Evidence from real-world data
Sentinel Initiative of US FDA

Darren Toh, ScD

Department of Population Medicine

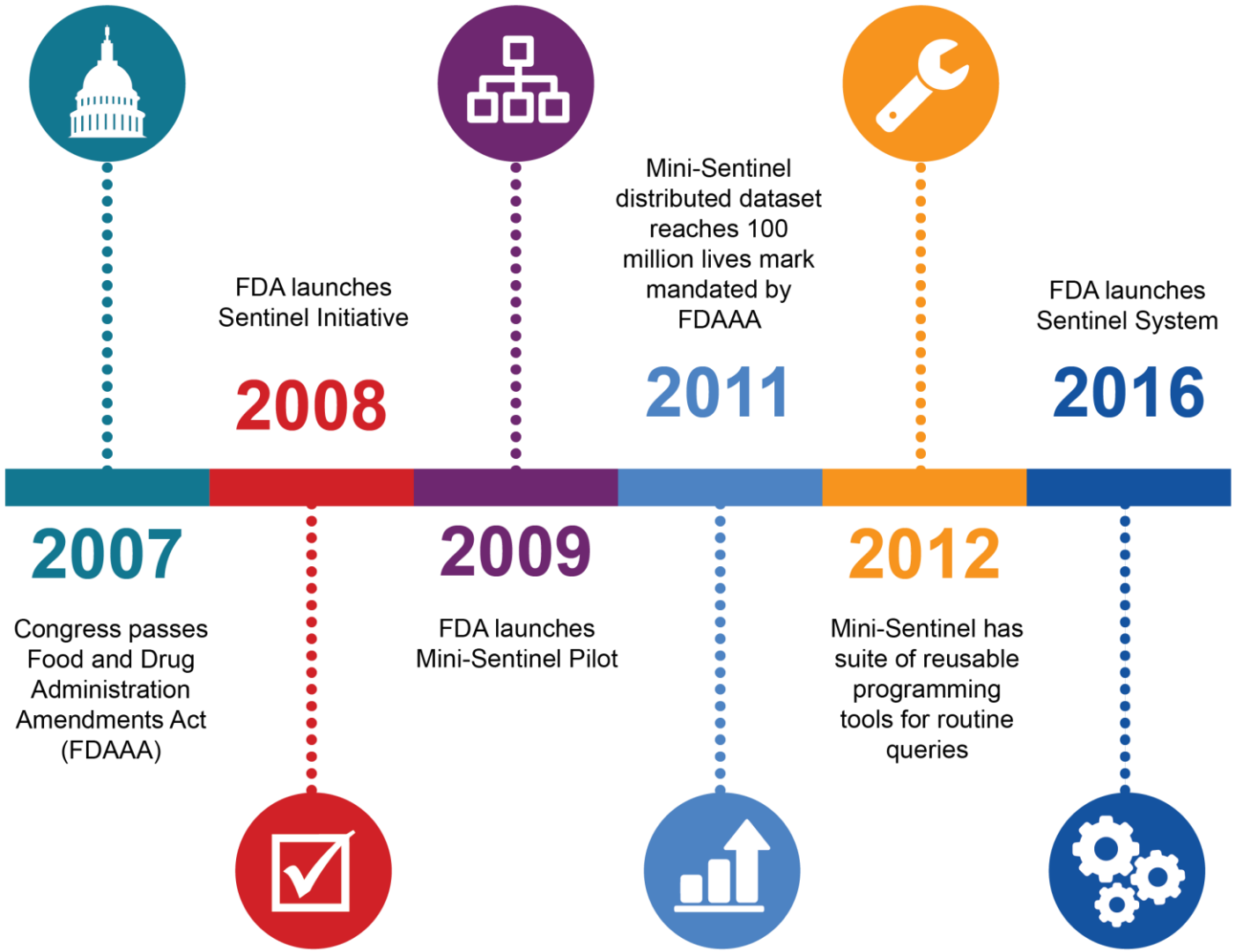
Harvard Medical School & Harvard Pilgrim Health Care Institute

February 20, 2019

Disclaimer

- The views expressed in this presentation are mine and do not represent the official views or policies of the U.S. Food and Drug Administration.

Timeline


2007
Congress passes Food and Drug Administration Amendments Act (FDAAA)
2008
FDA launches Sentinel Initiative
2009
FDA launches Mini-Sentinel Pilot
2011
Mini-Sentinel distributed dataset reaches 100 million lives mark mandated by FDAAA
2012
Mini-Sentinel has suite of reusable programming tools for routine queries
2016
FDA launches Sentinel System

Sentinel partner organizations

Sentinel

Lead – HPHC Institute

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

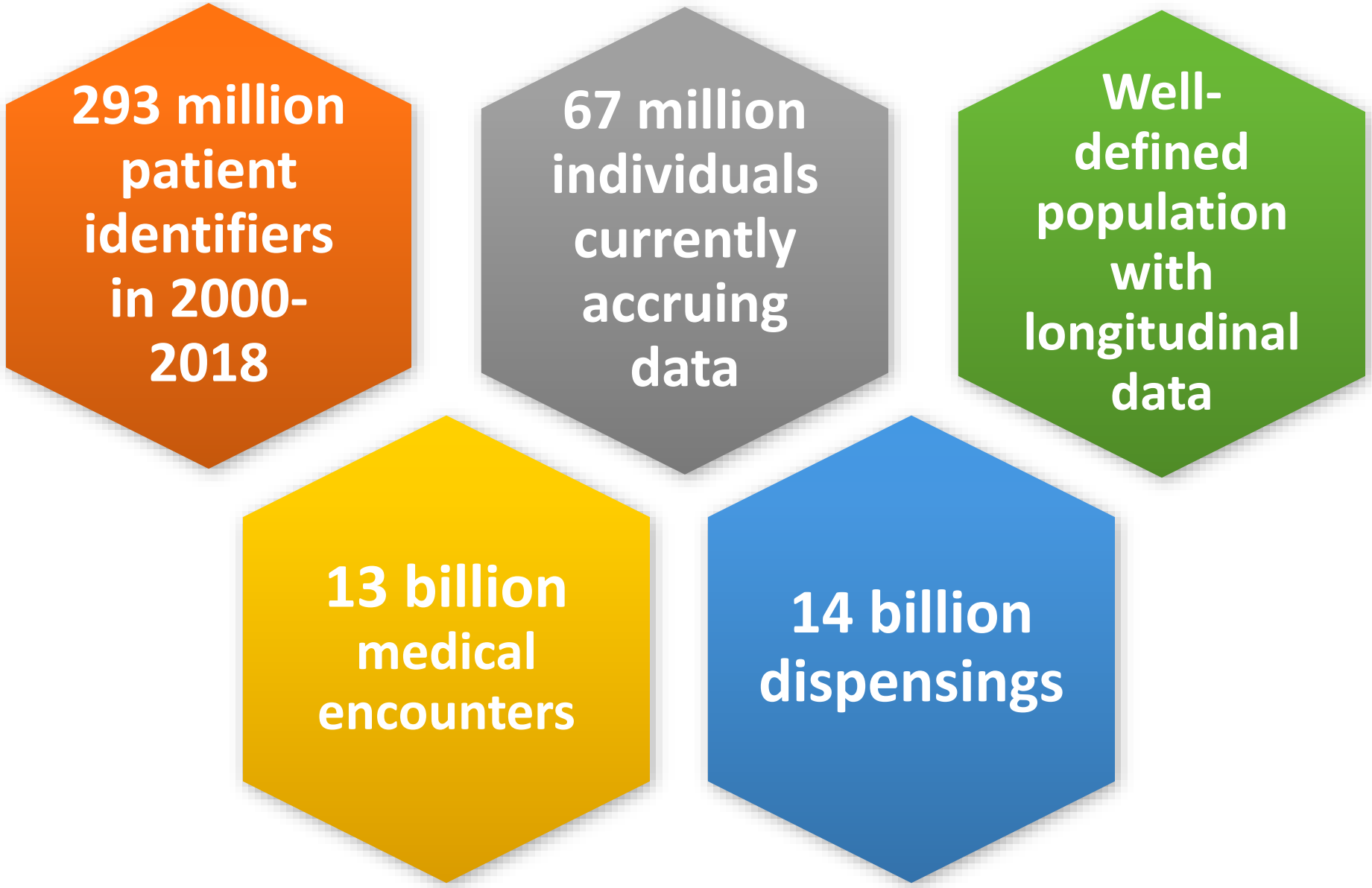
Data & scientific partners

MASSACHUSETTS
HealthCore Anthem
VANDERBILT SCHOOL OF MEDICINE
health care systems research network
HUMANA
HCA Hospital Corporation of America
CMS CENTERS FOR MEDICARE & MEDICAID SERVICES
OPTUM
KAISER PERMANENTE
aetna

Scientific partners

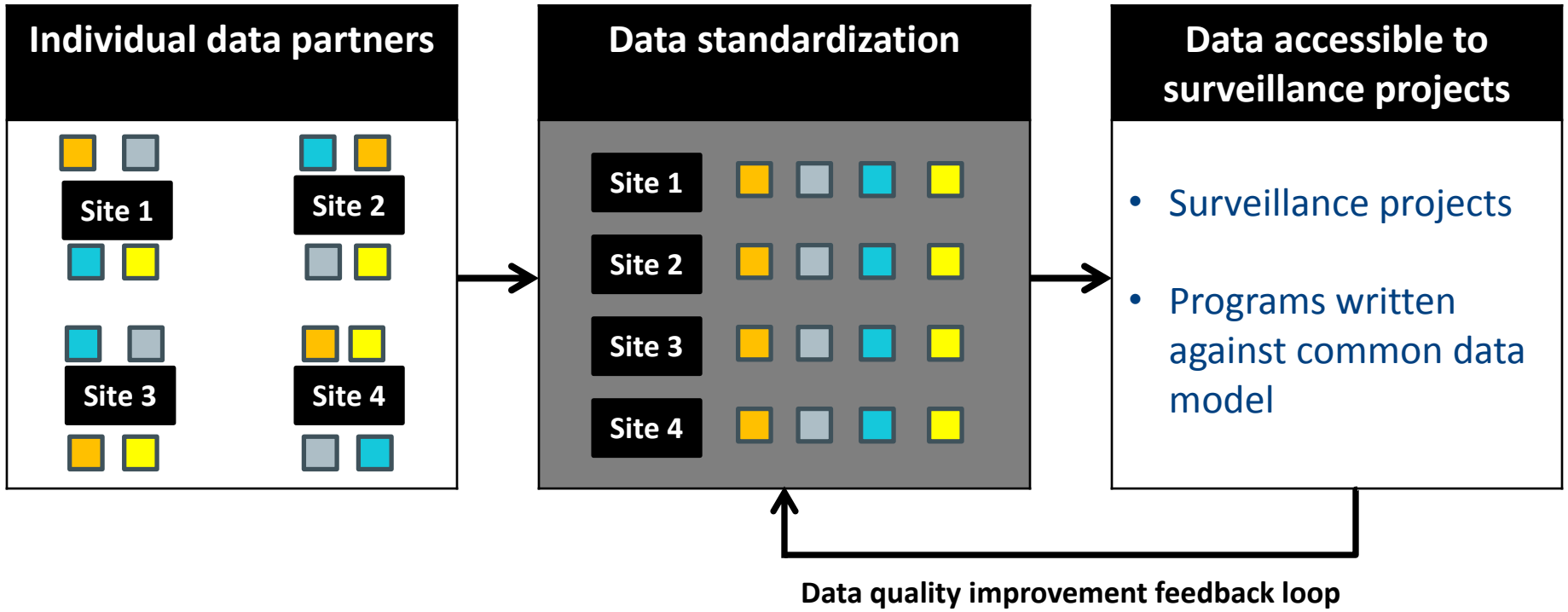
Penn Medicine
IQVIA
Cincinnati Children's change the outcome
DukeMedicine
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF MEDICINE BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL
AHIP America's Health Insurance Plans
UF College of Pharmacy UNIVERSITY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

Data snapshot



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

Harmonizing multiple databases



Adapted from: http://www.hcsrn.org/asset/b9efb268-eb86-400e-8c74-2d42ac57fa4F/VDW.Infographic031511.jpg

Sentinel data quality assurance and characterization

Guidance for Industry and FDA Staff

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

Submit Comment

Sentinel Data Quality Assurance Practices

Project Title	**Sentinel Data Quality Assurance Practices**
Date Posted	*Thursday, March 23, 2017*
Deliverables	Sentinel Data Quality Assurance Practices
Description	The Food and Drug Administration (FDA) set forth its current recommendations for data quality assurance (QA) in the following document: "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC)," in May 2013. This Guidance describes best practices that particularly apply to observational studies designed to assess the risk associated with a drug exposure using electronic healthcare data. The SOC has drafted a document describing the ways in which SOC data quality assurance procedures align with FDA's standards.

https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model/sentinel-data-quality-assurance-practices
https://www.fda.gov/downloads/drugs/guidances/ucm243537.pdf

Sentinel Common Data Model

Administrative Data

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

Clinical Data

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

Registry Data

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

Inpatient Data

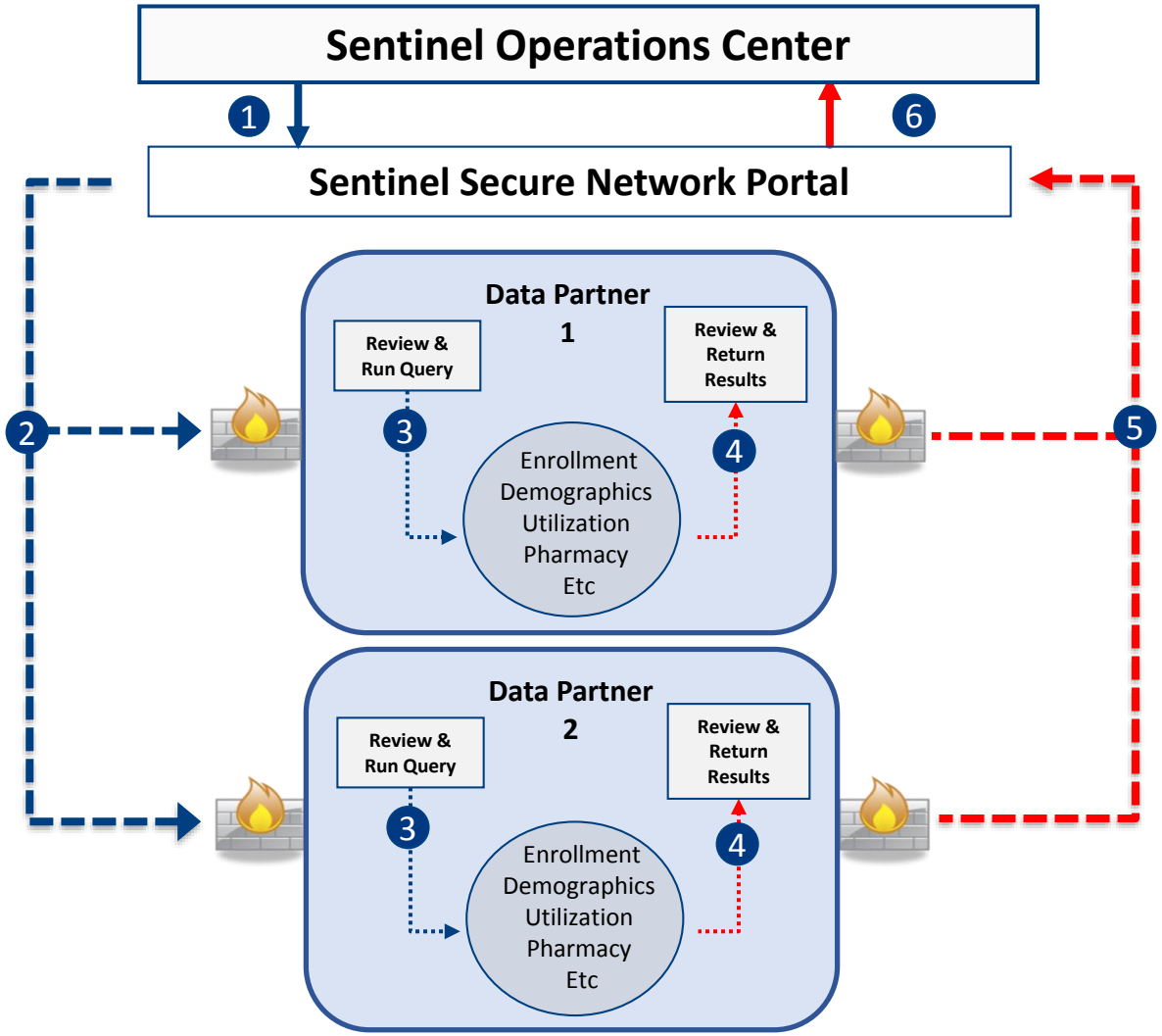
Inpatient Pharmacy	Inpatient Transfusion
Patient ID	Patient ID
Administration Date & Time	Administration Start & End Date & Time
Encounter ID	Encounter ID
National Drug Code (NDC)	Transfusion Administration ID
Route	Transfusion Product Code
Dose	Blood Type
Etc.	Etc.

Mother-Infant Linkage Data

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

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

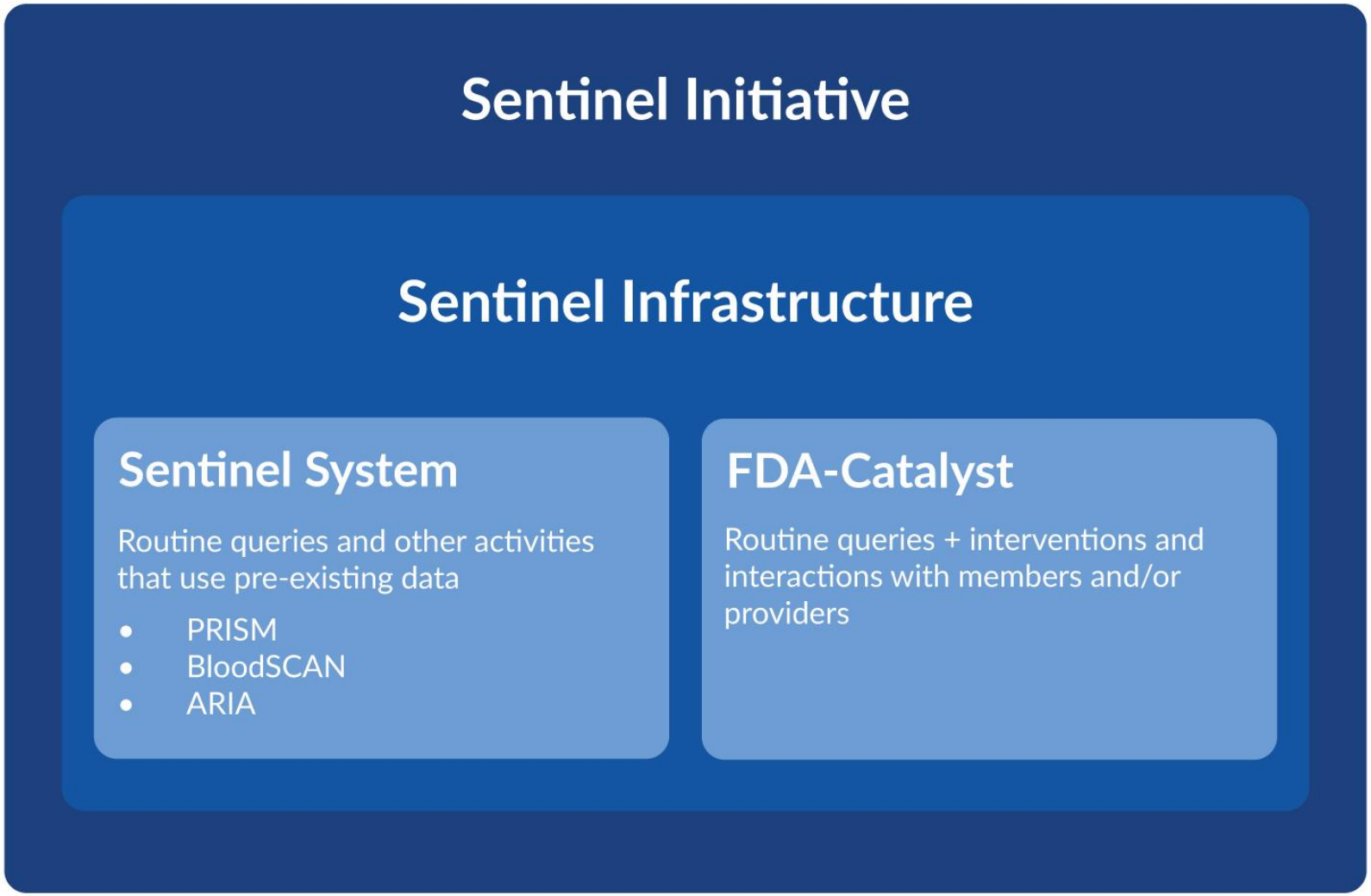
Distributed analysis in Sentinel



1. User creates and submits query
2. Data Partners retrieve query
3. Data Partners review and run query against their local data
4. Data Partners review results
5. Data Partners return results via secure network
6. Results are aggregated and returned

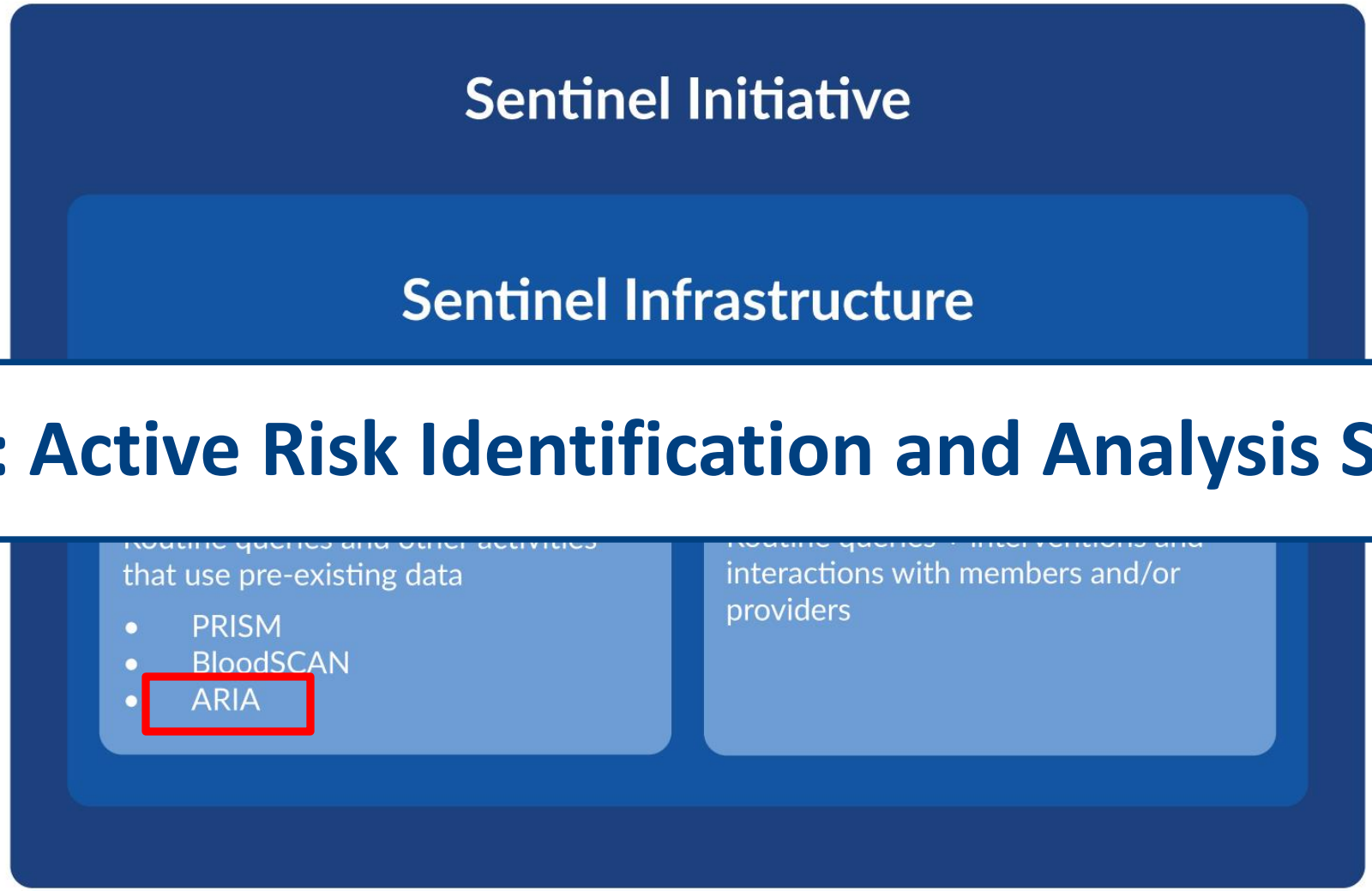
https://www.sentinelinitiative.org/privacy-and-security

Sentinel Initiative



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

Sentinel Initiative



ARIA: Active Risk Identification and Analysis System

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

Sentinel and FDA's mandate

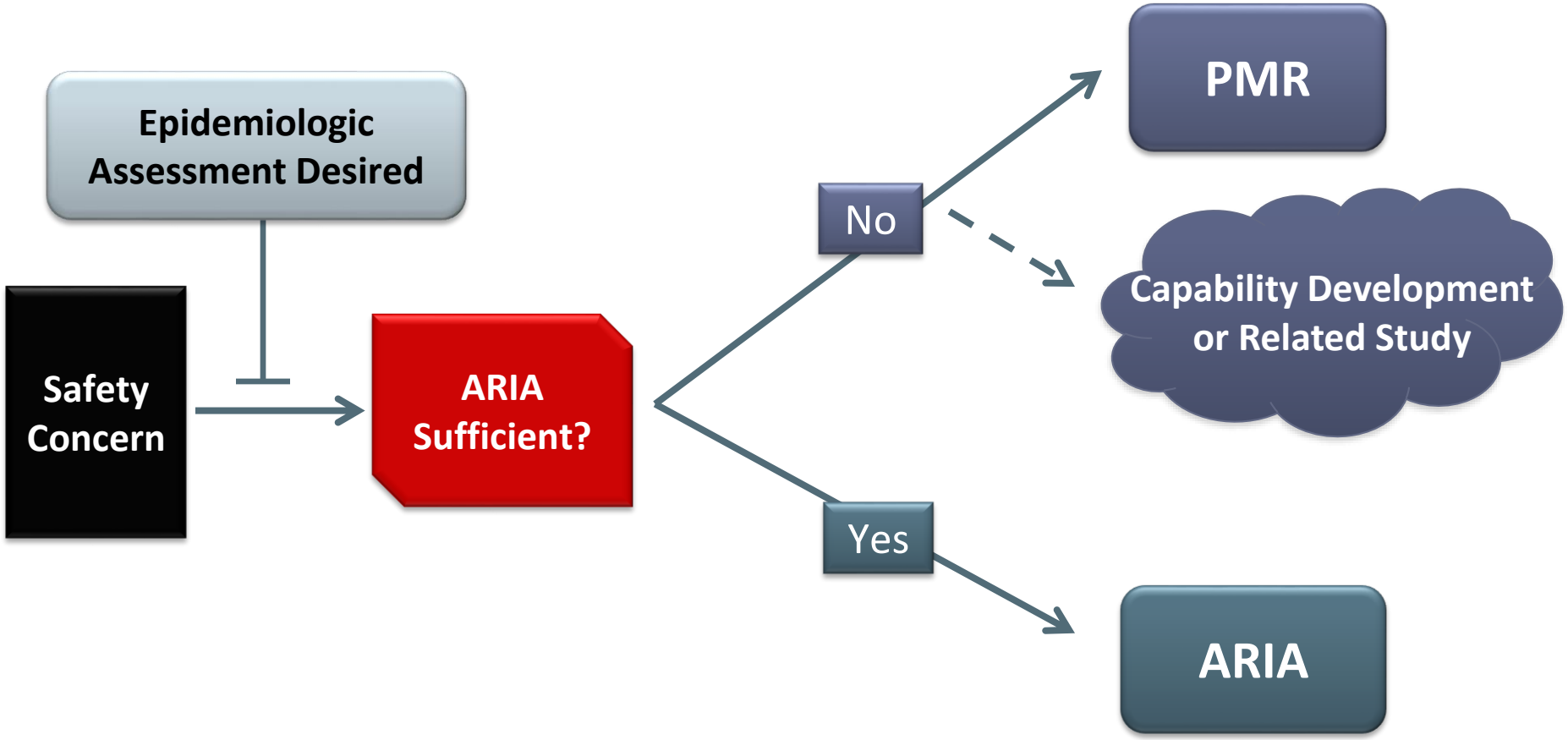
Section 905
Mandates creation of Sentinel

Section 901
New FDAAA PMR authority

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

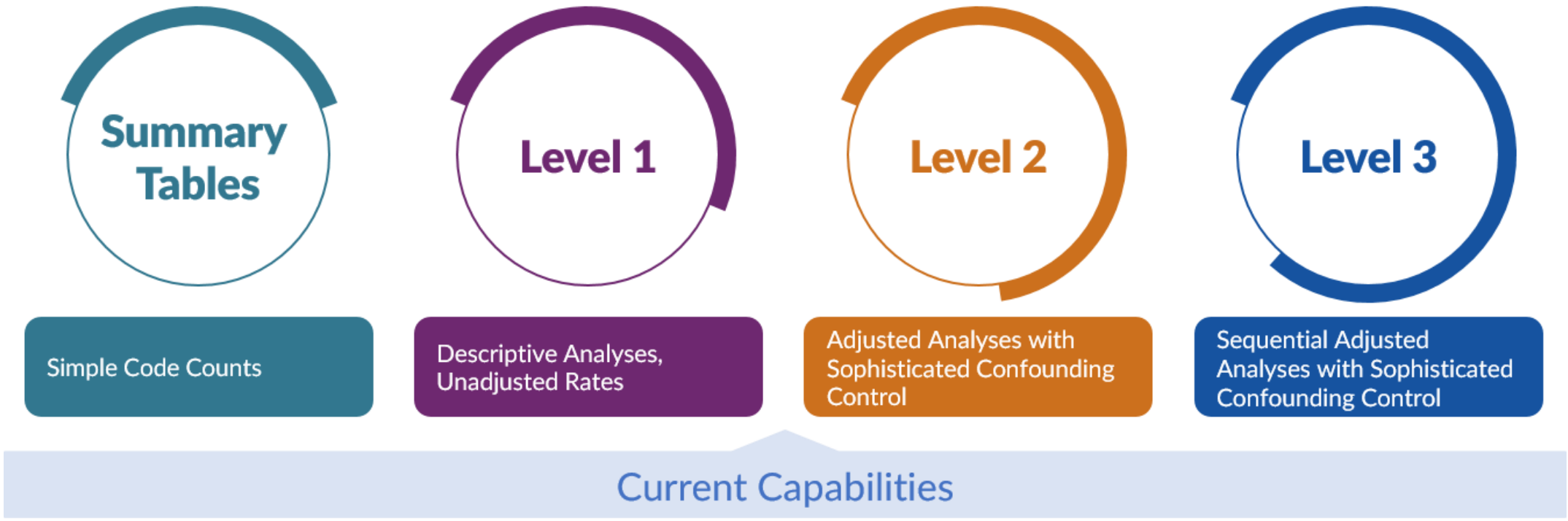
https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf

Sentinel and FDA's mandate



ARIA: Active Risk Identification and Analysis System

ARIA



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

How Sentinel has been used by FDA (selected)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207987

NDA APPROVAL

Belcher Pharmaceuticals, LLC
Attention: Mihir Taneja
Vice President
6911 Bryan Diary Road, Suite 210
Largo, FL 33777

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 the use of dehydrated alcohol 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: heart failure, ventricular fibrillation, atrioventricular block with and without permanent pacemaker insertion, subsequent septal myectomy, and death.

The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org. 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/2018/207987Orig1s000ltr.pdf

Ongoing ARIA assessments (selected)

Sentinel

ARIA Analyses for Safety Issues Identified During Review of New Applications and Supplements

Drug Name	Outcome Assessed	ARIA Analysis	Related Links	Date Posted
Ablysinol (Dehydrated alcohol)	• Number of percutaneous transluminal septal myocardial ablation procedures • Ventricular arrhythmia • Heart failure • Atrioventricular block • Septal myectomy • Death	Level 2	• Approval letter	10/22/2018
Annovera (segesterone acetate and ethinyl estradiol vaginal system)	• Early detection of a large increase in the risk of non-fatal venous thromboembolism or arterial thromboembolism in the United States population	Level 3 (Sequential safety monitoring)	• Approval letter	9/24/2018
Ilumya (tildrakizumab)	• Lymphoma	TBD		5/25/2018
Sinuva (mometasone furoate)	• Cataracts • Glaucoma • Nasal perforation	Level 1	• Approval letter	12/18/2017
Tremfya (guselkumab)	• Short term lymphoma e.g.,within 1-3 years	TBD		9/29/2017
Stelara (ustekinumab)	• Serious Infection	TBD		8/23/2017
Siliq (brodalumab)	• Neutropenia • Serious infections • Myocardial infarction and stroke	TBD		8/23/2017

https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments

How Sentinel has been used by FDA (selected)

The NEW ENGLAND JOURNAL of Perspective

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

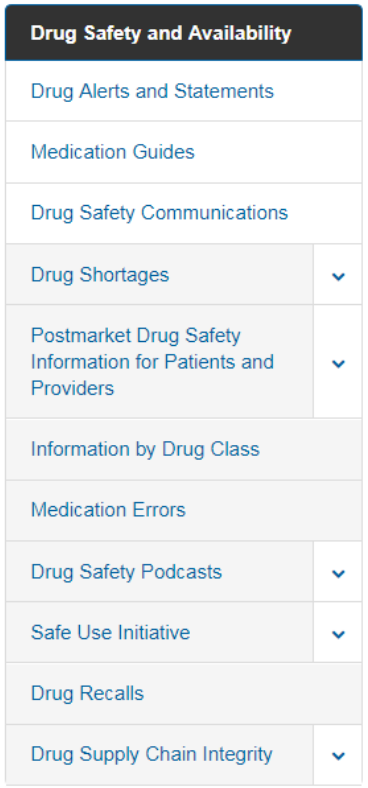
Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Southworth et al. N Engl J Med 2013;368:1272-1274

How Sentinel has been used by FDA (selected)

Sentinel



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.

Drug Safety Communication

https://wayback.archive-it.org/7993/20170112031650/http:/www.fda.gov/Drugs/DrugSafety/ucm326580.htm

How Sentinel has been used by FDA (selected)

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.

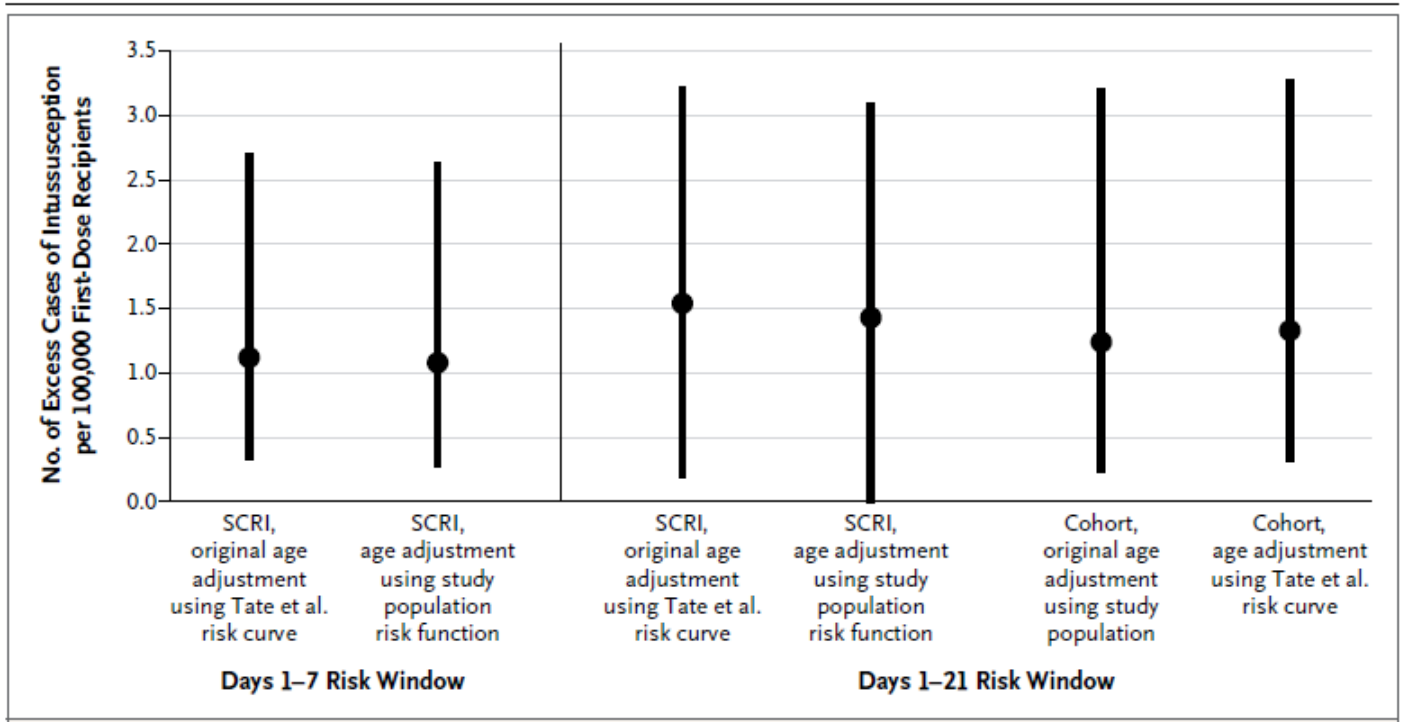


Figure 1. Attributable Risk of Intussusception after the First Dose of RotaTeq (RV5) Rotavirus Vaccine.

The attributable risk of intussusception after dose 1 of the RV5 vaccine, shown as the number of excess cases of intussusception per 100,000 recipients, was calculated for two study designs — a self-controlled risk-interval (SCRI) design and a cohort design — with the original age-adjustment method (based on the rates from Tate et al.[25] in the SCRI design and the quadratic risk function from the unexposed person-time in the cohort design) and an alternative age-adjustment method (based on the quadratic risk function from the unexposed cohort person-time in the SCRI design and the rates from Tate et al.[25] in the cohort design). For dose 1 of RV5, age adjustment with the use of the quadratic risk function obtained from the study population results in only slightly lower attributable risks than age adjustment with the use of hospital-discharge data from Tate et al.[25]

Yih et al. New Engl J Med 2014;370:503-512

How Sentinel has been used by FDA (selected)

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)

Label change

Post-Marketing Observational Safety Surveillance Studies

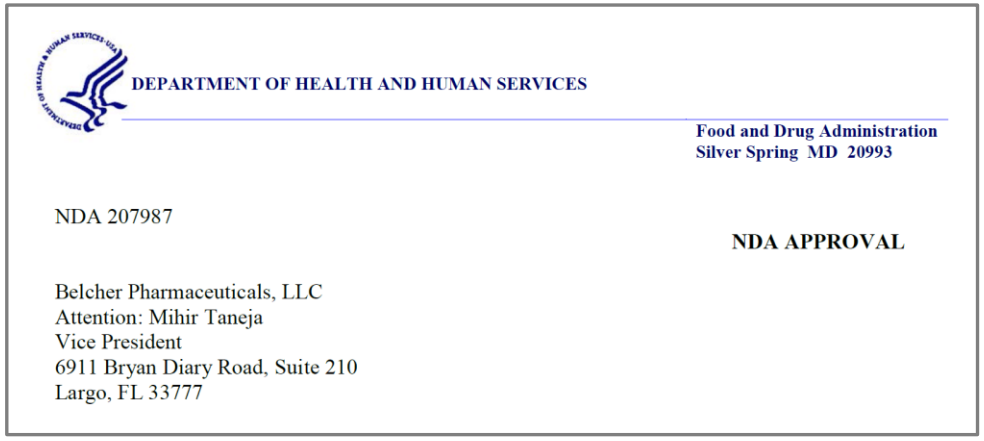
The temporal association between vaccination with RotaTeq and intussusception was evaluated in the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program[2], an electronic active surveillance program comprised of 3 US health insurance plans.

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

How Sentinel has been used by FDA (selected)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207987

NDA APPROVAL

Belcher Pharmaceuticals, LLC
Attention: Mihir Taneja
Vice President
6911 Bryan Diary Road, Suite 210
Largo, FL 33777

NDA approval letter

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https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/207987Orig1s000ltr.pdf

How Sentinel has been used by FDA (selected)

Sentinel

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.

Advisory Committee briefing document

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

How ARIA has been used by FDA (selected)

Drug Name	Outcome Assessed	ARIA Analysis	Regulatory Determination / Use	Date Posted
Ranexa (ranolazine)	Seizures	Level 1, Level 2	Combined with evidence from the Centers for Medicare & Medicaid Services, risk of seizure was determined to be driven primarily by underlying comorbidities. FDA decided that no action is necessary at this time, based on available information. • Results • 2017 ICPE Symposium	01/03/2019
Multiple sclerosis (MS) drugs	Exposure before, during, and after pregnancy	Level 1	Contextualized enrollment and recruitment in MS pregnancy registries. Described patterns of drug use before, during, and after pregnancy. • Results • 2018 ICPE Presentation	12/6/2018
Interleukin-1/-6 inhibitors	Pulmonary arterial hypertension and interstitial lung disease	Level 1	Feasibility assessment of ARIA to conduct a postmarket safety study. FDA decided that no action is necessary at this time, based on available information. • Results	12/3/2018
Forteo (teriparatide)	Duration of use	Level 1	Contributed to the decision regarding continuation of sponsor Postmarket Requirement for teriparatide • Results • Approval Letter with PMR/PMC Commitments • Supplemental Approval Letter with PMR/PMC Commitments	11/30/2018

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

Transparency

Analytic Request Packages Available for Download

Request ID	Summary
cder_mpl2p_wp001	Venous Thromboembolism after Continuous or Extended Cycle Contraceptive Use
cder_mpl2p_wp002	Ranexa (Ranolazine) and Seizures, Report 2
cder_mpl2p_wp006	Ranexa (Ranolazine) and Seizures, Report 3

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

Transparency

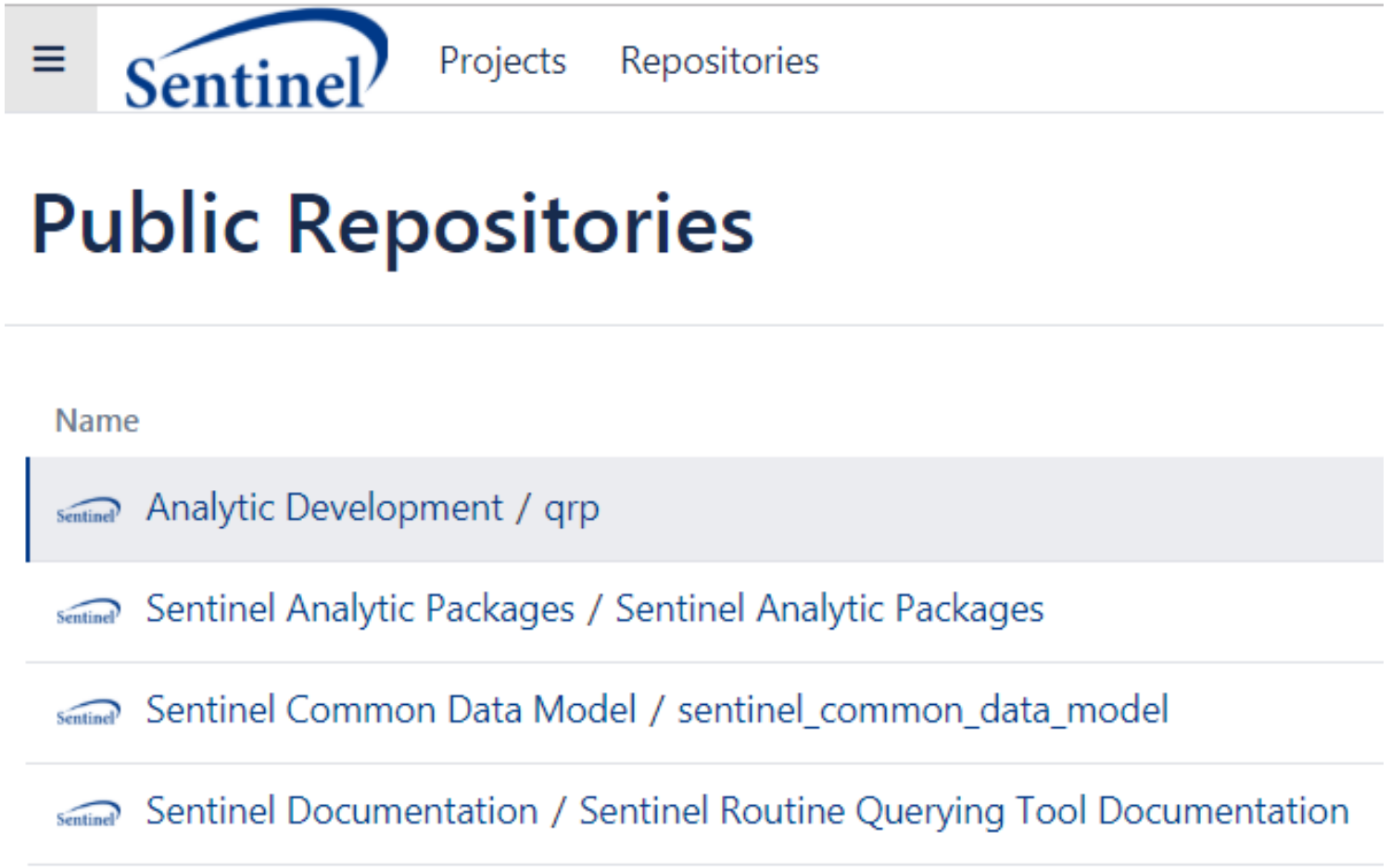
Table 1: Incident Ranolazine Use with Either Concomitant Beta Blocker, Calcium Channel Blocker, or Nitrate Use and Seizures in the Sentinel Distributed Database (SDD) between January 1, 2006 and September 30, 2015, by Strength of Ranolazine and Concomitant Exposure among All Individuals

	New Users	New Episodes	Dispensings	Days Supplied	Amount Supplied	Episode Duration	Years at Risk*	Episodes with Events	Episodes with Events per 10K Years at Risk*
Ranolazine (500 mg strength)									
Ranolazine With or Without Concomitant Use	49,256	49,256	199,812	7,344,143	15,257,873	7,634,313	20,902	32	15.31
With Concomitant Beta Blocker Use	30,679	30,679	na	na	na	3,698,827	10,127	23	22.71
With Concomitant Calcium Channel Blocker Use	2,476	2,476	na	na	na	268,127	734	1	13.62
With Concomitant Nitrates Use	26,853	26,853	na	na	na	2,569,997	7,036	18	25.58
Ranolazine (1000 mg strength)									
Ranolazine With or Without Concomitant Use	5,618	5,618	16,988	639,582	1,294,857	667,033	1,826	4	21.91
With Concomitant Beta Blocker Use	3,394	3,394	na	na	na	321,790	881	2	22.70
With Concomitant Calcium Channel Blocker Use	233	233	na	na	na	18,781	51	1	196.08
With Concomitant Nitrates Use	2,719	2,719	na	na	na	203,253	556	2	35.97

* Years at Risk stop accumulating when first event during episode is encountered

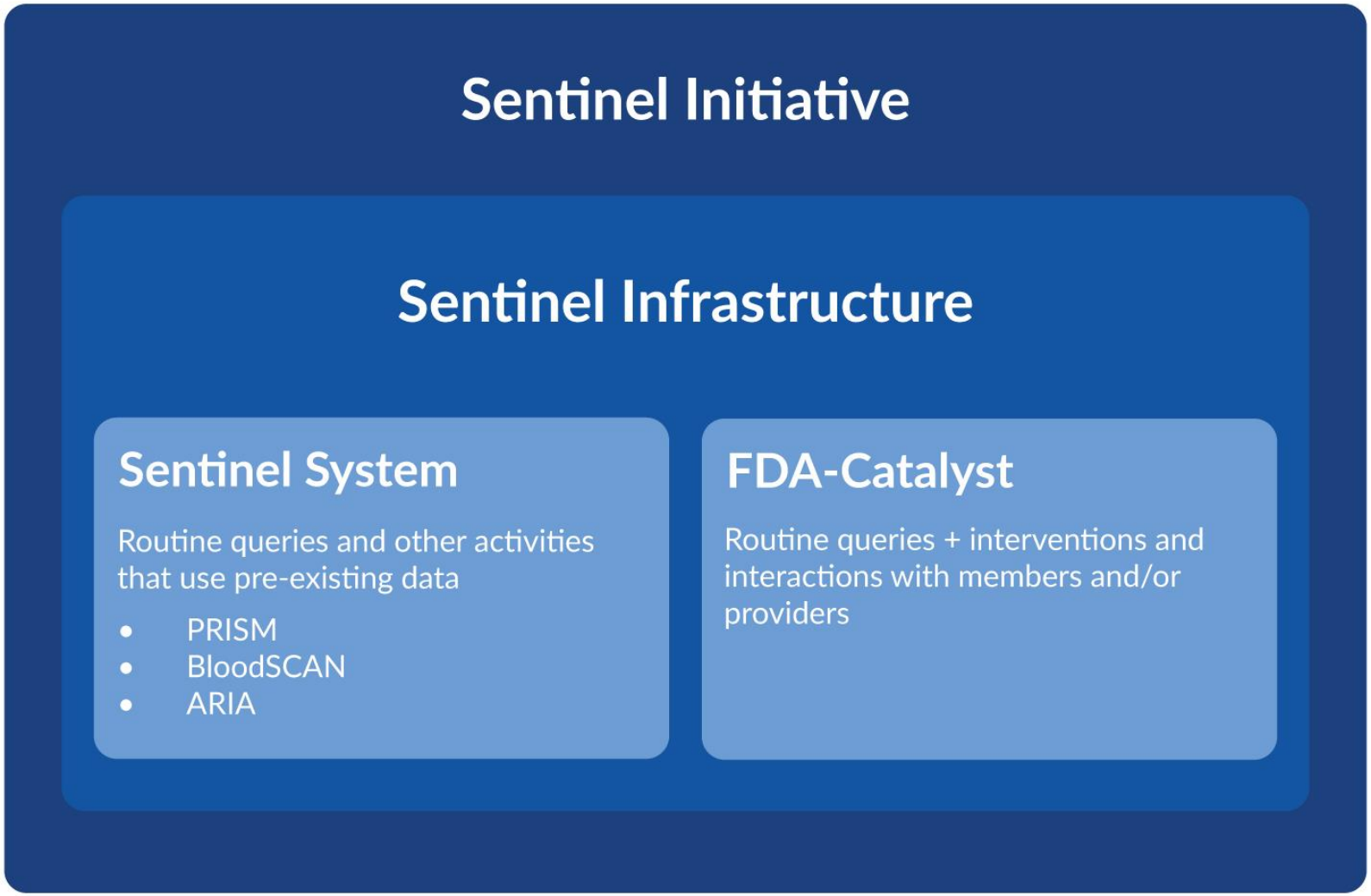
https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Sentinel_MP_Report_Ranexa_and_Seizures_L1.pdf

Transparency



https://dev.sentinelsystem.org/repos?visibility=public

Sentinel Initiative



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

Signal generation

What is TreeScan?

- A signal detection / data mining method
- Automatically adjusts for multiple hypothesis testing
- Scans electronic health data that are grouped into hierarchical tree structures

Evaluating impacts of FDA actions

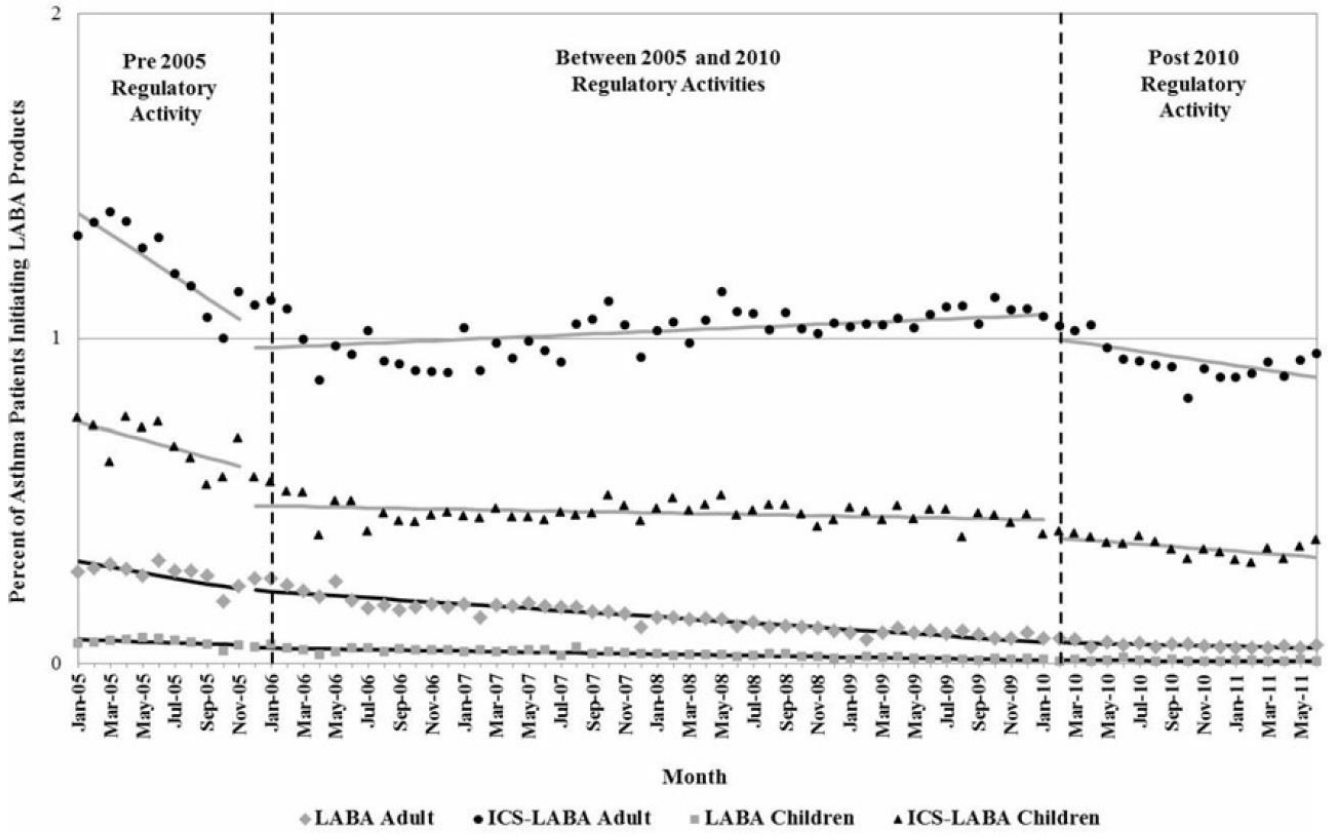
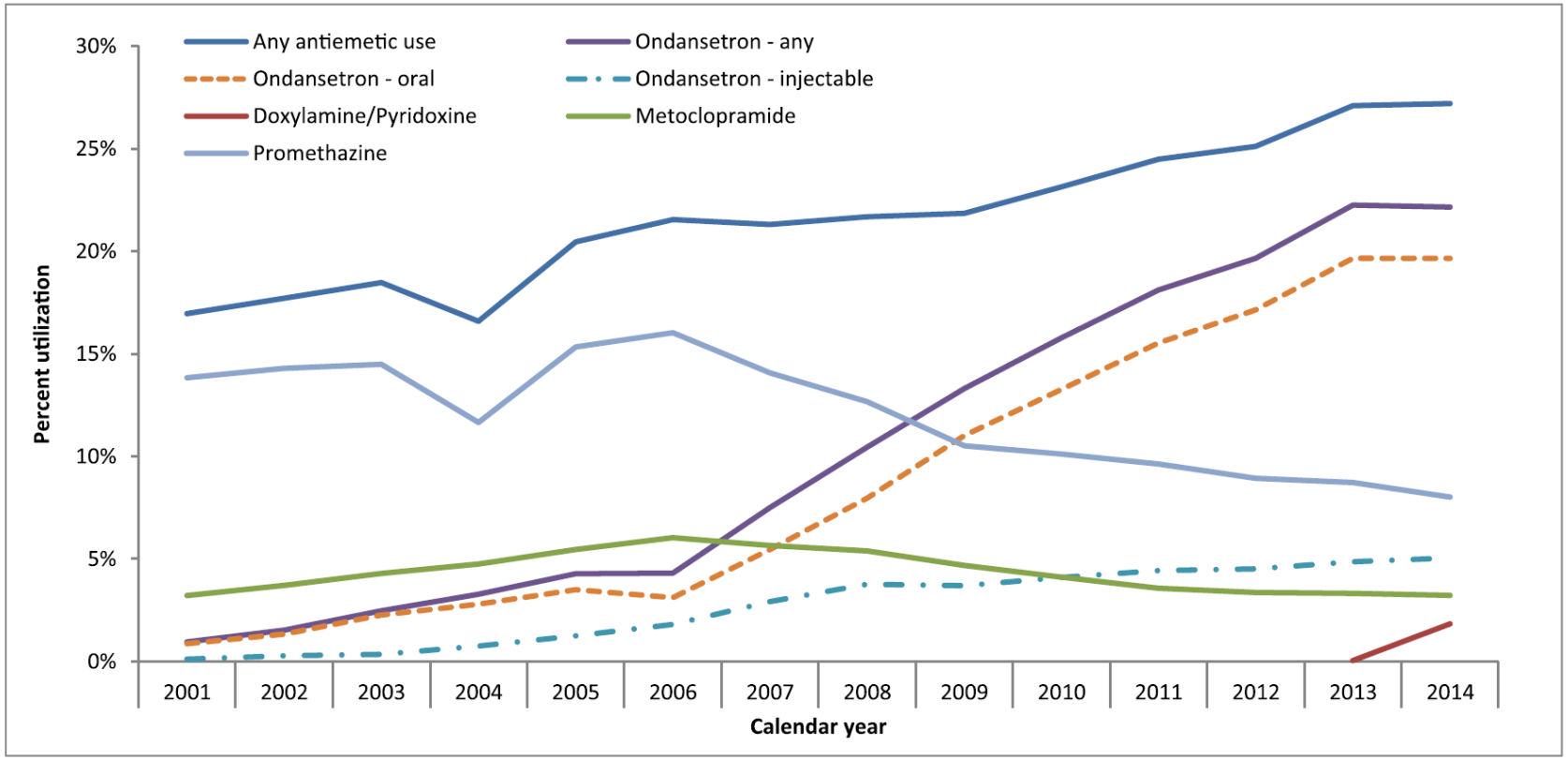


Figure 2. Percentage of LABA product initiation before, between and after the 2005 and 2010 FDA regulatory activities for LABA-containing agents in children and adults with asthma and no history of a LABA dispensing in 180 days.

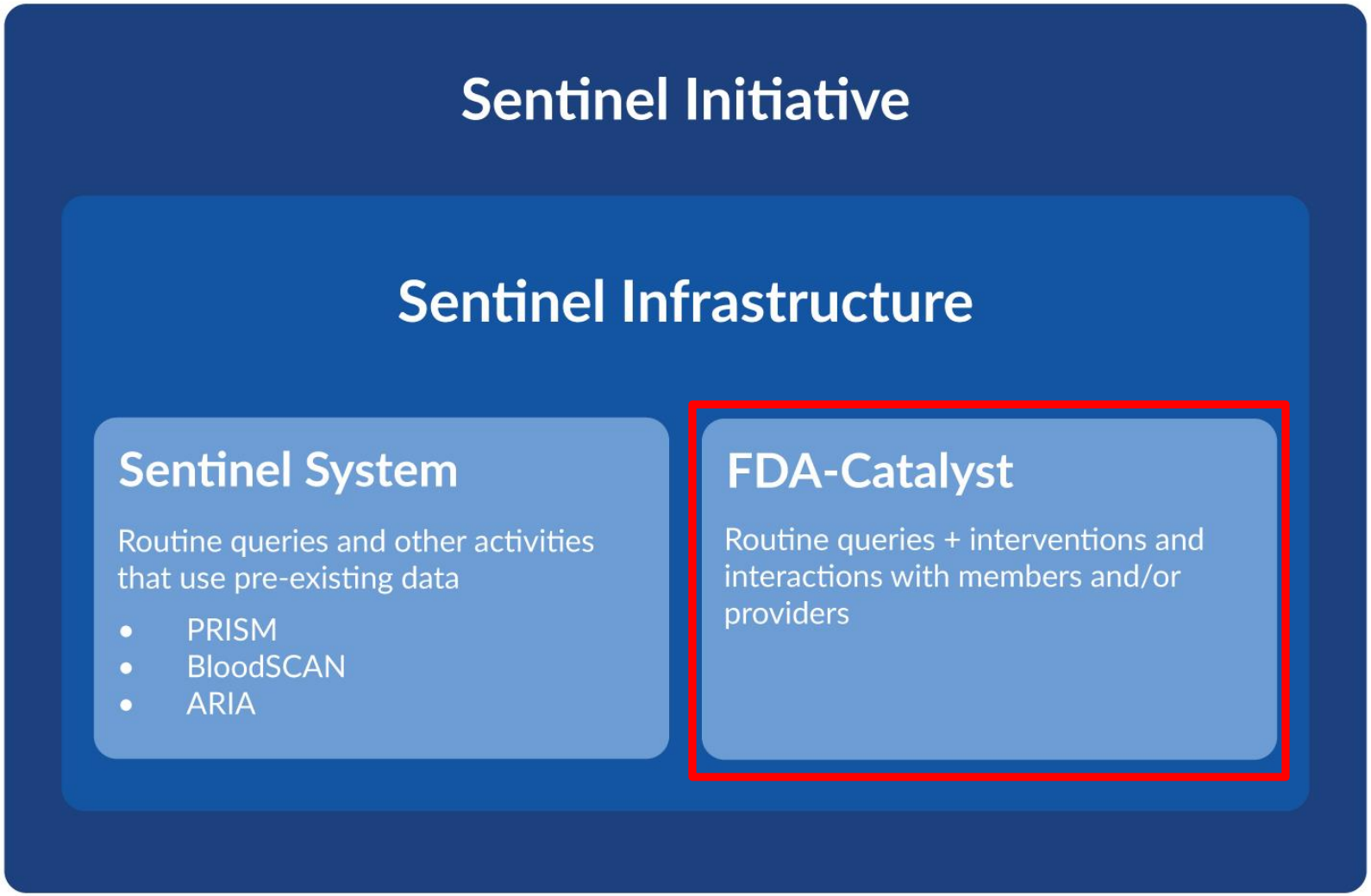
Baker et al. J Asthma 2018; 55:907-91

Medication exposure during pregnancy



Taylor et al. Pharmacoepidemiol Drug Saf 2017;26:592-596

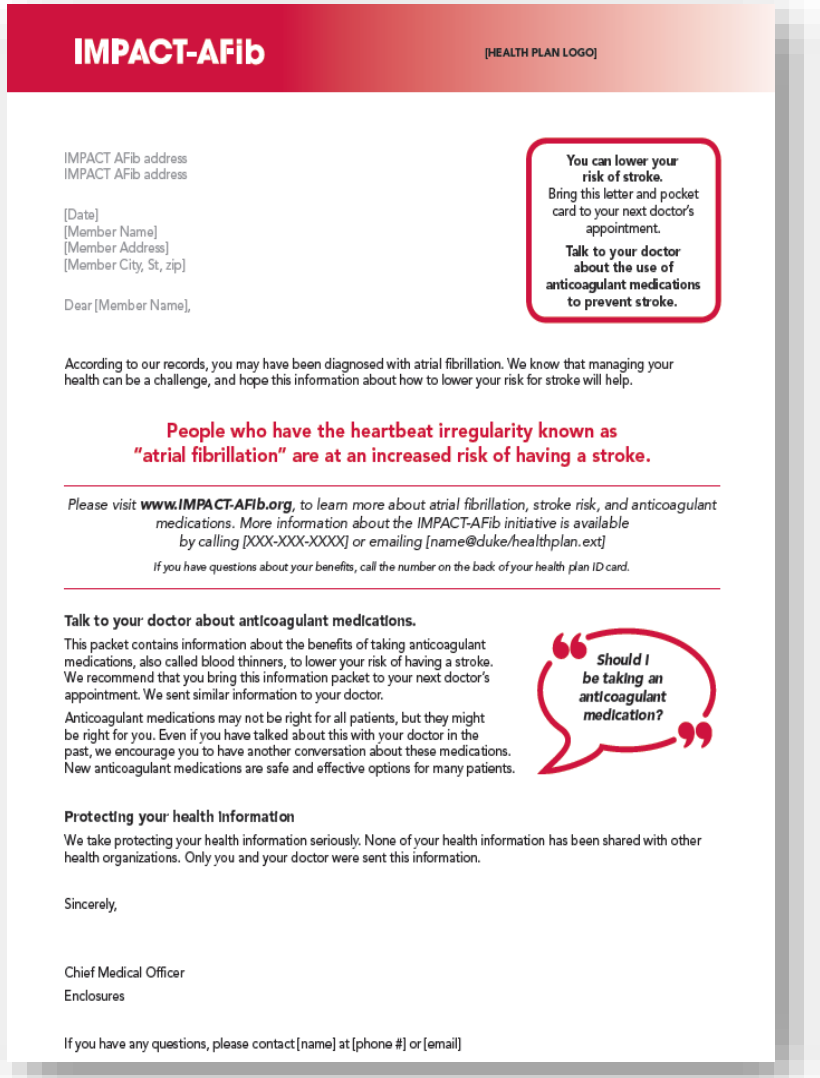
Sentinel Initiative



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

Pragmatic trial in Sentinel

MEMBER LETTER



IMPACT-AFib [HEALTH PLAN LOGO]

IMPACT AFib address
IMPACT AFib address

[Date]
[Member Name]
[Member Address]
[Member City, St, zip]

You can lower your risk of stroke.
Bring this letter and pocket card to your next doctor's appointment.
Talk to your doctor about the use of anticoagulant medications to prevent stroke.

Dear [Member Name],

According to our records, you may have been diagnosed with atrial fibrillation. We know that managing your health can be a challenge, and hope this information about how to lower your risk for stroke will help.

People who have the heartbeat irregularity known as "atrial fibrillation" are at an increased risk of having a stroke.

*Please visit **www.IMPACT-AFib.org**, to learn more about atrial fibrillation, stroke risk, and anticoagulant medications. More information about the IMPACT-AFib initiative is available by calling [XXX-XXX-XXXX] or emailing [name@duke/healthplan.ext]*

If you have questions about your benefits, call the number on the back of your health plan ID card.

Talk to your doctor about anticoagulant medications.

This packet contains information about the benefits of taking anticoagulant medications, also called blood thinners, to lower your risk of having a stroke. We recommend that you bring this information packet to your next doctor's appointment. We sent similar information to your doctor.

Anticoagulant medications may not be right for all patients, but they might be right for you. Even if you have talked about this with your doctor in the past, we encourage you to have another conversation about these medications. New anticoagulant medications are safe and effective options for many patients.

"Should I be taking an anticoagulant medication?"

Protecting your health information

We take protecting your health information seriously. None of your health information has been shared with other health organizations. Only you and your doctor were sent this information.

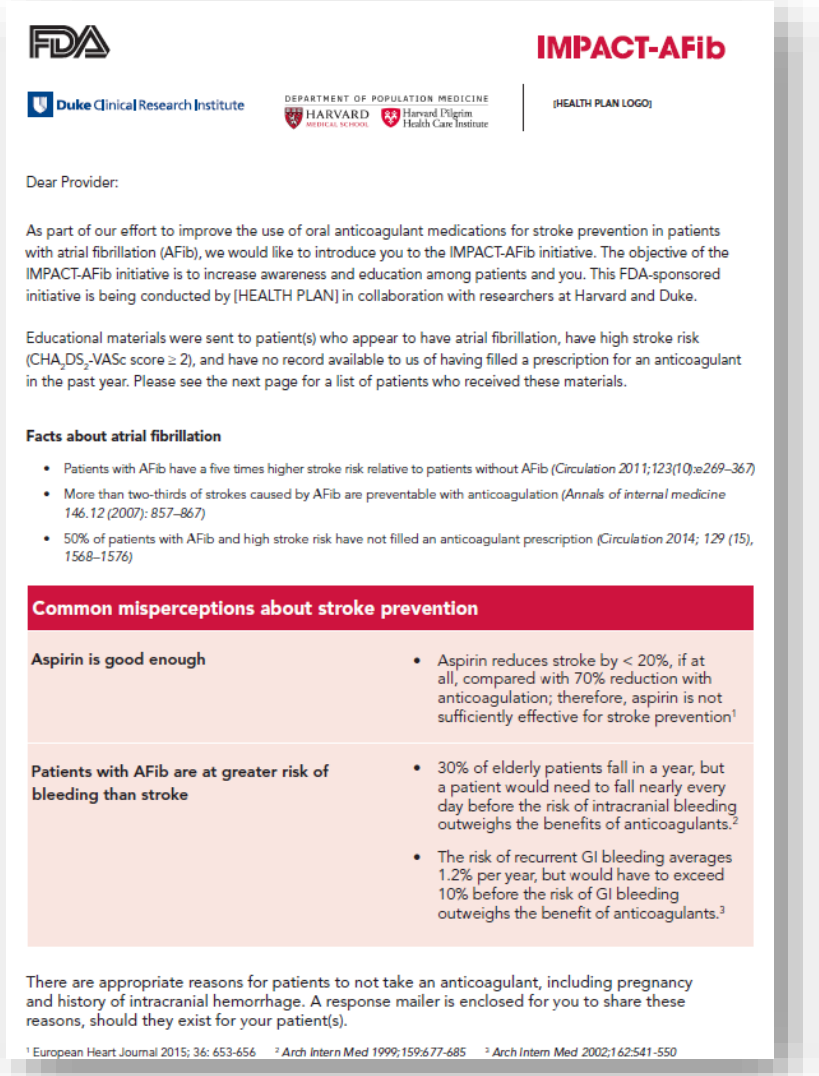
Sincerely,

Chief Medical Officer

Enclosures

If you have any questions, please contact [name] at [phone #] or [email]

PROVIDER LETTER



FDA

IMPACT-AFib

Duke Clinical Research Institute | Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Health Care Institute | [HEALTH PLAN LOGO]

Dear Provider:

As part of our effort to improve the use of oral anticoagulant medications for stroke prevention in patients with atrial fibrillation (AFib), we would like to introduce you to the IMPACT-AFib initiative. The objective of the IMPACT-AFib initiative is to increase awareness and education among patients and you. This FDA-sponsored initiative is being conducted by [HEALTH PLAN] in collaboration with researchers at Harvard and Duke.

Educational materials were sent to patient(s) who appear to have atrial fibrillation, have high stroke risk (CHA_2DS_2-VASc score ≥ 2), and have no record available to us of having filled a prescription for an anticoagulant in the past year. Please see the next page for a list of patients who received these materials.

Facts about atrial fibrillation

- Patients with AFib have a five times higher stroke risk relative to patients without AFib *(Circulation 2011;123(10):e269–367)*
- More than two-thirds of strokes caused by AFib are preventable with anticoagulation *(Annals of internal medicine 146.12 (2007): 857–867)*
- 50% of patients with AFib and high stroke risk have not filled an anticoagulant prescription *(Circulation 2014; 129 (15), 1568–1576)*

Common misperceptions about stroke prevention

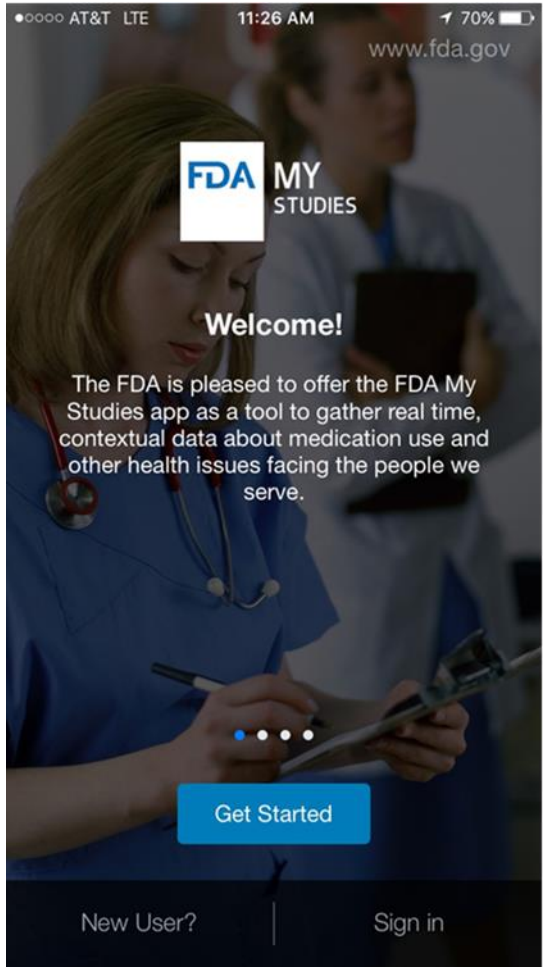
Aspirin is good enough	• Aspirin reduces stroke by < 20%, if at all, compared with 70% reduction with anticoagulation; therefore, aspirin is not sufficiently effective for stroke prevention[1]
Patients with AFib are at greater risk of bleeding than stroke	• 30% of elderly patients fall in a year, but a patient would need to fall nearly every day before the risk of intracranial bleeding outweighs the benefits of anticoagulants.[2] • The risk of recurrent GI bleeding averages 1.2% per year, but would have to exceed 10% before the risk of GI bleeding outweighs the benefit of anticoagulants.[3]

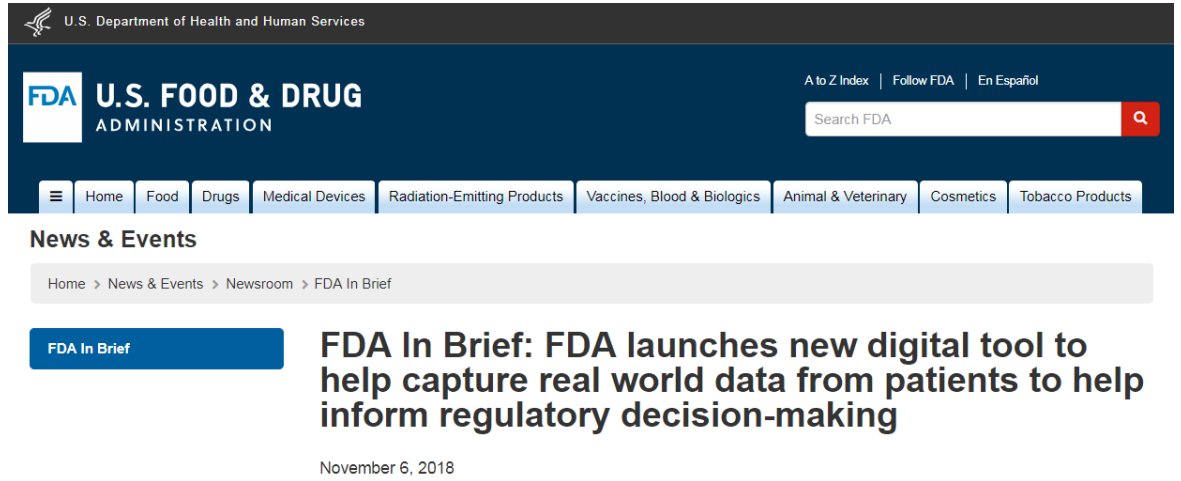
There are appropriate reasons for patients to not take an anticoagulant, including pregnancy and history of intracranial hemorrhage. A response mailer is enclosed for you to share these reasons, should they exist for your patient(s).

[1] European Heart Journal 2015; 36: 653-656 [2] *Arch Intern Med 1999;159:677-685* [3] *Arch Intern Med 2002;162:541-550*

https://www.sentinelinitiative.org/FDA-catalyst/projects/implementation-randomized-controlled-trial-improve-treatment-oral-anticoagulants-patients

Collecting patient-reported information





https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
https://www.sentinelinitiative.org/FDA-catalyst/projects/collection-patient-provided-information-through-mobile-device-application-use-comparative

The NEW ENGLAND JOURNAL of MEDICINE

Sentinel

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

“Opening up” Sentinel

REAGAN-UDALL FOUNDATION FOR THE FOOD AND DRUG ADMINISTRATION

INNOVATION IN MEDICAL EVIDENCE DEVELOPMENT AND SURVEILLANCE

http://reaganudall.org/innovation-medical-evidence-development-and-surveillance
https://www.sentinelinitiative.org/sentinel/reagan-udall-foundation-and-imeds

IMEDS

Sentinel

Received: 4 October 2017 | Revised: 5 December 2017 | Accepted: 21 December 2017

DOI: 10.1002/pds.4392

ORIGINAL REPORT

WILEY

Do FDA label changes work? Assessment of the 2010 class label change for proton pump inhibitors using the Sentinel System's analytic tools

Rachel E. Sobel[1] | Andrew Bate[1] | James Marshall[2] | Kevin Haynes[3] | Nandini Selvam[3] | Vinit Nair[4] | Gregory Daniel[5] | Jeffrey S. Brown[2] | Robert F. Reynolds[1]

IMEDS

TAGS: Regulation | Safety | FDA

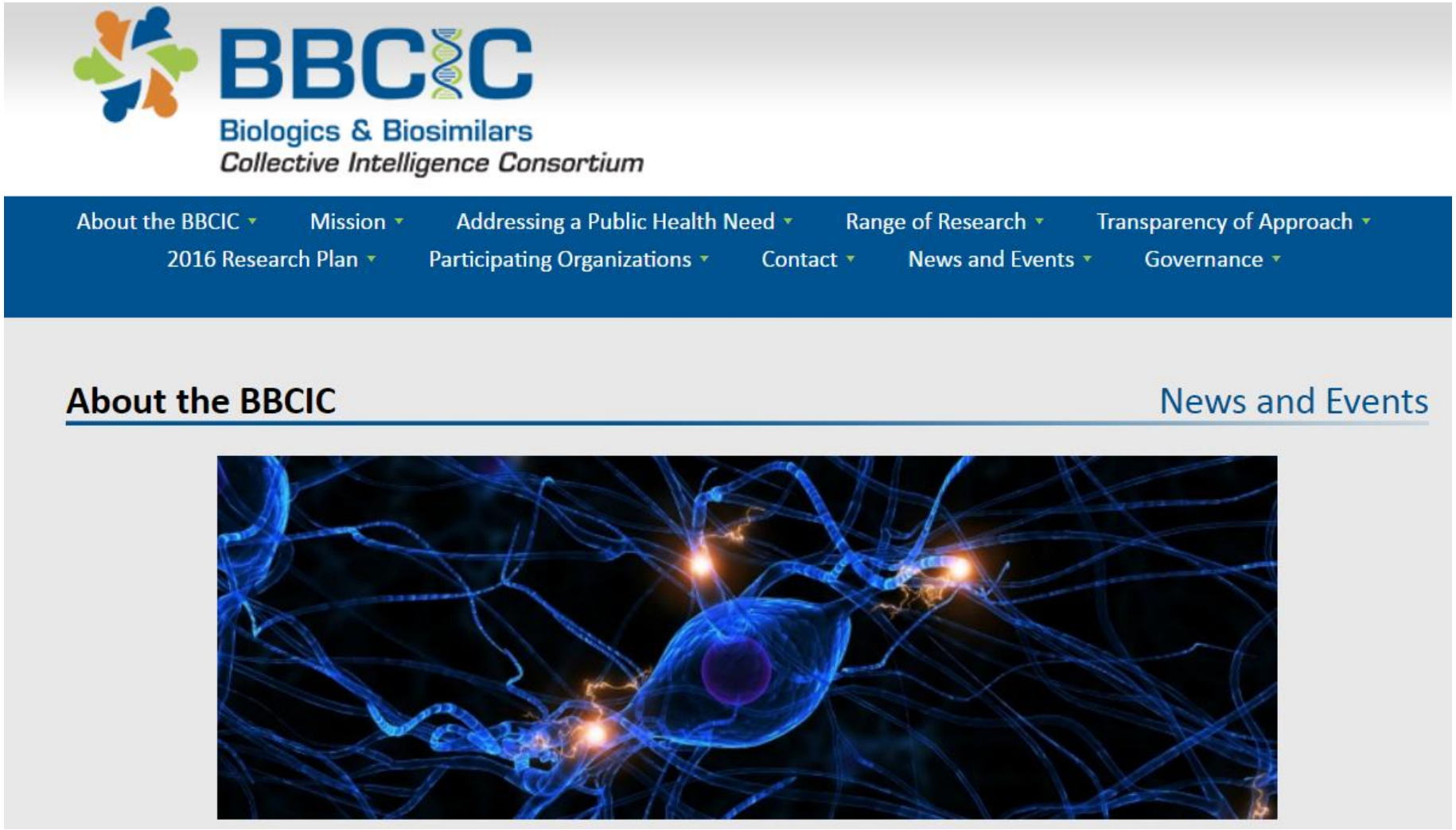
ASK THE ANALYST

Lilly's Olumiant Resubmission Includes Safety Data From US FDA's Sentinel Network

22 Feb 2018 | ANALYSIS

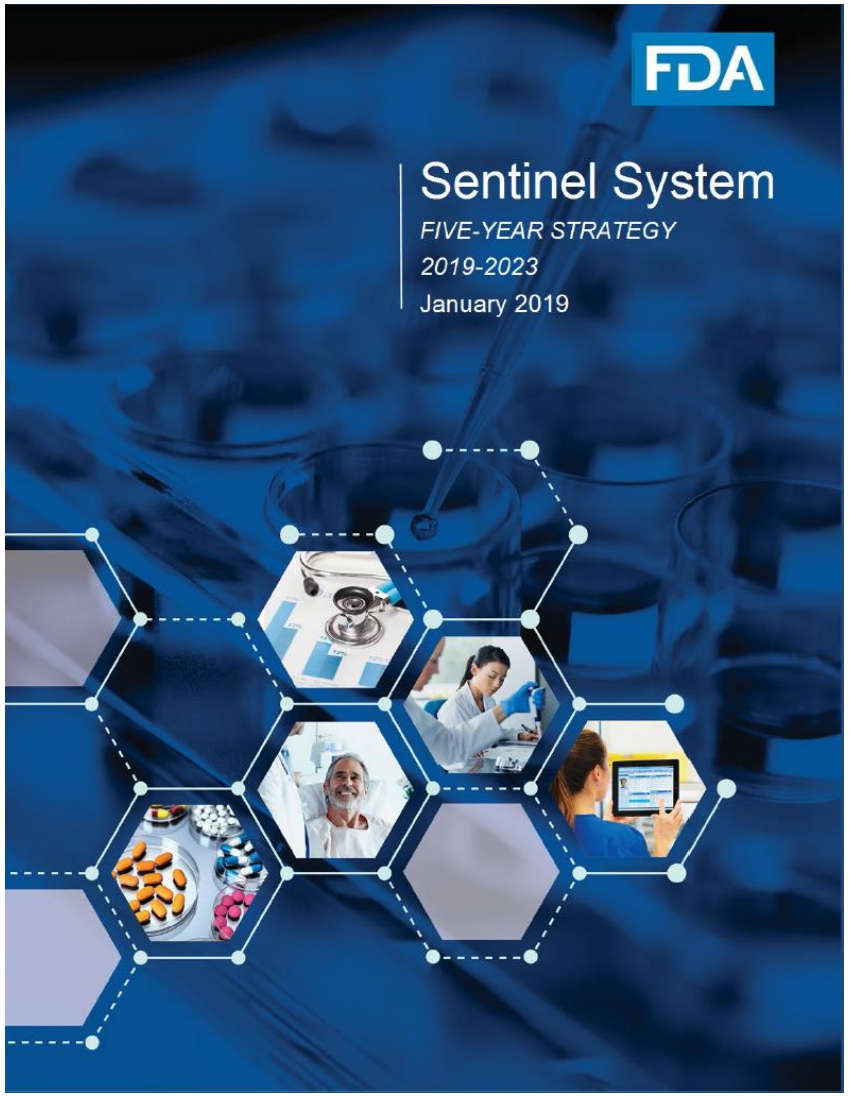
https://pink.pharmaintelligence.informa.com/PS122553/Lillys-Olumiant-Resubmission-Includes-Safety-Data-From-US-FDAs-Sentinel-Network
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000OtherR.pdf

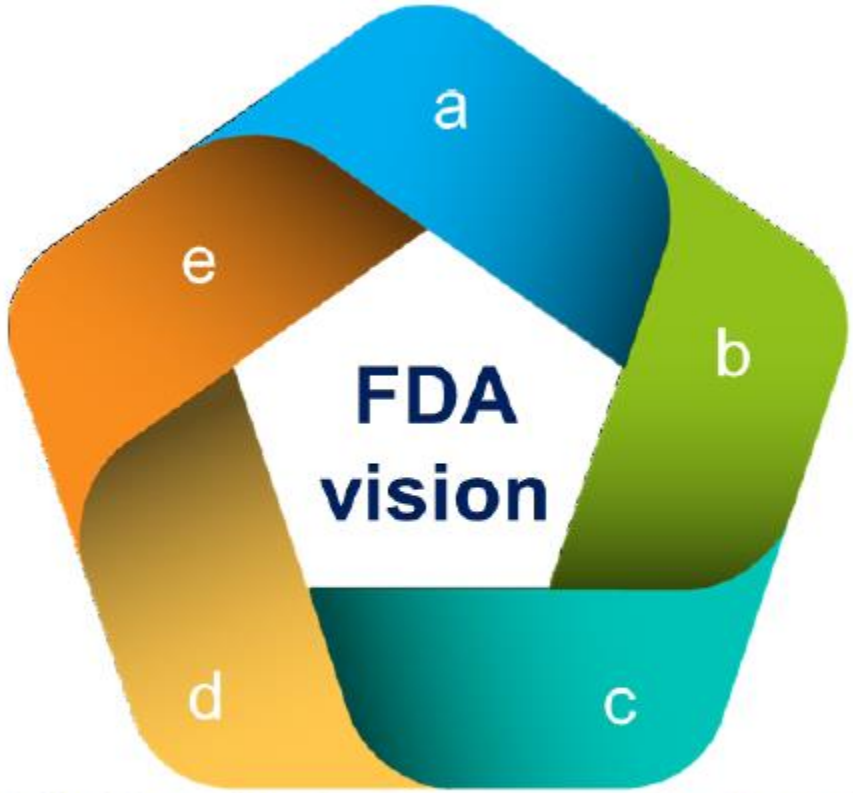
BBCIC



https://bbcic.org/

Sentinel System 5-year strategic plan

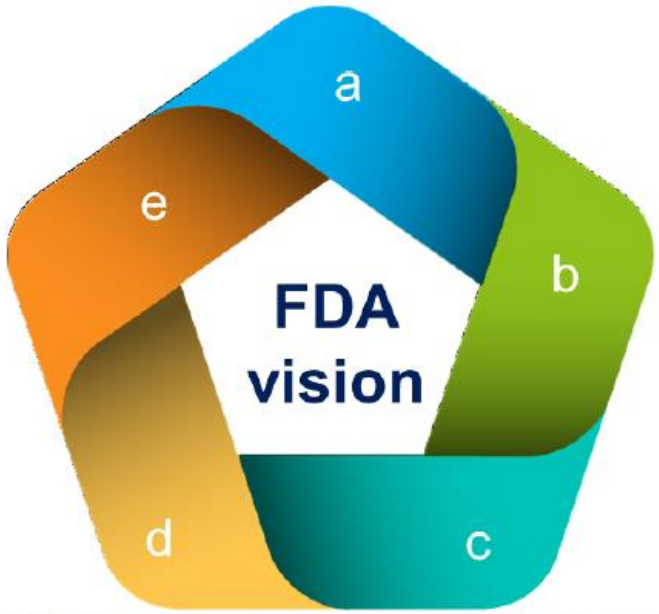




A sustainable national resource to monitor the safety of marketed medical products, and expand real-world data sources used to evaluate medical product performance

https://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM629243.pdf

Sentinel System 5-year strategic plan



A sustainable national resource to monitor the safety of marketed medical products, and expand real-world data sources used to evaluate medical product performance

a

Enhance the foundation of the Sentinel System

- Expand data sources and linkages
- Improve data infrastructure and methods development
- Enable more effective use through operational improvements

b

Further enhance safety analysis capabilities

- Increase ARIA sufficiency
- Leverage advances in data science and signal detection

c

Accelerate access to and broader use of real-world data

- Enable new avenues for generating real-world evidence by investing in access to and approaches to use of electronic health records
- Conduct specific real-world data-driven demonstration projects to explore the universe of addressable effectiveness questions

d

Create a national resource by broadening the Sentinel user base

- Improve operations and procedures for accessing tools, methods, and results
- Evolve the Sentinel System operating model
- Engage directly with potential users and develop a Sentinel scientific community

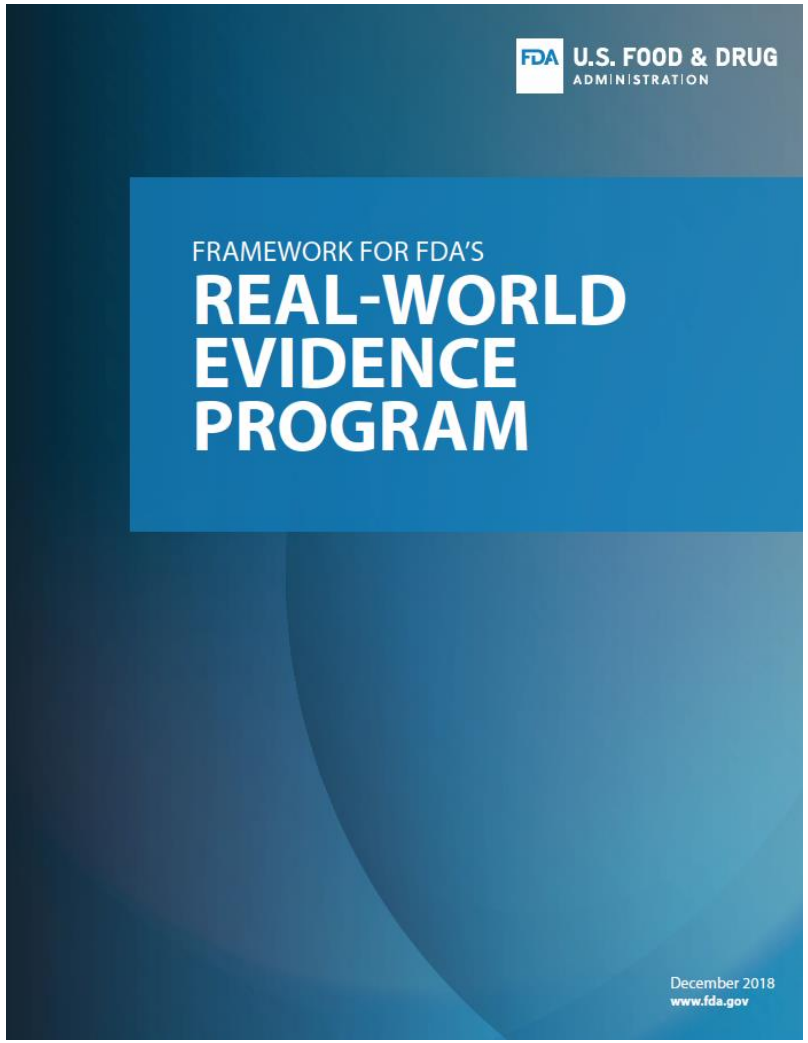
e

Disseminate knowledge, and advance regulatory science

- External outreach and convening across the learning healthcare ecosystem
- Provide transparency, and encourage innovation and collaboration

https://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM629243.pdf

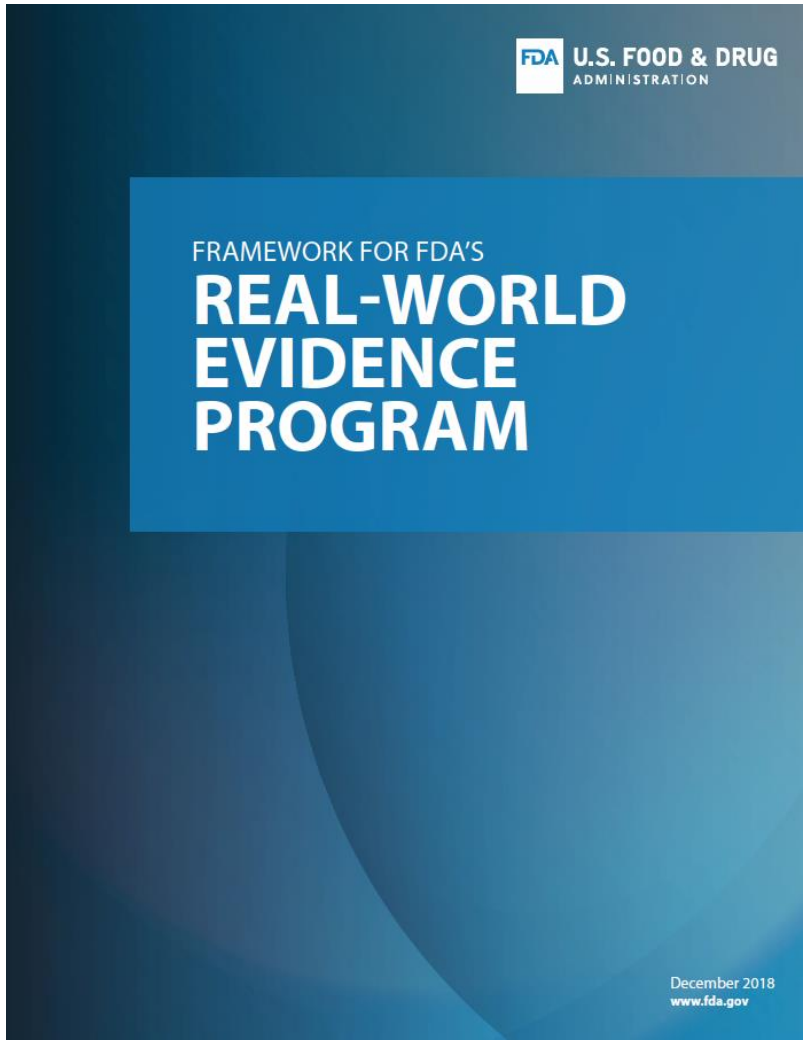
RWD/RWE and regulatory science



- Using trials or studies with RWD/RWE for effectiveness decisions
- Assessing fitness of RWD for use in regulatory decisions
- Potential for study designs using RWD to support effectiveness
- Regulatory consideration for study design using RWD
- Data standards – appropriate data standards for integration and submission to FDA

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

RWD/RWE and regulatory science



Specifically, FDA's RWE Program will evaluate the potential use of RWE to support changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information.

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

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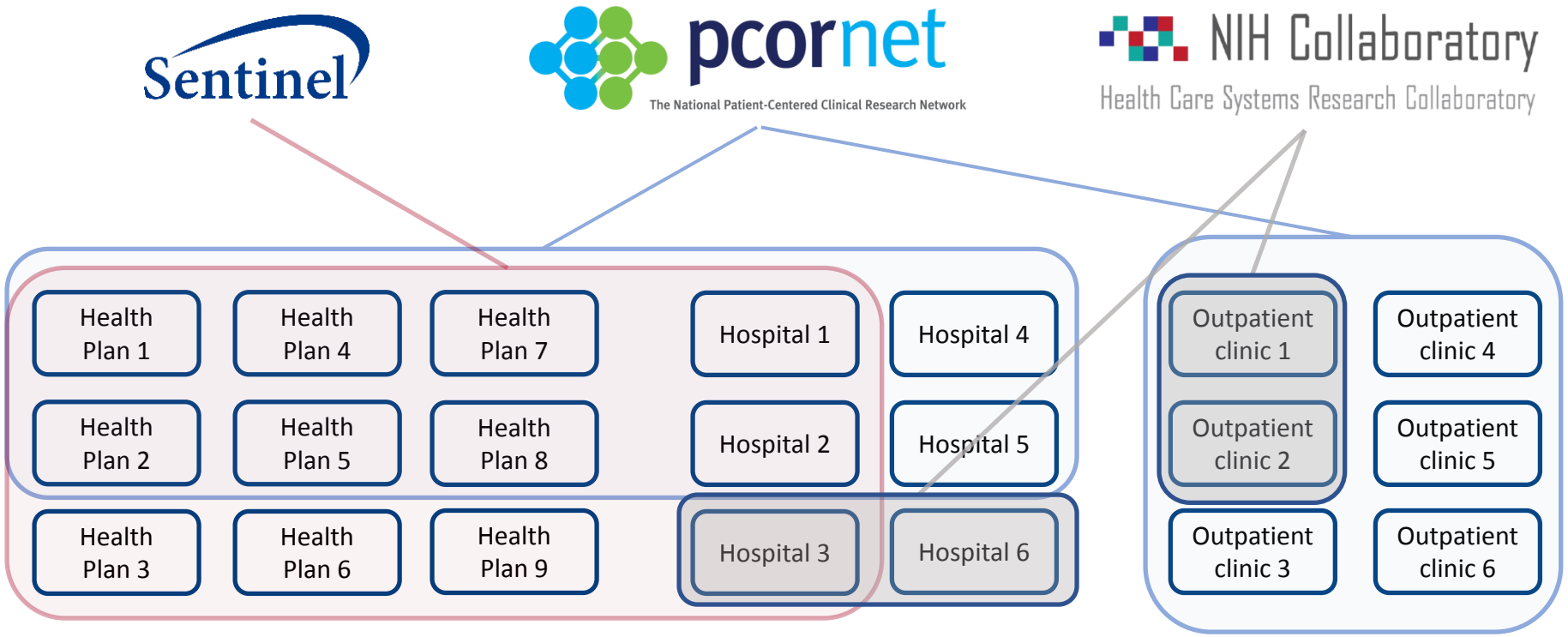
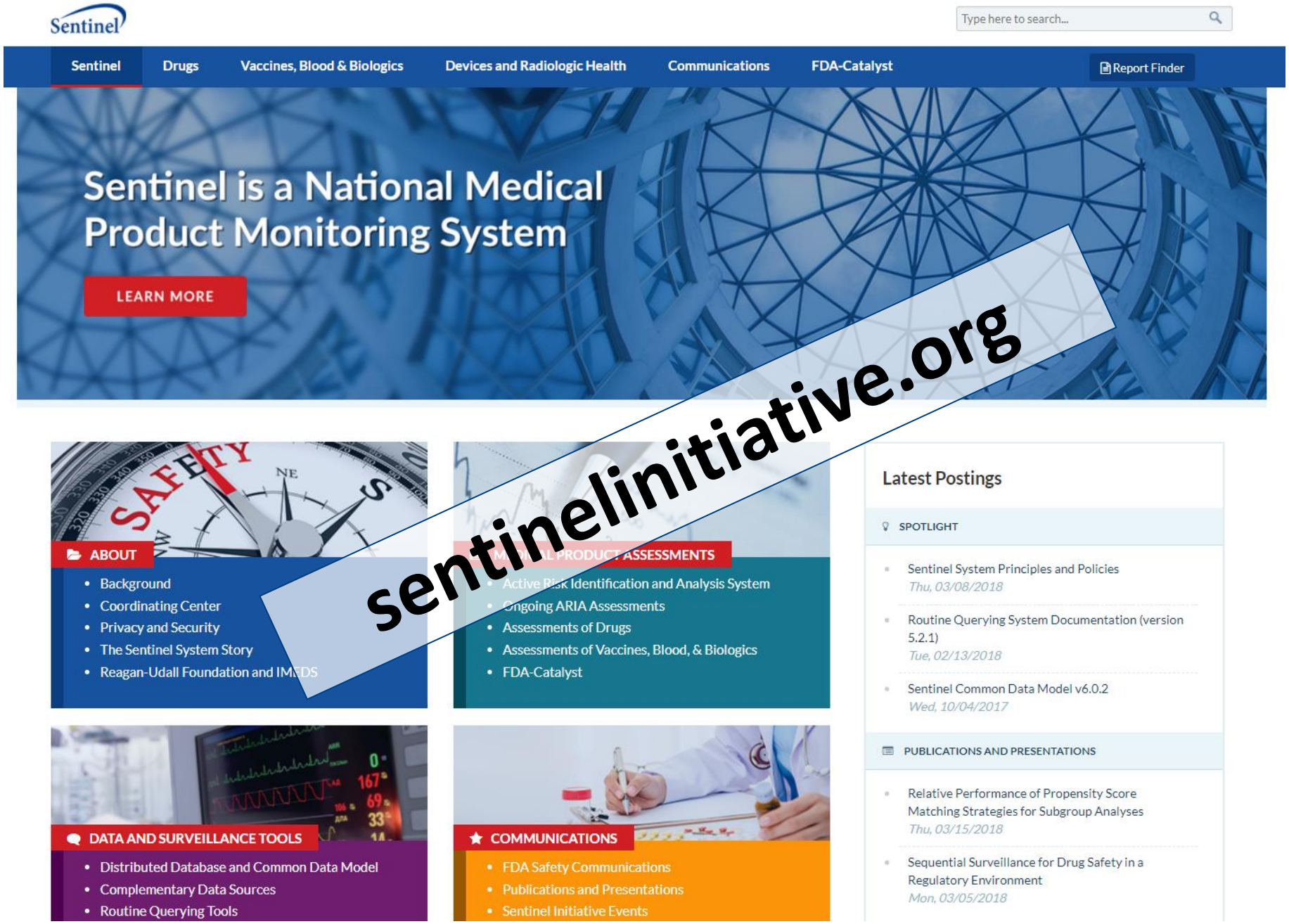
N Engl J Med 2018; 379:2091-2093

A national infrastructure for evidence generation



- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, analytics, lessons, security, software

Adapted from a slide by Dr. Janet Woodcock, CDER, FDA; https://healthpolicy.duke.edu/sentinel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Thu, 03/08/2018
Routine Querying System Documentation (version 5.2.1)
Tue, 02/13/2018
Sentinel Common Data Model v6.0.2
Wed, 10/04/2017
PUBLICATIONS AND PRESENTATIONS
Relative Performance of Propensity Score Matching Strategies for Subgroup Analyses
Thu, 03/15/2018
Sequential Surveillance for Drug Safety in a Regulatory Environment
Mon, 03/05/2018

Darren_Toh@harvardpilgrim.org

@darrentoh_epi

https://www.distributedanalysis.org