Real-world data
Data networks, standardization, and federated analysis

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January 18, 2022

When or why do we need large amount of real-world data?

To study rare exposures

To study rare exposures

To study rare outcomes

To study rare exposures

To study rare outcomes

To study specific patient subgroups

To study rare exposures

To study rare outcomes

To study specific patient subgroups

To study newly approved medical products

How do we get large amount of real-world data?

Wait for the data to accrue over time…

Bring multiple real-world data sources together

How do we bring multiple real-world data sources together?

Ask everyone to send all their data to a centralized location

But is that feasible?

Loss of patient privacy

Loss of patient privacy

Unauthorized uses of transferred data

Loss of patient privacy

Unauthorized uses of transferred data

Inaccurate analysis or interpretation of data

Loss of patient privacy

Unauthorized uses of transferred data

Inaccurate analysis or interpretation of data

Disclosure of sensitive corporate information

Loss of patient privacy

Unauthorized uses of transferred data

Inaccurate analysis or interpretation of data

Disclosure of sensitive corporate information

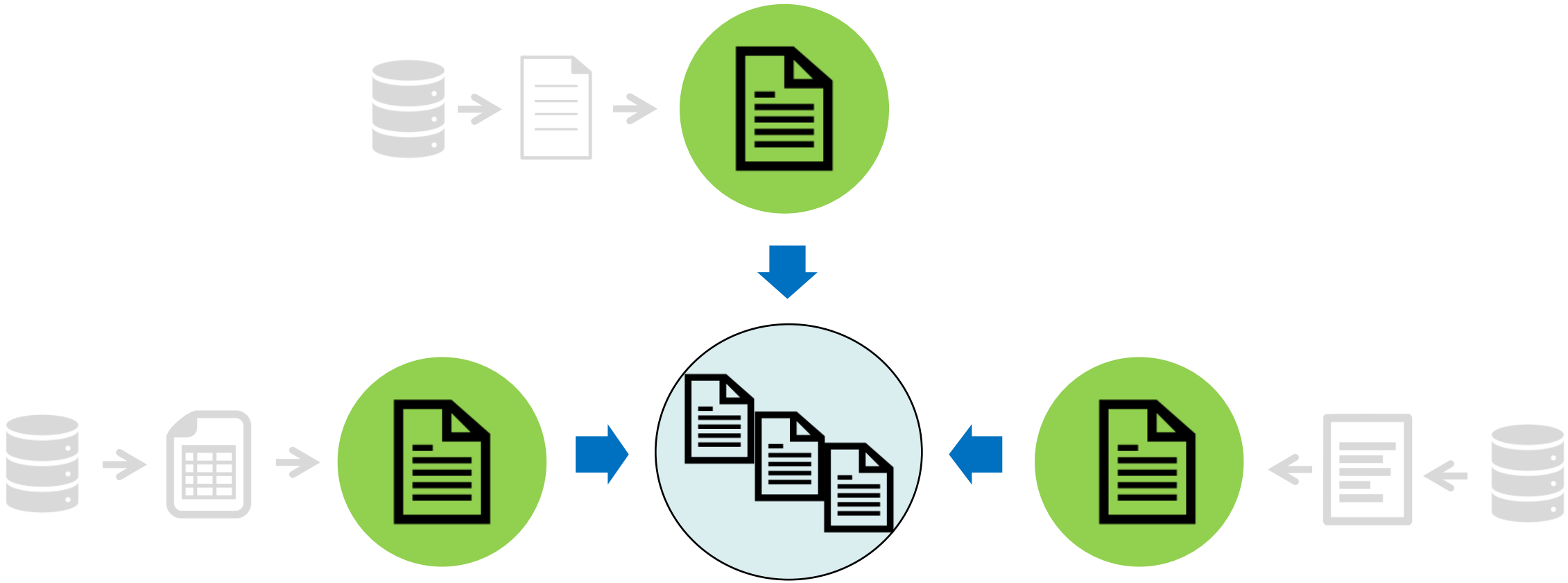
Regulatory or contractual restrictions

Annals of Internal Medicine | Academia and Clinic

Design of a National Distributed Health Data Network

Judith C. Maro, MS; Richard Platt, MD, MSc; John H. Holmes, PhD; Brian L. Strom, MD, MPH; Sean Hennessy, PharmD, PhD; Ross Lazarus, MBBS, MPH; and Jeffrey S. Brown, PhD

Ann Intern Med. 2009;151:341-344



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

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

Sentinel

- How Sentinel gets, standardizes, and checks its data
- How Sentinel performs privacy-protecting analysis
- How Sentinel contributes to FDA's regulatory mission
- How Sentinel builds trust through transparency
- How Sentinel continues to innovate and expand its capabilities
- Discussion

Sentinel

- **How Sentinel gets, standardizes, and checks its data**
- How Sentinel performs privacy-protecting analysis
- How Sentinel contributes to FDA's regulatory mission
- How Sentinel builds trust through transparency
- How Sentinel continues to innovate and expand its capabilities
- Discussion

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

Harvard Pilgrim Health Care Institute

Healthagen

aetna™

HealthCore

Anthem

OPTUM®

Humana Healthcare Research

RTI INTERNATIONAL

veradigm

TriNetX

TennCare

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

OPTUM Labs®

pcornet®

MASSACHUSETTS

ADVANCE Collaborative

Booz | Allen | Hamilton

BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S HOSPITAL

KAISER PERMANENTE®

Colorado
Hawaii
Mid-Atlantic
Northern California
Northwest
Washington

CAPriCORN

GPC Greater Plains Collaborative

Marshfield Clinic Research Institute

HCA Healthcare

GDIT

NYC-CDRN New York City Clinical Data Research Network

UF College of Pharmacy UNIVERSITY of FLORIDA

VANDERBILT UNIVERSITY MEDICAL CENTER

The Meyers Primary Care Institute

RUTGERS

OneFlorida Clinical Research Consortium

REACHnet Research Action for Health Network

IBM Watson Health

PaTH Network patient empowered research

PEDSnet A Pediatric Learning Health System

HealthPartners Institute

SCHOOL OF PUBLIC HEALTH UNIVERSITY of WASHINGTON

UAB

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

STAR Stakeholders, Technology, and Research CRN

Duke Clinical Research Institute

Penn Medicine

THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH


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

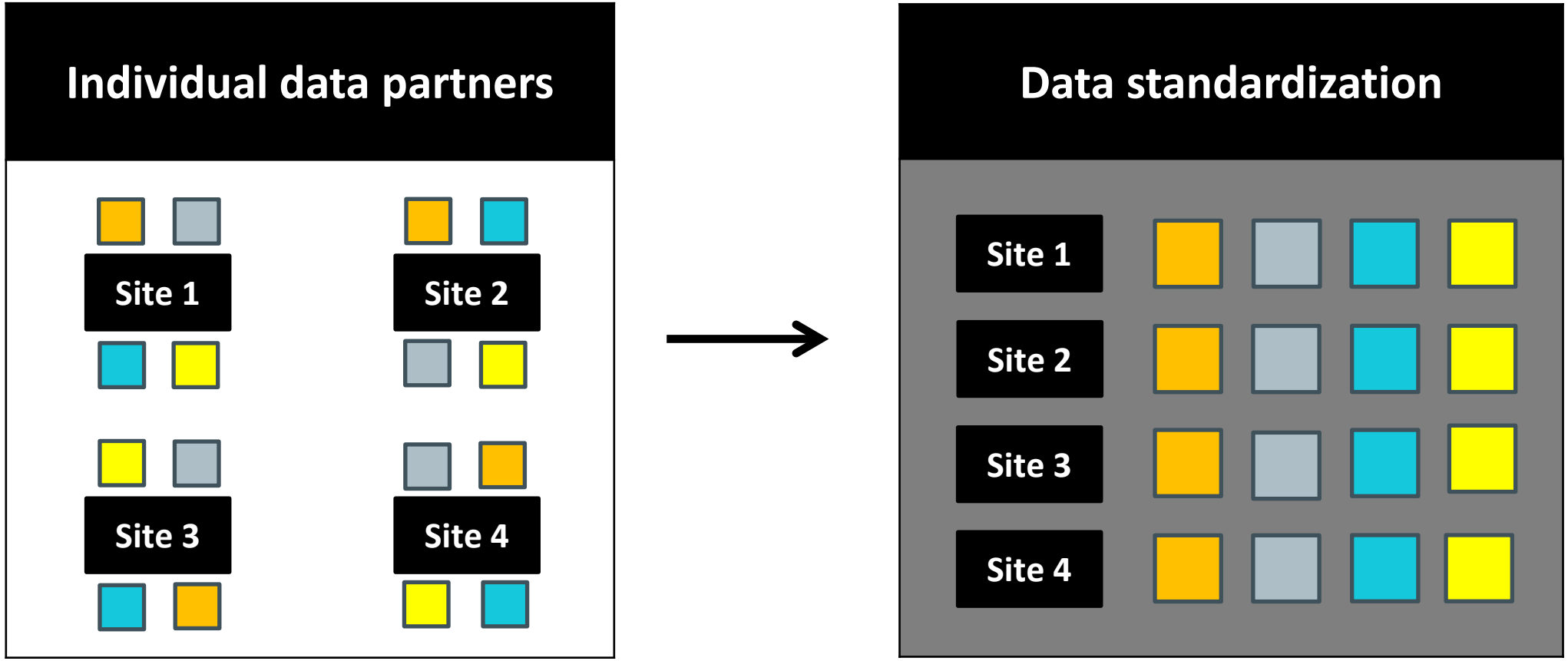
PROCEDURE

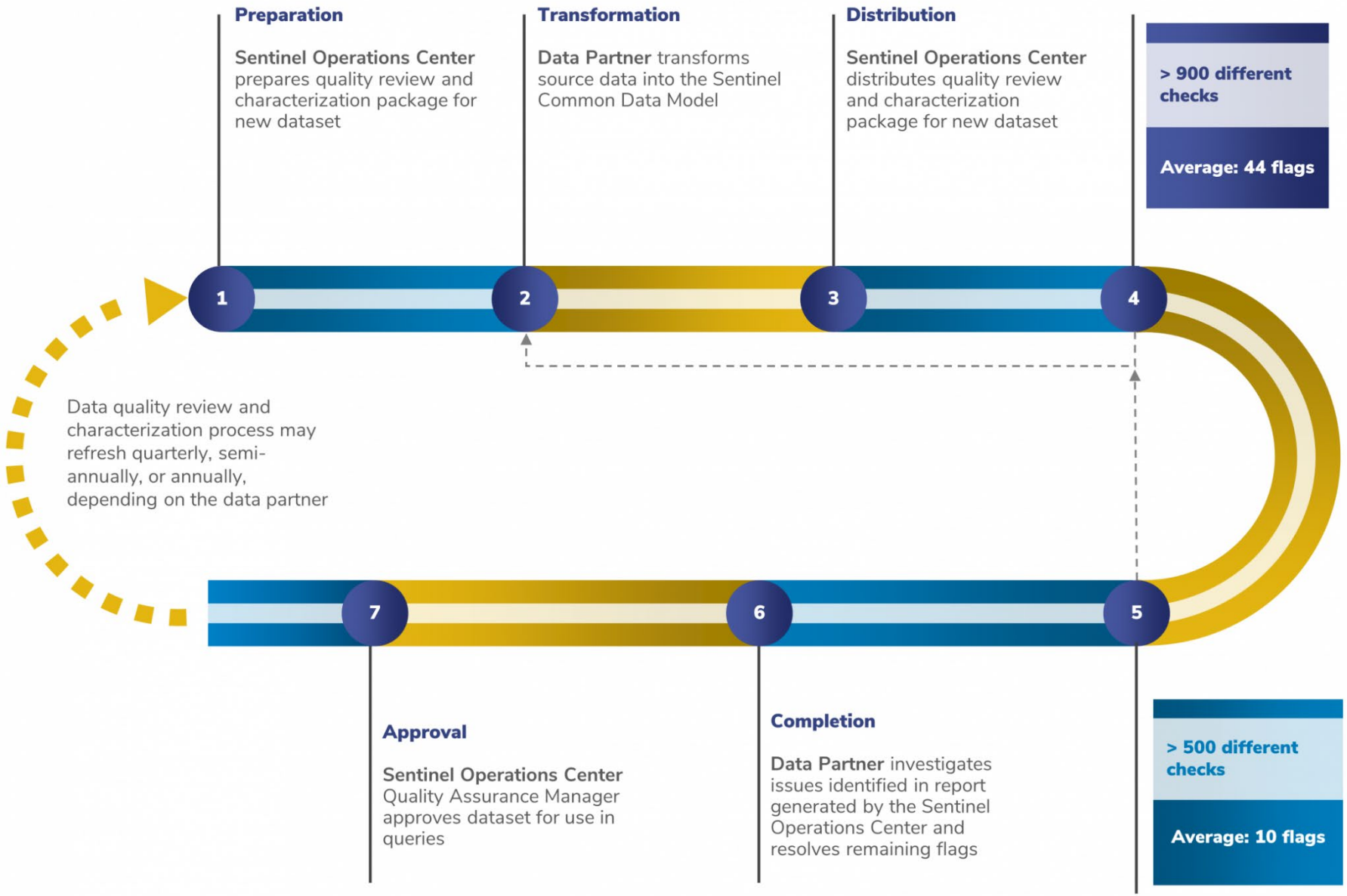
PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99222	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99238	C4
PatID1	EncID1	10/18/2005	Provider2	IP	27445	C4

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

Guidance for Industry and FDA Staff

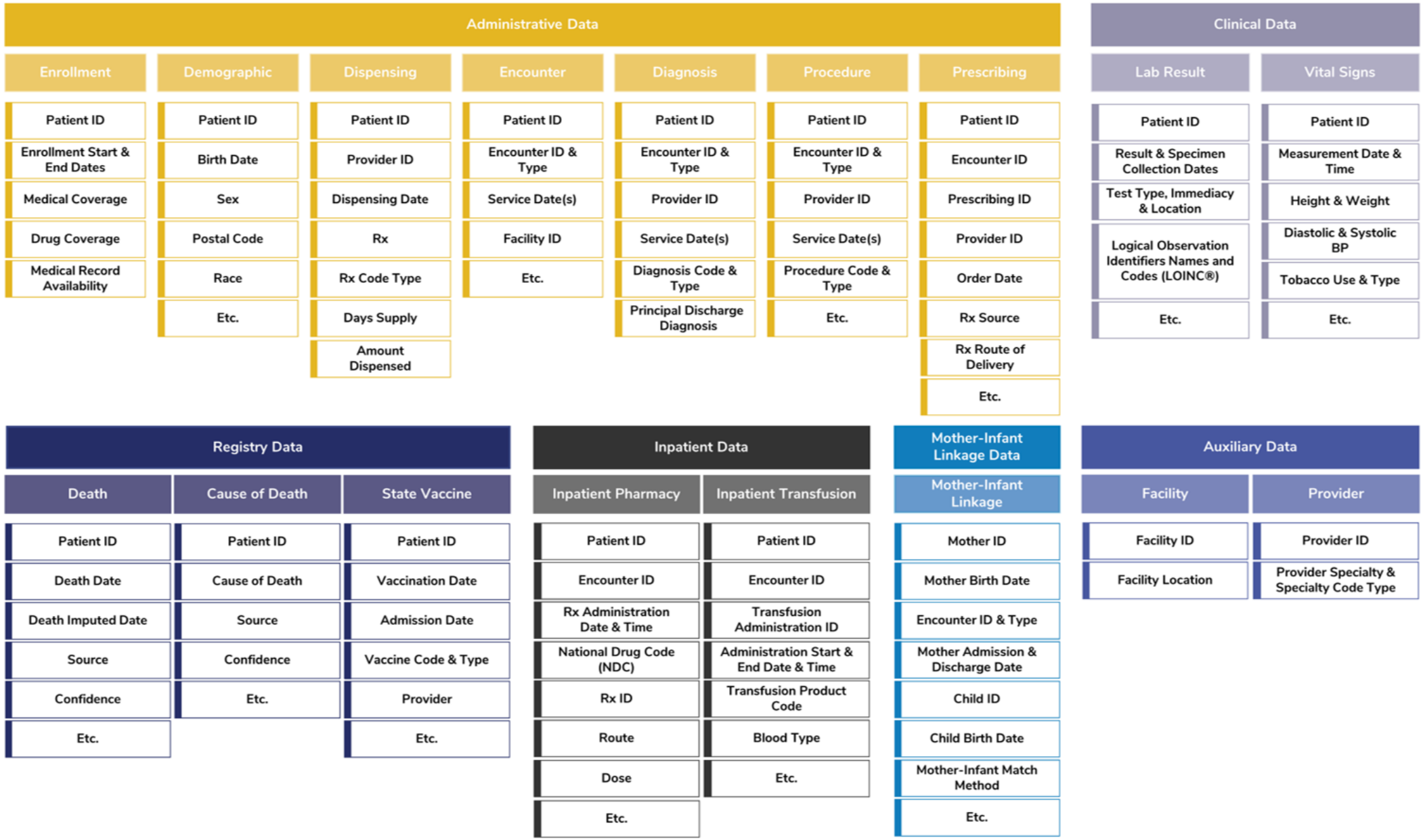
Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

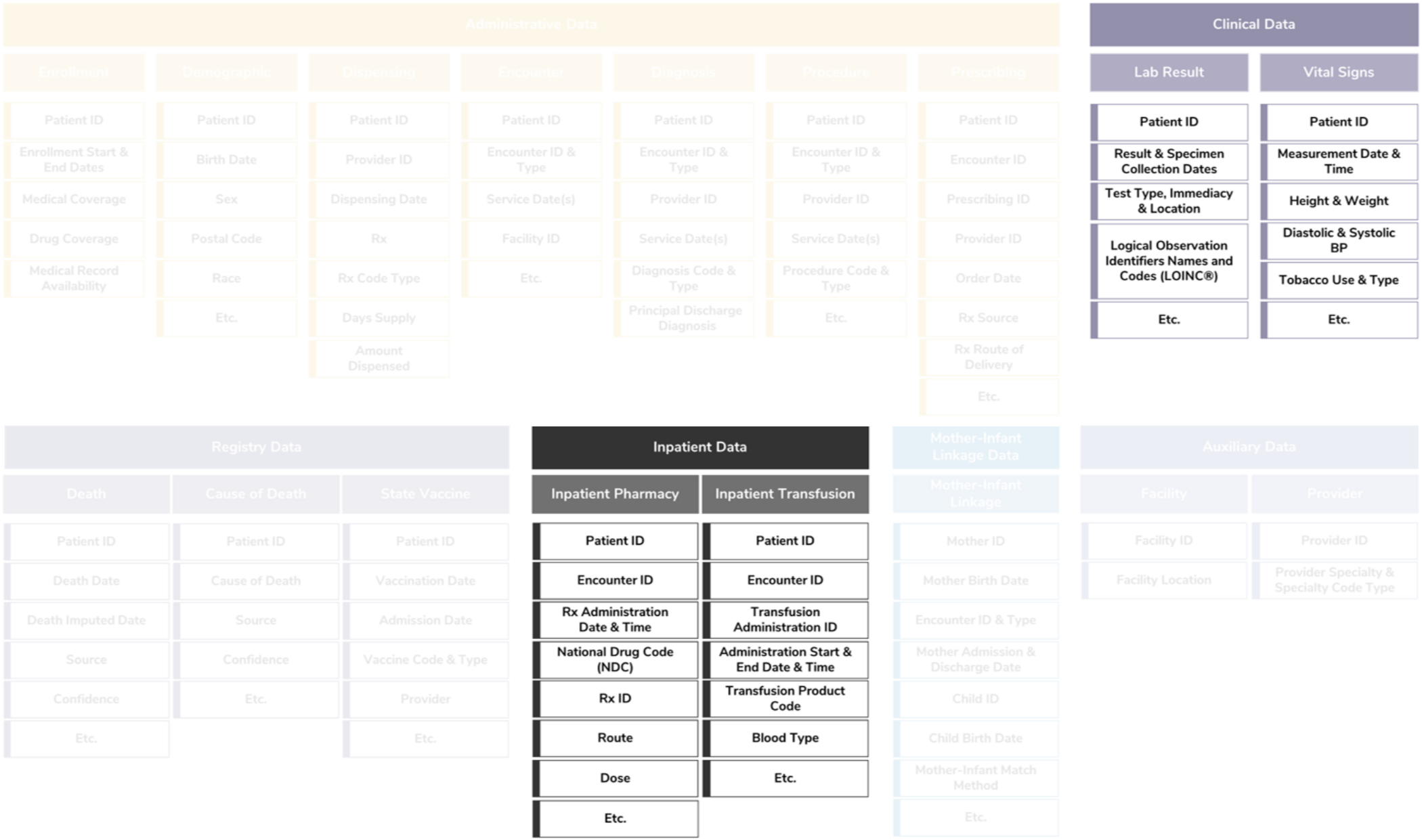
Sentinel

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"

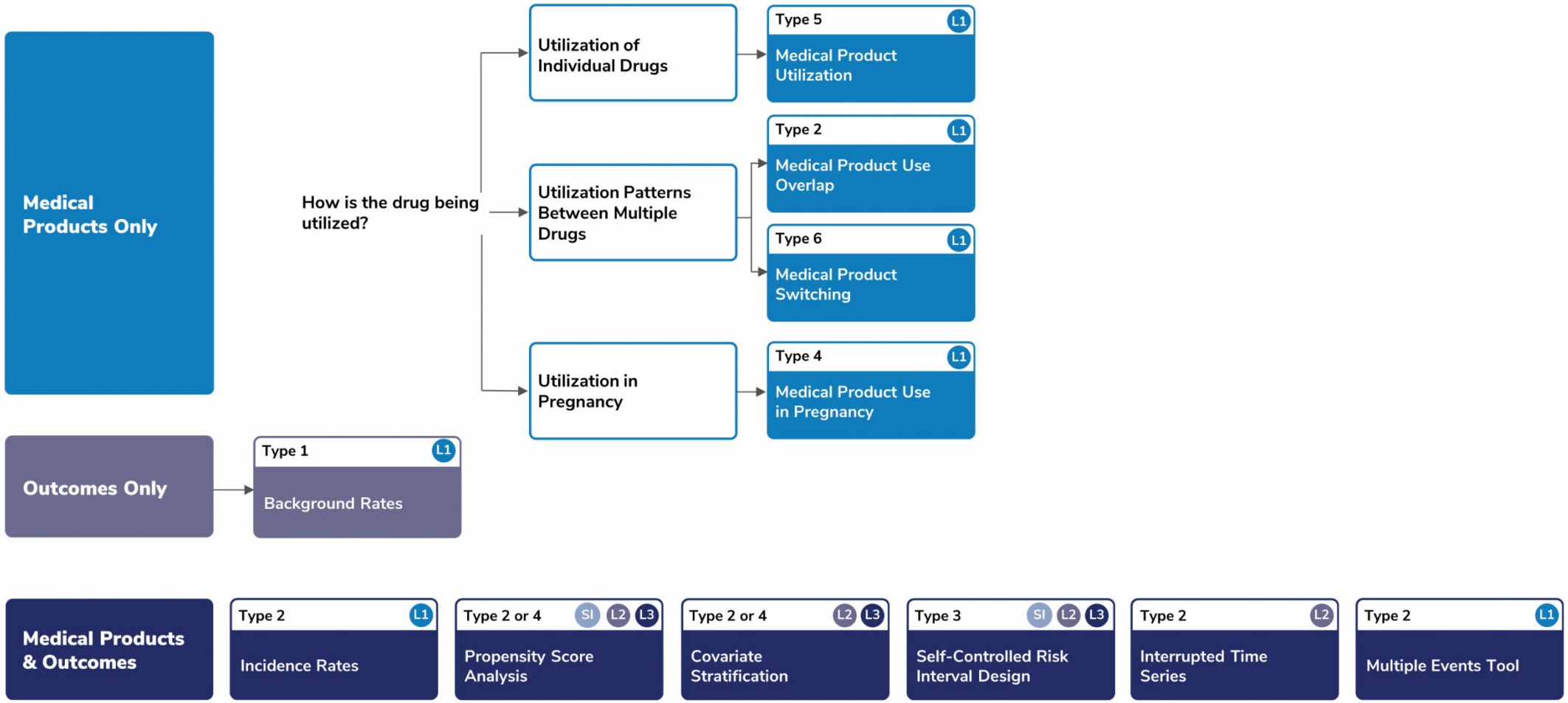
https://www.sentinelinitiative.org/sites/default/files/data/distributed-database/Sentinel_DataQAPractices_Memo.pdf
https://www.fda.gov/downloads/drugs/guidances/ucm243537.pdf

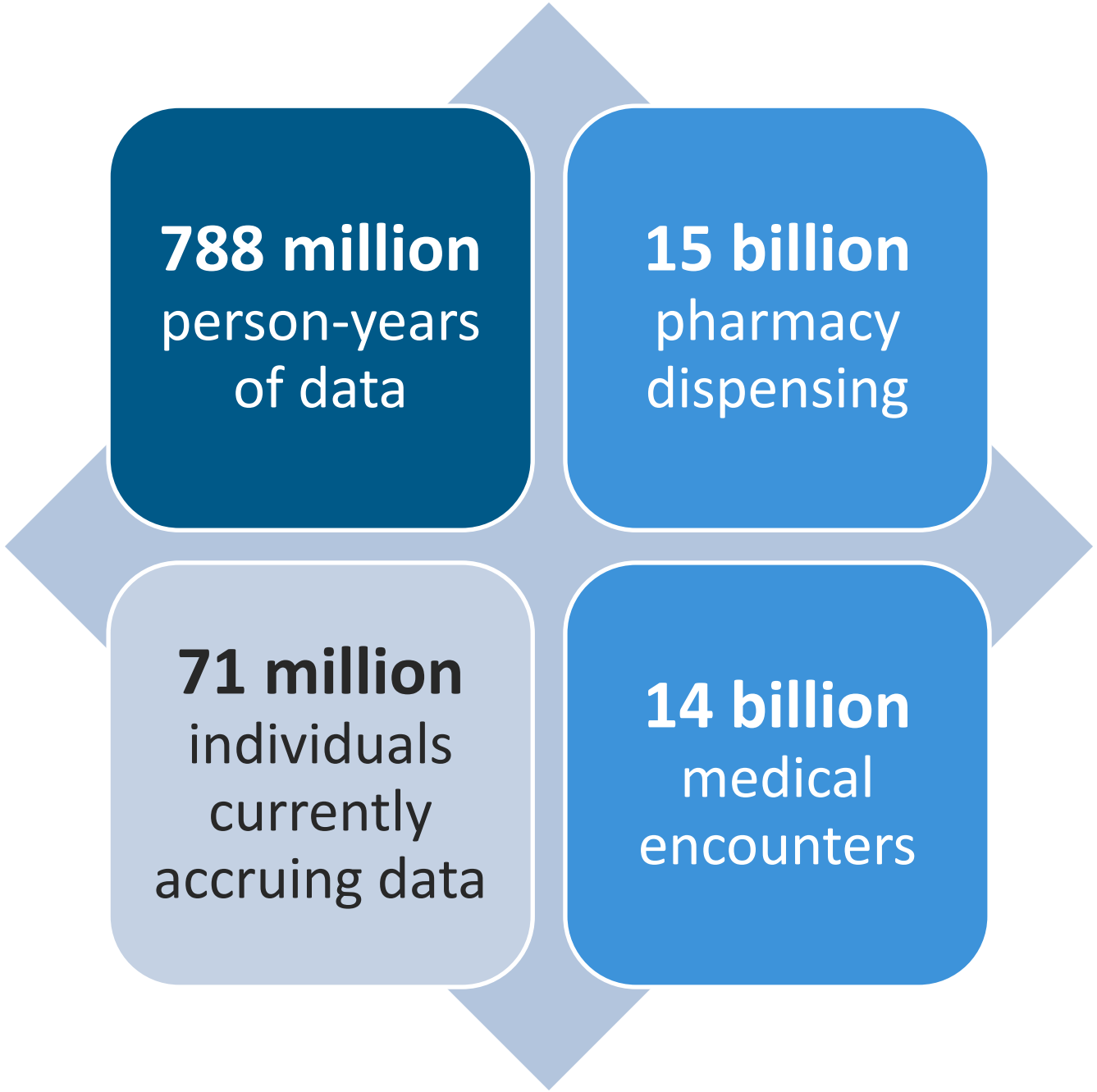

Administrative Data
Enrollment
Patient ID
Enrollment Start & End Dates
Medical Coverage
Drug Coverage
Medical Record Availability
Demographic
Patient ID
Birth Date
Sex
Postal Code
Race
Etc.
Dispensing
Patient ID
Provider ID
Dispensing Date
Rx
Rx Code Type
Days Supply
Amount Dispensed
Encounter
Patient ID
Encounter ID & Type
Service Date(s)
Facility ID
Etc.
Diagnosis
Patient ID
Encounter ID & Type
Provider ID
Service Date(s)
Diagnosis Code & Type
Principal Discharge Diagnosis
Procedure
Patient ID
Encounter ID & Type
Provider ID
Service Date(s)
Procedure Code & Type
Etc.
Prescribing
Patient ID
Encounter ID
Prescribing ID
Provider ID
Order Date
Rx Source
Rx Route of Delivery
Etc.
Clinical Data
Lab Result
Patient ID
Result & Specimen Collection Dates
Test Type, Immediacy & Location
Logical Observation Identifiers Names and Codes (LOINC®)
Etc.
Vital Signs
Patient ID
Measurement Date & Time
Height & Weight
Diastolic & Systolic BP
Tobacco Use & Type
Etc.
Registry Data
Death
Patient ID
Death Date
Death Imputed Date
Source
Confidence
Etc.
Cause of Death
Patient ID
Cause of Death
Source
Confidence
Etc.
State Vaccine
Patient ID
Vaccination Date
Admission Date
Vaccine Code & Type
Provider
Etc.
Inpatient Data
Inpatient Pharmacy
Patient ID
Encounter ID
Rx Administration Date & Time
National Drug Code (NDC)
Rx ID
Route
Dose
Etc.
Inpatient Transfusion
Patient ID
Encounter ID
Transfusion Administration ID
Administration Start & End Date & Time
Transfusion Product Code
Blood Type
Etc.
Mother-Infant Linkage Data
Mother-Infant Linkage
Mother ID
Mother Birth Date
Encounter ID & Type
Mother Admission & Discharge Date
Child ID
Child Birth Date
Mother-Infant Match Method
Etc.
Auxiliary Data
Facility
Facility ID
Facility Location
Provider
Provider ID
Provider Specialty & Specialty Code Type


Administrative Data
Enrollment
Patient ID
Enrollment Start & End Dates
Medical Coverage
Drug Coverage
Medical Record Availability
Demographic
Patient ID
Birth Date
Sex
Postal Code
Race
Etc.
Dispensing
Patient ID
Provider ID
Dispensing Date
Rx
Rx Code Type
Days Supply
Amount Dispensed
Encounter
Patient ID
Encounter ID & Type
Service Date(s)
Facility ID
Etc.
Diagnosis
Patient ID
Encounter ID & Type
Provider ID
Service Date(s)
Diagnosis Code & Type
Principal Discharge Diagnosis
Procedure
Patient ID
Encounter ID & Type
Provider ID
Service Date(s)
Procedure Code & Type
Etc.
Prescribing
Patient ID
Encounter ID
Prescribing ID
Provider ID
Order Date
Rx Source
Rx Route of Delivery
Etc.
Clinical Data
Lab Result
Patient ID
Result & Specimen Collection Dates
Test Type, Immediacy & Location
Logical Observation Identifiers Names and Codes (LOINC®)
Etc.
Vital Signs
Patient ID
Measurement Date & Time
Height & Weight
Diastolic & Systolic BP
Tobacco Use & Type
Etc.
Registry Data
Death
Patient ID
Death Date
Death Imputed Date
Source
Confidence
Etc.
Cause of Death
Patient ID
Cause of Death
Source
Confidence
Etc.
State Vaccine
Patient ID
Vaccination Date
Admission Date
Vaccine Code & Type
Provider
Etc.
Inpatient Data
Inpatient Pharmacy
Patient ID
Encounter ID
Rx Administration Date & Time
National Drug Code (NDC)
Rx ID
Route
Dose
Etc.
Inpatient Transfusion
Patient ID
Encounter ID
Transfusion Administration ID
Administration Start & End Date & Time
Transfusion Product Code
Blood Type
Etc.
Mother-Infant Linkage Data
Mother-Infant Linkage
Mother ID
Mother Birth Date
Encounter ID & Type
Mother Admission & Discharge Date
Child ID
Child Birth Date
Mother-Infant Match Method
Etc.
Auxiliary Data
Facility
Facility ID
Facility Location
Provider
Provider ID
Provider Specialty & Specialty Code Type

What are you investigating?

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




788 million
person-years
of data
15 billion
pharmacy
dispensing
71 million
individuals
currently
accruing data
14 billion
medical
encounters

Sentinel's Multi-Modal Response System

Claims (with Limited EHR Network)

Active Risk Identification and Analysis (ARIA)*

- Sentinel Distributed Database
- IBM® MarketScan® Research Databases

- Sentinel Common Data Model
- Sentinel Analytic Tools
- Access to Medical Records within the Sentinel Distributed Database

EHR Data Aggregators

- TriNetX
- IBM Watson Health

- Proprietary Common Data Models
- Web-Based Query Interface & Custom Programming
- Access to Medical Records varies by Source

EHR Data Warehouse

- HCA Healthcare
- Veradigm

- Data Warehouse for Multiple Healthcare Organizations in a System
- Custom Programming
- Access to Medical Records

EHR Networks

- PCORnet

- PCORnet Common Data Model
- PCORnet Analytic Tools
- Access to Medical Records

**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.*

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**: 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]

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]

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]

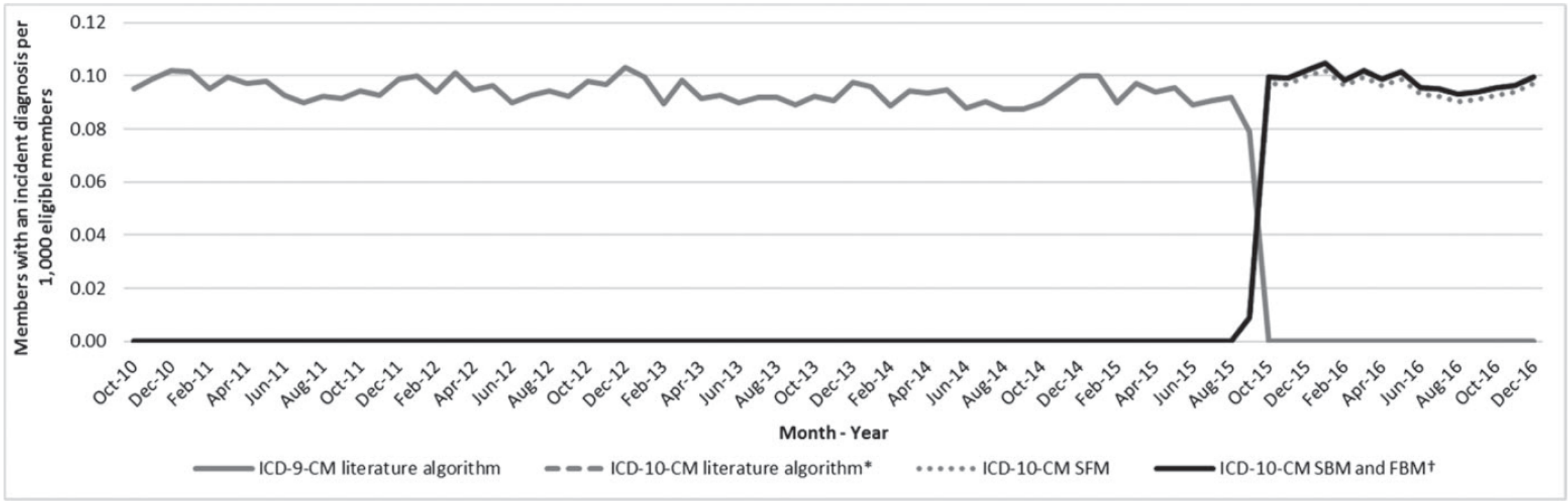
Received: 17 August 2017 | Revised: 28 February 2018 | Accepted: 29 April 2018
DOI: 10.1002/pds.4563

ORIGINAL REPORT

WILEY

Early impact of the ICD-10-CM transition on selected health outcomes in 13 electronic health care databases in the United States

Catherine A. Panozzo[1] | Tiffany S. Woodworth[1] | Emily C. Welch[1] | Ting-Ying Huang[1] | Qoua L. Her[1] | Kevin Haynes[2] | Catherine Rogers[1] | Talia J. Menzin[1] | Max Ehrmann[1] | Katherine E. Freitas[1] | Nicole R. Haug[1] | Sengwee Toh[1]



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]

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

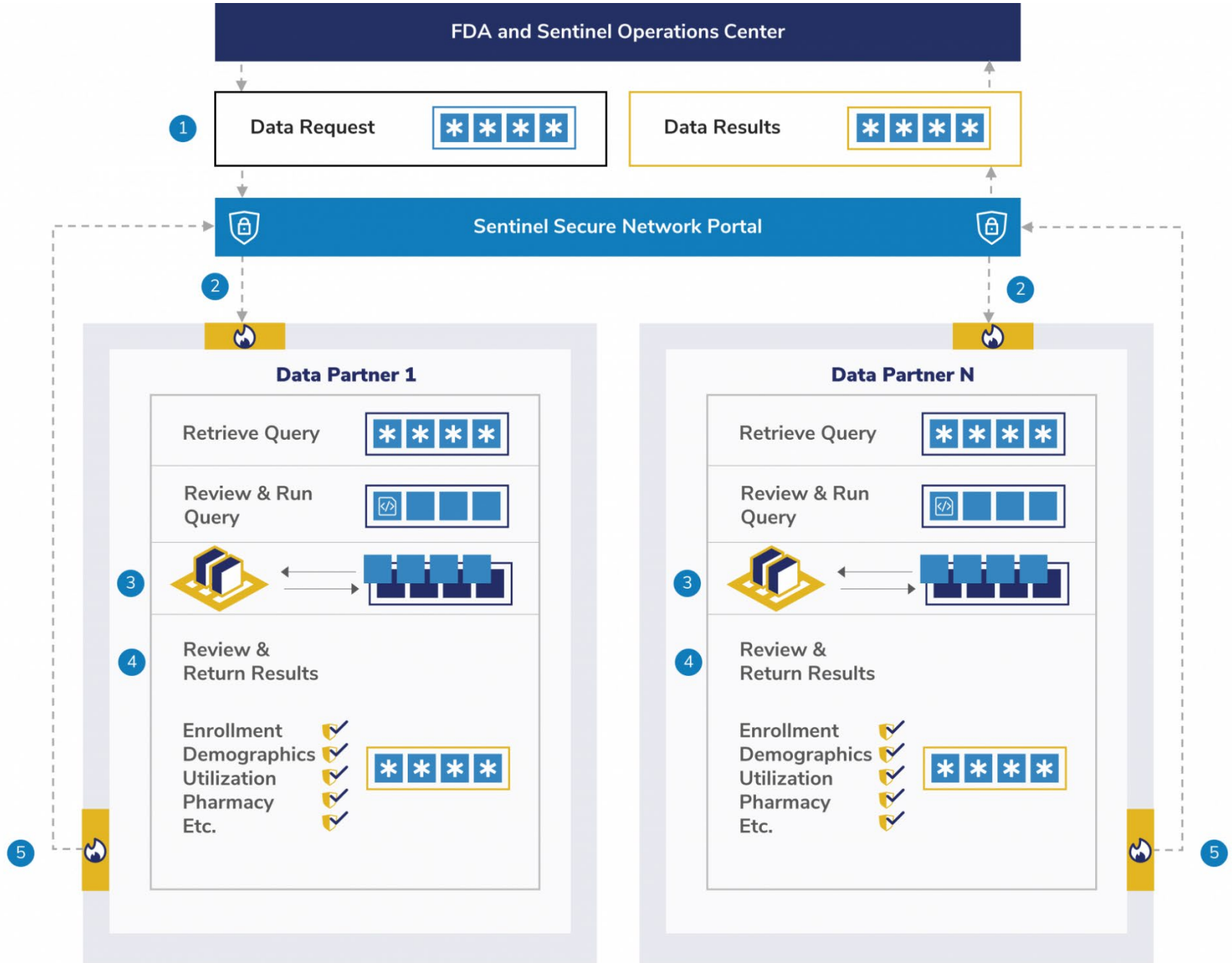
- How Sentinel gets, standardizes, and checks its data
- **How Sentinel performs privacy-protecting analysis**
- How Sentinel contributes to FDA's regulatory mission
- How Sentinel builds trust through transparency
- How Sentinel continues to innovate and expand its capabilities
- Discussion

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



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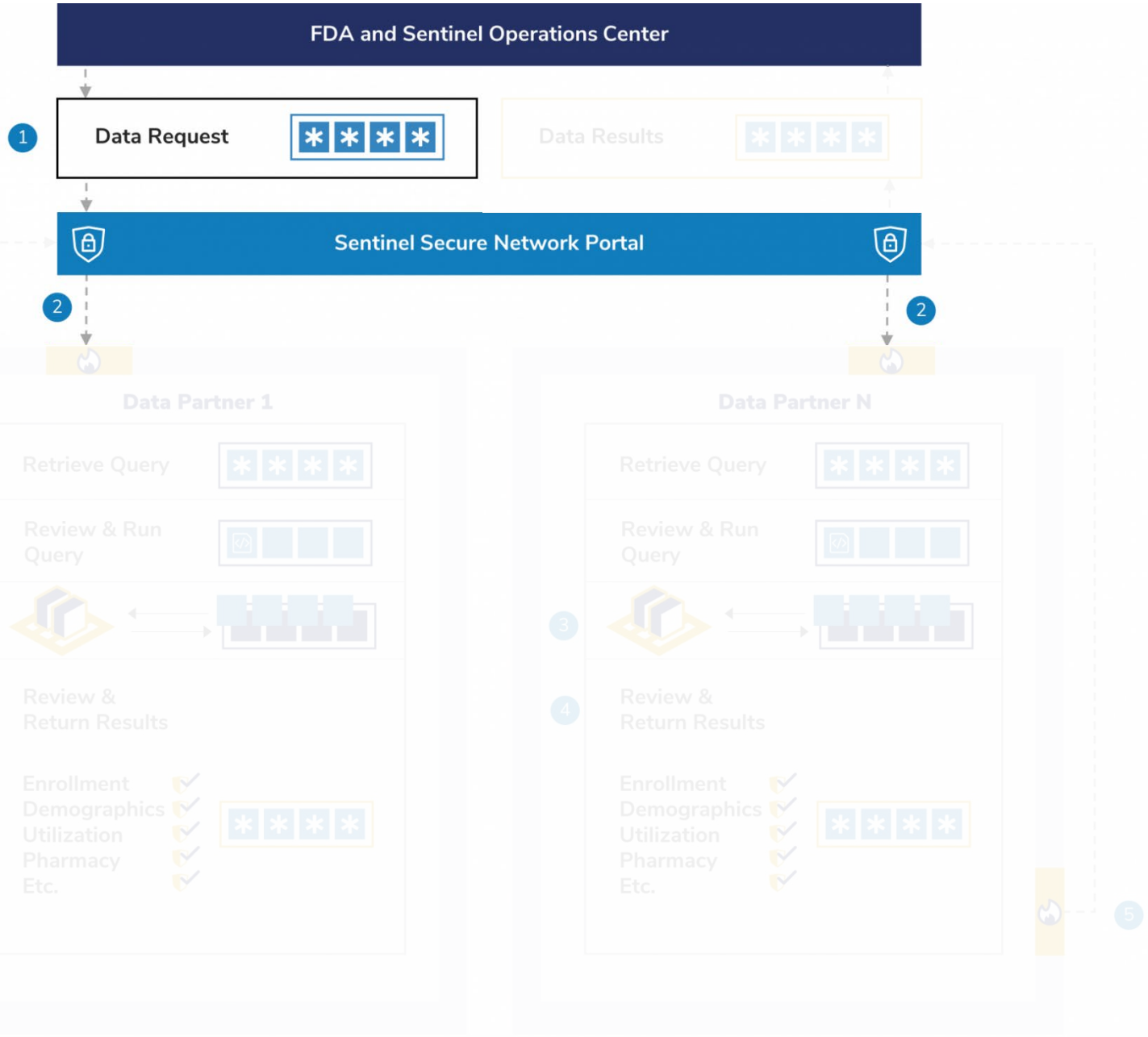

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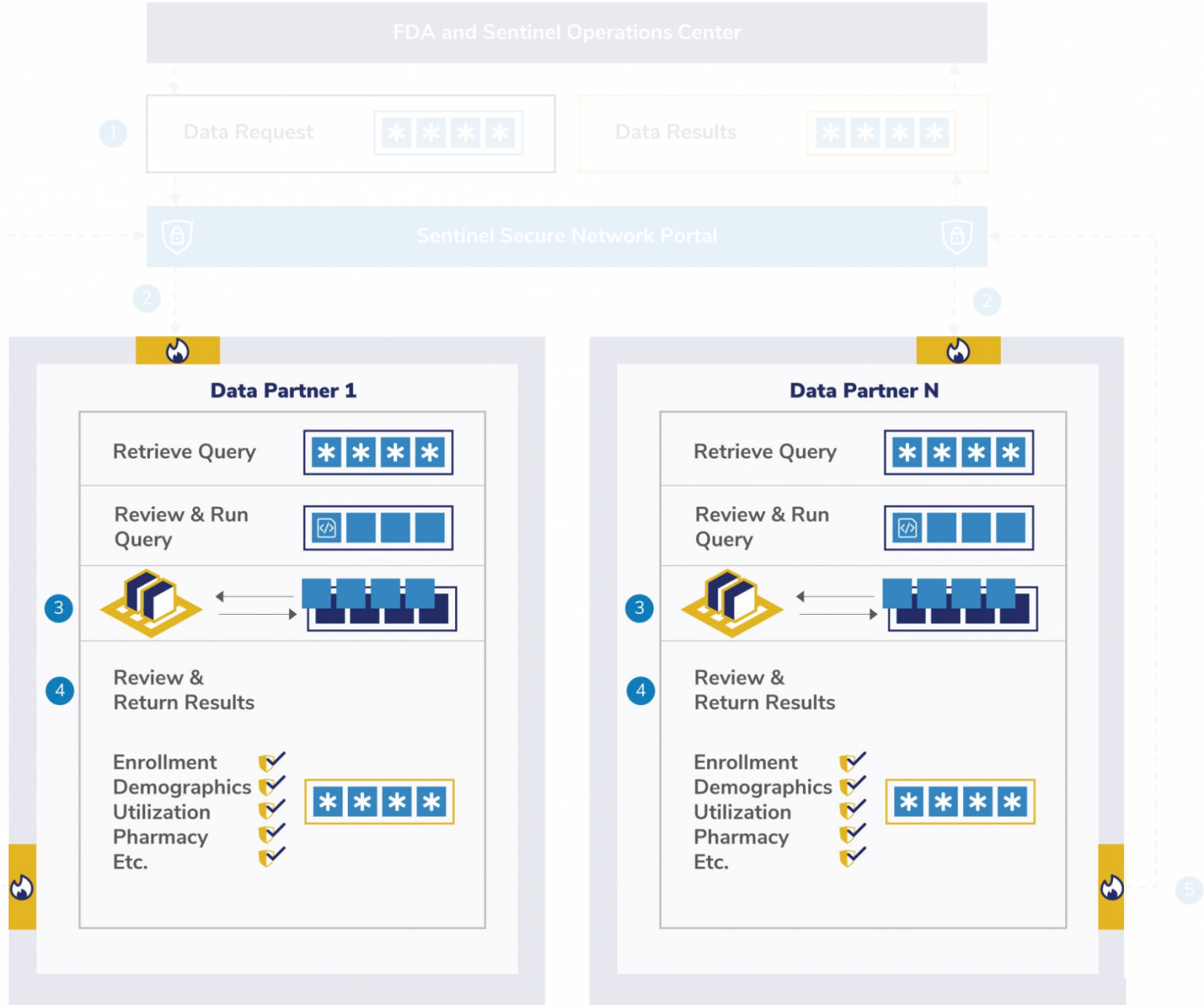

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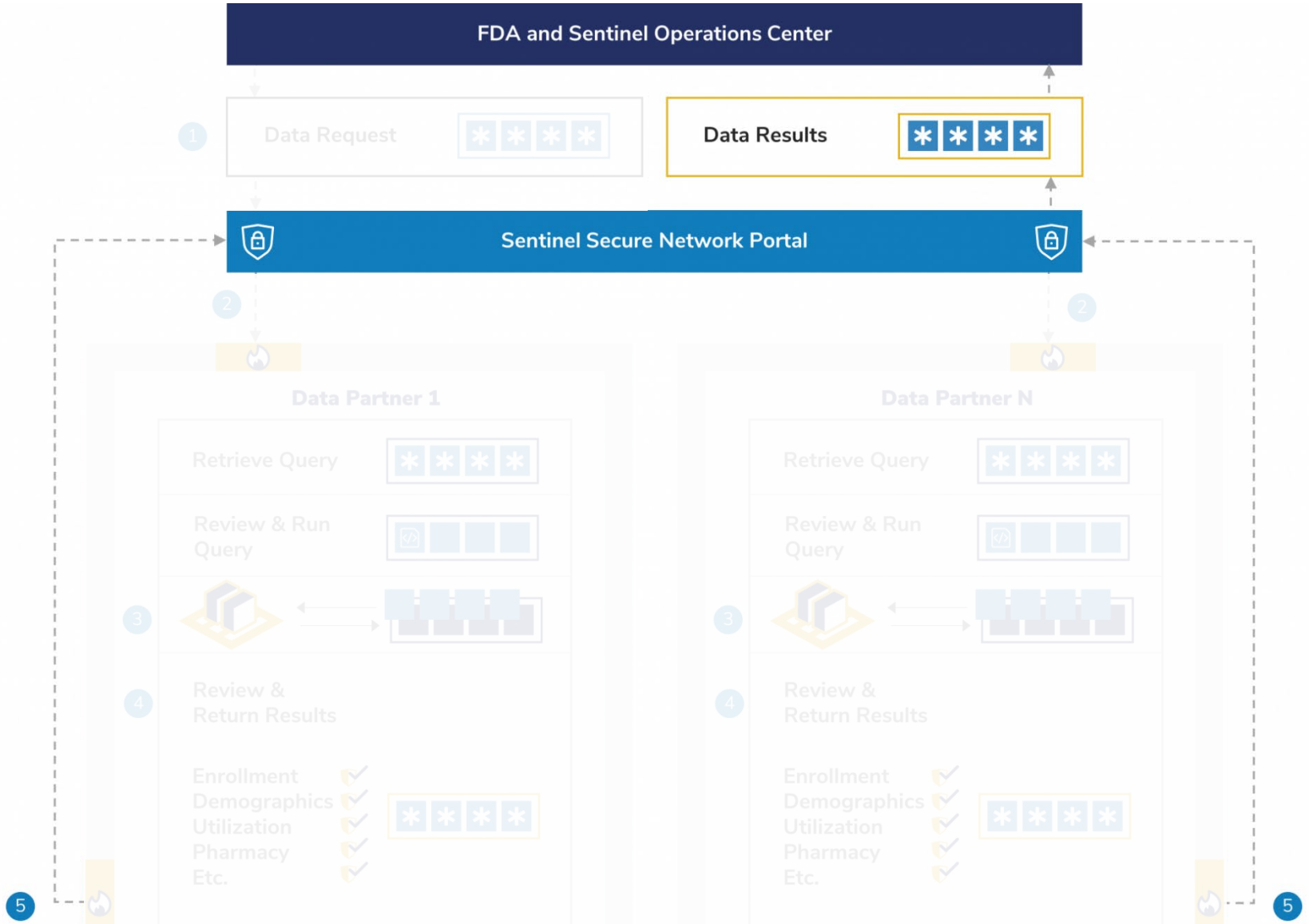

Firewall

Local Data

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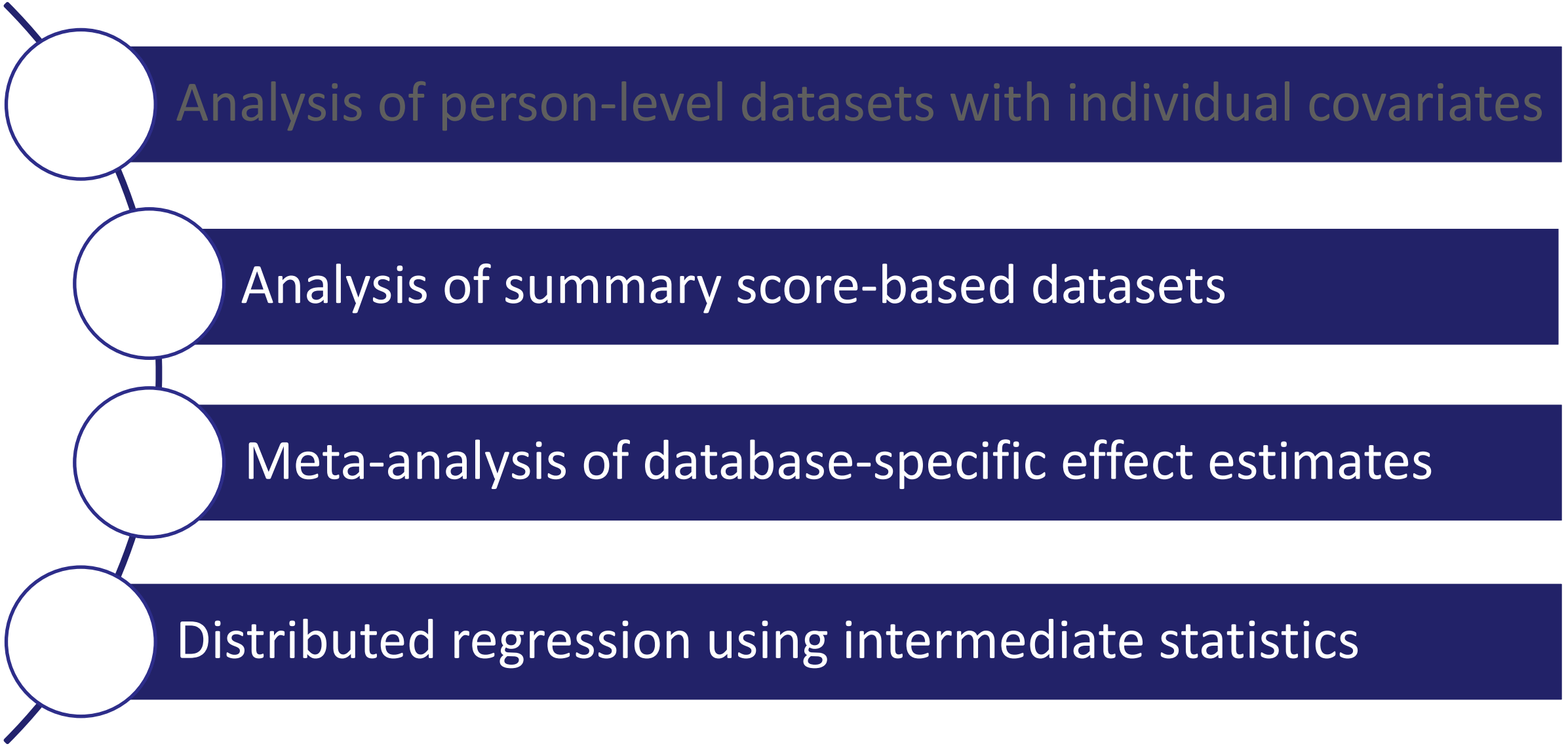
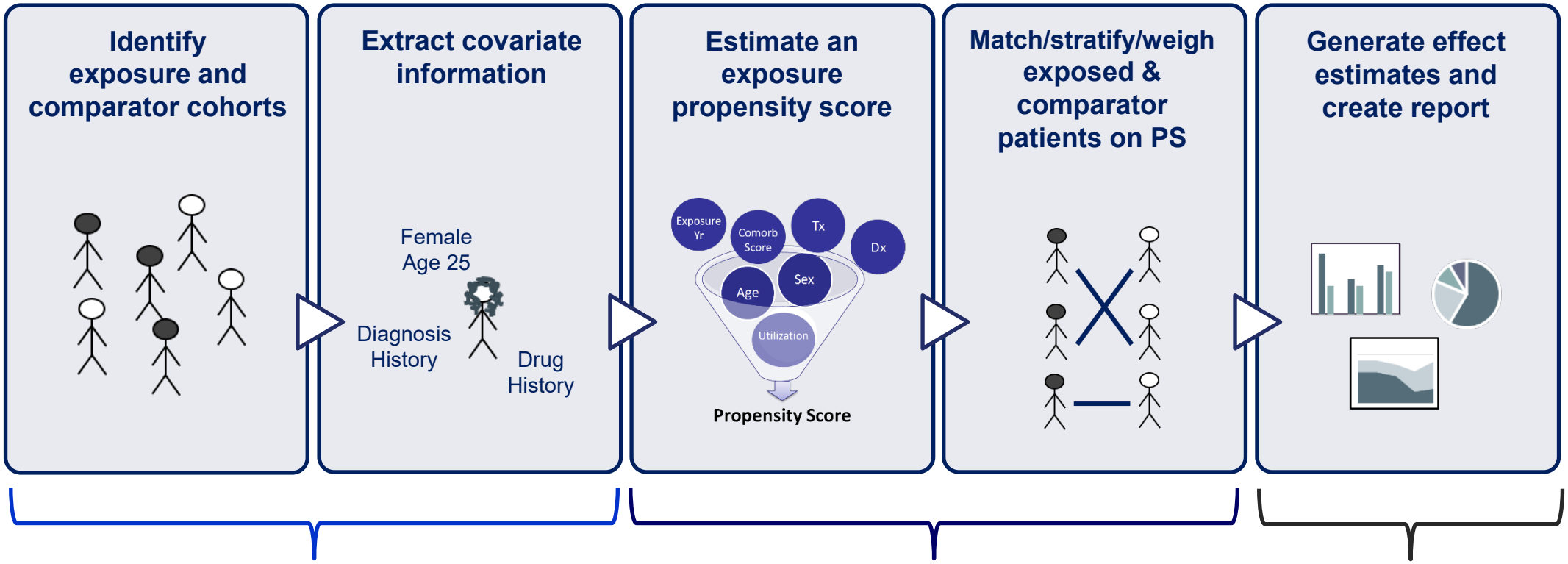
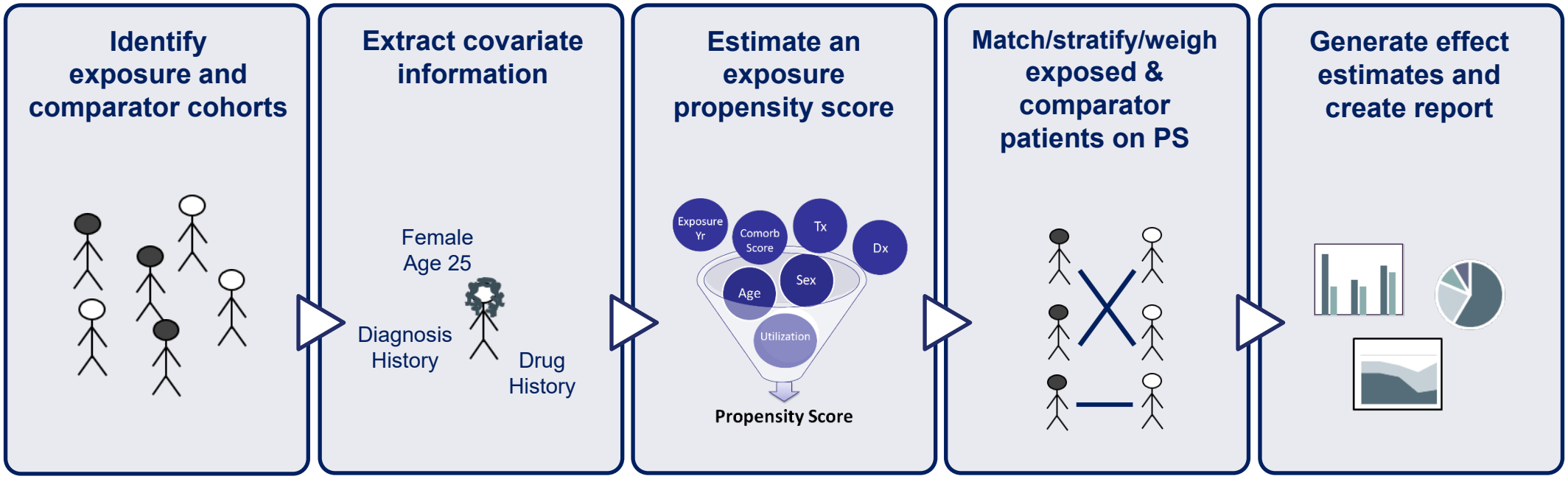

Analysis of person-level datasets with individual covariates
Analysis of summary score-based datasets
Meta-analysis of database-specific effect estimates
Distributed regression using intermediate statistics



Cohort Identification and Descriptive Analysis Tool

Propensity Score Analysis Tool

Other Tools (depending on analysis)


Identify exposure and comparator cohorts
Extract covariate information
Female
Age 25
Diagnosis History
Drug History
Estimate an exposure propensity score
Exposure Yr
Comorb Score
Tx
Dx
Sex
Age
Utilization
Propensity Score
Match/stratify/weigh exposed & comparator patients on PS
Generate effect estimates and create report
Performed at the data partner sites
Performed at the analysis center

REVIEW

Analytic and Data Sharing Options in Real-World Multidatabase Studies of Comparative Effectiveness and Safety of Medical Products

Sengwee Toh[1,*]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 107 NUMBER 4 | April 2020

Sentinel

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- **How Sentinel contributes to FDA's regulatory mission**
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- How Sentinel continues to innovate and expand its capabilities
- Discussion

Risk of Psychiatric Adverse Events Among Montelukast Users

Veronica Sansing-Foster, PhD[a], Nicole Haug, MS[b], Andrew Mosholder, MD, MPH[a], Noelle M. Cocoros, PhD[b], Marie Bradley, PhD[a], Yong Ma, PhD[c], Dinci Pennap, PhD[a], Elizabeth C. Dee, MPH[b], Sengwee Toh, ScD[b], Ella Pestine, MPH[b], Andrew B. Petrone, MPH[b], Ivone Kim, MD[d], Jennifer G. Lyons, PhD[b], and Efe Eworuke, PhD[a] *Silver Spring, Md; and Boston, Mass*

J Allergy Clin Immunol Pract 2021;9:385-93

TABLE I. Baseline characteristics before and after 1:1 propensity score matching

	Before matching				After matching			
	Montelukast		ICSs		Montelukast		ICSs	
Characteristic	(n = 513,519)	%	(n = 1,332,531)	%	(n = 457,377)	%	(n = 457,377)	%
Mean age (y), mean ± SD	38.9 ± 18.3		37 ± 19.8		38.5 ± 18.3		38.5 ± 19.3	
Age group (y)								
6-11	92,294	18.0	269,772	21.1	83,372	18.2	96,887	21.2
12-17	61,854	12.0	152,571	13.5	56,576	12.4	50,311	11.0
18+	359,371	70.0	910,188	65.4	318,009	69.4	310,759	67.9
Female	321,937	62.7	789,900	60.4	283,584	61.9	283,502	61.9
Male	191,582	37.3	542,631	39.6	174,373	38.1	174,455	38.1
Pre-DSC/labeling change (2000-2007)	53,082	10.3	380,780	46.0	45,949	10.0	45,405	10.2
Post-DSC/labeling change (2008-2015)	460,437	89.7	951,751	54.0	412,008	90.0	411,497	89.9
Combined comorbidity score, mean ± SD	1.2 ± 1.1		1.2 ± 0.8		1.3 ± 1.1		1.3 ± 1.1	
Psychiatric disorder	191,922	37.4	421,649	34.7	168,654	36.8	168,435	36.8
Any other psychiatric event	136,101	26.5	300,278	25.4	119,790	26.2	120,723	26.4
Self-harm	366	0.1	774	0.1	337	0.1	328	0.1
Psychiatric and psychotropic drugs	151,108	29.4	325,423	26.5	132,614	30.0	131,852	28.8
Substance abuse	3,607	0.7	15,230	2.1	3,310	0.7	3,256	0.7
Allergic rhinitis	249,160	48.5	366,987	23.8	198,702	43.4	198,406	43.3
At least 2 respiratory disorders (not COPD or asthma)	260,341	50.7	465,933	34.7	221,671	48.4	220,988	48.3
Asthma—Emergency	42,512	8.3	89,980	9.1	2,001	0.4	1,992	0.4
Asthma—Inpatient primary	2,190	0.4	4,443	0.5	17,113	3.7	17,067	3.7
Asthma—Inpatient secondary/unknown	19,003	3.7	40,224	3.0	134,486	29.4	135,549	29.6
Asthma—Outpatient	149,886	29.2	308,554	23.4	52,674	11.5	52,385	11.4
Asthma exacerbation	55,780	10.9	147,857	13.8	2,001	0.4	1,992	0.4
History of other asthma medications								
Oral corticosteroids	109,785	21.4	193,116	16.7	94,602	20.7	94,240	20.6
Short-acting beta-agonists	296,329	57.7	1,041,200	82.5	288,348	63.0	287,982	62.9
Anticholinergic agents	5,578	1.1	7,904	0.3	4,984	1.1	5,008	1.1
Phosphodiesterase inhibitors	3,039	0.6	6,091	0.9	2,583	0.6	2,589	0.6

COPD, Chronic obstructive pulmonary disease, *DSC*, Drug Safety Communication.

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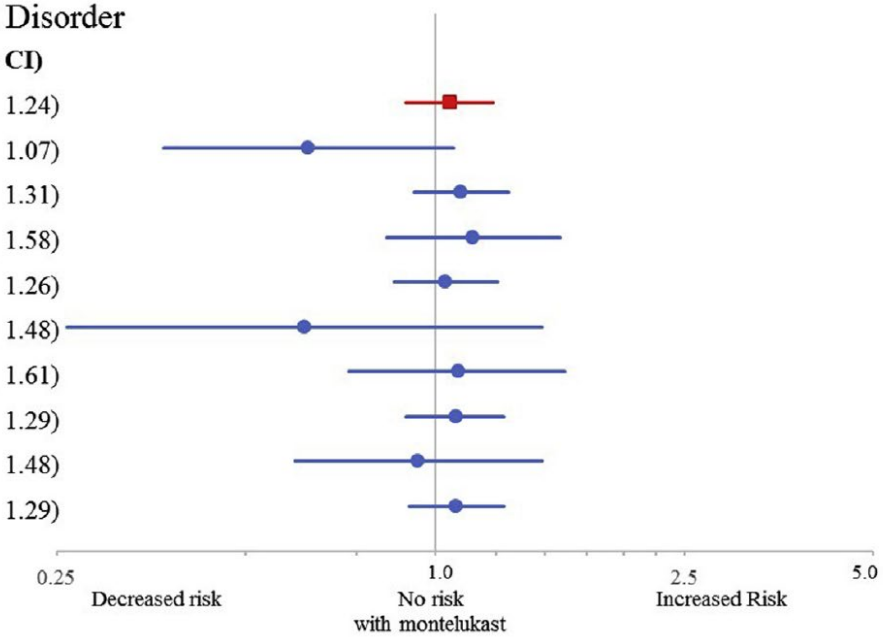
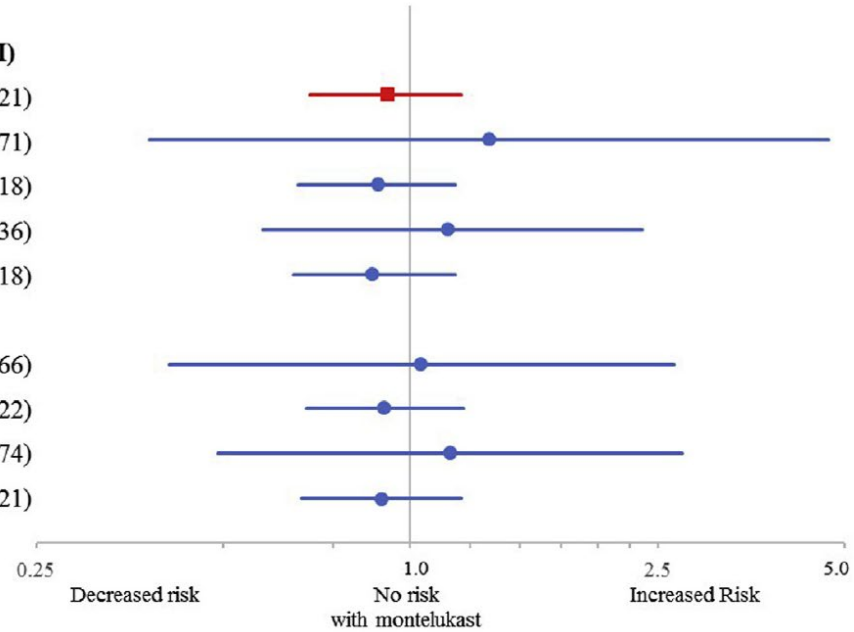
Inpatient Depressive Disorder

	HR (95% CI)
Overall	1.06 (0.90, 1.24)
No psych hx	0.63 (0.37, 1.07)
Psych hx	1.10 (0.93, 1.31)
Male	1.15 (0.84, 1.58)
Female	1.04 (0.86, 1.26)
Age 6-11	0.62 (0.26, 1.48)
Age 12-17	1.09 (0.73, 1.61)
Age 18+	1.08 (0.90, 1.29)
Pre: 2000-2007	0.94 (0.60, 1.48)
Post: 2008-2015	1.08 (0.91, 1.29)



Self-Harm

	HR (95% CI)
Overall	0.92 (0.69, 1.21)
No psych hx	1.34 (0.38, 4.71)
Psych hx	0.89 (0.66, 1.18)
Male	1.16 (0.58, 2.36)
Female	0.87 (0.65, 1.18)
Age 6-11	- -
Age 12-17	1.04 (0.41, 2.66)
Age 18+	0.91 (0.68, 1.22)
Pre: 2000-2007	1.16 (0.49, 2.74)
Post: 2008-2015	0.90 (0.67, 1.21)



FDA NEWS RELEASE

FDA Requires Stronger Warning About Risk of Neuropsychiatric Events Associated with Asthma and Allergy Medication Singulair and Generic Montelukast

https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warning-about-risk-neuropsychiatric-events-associated-asthma-and-allergy

The FDA updated the product labeling in 2008 to include information about neuropsychiatric events reported with use of montelukast. In response to continued reports of suicide and other adverse events, the FDA evaluated available data regarding the risk of neuropsychiatric events, including reports submitted through the FDA Adverse Event Reporting System (FAERS) and observational studies in the published literature. The FDA also conducted an observational study using data in the Sentinel Distributed Database and presented the findings at an FDA advisory committee meeting in 2019.

As part of its review, the FDA re-evaluated the benefits and risks of montelukast as the treatment landscape has evolved since the drug was first approved in 1998. Based upon this assessment, the FDA determined the risks of montelukast may outweigh the benefits in some patients, particularly when the symptoms of the disease are mild and can be adequately treated with alternative therapies. For allergic rhinitis in particular, the FDA has determined that montelukast should be reserved for patients who have not responded adequately to other therapies — or who cannot tolerate these therapies.

https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warning-about-risk-neuropsychiatric-events-associated-asthma-and-allergy

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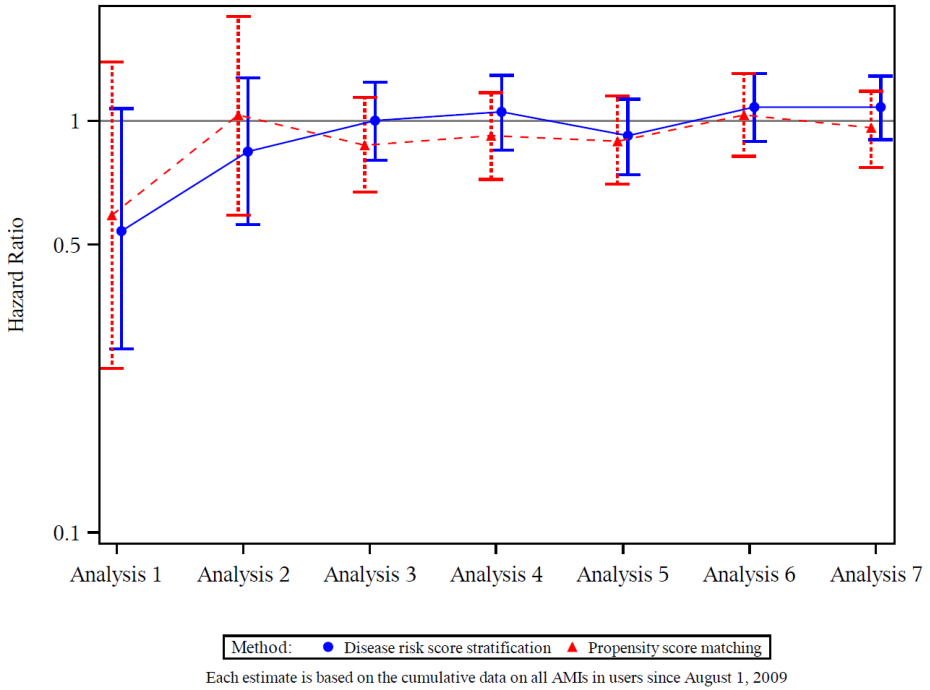
https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warning-about-risk-neuropsychiatric-events-associated-asthma-and-allergy

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]

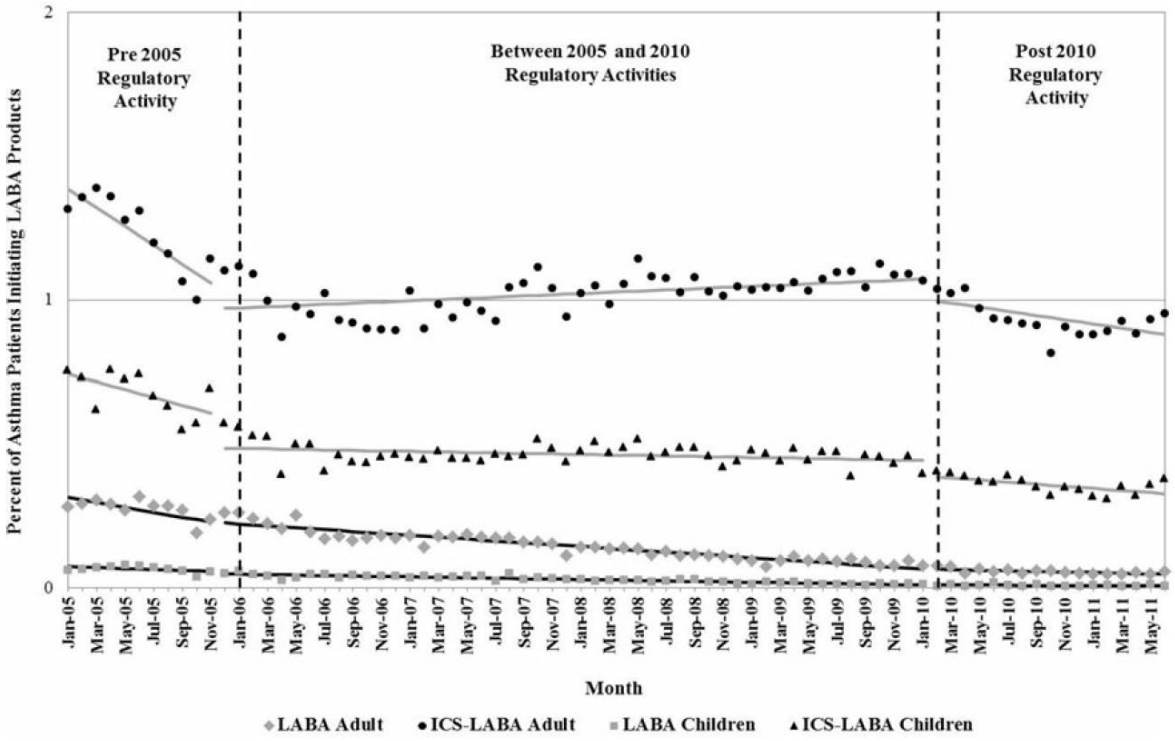


Figure 2. Percentage of LABA product initiation before, between and after the 2005 and 2010 FDA regulatory activities for LABA-containing agents in children and adults with asthma and no history of a LABA dispensing in 180 days.

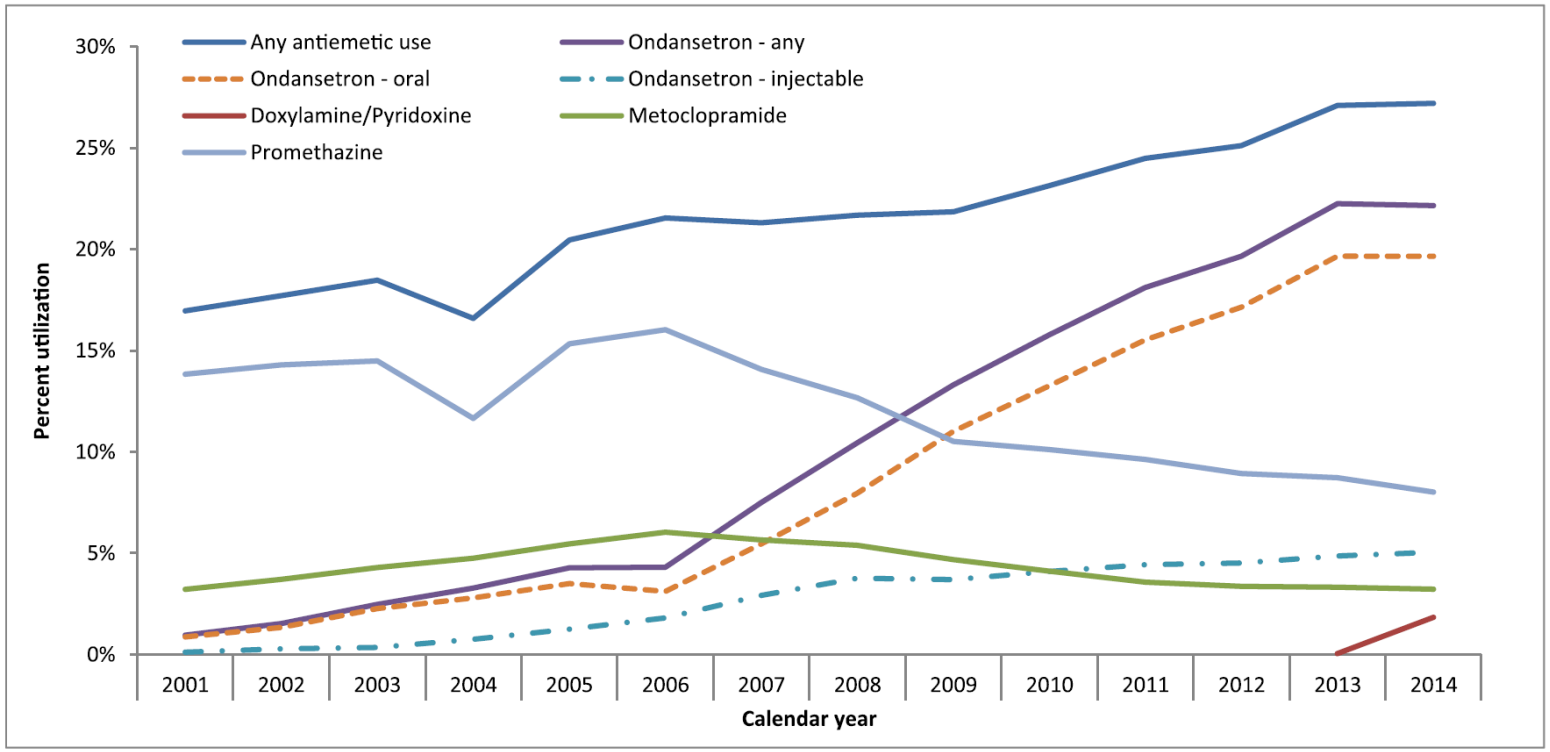
Examine medication exposure during pregnancy

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]



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

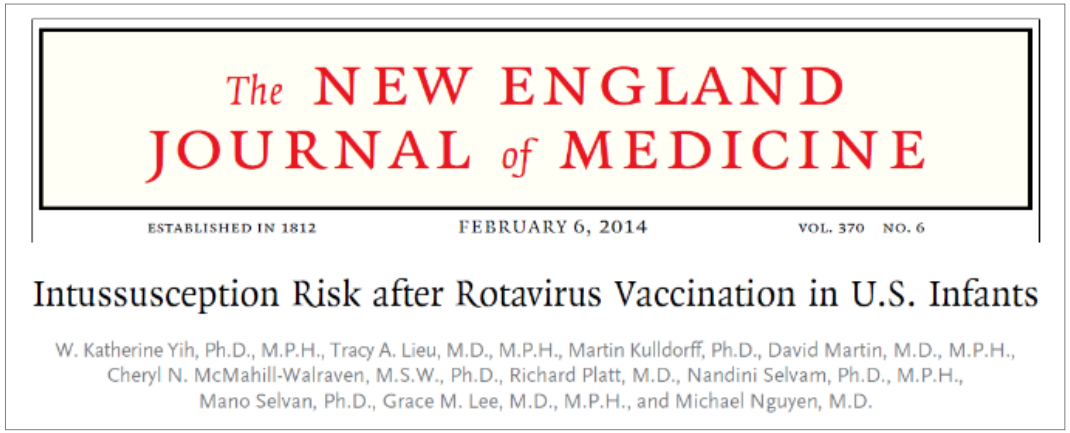
----------INDICATIONS AND USAGE----------
RotaTeq® is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9. (1)

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

Generate timely evidence during pandemic

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

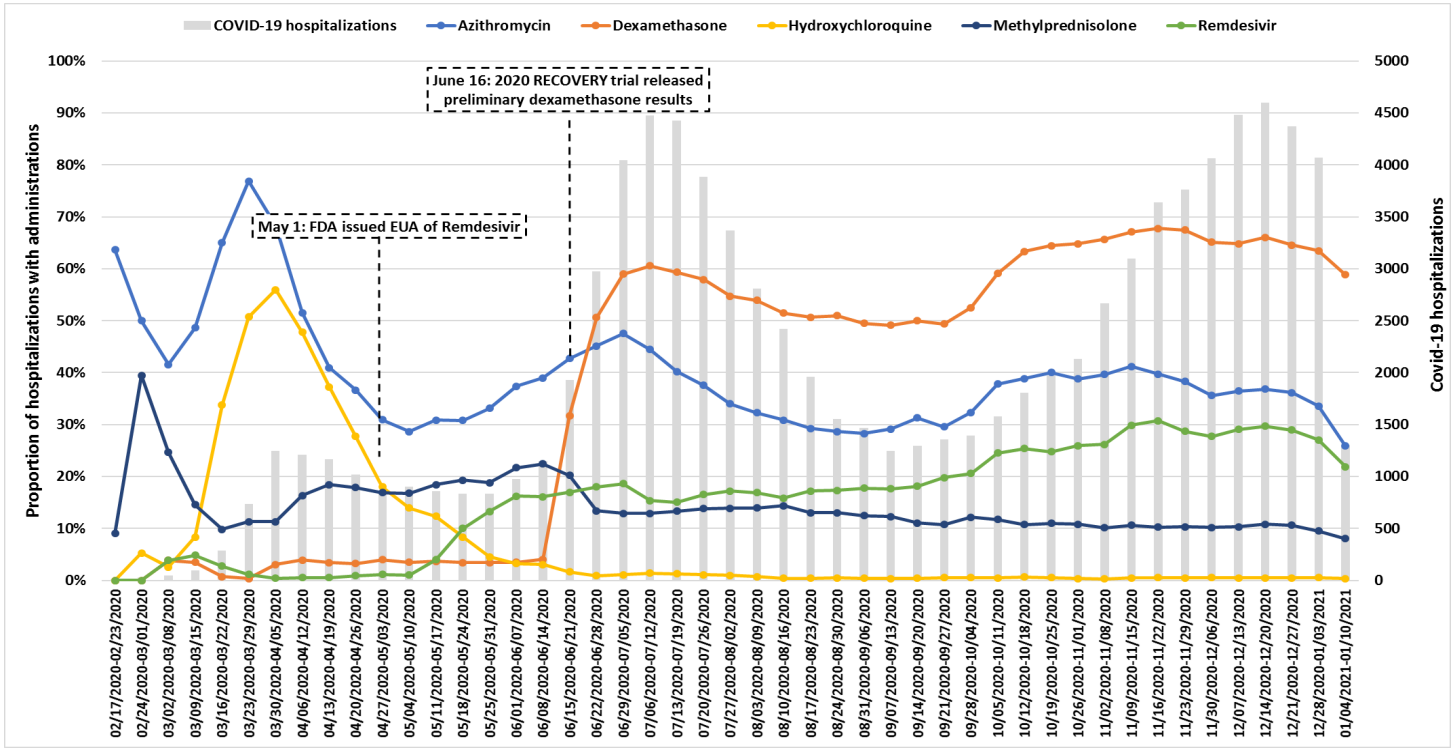
REVIEW

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.



Enable international collaboration during pandemic

COVID-19 Coagulopathy Study

- Assessment of arterial and venous thrombotic events among COVID-19 patients

Natural History of COVID-19 among Pregnant Women

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

Outpatient Corticosteroid Use Among a Non-Hospitalized COVID+ Population

- Initial US-based study done with 4 sources (Sentinel, CMS, HealthVerity, VA)

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

Quantitative Assessment of the Impact of Nitrosamine Contamination and Angiotensin Receptor Blockers (ARB) Recall on ARB Utilization: A Multinational Study

Details | **Additional Information** | **Contributors**

Date Posted: Tuesday, August 18, 2020

Status: IN PROGRESS

Medical Product: angiotensin II receptor blocker (ARB), angiotensin receptor blocker, angiotensin-converting enzyme (ACE) inhibitor, calcium channel blockers (CCB)

https://www.sentinelinitiative.org/methods-data-tools/methods/quantitative-assessment-impact-nitrosamine-contamination-and-angiotensin

Sentinel

- How Sentinel gets, standardizes, and checks its data
- How Sentinel performs privacy-protecting analysis
- How Sentinel contributes to FDA's regulatory mission
- **How Sentinel builds trust through transparency**
- How Sentinel continues to innovate and expand its capabilities
- 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

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

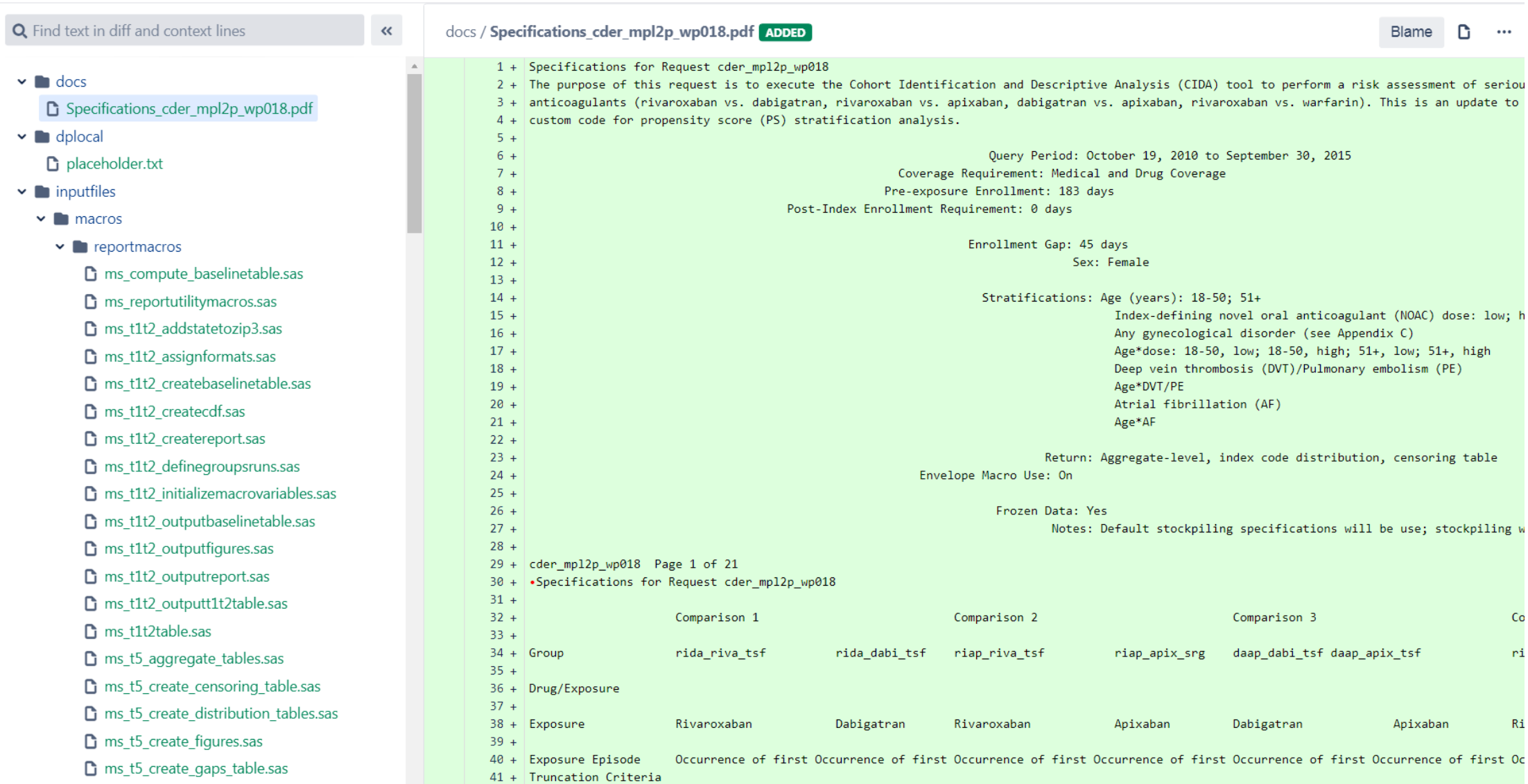
Regulatory Determination / Use:

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://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

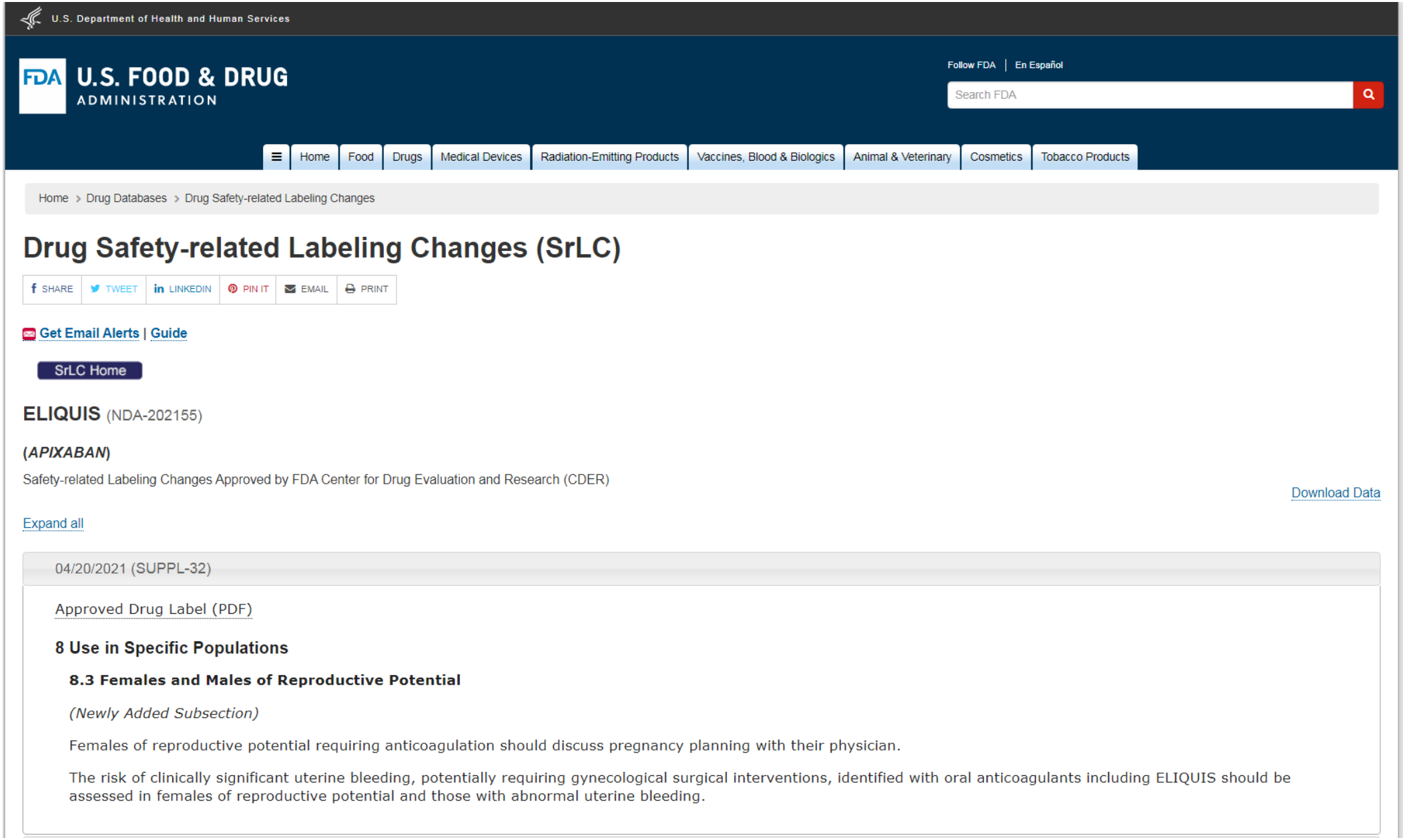
Regulatory Link(s) (3)

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



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

Related Publication(s) and/or Presentation(s) (1)

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

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

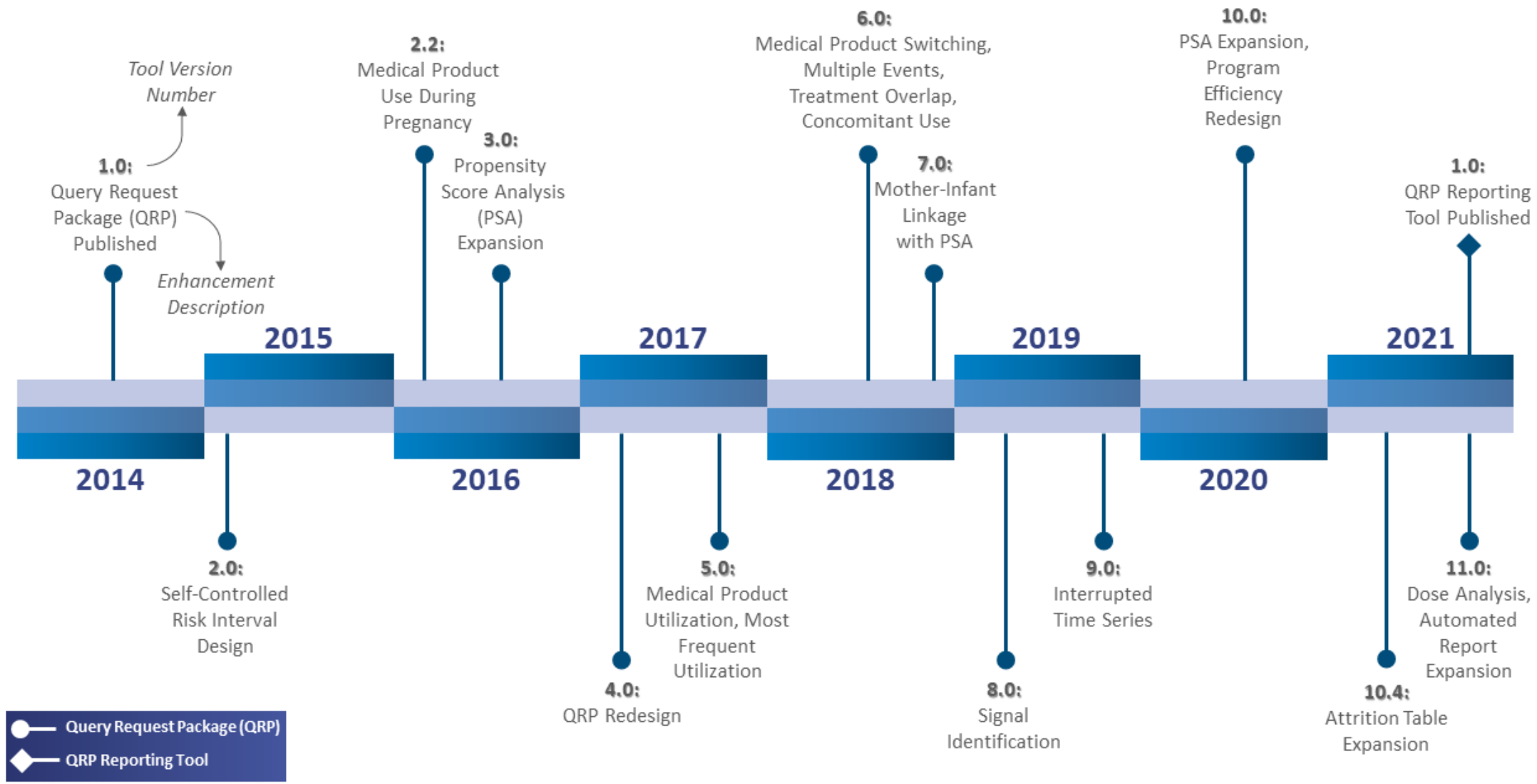
Risk of Severe Abnormal Uterine Bleeding Associated with Rivaroxaban Compared with Apixaban, Dabigatran and Warfarin

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

- How Sentinel gets, standardizes, and checks its data
- How Sentinel performs privacy-protecting analysis
- How Sentinel contributes to FDA's regulatory mission
- How Sentinel builds trust through transparency
- **How Sentinel continues to innovate and expand its capabilities**
- Discussion

Enhancements to Routine Querying Tools



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]

Use of The Tree-Based Scan Statistic for Surveillance of Maternal Outcomes Following Medication Use During Gestation

Sentinel Methods

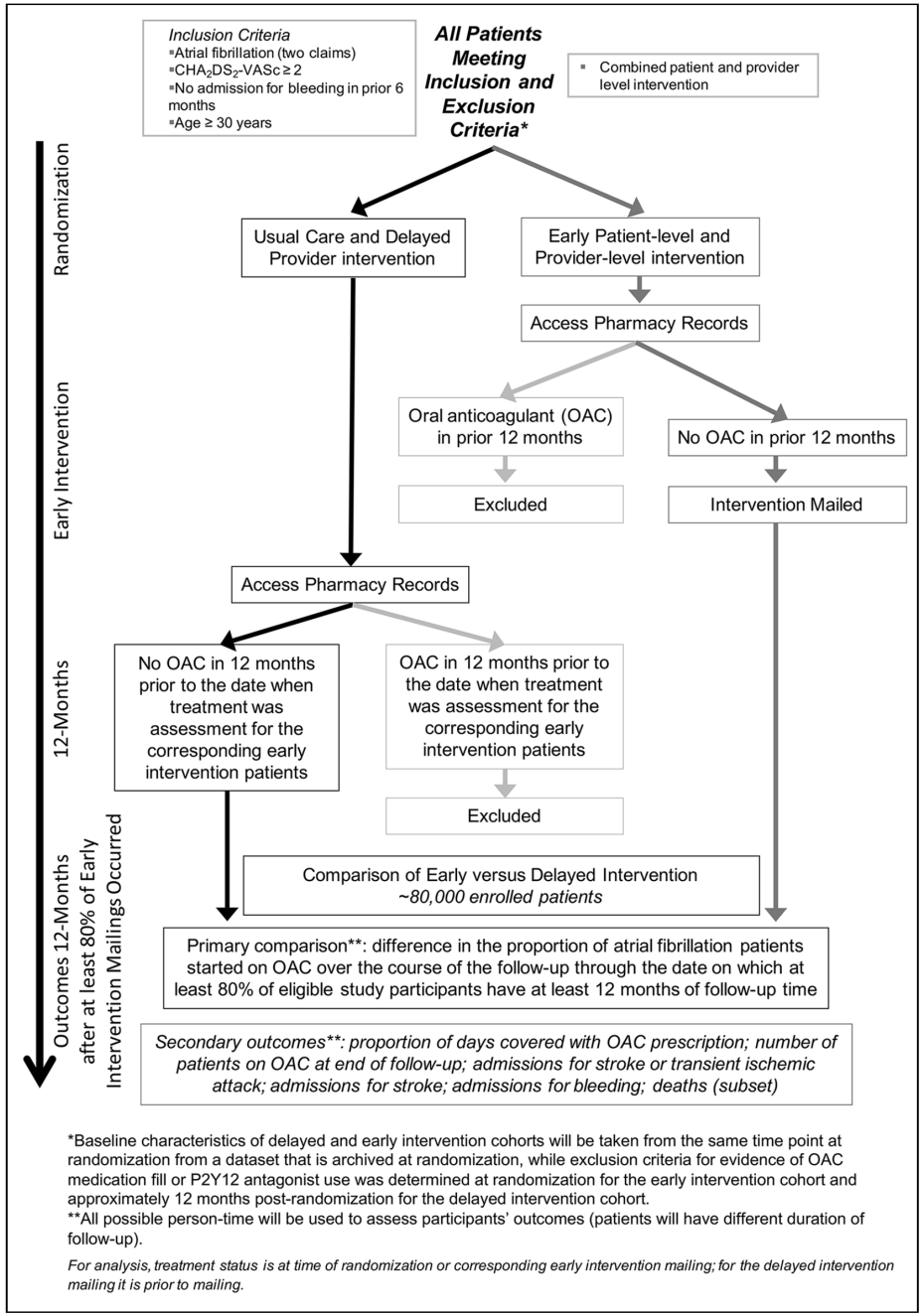
Thuy N Thai[1], Almut G Winterstein[1,2,3], Elizabeth A Suarez[4], Michael Nguyen[5], Danijela Stojanovic[5], Jane Liedtka[6], Abby Anderson[7], Di Zhang[8], Yueqin Zhao[8], Monica Munoz[9], Wei Liu[10], Steven Bird[10], Inna Dashevsky[4], David Cole[4], Talia Menzin[4], Sandra DeLuccia[4], Jennifer Noble[4], Judith C Maro[4]

Use of the Tree-Based Scan Statistic for Surveillance of Infant Outcomes Following Maternal Perinatal Medication Use

Sentinel Methods

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], Steven Bird[7], Inna Dashevsky[1], David Cole[1], Sandra DeLuccia[1], Talia Menzin[1], Jennifer Noble[1], Judith C Maro[1]

https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Protocol_TreeScan_Pregnancy_V3.pdf
https://www.sentinelinitiative.org/sites/default/files/documents/Sentinel_Protocol_TreeScan_Pregnancy_Maternal-Outcomes_v2.1.pdf



Clinical Trials
2019, Vol. 16(1) 90–97

DOI: 10.1177/1740774518812776
journals.sagepub.com/home/ctj
SAGE

FDA-Catalyst—Using FDA's Sentinel Initiative for large-scale pragmatic randomized trials: Approach and lessons learned during the planning phase of the first trial

Noelle M Cocoros[1], Sean D Pokorney[2], Kevin Haynes[3], Crystal Garcia[1], Hussein R Al-Khalidi[4], Sana M Al-Khatib[2], Patrick Archdeacon[5], Jennifer C Goldsack[6], Thomas Harkins[7], Nancy D Lin[8], David Martin[5], Debbe McCall[9], Vinit Nair[7], Lauren Parlett[3], Robert Temple[5], Cheryl McMahill-Walraven[10], Christopher B Granger[2] and Richard Platt[1]

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

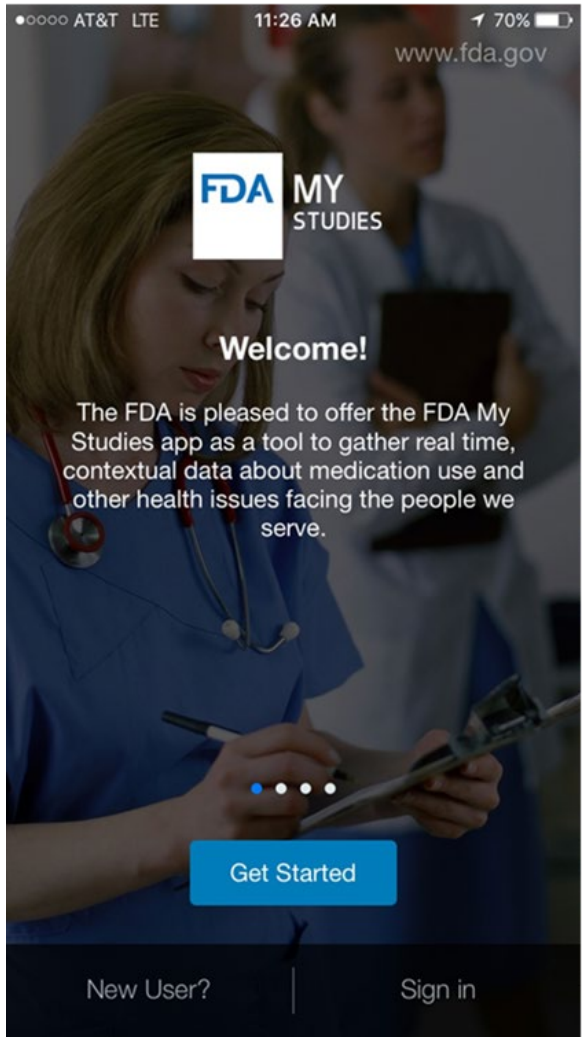
DOI: 10.1002/pds.5320

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]

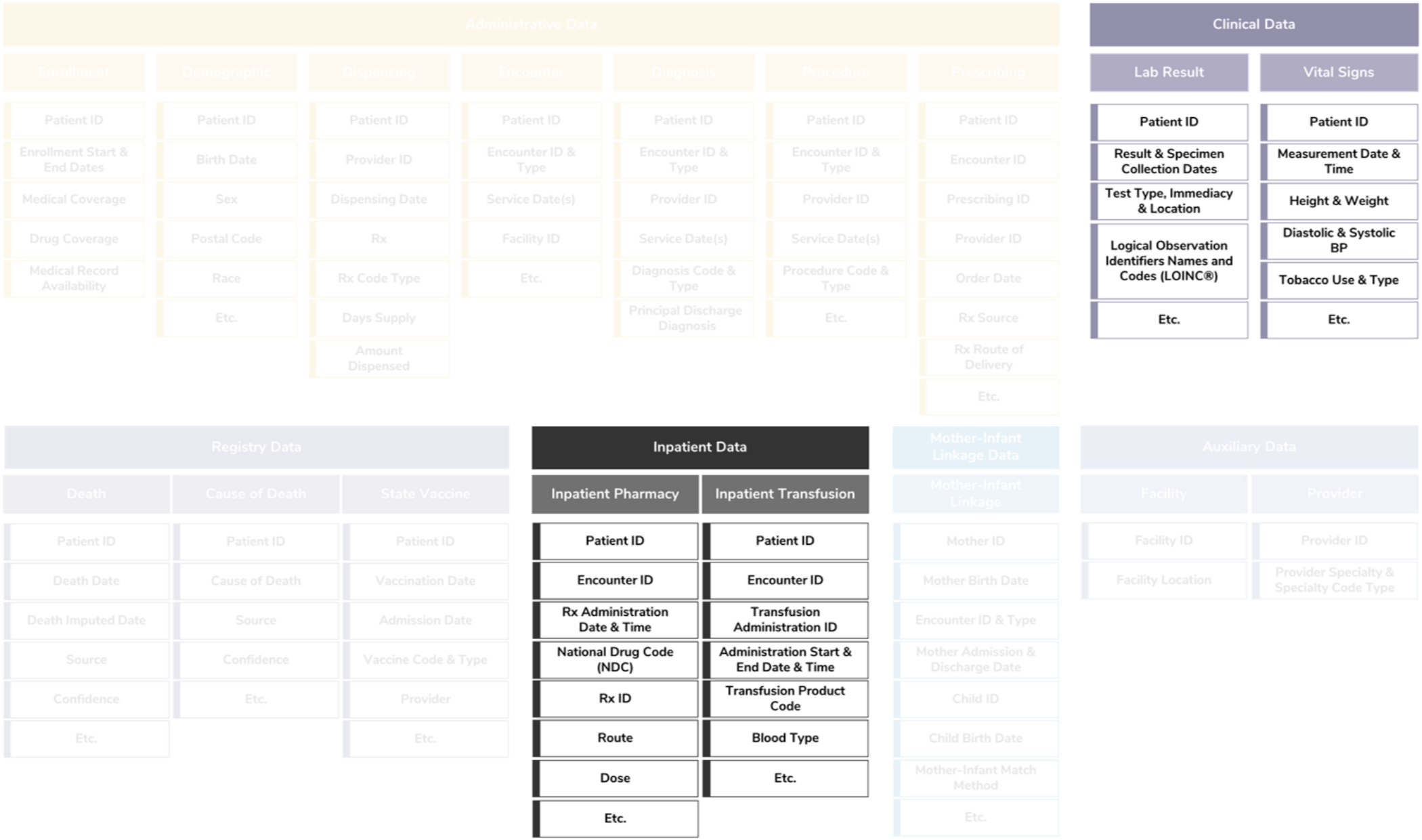


PERSPECTIVE OPEN

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


Administrative Data
Enrollment
Patient ID
Enrollment Start & End Dates
Medical Coverage
Drug Coverage
Medical Record Availability
Demographic
Patient ID
Birth Date
Sex
Postal Code
Race
Etc.
Dispensing
Patient ID
Provider ID
Dispensing Date
Rx
Rx Code Type
Days Supply
Amount Dispensed
Encounter
Patient ID
Encounter ID & Type
Service Date(s)
Facility ID
Etc.
Diagnosis
Patient ID
Encounter ID & Type
Provider ID
Service Date(s)
Diagnosis Code & Type
Principal Discharge Diagnosis
Procedure
Patient ID
Encounter ID & Type
Provider ID
Service Date(s)
Procedure Code & Type
Etc.
Prescribing
Patient ID
Encounter ID
Prescribing ID
Provider ID
Order Date
Rx Source
Rx Route of Delivery
Etc.
Clinical Data
Lab Result
Patient ID
Result & Specimen Collection Dates
Test Type, Immediacy & Location
Logical Observation Identifiers Names and Codes (LOINC®)
Etc.
Vital Signs
Patient ID
Measurement Date & Time
Height & Weight
Diastolic & Systolic BP
Tobacco Use & Type
Etc.
Registry Data
Death
Patient ID
Death Date
Death Imputed Date
Source
Confidence
Etc.
Cause of Death
Patient ID
Cause of Death
Source
Confidence
Etc.
State Vaccine
Patient ID
Vaccination Date
Admission Date
Vaccine Code & Type
Provider
Etc.
Inpatient Data
Inpatient Pharmacy
Patient ID
Encounter ID
Rx Administration Date & Time
National Drug Code (NDC)
Rx ID
Route
Dose
Etc.
Inpatient Transfusion
Patient ID
Encounter ID
Transfusion Administration ID
Administration Start & End Date & Time
Transfusion Product Code
Blood Type
Etc.
Mother-Infant Linkage Data
Mother-Infant Linkage
Mother ID
Mother Birth Date
Encounter ID & Type
Mother Admission & Discharge Date
Child ID
Child Birth Date
Mother-Infant Match Method
Etc.
Auxiliary Data
Facility
Facility ID
Facility Location
Provider
Provider ID
Provider Specialty & Specialty Code Type

Sentinel's Multi-Modal Response System

Claims (with Limited EHR Network)

Active Risk Identification and Analysis (ARIA)*

- Sentinel Distributed Database
- IBM® MarketScan® Research Databases

- Sentinel Common Data Model
- Sentinel Analytic Tools
- Access to Medical Records within the Sentinel Distributed Database

EHR Data Aggregators

- TriNetX
- IBM Watson Health

- Proprietary Common Data Models
- Web-Based Query Interface & Custom Programming
- Access to Medical Records varies by Source

EHR Data Warehouse

- HCA Healthcare
- Veradigm

- Data Warehouse for Multiple Healthcare Organizations in a System
- Custom Programming
- Access to Medical Records

EHR Networks

- PCORnet

- PCORnet Common Data Model
- PCORnet Analytic Tools
- Access to Medical Records

**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.*

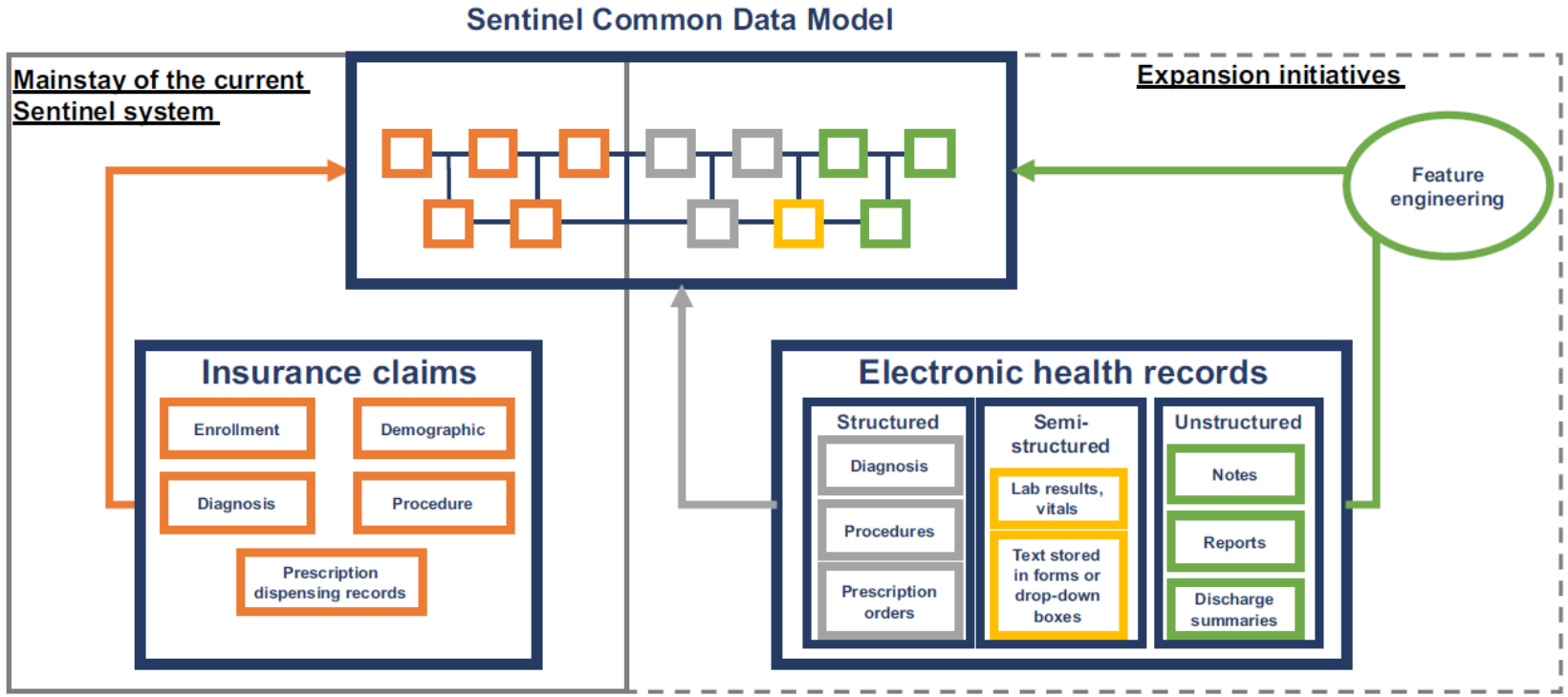


Fig. 1 Conceptual overview of the integration of claims data and electronic health records in Sentinel. Solid box on the left indicates data elements currently available in the Sentinel common data model, dotted box on the right indicates elements from electronic health records that will be considered for inclusion.

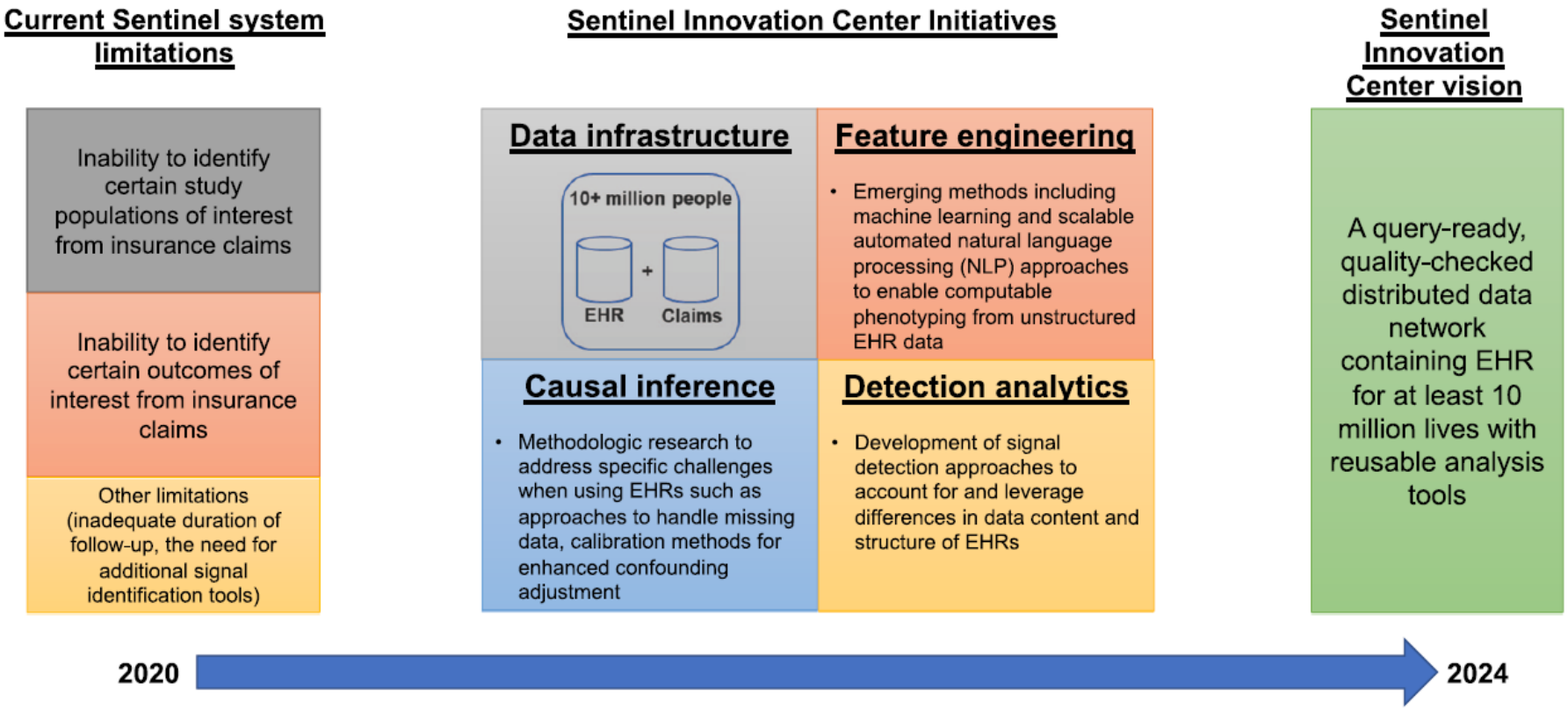


Fig. 3 The Sentinel Innovation Center initiatives and vision. Arrow at the bottom indicates timeline for the proposed activities.

Sentinel

- How Sentinel gets, standardizes, and checks its data
- How Sentinel performs privacy-protecting analysis
- How Sentinel contributes to FDA's regulatory mission
- How Sentinel builds trust through transparency
- How Sentinel continues to innovate and expand its capabilities
- **Discussion**

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

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

Real-world data

Data networks, standardization, and federated analysis

Darren Toh, ScD


https://www.sentinelinitiative.org/


darren_toh@harvardpilgrim.org


@darrentoh_epi