President, Regulatory Affairs and Quality Assurance
34175 Ardenwood Blvd.
Suite 100
Fremont, CA 94555

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate tenapanor in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the following serious risks: risk of inflammatory bowel disease.

The ARIA safety assessment will be posted to the Sentinel website.[3] Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/211801Orig1s000ltr.pdf

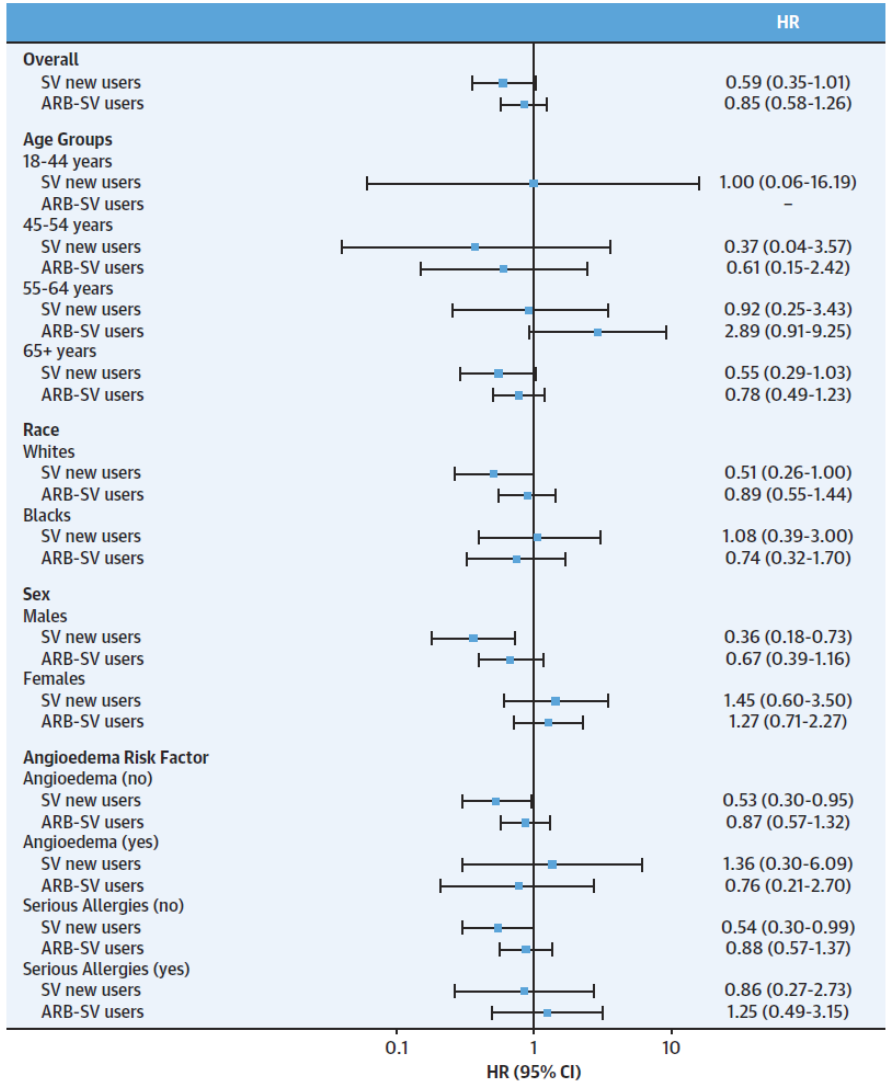
Conduct retrospective studies of medication safety

Comparative Risk of Angioedema With Sacubitril-Valsartan vs Renin-Angiotensin-Aldosterone Inhibitors

Efe Eworuke, PHD,[a] Emily C. Welch, MPH,[b] Nicole Haug, MPH,[b] Casie Horgan, MPH,[b] Hye Seung Lee, PHD,[c] Yueqin Zhao, PHD,[c] Ting-Ying Huang, PHD[b]

JACC VOL. 81, NO. 4, 2023
JANUARY 31, 2023:321–331

FIGURE 3 Angioedema Risk Among SV and ARB Users



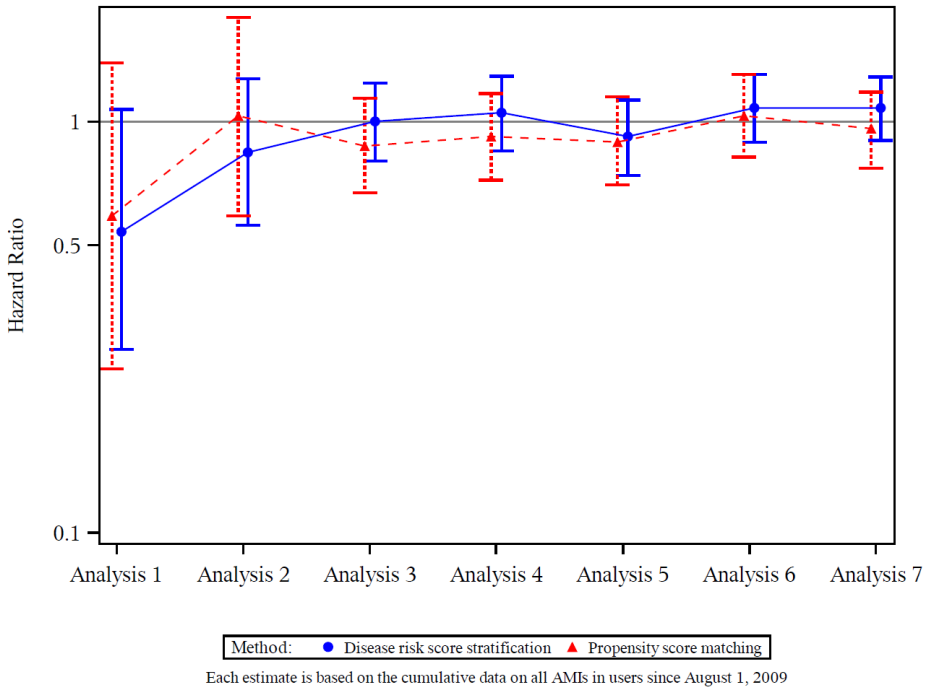
The propensity score adjusted HRs and 95% CIs compare the incidence of angioedema among SV new users and ARB-SV users to new ARB users. Adjusted HRs reported for the overall population and by various subgroups show no difference in risk between SV and ARB users. Abbreviations as in Figure 1.

Conduct prospective safety surveillance of new medications

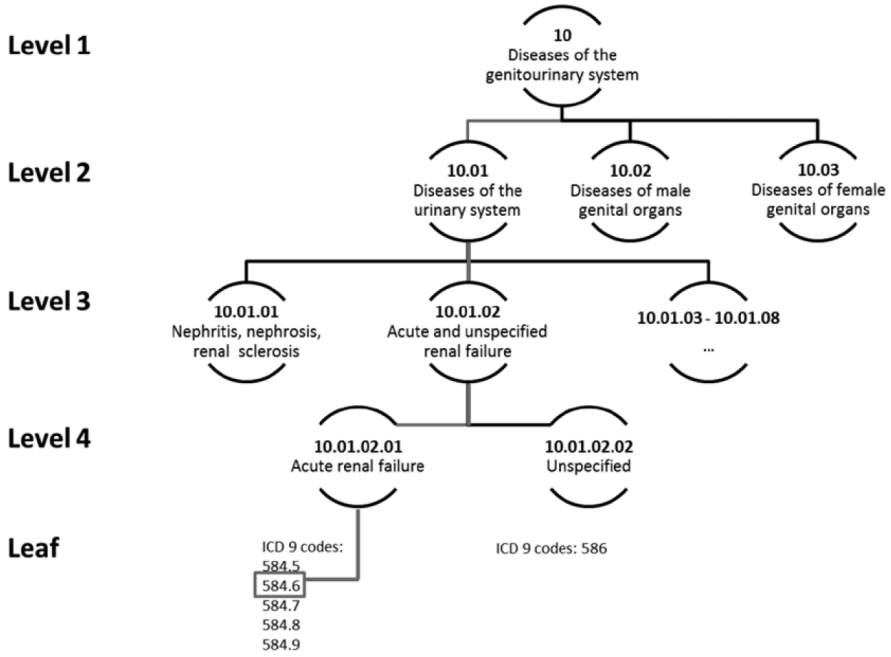
Prospective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study

*Sengwee Toh,[1] Marsha E. Reichman,[2] David J. Graham,[2] Christian Hampp,[2] Rongmei Zhang,[3] Melissa G. Butler,[4] Aarthi Iyer,[1] Malcolm Rucker,[1] Madelyn Pimentel,[1] Jack Hamilton,[5] Samuel Lendle,[5] and Bruce H. Fireman,[5] for the Mini-Sentinel Saxagliptin-AMI Surveillance Writing Group**

Diabetes Care 2018;41:39–48 | https://doi.org/10.2337/dc17-0476



Conduct signal identification studies



ORIGINAL ARTICLE

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

Shirley V. Wang,[a] *Judith C. Maro,*[b] *Elande Baro,*[c] *Rima Izem,*[c] *Inna Dashevsky,*[b] *James R. Rogers,*[a] *Michael Nguyen,*[d] *Joshua J. Gagne,*[a] *Elisabetta Patorno,*[a] *Krista F. Huybrechts,*[a] *Jacqueline M. Major,*[d] *Esther Zhou,*[d] *Megan Reidy,*[b] *Austin Cosgrove,*[b] *Sebastian Schneeweiss,*[a] *and Martin Kulldorff*[a]

Epidemiology 2018;29: 895–903

Evaluate impact of FDA regulatory actions

JOURNAL OF ASTHMA
2018, VOL. 55, NO. 8, 907–914
https://doi.org/10.1080/02770903.2017.1378355

The impact of FDA regulatory activities on incident dispensing of LABA-containing medication: 2005–2011

Meghan A. Baker, MD, ScD[a,b,†], Melissa G. Butler, PharmD, MPH, PhD [c,d,†], Sally Seymour, MD[e], Fang Zhang, PhD[a], Yute Wu, PhD[f], Ann Chen Wu, MD, MPH[a], Mark S. Levenson, PhD[f], Pingsheng Wu, PhD[g], Aarthi Iyer, MPH[a], Sengwee Toh, ScD[a], Solomon Iyasu, MD, MPH[h,*], and Esther H. Zhou, MD, PhD[h]

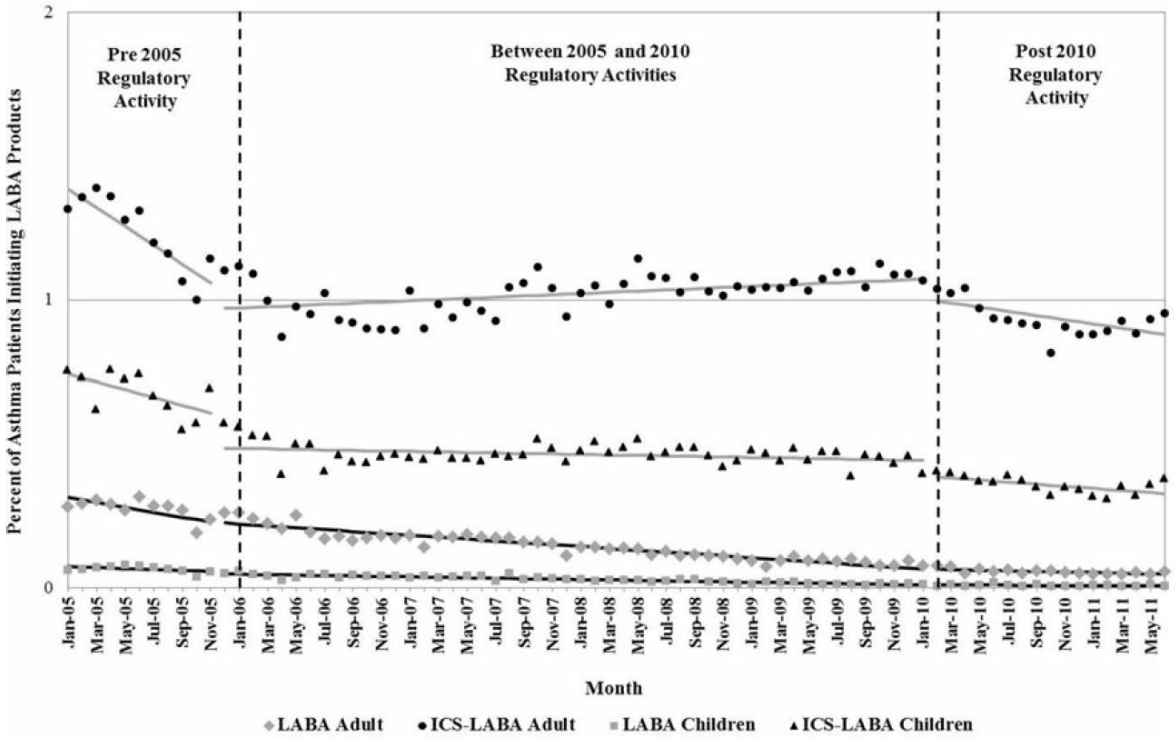


Figure 2. Percentage of LABA product initiation before, between and after the 2005 and 2010 FDA regulatory activities for LABA-containing agents in children and adults with asthma and no history of a LABA dispensing in 180 days.

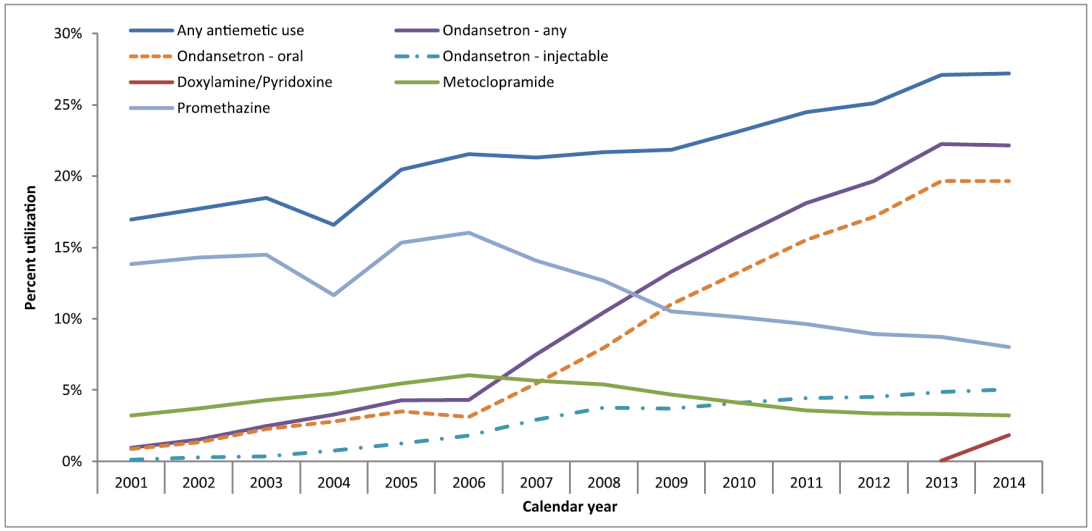
Examine medication exposure during pregnancy

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 592–596
Published online 21 February 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4185

BRIEF REPORT

Antiemetic use among pregnant women in the United States: the escalating use of ondansetron

Lockwood G. Taylor[1]*, Steven T. Bird[1], Leyla Sahin[1], Melissa S. Tassinari[1], Patty Greene[1], Marsha E. Reichman[1], Susan E. Andrade[2], Katherine Haffenreffer[3] and Sengwee Toh[3]

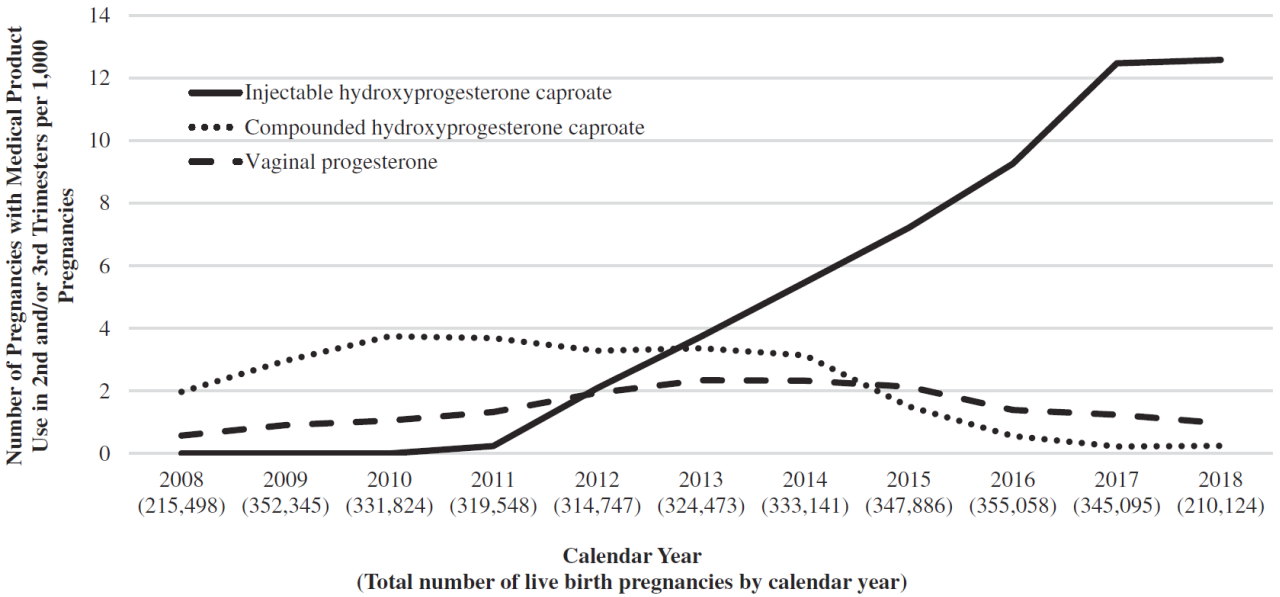


THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
https://doi.org/10.1080/14767058.2021.1910669

ORIGINAL ARTICLE

Utilization of hydroxyprogesterone caproate among pregnancies with live birth deliveries in the sentinel distributed database

Mayura Shinde[a], Austin Cosgrove[a], Corinne M. Woods[b], Christina Chang[c], Christine P. Nguyen[c], David Moeny[b], Adebola Ajao[b], Joy Kolonoski[a] and Huei-Ting Tsai[b]



Examine medication safety during pregnancy

Duke | MARGOLIS CENTER for Health Policy

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Home › Events › Optimizing the Use of Postapproval Pregnancy Safety Studies

Event

FDA Convening

Optimizing the Use of Postapproval Pregnancy Safety Studies

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

Contact Information
Luke Durocher

Received: 11 April 2022 | Revised: 14 July 2022 | Accepted: 21 July 2022

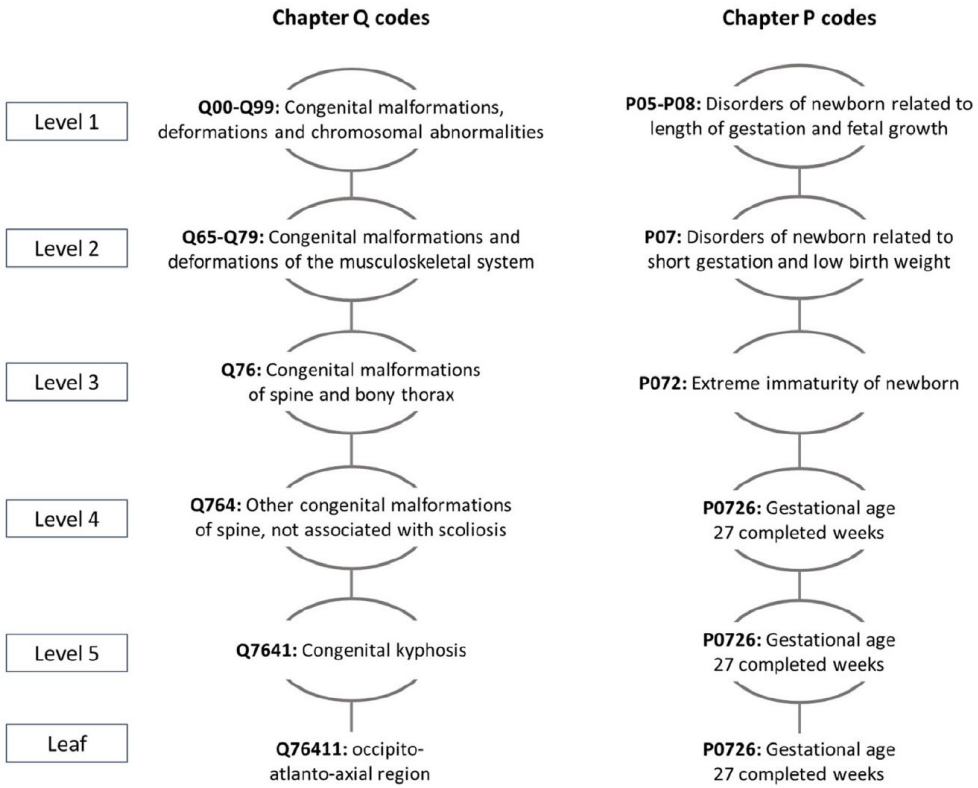
DOI: 10.1002/pds.5512

WILEY

ORIGINAL ARTICLE

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

Elizabeth A. Suarez[1] | Michael Nguyen[2] | Di Zhang[3] | Yueqin Zhao[3] | Danijela Stojanovic[2] | Monica Munoz[4] | Jane Liedtka[5] | Abby Anderson[6] | Wei Liu[7] | Inna Dashevsky[1] | David Cole[1] | Sandra DeLuccia[1] | Talia Menzin[1] | Jennifer Noble[1] | Judith C. Maro[1]



Contribute to surveillance of infectious diseases

INT J TUBERC LUNG DIS 26(12):1170–1176

http://dx.doi.org/10.5588/ijtld.22.0259

Using the Food and Drug Administration's Sentinel System for surveillance of TB infection

W. L. Walker,[1] K. M. Schmit,[1] E. C. Welch,[2] L. A. Vonnahme,[1] A. Talwar,[1] M. Nguyen,[3] D. Stojanovic,[3] A. J. Langer,[1] N. M. Cocoros[2]

Table 2 Diagnoses, risk factors, and diagnostic evaluations for persons who filled prescriptions consistent with treatment of LTBI, United States, 2008–2019

Characteristic	Isoniazid-only (n = 90,377) n (%)	Rifampin-only* (n = 21,235) n (%)	Isoniazid + rifapentine (n = 1,726) n (%)	Total† (N = 113,338) N (%)
Diagnoses of LTBI and selected risk factors for progression to TB disease				
HIV test				
0–365 days before prescription filled	14,160 (16)	3,025 (14)	360 (21)	17,545 (15)
1–365 days after prescription filled	9,254 (10)	1,733 (8)	138 (8)	11,125 (10)
HIV diagnosis				
0–365 days before prescription filled	3,380 (4)	212 (1)	21 (1)	3,613 (3)
1–365 days after prescription filled	3,398 (4)	213 (1)	21 (1)	3,632 (3)
Diabetes				
0–365 days before prescription filled	21,972 (24)	4,869 (23)	386 (22)	27,227 (24)
1–365 days after prescription filled	22,265 (25)	4,964 (23)	387 (22)	27,616 (24)
Tumor necrosis factor-α inhibitor use				
0–365 days before prescription filled	2,778 (3)	516 (2)	60 (4)	3,354 (3)
1–365 days after prescription filled	4,423 (5)	677 (3)	105 (6)	5,205 (5)
Diagnostic evaluation during 365 days before prescription filled				
Encounter screening for LTBI	24,681 (27)	3,606 (17)	585 (34)	28,872 (26)
TST	62,919 (70)	9,754 (46)	1,428 (83)	74,101 (65)
IGRA test	30,042 (33)	5,786 (27)	791 (46)	36,619 (32)
Patients with either TST or IGRA	71,207 (79)	11,496 (54)	1,574 (91)	84,277 (74)
Patients with both TST and IGRA	21,754 (24)	4,044 (19)	645 (37)	26,443 (23)
Patients with neither TST nor IGRA	19,170 (21)	9,739 (46)	152 (9)	29,061 (26)
CXR	75,793 (84)	13,722 (65)	1,411 (82)	90,926 (80)
Thoracic CT scan	14,923 (17)	6,159 (29)	167 (10)	21,249 (19)
CXR or thoracic CT scan	77,174 (85)	14,535 (68)	1,434 (83)	93,143 (82)
Sputum culture	7,564 (8)	4,989 (24)	82 (5)	12,635 (11)
Sputum smear microscopy	150 (0)	70 (0)	—‡	—‡
TB testing in relation to LTBI treatment initiation				
Any testing (−365 to −1 days before prescription filled)	81,502 (90)	16,062 (76)	1,615 (94)	99,179 (88)
Any testing (0 to 365 days after prescription filled)	66,588 (74)	14,570 (69)	1,243 (72)	82,401 (73)

* Rifampin cohort is among those meeting 20-day minimum supply and has certain exclusions (see Appendix D of the full report for specific codes; https://www.sentinelinitiative.org/sites/default/files/Methods/Report_cder_mpl1p_wp039.pdf).
† The same patient might appear in more than one treatment cohort if the patient switches treatment regimens and also meets the incidence criteria of having filled no other prescription for a regimen used to treat LTBI in the previous 365 days.
‡ Cell counts are too small to report.
LTBI = latent TB infection; TST = tuberculin skin test; IGRA = interferon-gamma release assay; CXR = chest X-ray; CT = computed tomography.

Identify potential medication errors

Received: 31 December 2018 | Revised: 7 May 2019 | Accepted: 12 June 2019
DOI: 10.1002/pds.4858

ORIGINAL REPORT

WILEY

Development of an algorithm to detect methotrexate wrong frequency error using computerized health care data

Lisa J. Herrinton[1] | Tiffany S. Woodworth[2] | Efe Eworuke[3] | Laura B. Amsden[1] | Liyan Liu[1] | Jo Wyeth[3] | Andrew Petrone[2] | Talia J. Menzin[2] | James Williams[2] | Robert Goldfien[1] | Michael Nguyen[3]

Received: 15 April 2019 | Revised: 7 August 2019 | Accepted: 18 August 2019
DOI: 10.1002/pds.4891

ORIGINAL REPORT

WILEY

Identification of potential drug name confusion errors in the Sentinel System

Noelle M. Cocoros[1] | Kevin Haynes[2] | Qoua Her[1] | Austin Cosgrove[1] | Elizabeth Dee[1] | Nancy D. Lin[3] | Chi-Ming Tu[4] | Yulan Ding[4] | Michael Nguyen[4] | Sengwee Toh[1]

Inform label change

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RotaTeq safely and effectively. See full prescribing information for RotaTeq.

RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent)
Oral Solution
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) 02/2017

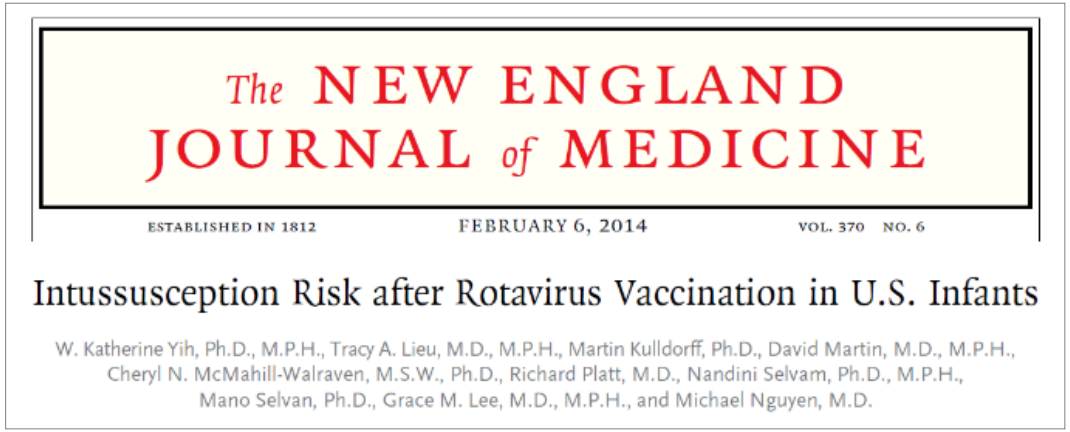
----------INDICATIONS AND USAGE----------
RotaTeq® is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9. (1)

RotaTeq is approved for use in infants 6 weeks to 32 weeks of age. (1)

----------DOSAGE AND ADMINISTRATION----------
- FOR ORAL USE ONLY. NOT FOR INJECTION. (2)
- The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age,

----------WARNINGS AND PRECAUTIONS----------
- No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised (e.g., HIV/AIDS). (5.2)
- In a post-marketing study, cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. (5.3, 6.2)
- No safety or efficacy data are available for the administration of RotaTeq to infants with a history of gastrointestinal disorders (e.g., active acute gastrointestinal illness, chronic diarrhea, failure to thrive, history of congenital abdominal disorders, and abdominal surgery). (5.4)
- Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient contacts. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse events included diarrhea, vomiting, irritability, otitis media, nasopharyngitis, and bronchospasm. (6.1)


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 6, 2014 VOL. 370 NO. 6

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Mano Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.

Post-Marketing Observational Safety Surveillance Studies

The temporal association between vaccination with RotaTeq and intussusception was evaluated in the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program[2], an electronic active surveillance program comprised of 3 US health insurance plans.

More than 1.2 million RotaTeq vaccinations (507,000 of which were first doses) administered to infants 5 through 36 weeks of age were evaluated. From 2004 through 2011, potential cases of intussusception in either the inpatient or emergency department setting and vaccine exposures were identified through electronic procedure and diagnosis codes. Medical records were reviewed to confirm intussusception and rotavirus vaccination status.

The risk of intussusception was assessed using self-controlled risk interval and cohort designs, with adjustment for age. Risk windows of 1-7 and 1-21 days were evaluated. Cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. Based on the results, approximately 1 to 1.5 excess cases of intussusception occur per 100,000 vaccinated US infants within 21 days following the first dose of RotaTeq. In the first year of life, the background rate of intussusception hospitalizations in the US has been estimated to be approximately 34 per 100,000 infants.[3]

https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142288.pdf

Inform label change

OXFORD

JNCI Cancer Spectrum (2021) 5(2): pkab009

doi: 10.1093/jncics/pkab009
First published online 4 February 2021
Article

Risk of Nonmelanoma Skin Cancer in Association With Use of Hydrochlorothiazide-Containing Products in the United States

Efe Eworuke, PhD,[1,*] Nicole Haug, MPH,[2] Marie Bradley, PhD,[1] Austin Cosgrove, BS,[2] Tancy Zhang, MPH,[2] Elizabeth C. Dee, MPH,[2] Sruthi Adimadhyam, PhD[2] Andrew Petrone, MPH,[2] Hana Lee, PhD,[3] Tiffany Woodworth, MPH,[2] Sengwee Toh, ScD[2]

Postmarketing Experience:

Non-melanoma Skin Cancer

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000 mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=02e96a51-1d56-460c-8c20-3d6f37e0ce46

Contribute to FDA advisory committee meeting

FDA Briefing Document

ARTHRITIS ADVISORY COMMITTEE
AND DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE MEETING
January 11, 2019

NDA 21856
Febuxostat
Xanthine oxidase (XO) inhibitor for the chronic management of hyperuricemia in patients with gout

Takeda

EXECUTIVE SUMMARY

Febuxostat (Uloric®), a selective inhibitor of xanthine oxidase, lowers serum uric acid levels by inhibiting the conversion of xanthine to uric acid. It was approved by the FDA in February 2009 for the management of chronic hyperuricemia in patients with gout. Preliminary results from a post-approval safety trial (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidity (CARES)) showed an increased risk of cardiovascular-related death and all-cause death in febuxostat users. As a result, FDA issued a drug safety communication in November 2017. An advisory committee (AC) meeting is scheduled for January 11, 2019 to discuss potential regulatory action to address the safety of febuxostat. For context, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested the Division of Epidemiology (DEPI) to investigate the characteristics of the gout population and use of febuxostat and allopurinol in real-world settings using the Sentinel Distributed Database (SDD) since the CARES trial was enriched for patients with CVD.

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM629362.pdf

Contribute to FDA Drug Safety Communication

Drug Safety and Availability

- Drug Alerts and Statements
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- Drug Supply Chain Integrity

FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran)

The FDA has issued new information about this safety issue, see the **FDA Drug Safety Communication issued 05-13-2014**.

This update is a follow-up to the **FDA Drug Safety Communication of 12/7/2011**: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
References

Safety Announcement

[11-02-2012] The U.S. Food and Drug Administration (FDA) has evaluated new information about the risk of serious bleeding associated with use of the anticoagulants (blood thinners) dabigatran (Pradaxa) and warfarin (Coumadin, Jantoven, and generics). Following the approval of Pradaxa, FDA received a large number of post-marketing reports of bleeding among Pradaxa users. As a result, FDA investigated the actual rates of gastrointestinal bleeding (occurring in the stomach and intestines) and intracranial hemorrhage (a type of bleeding in the brain) for new users of Pradaxa compared to new users of warfarin. This assessment was done using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).[1] (see Data Summary). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

Southworth et al. N Engl J Med 2013;368:1272-1274
https://wayback.archive-it.org/7993/20170112031650/http:/www.fda.gov/Drugs/DrugSafety/ucm326580.htm

Address emerging safety issues

Trial of erectile dysfunction drug on pregnant women stopped after 11 babies die

By Debra Goldschmidt and Michael Nedelman, CNN

Updated 3:45 PM ET, Wed July 25, 2018

Received: 13 November 2019 | Revised: 11 August 2020 | Accepted: 17 August 2020

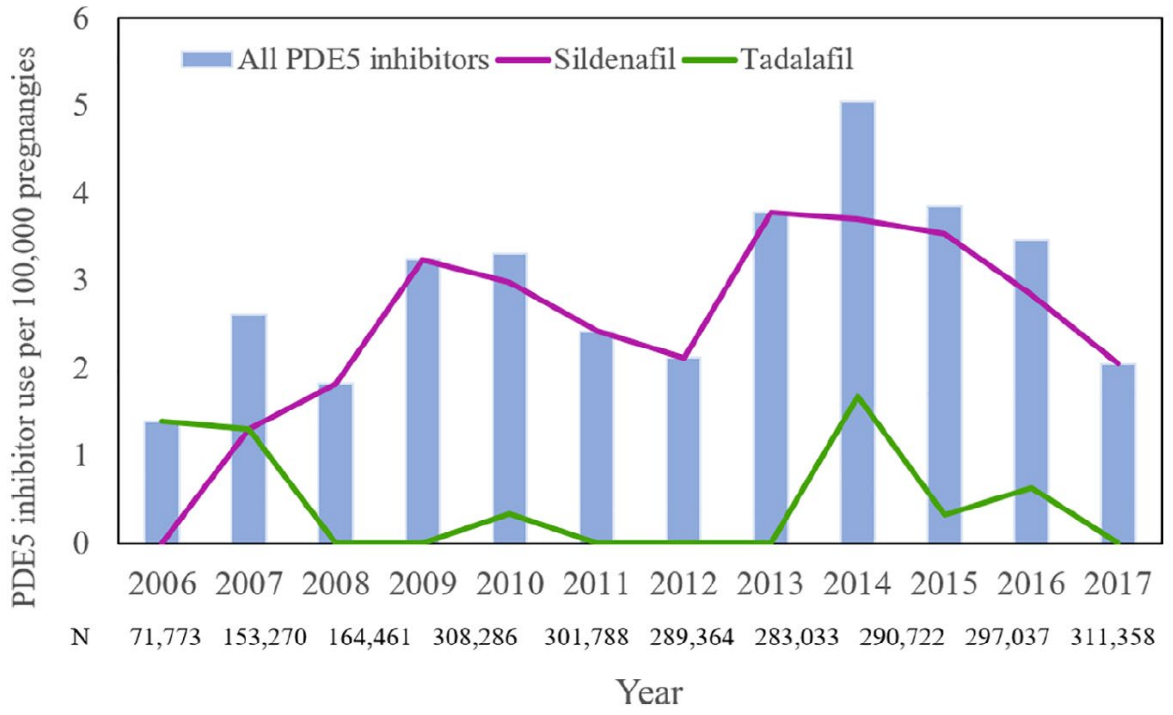
DOI: 10.1002/pds.5112

ORIGINAL REPORT

WILEY

Phosphodiesterase type 5 inhibitor use among pregnant and reproductive-age women in the United States

Wei Liu[1] | Talia J. Menzin[2] | Corinne M. Woods[1] | Nicole R. Haug[2] | Jie Li[1] | Justin A. Mathew[1] | Christine P. Nguyen[3] | Grace P. Chai[1] | David G. Moeny[1] | Mayura Shinde[2]



https://www.cnn.com/2018/07/24/health/viagra-clinical-trial-stopped-baby-deaths-bn/index.html

Conduct pragmatic trials (FDA Catalyst*)

JAMA Network Open

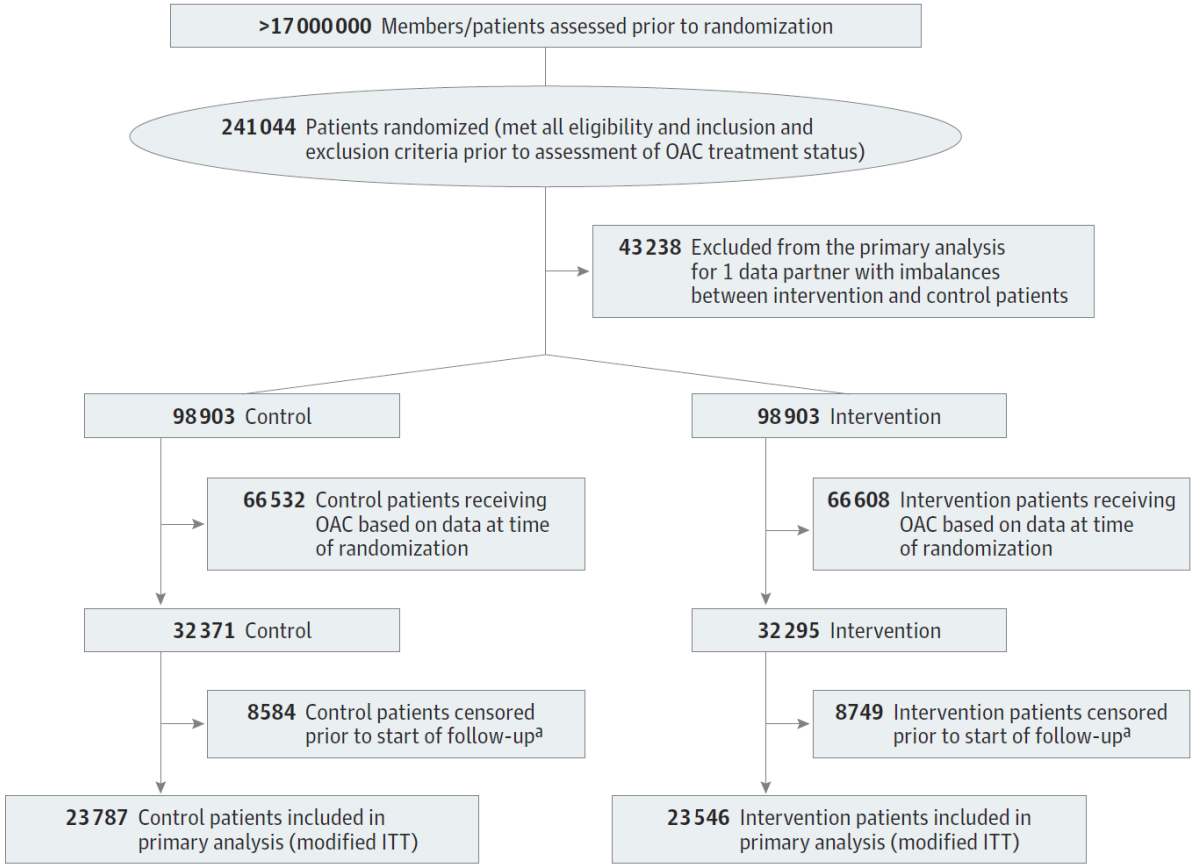
Original Investigation | Cardiology

Effect of Mailing Educational Material to Patients With Atrial Fibrillation and Their Clinicians on Use of Oral Anticoagulants

A Randomized Clinical Trial

Sean D. Pokorney, MD, MBA; Noelle Cocoros, DSc, MPH; Hussein R. Al-Khalidi, PhD; Kevin Haynes, PharmD, MSCE; Shuang Li, MS; Sana M. Al-Khatib, MD, MHS; Jacqueline Corrigan-Curay, MD; Meighan Rogers Driscoll, MPH; Crystal Garcia, MPH; Sara B. Calvert, PharmD; Thomas Harkins, MPH, MA; Robert Jin, MS; Daniel Knecht, MD, MBA; Mark Levenson, PhD; Nancy D. Lin, ScD; David Martin, MD, MPH; Debbe McCall, BS, MBA; Cheryl McMahill-Walraven, PhD, MSW; Vinit Nair, BPharm, MS, RPh; Lauren Parlett, PhD; Andrew Petrone, MPH; Robert Temple, MD; Rongmei Zhang, PhD; Yunping Zhou, MS; Richard Platt, MD, MSc; Christopher B. Granger, MD

JAMA Network Open. 2022;5(5):e2214321.



*FDA-Catalyst is a component of the Sentinel Initiative that supplements the Sentinel System. FDA Catalyst projects combine data from interactions with patients and/or providers with data included in the Sentinel infrastructure.

Collect information directly from patients (FDA Catalyst*)

Received: 18 April 2020 | Revised: 4 June 2021 | Accepted: 25 June 2021

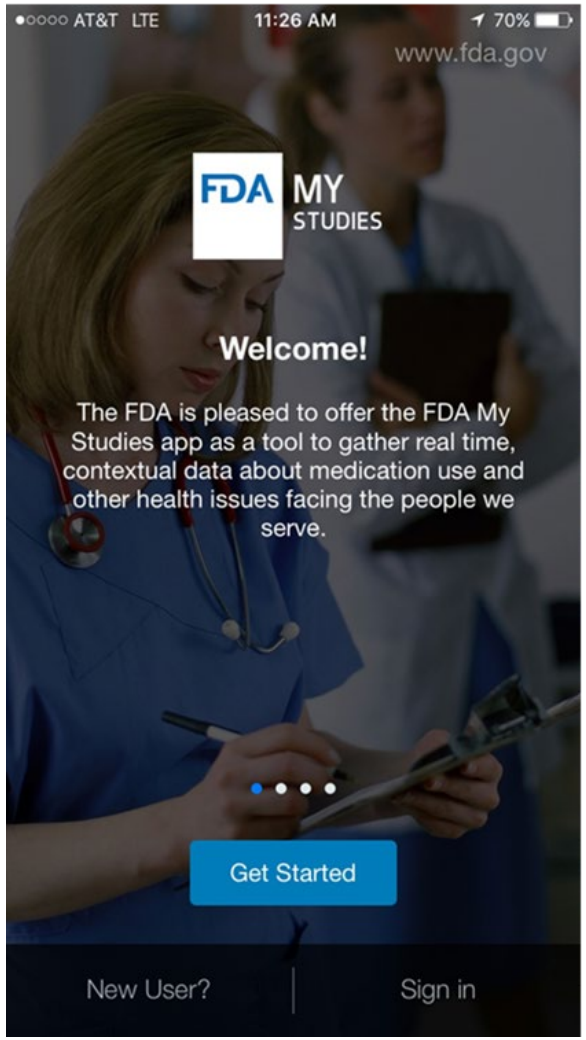
DOI: 10.1002/pds.5320

ORIGINAL ARTICLE

WILEY

Use of a mobile app to capture supplemental health information during pregnancy: Implications for clinical research

Claire W. Rothschild[1] | Sascha Dublin[1,2] | Jeffrey S. Brown[3,4] | Predrag Klasnja[2] | Chayim Herzig-Marx[3,4] | Juliane S. Reynolds[3,4] | Zachary Wyner[3,4] | Christina Chambers[5] | David Martin[6]



*FDA-Catalyst is a component of the Sentinel Initiative that supplements the Sentinel System. FDA Catalyst projects combine data from interactions with patients and/or providers with data included in the Sentinel infrastructure.

Prepare for the next pandemic

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; **25**: 481–492
Published online 17 November 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3908

ORIGINAL REPORT

Prospective influenza vaccine safety surveillance using fresh data in the Sentinel System†

Weiling Katherine Yih[1]*, Martin Kulldorff[1], Sukhminder K. Sandhu[2], Lauren Zichittella[1], Judith C. Maro[1], David V. Cole[1], Robert Jin[1], Alison Tse Kawai[1], Meghan A. Baker[1], Chunfu Liu[3], Cheryl N. McMahill-Walraven[4], Mano S. Selvan[5], Richard Platt[1], Michael D. Nguyen[2,‡] and Grace M. Lee[1,‡]

Generate timely evidence during pandemic

Received: 3 March 2021 | Revised: 25 March 2021 | Accepted: 26 March 2021
DOI: 10.1002/pds.5240

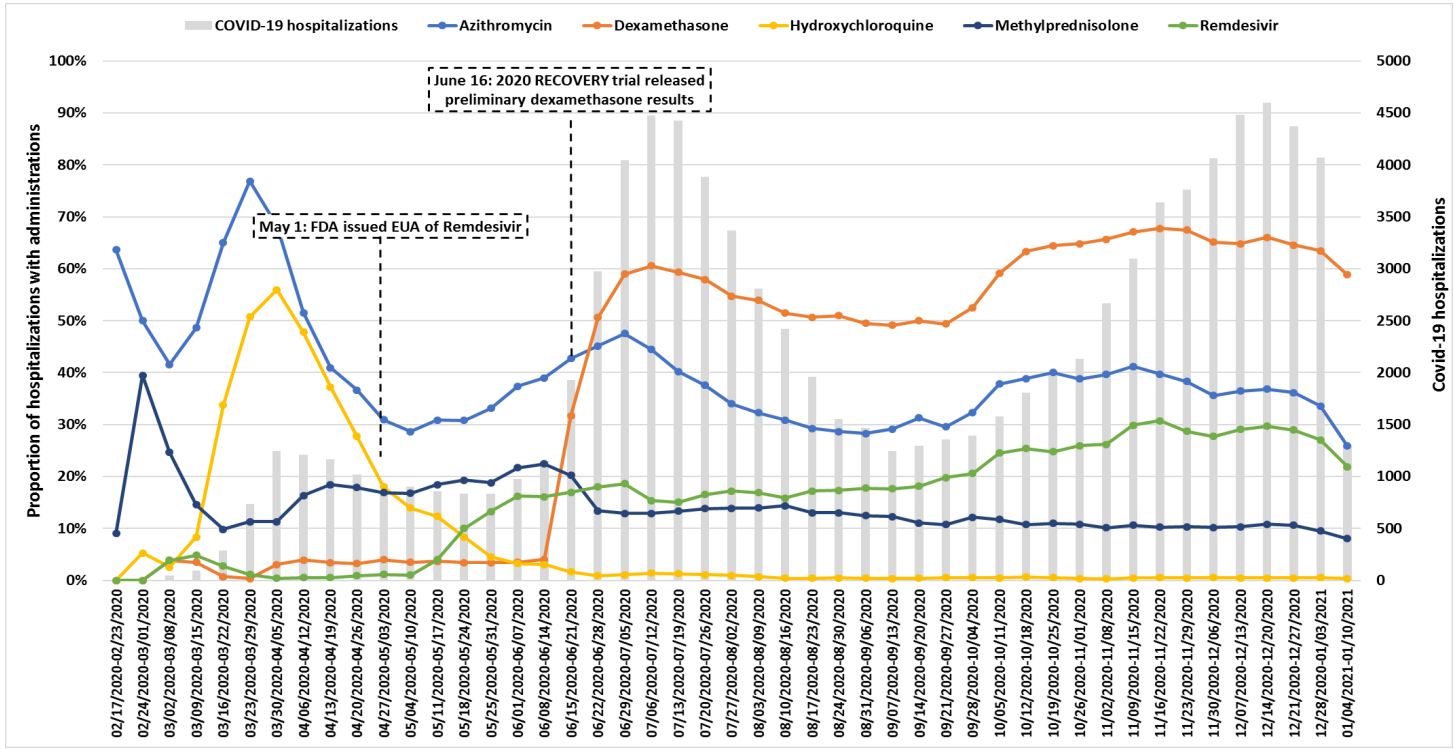
REVIEW

WILEY

A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System

Noelle M. Cocoros[1] | Candace C. Fuller[1] | Sruthi Adimadhyam[1] | Robert Ball[2] | Jeffrey S. Brown[1] | Gerald J. Dal Pan[2] | Sheryl A. Kluberg[1] | Vincent Lo Re 3rd[3] | Judith C. Maro[1] | Michael Nguyen[2] | Robert Orr[2] | Dianne Paraoan[2] | Jonathan Perlin[4] | Russell E. Poland[1,4] | Meighan Rogers Driscoll[1] | Kenneth Sands[1,4] | Sengwee Toh[1] | W. Katherine Yih[1] | Richard Platt[1] | And the FDA-Sentinel COVID-19 Working Group

Pharmacoepidemiol Drug Saf. 2021;30:827–837.



Generate timely evidence during pandemic

Research Letter

April 8, 2022

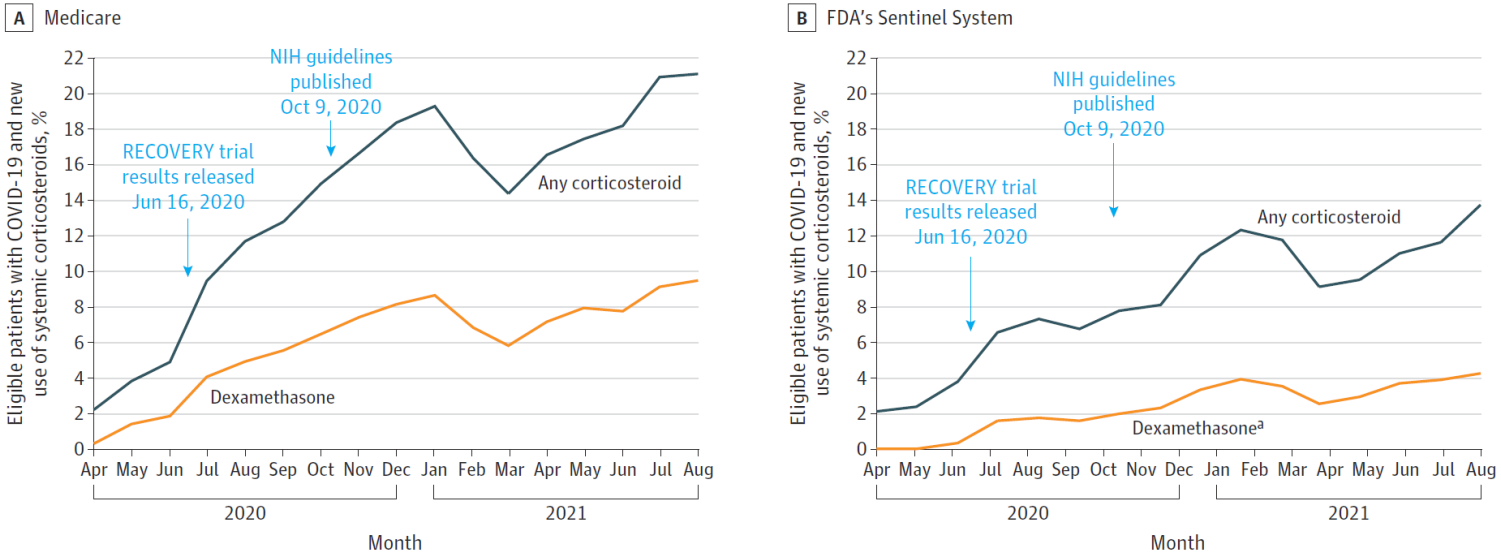
Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021

Marie C. Bradley, PhD, MPharm, MScPH[1]; Silvia Perez-Vilar, PhD, PharmD[1]; Yoganand Chillarige, MPA[2]; Diane Dong, RN, MPH[3]; Ashley I. Martinez, PharmD, PhD[4]; Andrew R. Weckstein, BA[5]; Gerald J. Dal Pan, MD, MHS[1]

Author Affiliations | Article Information

JAMA. 2022;327(20):2015-2018. doi:10.1001/jama.2022.4877

Figure. Proportion of Patients With COVID-19 Initiating Systemic Corticosteroids Within 14 Days of Diagnosis



FDA indicates Food and Drug Administration; NIH, National Institutes of Health; RECOVERY, Randomised Evaluation of COVID-19 Therapy.

[a] The name of the corticosteroid was only available for pharmacy dispensings.

Generate timely evidence during pandemic

Original Investigation

August 16, 2022

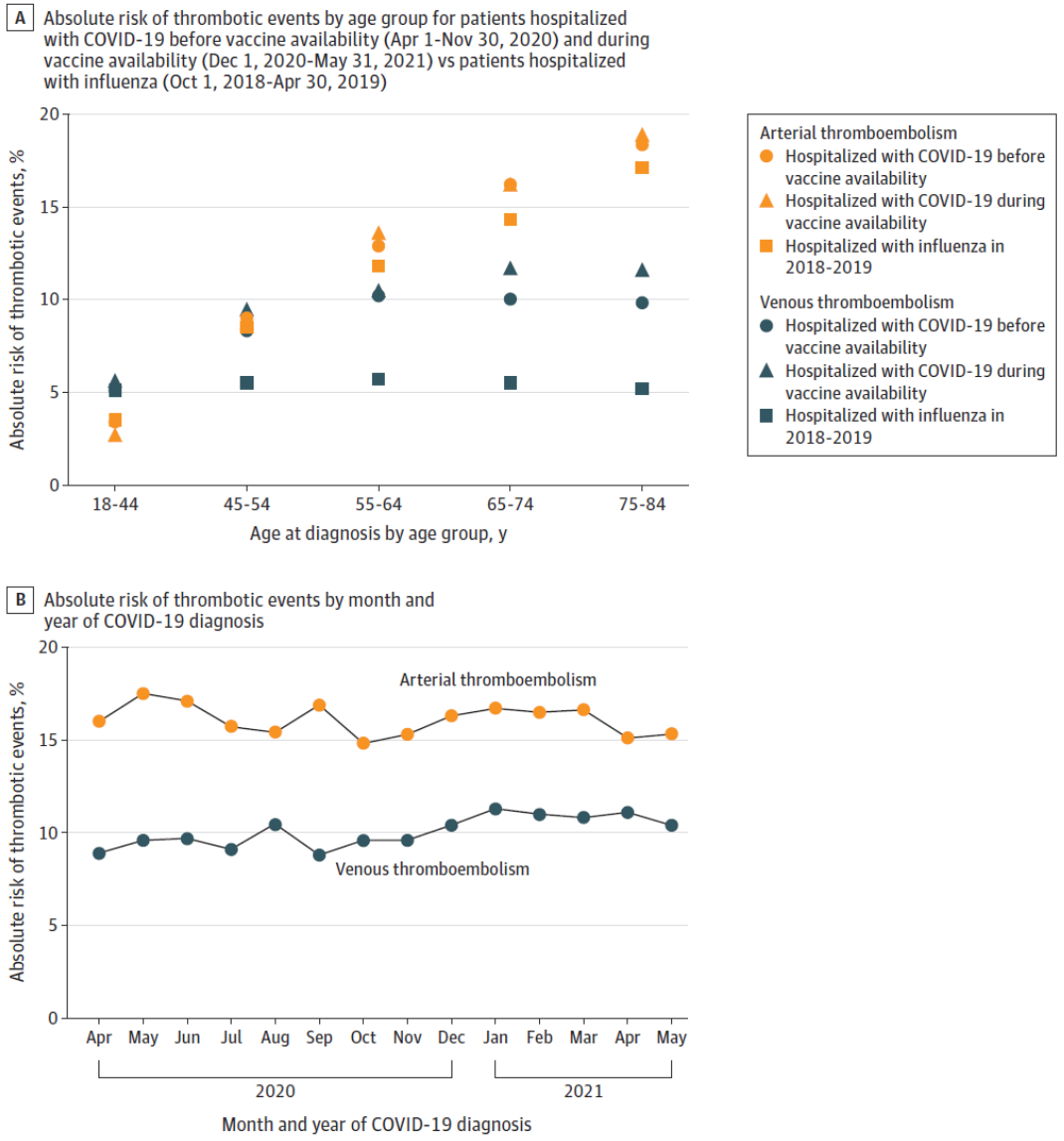
Association of COVID-19 vs Influenza With Risk of Arterial and Venous Thrombotic Events Among Hospitalized Patients

Vincent Lo Re III, MD, MSCE[1,2]; Sarah K. Dutcher, PhD[3]; John G. Connolly, ScD[4]; Silvia Perez-Vilar, PharmD, PhD[3]; Dena M. Carbonari, MS[2]; Terese A. DeFor, MS[5]; Djeneba Audrey Djibo, PhD[6]; Laura B. Harrington, PhD, MPH[7]; Laura Hou, MS[4]; Sean Hennessy, PharmD, PhD[2]; Rebecca A. Hubbard, PhD[2]; Maria E. Kempner, BA[4]; Jennifer L. Kuntz, PhD[8]; Cheryl N. McMahill-Walraven, PhD[6]; Jolene Mosley, MS[4]; Pamala A. Pawloski, PharmD[5]; Andrew B. Petrone, MPH[4]; Allyson M. Pishko, MD, MSCE[9]; Meighan Rogers Driscoll, MPH[4]; Claudia A. Steiner, MD, MPH[10]; Yunping Zhou, MS[11]; Noelle M. Cocoros, DSc, MPH[4]

Author Affiliations | Article Information

JAMA. 2022;328(7):637-651. doi:10.1001/jama.2022.13072

Figure. Absolute Risk of Inpatient Arterial and Venous Thrombotic Events



Enable international collaboration during pandemic

Natural History of COVID-19 among Pregnant Women

- **CONSIGN (Covid-19 infectiON and medicineS In pregnancy) conceptual replication**

ICMRA
International Coalition of Medicines Regulatory Authorities

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Health Canada Santé Canada

CNODES
CANADIAN NETWORK FOR OBSERVATIONAL DRUG EFFECT STUDIES

http://www.icmra.info/drupal/covid-19/10may2021

Enable international collaboration to address global issues

Open access Original research

BMJ Open

Valsartan, Losartan and Irbesartan use in the USA, UK, Canada and Denmark after the nitrosamine recalls: a descriptive cohort study

Efe Eworuke ,[1] Mayura Shinde,[2] Laura Hou,[2] Michael J Paterson,[3] Peter Bjødstrup Jensen,[4] Judith C Maro,[2] Ashish Rai,[2] Daniel Scarnecchia ,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca E Ghosh,[5] Stephen Welburn ,[5] Anton Pottegard,[6,7] Robert W Platt,[2] Hana Lee,[1] Marie C Bradley [1]

Eworuke E, *et al. BMJ Open* 2023;**13**:e070985.

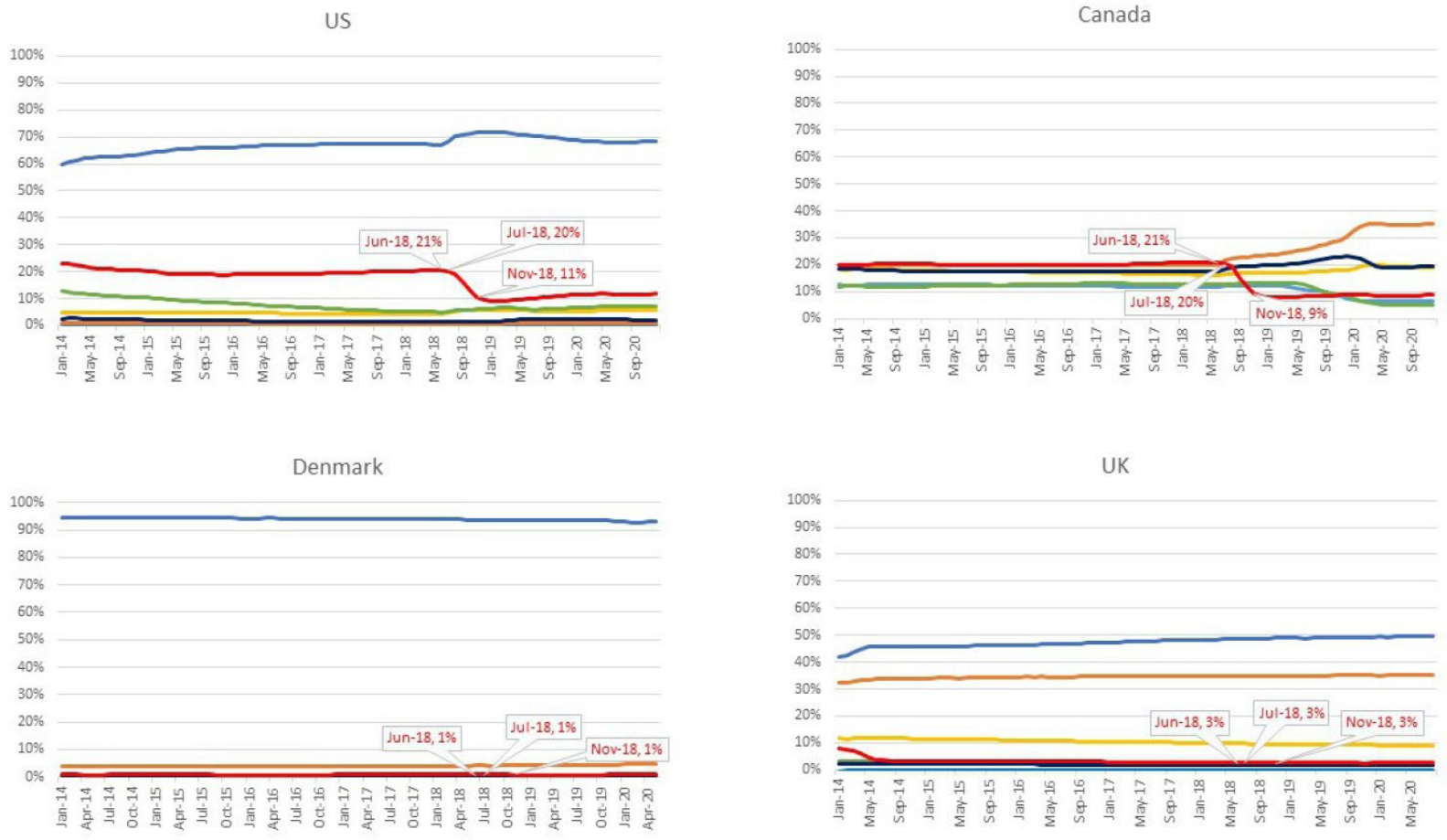


Figure 2 Monthly Angiotensin-Receptor-Blockers use trends between January 2014 and end of available data or December 2020 by country. Monthly ARB proportions represent the number of individual ARB episodes that span the month divided by the total number of any ARB episodes that span the same month. Data callouts represent the month-year, monthly percentage (%) for valsartan only.

Sentinel

- What Sentinel is
- How Sentinel gets, standardizes, and checks its data
- How Sentinel supports post-market surveillance
- **How Sentinel builds trust through transparency**
- Discussion

Received: 21 July 2017 | Revised: 25 July 2017 | Accepted: 25 July 2017
DOI: 10.1002/pds.4295

WILEY

ORIGINAL REPORT

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2] | Sebastian Schneeweiss[1,2] | Marc L. Berger[3] | Jeffrey Brown[4] | Frank de Vries[5] | Ian Douglas[6] | Joshua J. Gagne[1,2] | Rosa Gini[7] | Olaf Klungel[8] | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |
on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Graphical Depiction of Longitudinal Study Designs in Health Care Databases

Sebastian Schneeweiss, MD, ScD; Jeremy A. Rassen, ScD; Jeffrey S. Brown, PhD; Kenneth J. Rothman, DrPH; Laura Happe, PharmD, MPH; Peter Arlett, MD; Gerald Dal Pan, MD, MHS; Wim Goettsch, PhD; William Murk, PhD; and Shirley V. Wang, PhD

Ann Intern Med. 2019;170:398-406.

The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE)

Sinéad M Langan,[1] Sigrún AJ Schmidt,[2] Kevin Wing,[1] Vera Ehrenstein,[2] Stuart G Nicholls,[3,4] Kristian B Filion,[5,6] Olaf Klungel,[7] Irene Petersen,[2,8] Henrik T Sorensen,[2] William G Dixon,[9] Astrid Guttmann,[10,11] Katie Harron,[12] Lars G Hemkens,[13] David Moher,[3] Sebastian Schneeweiss,[14] Liam Smeeth,[1] Miriam Sturkenboom,[15] Erik von Elm,[16] Shirley V Wang,[14] Eric I Benchimol[10,17,18]

BMJ 2018;363:k3532

STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies

Shirley V Wang,[1] Simone Pinheiro,[2] Wei Hua,[2] Peter Arlett,[3,4] Yoshiaki Uyama,[5] Jesse A Berlin,[6] Dorothee B Bartels,[7] Kristijan H Kahler,[9] Lily G Bessette,[1] Sebastian Schneeweiss[1]

BMJ 2021;372:m4856

Sentinel

https://www.sentinelinitiative.org/assessments/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2

Eliquis (Apixaban), Pradaxa (Dabigatran), and Xarelto (Rivaroxaban) & Severe Uterine Bleed

Details

Status: Complete

Last Updated: Monday, May 24, 2021

Original Posting Date: Thursday, April 18, 2019

Health Outcome(s):

severe uterine bleed

Purpose: Drug and Outcome Analysis

https://www.sentinelinitiative.org/assessments/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2

Regulatory Determination / Use:

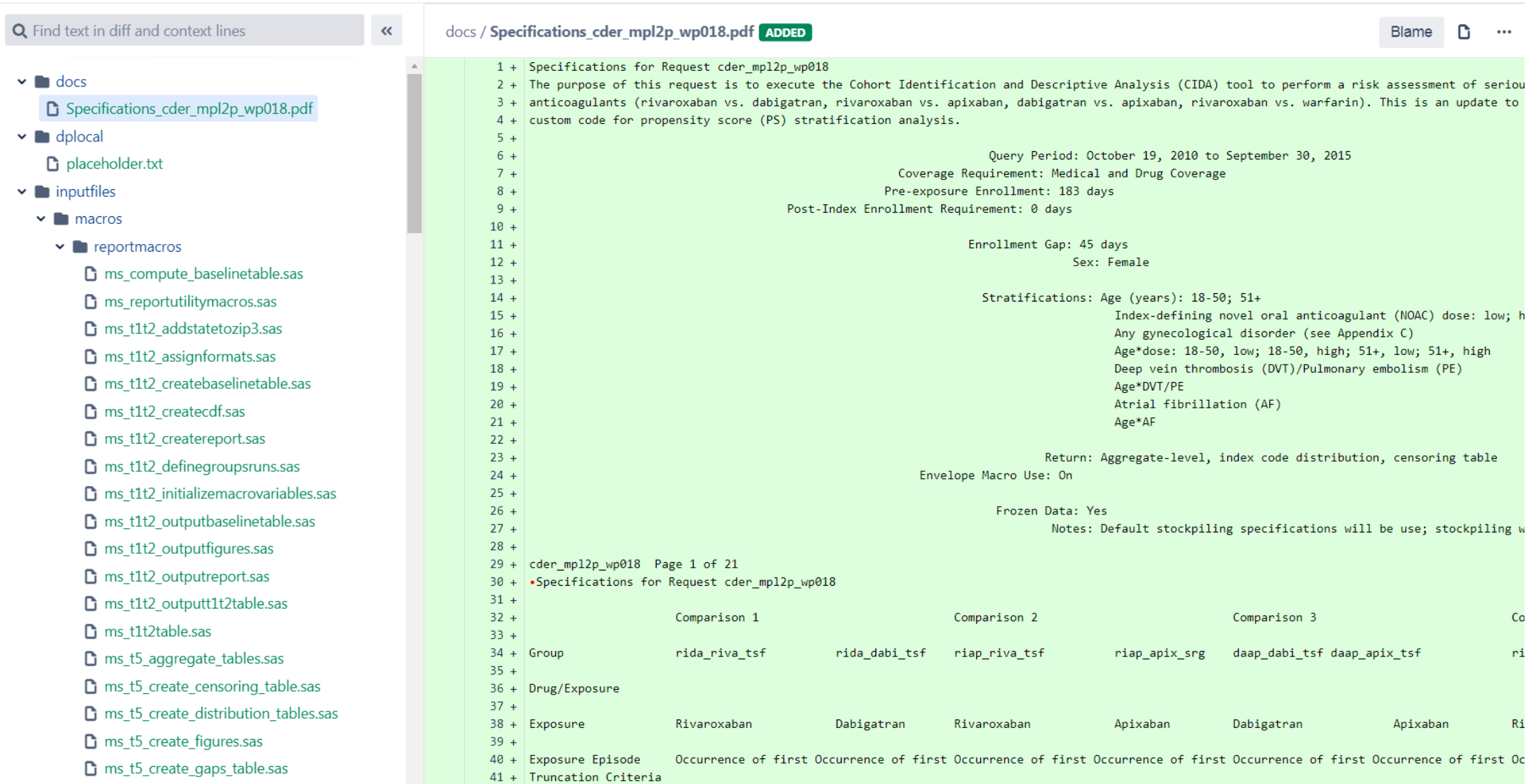
Cases of severe uterine bleeding associated with use of novel oral anticoagulants (ACs) have been reported in the FDA Adverse Event Reporting System (FAERS) and the medical literature. FDA conducted a Sentinel study to examine severe uterine bleeding events requiring medical intervention in women treated with oral ACs. Among 1,050,192 new users of oral ACs, the incidence rates of severe uterine bleeding with medical, transfusion, and surgical (e.g., hysterectomy, myomectomy) management were 0.6, 1.7, and 5.0 per 1000 person-years, respectively. These findings contributed to the following class-wide label change for oral ACs in Section 8.3, "The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including [PRODUCT name] should be assessed in females of reproductive potential and those with abnormal uterine bleeding."

https://www.sentinelinitiative.org/assessments/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2

Analytic Code Link(s) (1)

Severe Uterine Bleed Following Novel Oral Anticoagulants Use: A Propensity Score Analysis

https://www.sentinelinitiative.org/assessments/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2



https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/commits/2e632643a9a4320f2ea1cc4998f61d71682e7413

Result(s) (3)

Incidence of Severe Uterine Bleed Following Novel Oral Anticoagulants Use: A Descriptive Analysis

Severe Uterine Bleed Following Novel Oral Anticoagulants Use: A Propensity Score Analysis

Incidence Rate of Severe Uterine Bleeding Among New Users of Oral Anticoagulants: A Descriptive Analysis

https://www.sentinelinitiative.org/assessments/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2

Table 2a. Effect Estimates for Severe Uterine Bleed (SUB) Defined by Surgical Management in the Sentinel Distributed Database (SDD) between October 19, 2010 to September 30, 2015, by Analysis Type, Rivaroxaban vs. Dabigatran

Medical Product	Number of New Users	Person-Years at Risk	Average Person-Days at Risk	Average Person-Years at Risk	Number of Events	Incidence Rate per 1,000 Person-Years	Risk per 1,000 New Users	Incidence Rate Difference per 1,000 Person-Years	Difference in Risk per 1,000 New Users	Hazard Ratio (95% Confidence Interval)	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Rivaroxaban	289,011	155,142.97	196.07	0.54	801	5.16	2.77	1.54	-1.05	1.35 (1.17, 1.54)	<0.001
Dabigatran	80,844	85,311.95	385.44	1.06	309	3.62	3.82				
1:1 Matched Conditional Predefined Analysis; Caliper= 0.05											
Rivaroxaban	80,844	27,967.12	126.35	0.35	120	4.29	1.48	0.57	0.20	1.15 (0.89, 1.50)	0.285
Dabigatran	80,844	27,967.12	126.35	0.35	104	3.72	1.29				
1:1 Matched Unconditional Predefined Analysis; Caliper= 0.05											
Rivaroxaban	80,844	55,251.85	249.63	0.68	224	4.05	2.77	0.43	-1.05	1.09 (0.91, 1.30)	0.344
Dabigatran	80,844	85,311.95	385.44	1.06	309	3.62	3.82				
Predefined Percentile Analysis; Percentile = 10											
Rivaroxaban	289,011									1.21 (1.05, 1.39)	0.008
Dabigatran	80,844										

Data are not presented in shaded cells due to their inability to be calculated.

https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Sentinel-Report_cder_mpl2p_wp007.pdf

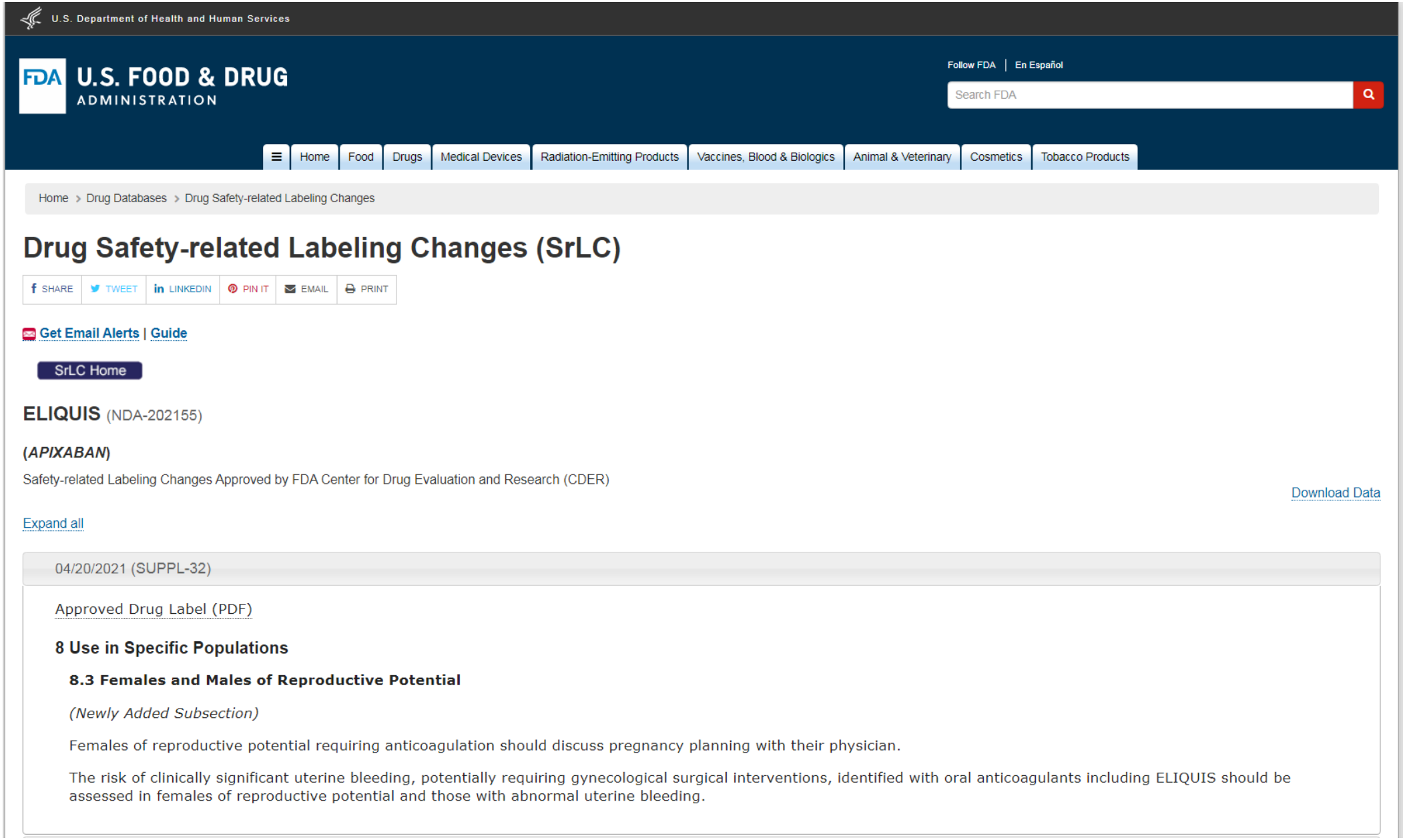
Regulatory Link(s) (3)

Drug Safety-related Labeling Change (Xarelto)

Drug Safety-related Labeling Change (Pradaxa)

Drug Safety-related Labeling Change (Eliquis)

https://www.sentinelinitiative.org/assessments/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2



U.S. Department of Health and Human Services

U.S. FOOD & DRUG ADMINISTRATION

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Drug Safety-related Labeling Changes (SrLC)

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SrLC Home

ELIQUIS (NDA-202155)

(*APIXABAN*)

Safety-related Labeling Changes Approved by FDA Center for Drug Evaluation and Research (CDER)

Download Data

Expand all

04/20/2021 (SUPPL-32)

Approved Drug Label (PDF)

8 Use in Specific Populations

8.3 Females and Males of Reproductive Potential

(Newly Added Subsection)

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including ELIQUIS should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=312

Related Publication(s) and/or Presentation(s) (3)

Publication: Risk of Severe Abnormal Uterine Bleeding Associated with Rivaroxaban Compared with Apixaban, Dabigatran and Warfarin

Publication: Incidence of Uterine Bleeding following Oral Anticoagulant Use in Food and Drug Administration's Sentinel System

Publication: Incidence of Severe Uterine Bleeding Outcomes among Oral Anticoagulant Users and Nonusers

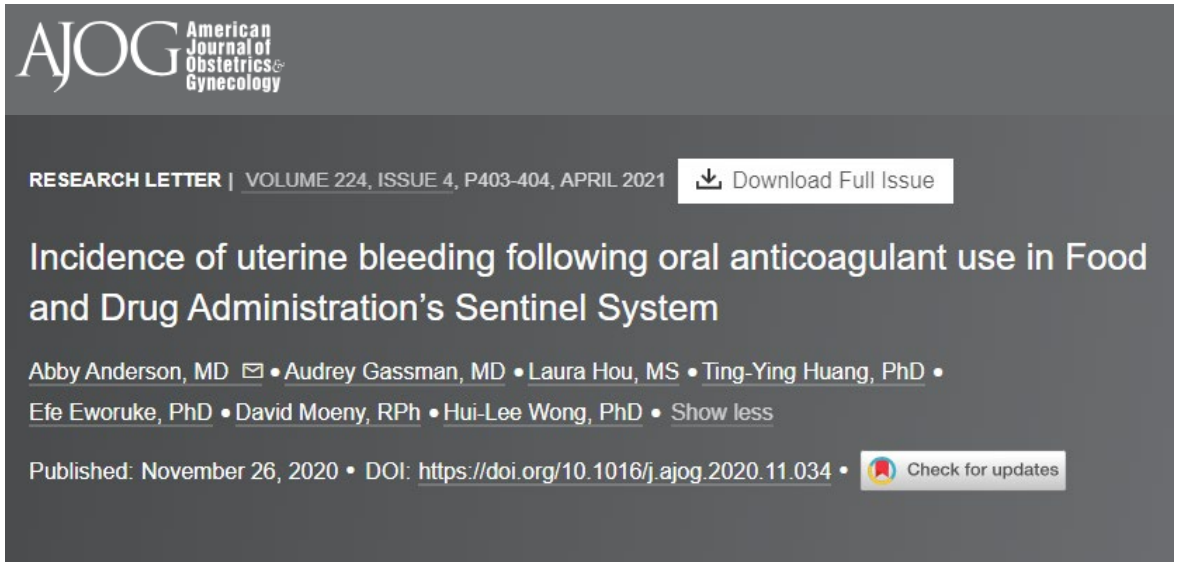
https://www.sentinelinitiative.org/assessments/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2

Drug Safety (2021) 44:753–763
https://doi.org/10.1007/s40264-021-01072-0

ORIGINAL RESEARCH ARTICLE

Risk of Severe Abnormal Uterine Bleeding Associated with Rivaroxaban Compared with Apixaban, Dabigatran and Warfarin

Efe Eworuke[1] · Laura Hou[2] · Rongmei Zhang[3] · Hui-Lee Wong[4] · Peter Waldron[5] · Abby Anderson[6] · Audrey Gassman[6] · David Moeny[1] · Ting-Ying Huang[2]



Sentinel

- What Sentinel is
- How Sentinel gets, standardizes, and checks its data
- How Sentinel supports post-market surveillance
- How Sentinel builds trust through transparency
- **Discussion**

Developing the Sentinel System — A National Resource for Evidence Development

Rachel E. Behrman, M.D., M.P.H., Joshua S. Benner, Pharm.D., Sc.D., Jeffrey S. Brown, Ph.D., Mark McClellan, M.D., Ph.D., Janet Woodcock, M.D., and Richard Platt, M.D.

N Engl J Med 2011; 364:498-499

The FDA Sentinel Initiative — An Evolving National Resource

Richard Platt, M.D., Jeffrey S. Brown, Ph.D., Melissa Robb, M.S., Mark McClellan, M.D., Ph.D., Robert Ball, M.D., M.P.H., Michael D. Nguyen, M.D., and Rachel E. Sherman, M.D., M.P.H.

N Engl J Med 2018; 379:2091-2093

The US Food and Drug Administration Sentinel System: a national resource for a learning health system

Jeffrey S. Brown [1], Aaron B. Mendelsohn[1], Young Hee Nam[1], Judith C. Maro [1], Noelle M. Cocoros[1], Carla Rodriguez-Watson[2], Catherine M. Lockhart[3], Richard Platt[1], Robert Ball [4], Gerald J. Dal Pan[4], and Sengwee Toh[1]

Journal of the American Medical Informatics Association, 00(0), 2022, 1–10
https://doi.org/10.1093/jamia/ocac153

The FDA Sentinel System

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