

FDA's Sentinel Initiative

LCDR Danijela Stojanovic, PharmD, PhD
Epidemiologist, Sentinel Core Team
Office of Surveillance and Epidemiology
CDER | US FDA

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The opinions expressed in this lecture are those of the presenter, and do not necessarily represent the views of the US Food and Drug Administration or the US Government

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Learning Objectives

- Describe Sentinel's history and implementation
- Identify key elements of Sentinel
- Describe Sentinel's three centers

SENTINEL'S HISTORY AND IMPLEMENTATION

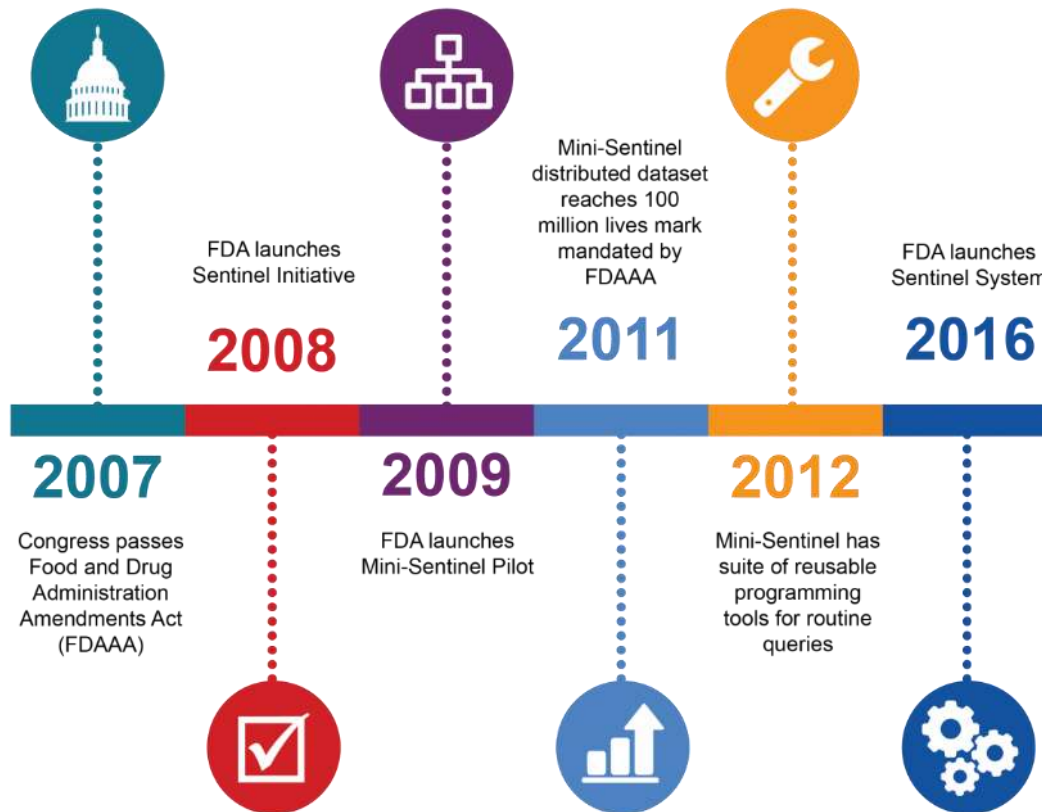


What is Sentinel?



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

Sentinel Timeline



FDA Amendments Act of 2007



Sec. 905. Active Postmarket Risk Identification and Analysis

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

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

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

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

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

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

FDA Amendments Act of 2007



Section 905

Mandates creation of Sentinel



Section 901

New FDAAA PMR authority

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

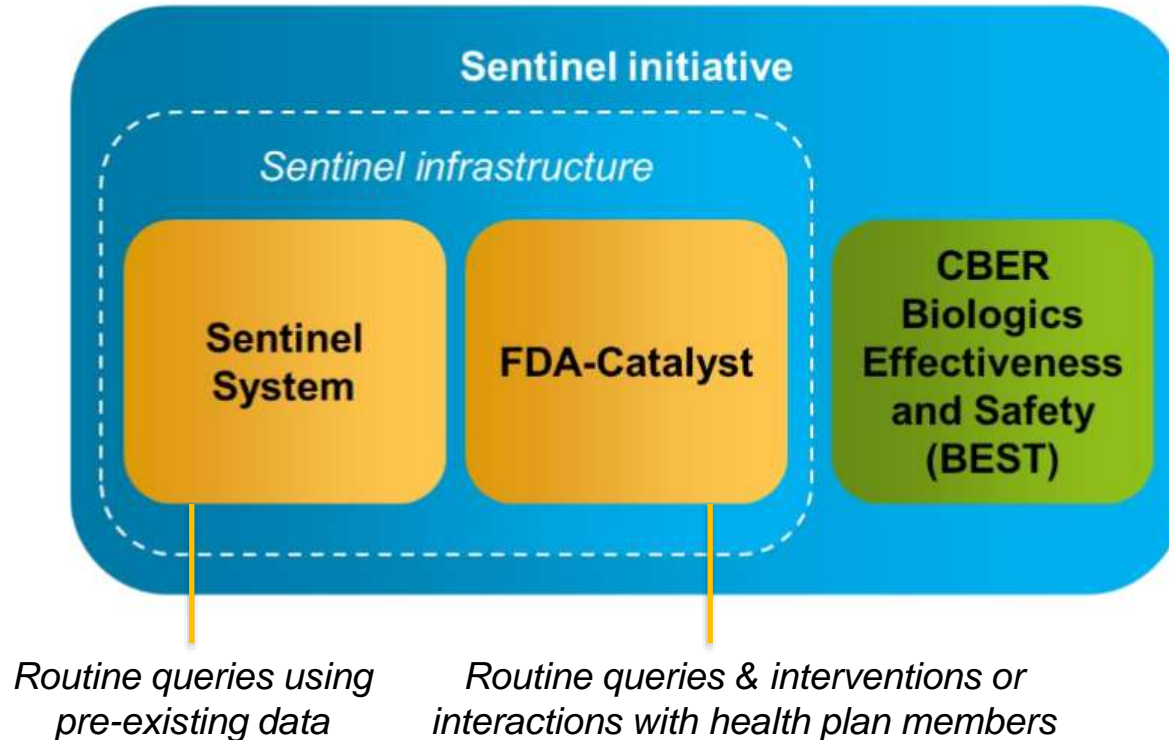
“The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient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

PMR Guidance



- Guidance for Industry: Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act
- Postmarketing studies may be required:
 - To assess a known serious risk
 - To assess signals of serious risk
 - To identify an unexpected serious risk when available data indicate the potential for a serious risk
- Details FDA considerations for determining ARIA sufficiency

Components of Sentinel Initiative



Knowledge check #1



The Sentinel Initiative was developed in response to what legislative mandate? Select one:

- A. Food and Drug Administration Amendments Act of 2007
- B. Draft guidance on postmarketing studies and clinical trials published in 2019
- C. Family Smoking Prevention and Tobacco Control Act of 2009

KEY ELEMENTS OF SENTINEL

Key Elements of the Sentinel System

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

Electronic Healthcare Data



- Sentinel relies on data generated from patient interactions with the U.S. healthcare system through health insurers and providers
- Principal source of data used in Sentinel is healthcare administrative claims data
- Additional types of healthcare data that complement the claims data in Sentinel include:
 - Electronic health records (EHRs), immunization registries, disease registries, birth and death registries

Snapshot of Database Statistics



- **The Sentinel Distributed Database (SDD) has:**
 - **310.8 million** cumulative patient identifiers between 2000 and 2018
- Of members with medical and drug coverage, there are:
 - **70.1 million** members are currently accruing new data
 - **11.7 billion** pharmacy dispensings
 - **15.0 billion** unique medical encounters
 - **48.5 million** members with at least one laboratory test result
 - **668 million** person-years of data
 - **4.1 million** linked deliveries

Sentinel Common Data Model

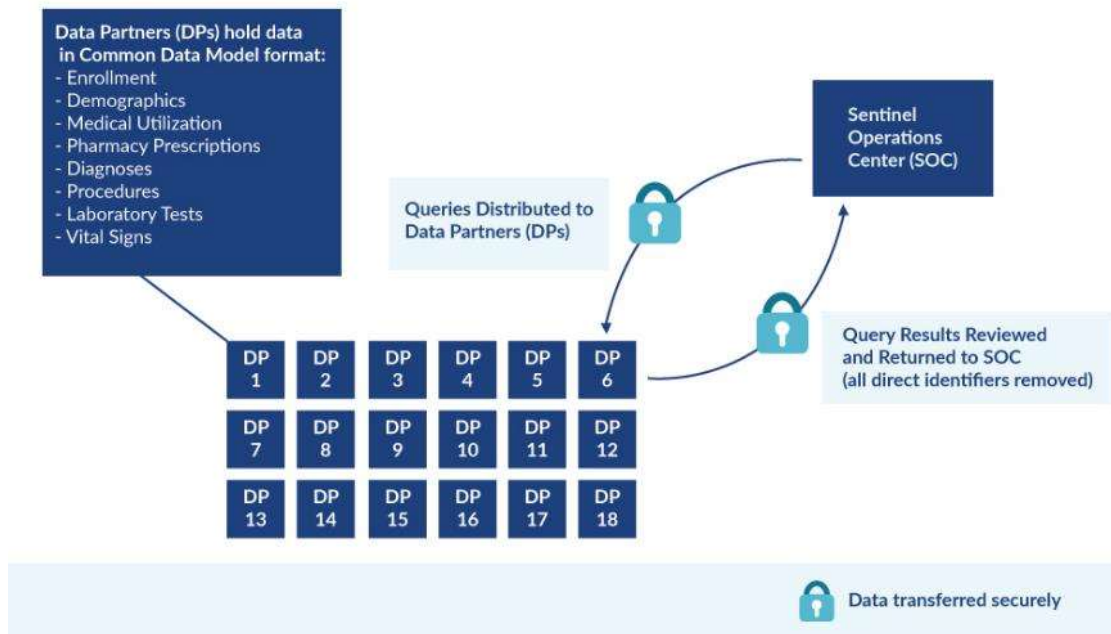


Administrative Data						Clinical Data	
Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure	Lab Result	Vital Signs
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID
Enrollment Start & End Dates	Birth Date	Dispensing Date	Service Date(s)	Service Date(s)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

Sentinel's Distributed Database



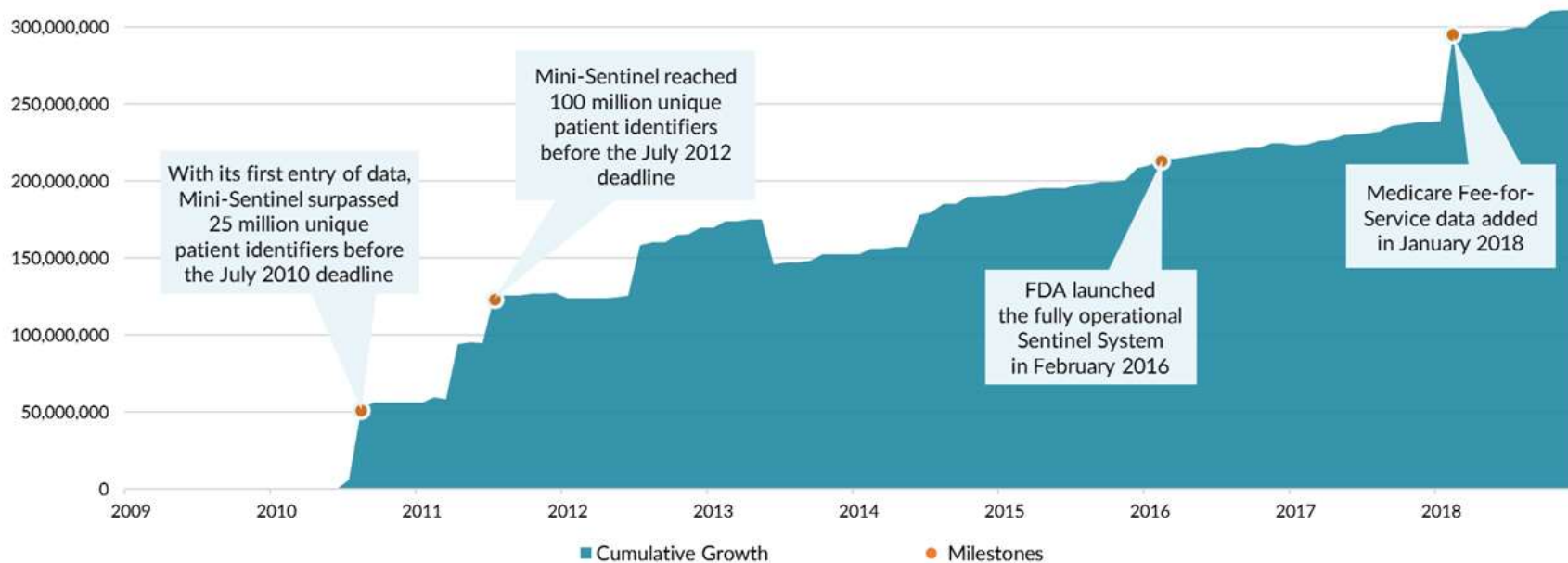
- Data Partners maintain physical and operational control over their data
- Data Partners execute standardized queries against their own data and return aggregate results to the Sentinel Operations Center
- Preserves patient privacy and institutional proprietary interests



Sentinel's Distributed Database



Growth of the Sentinel Distributed Database



Routine Querying Tools

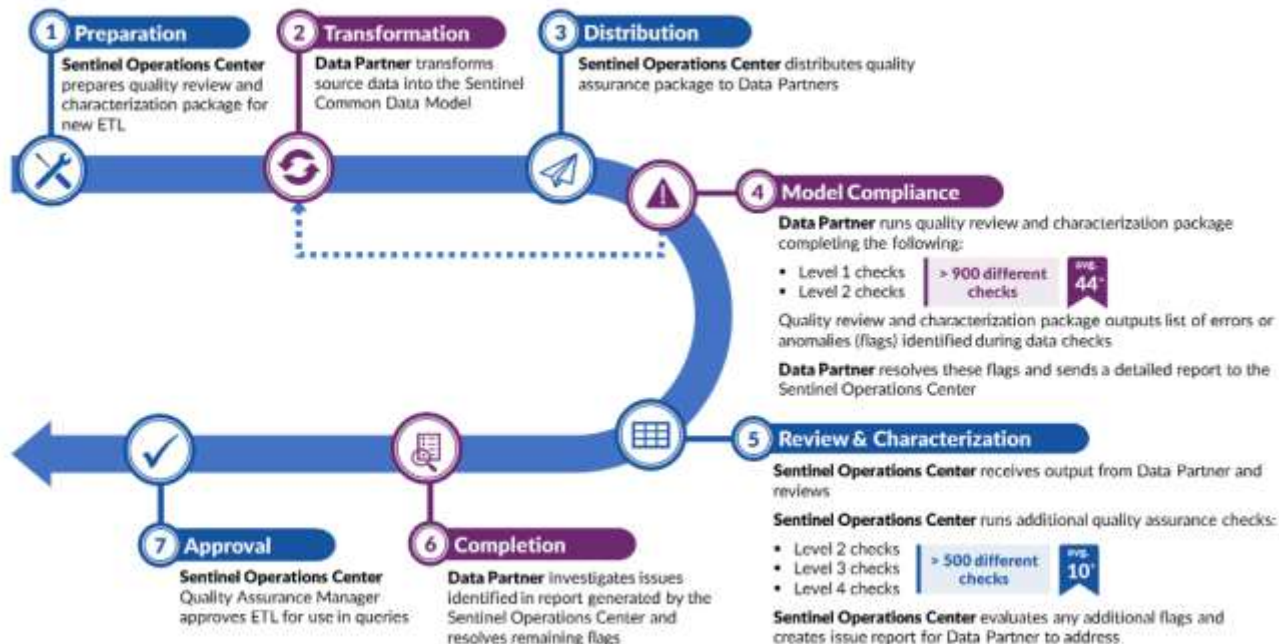
- Sentinel uses pre-defined, parameterized, reusable routine querying tools to conduct medical product safety surveillance
- Using routine querying tools shortens the turn around time for Sentinel queries compared to full protocol-based observational studies that require de novo analytic programming
- All Sentinel tools are pre-tested and validated prior to being used for analyses

Routine Querying Tools



Data Quality Assurance Process

Sentinel Data Quality Review and Characterization Process



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

Example Questions Addressed in Sentinel

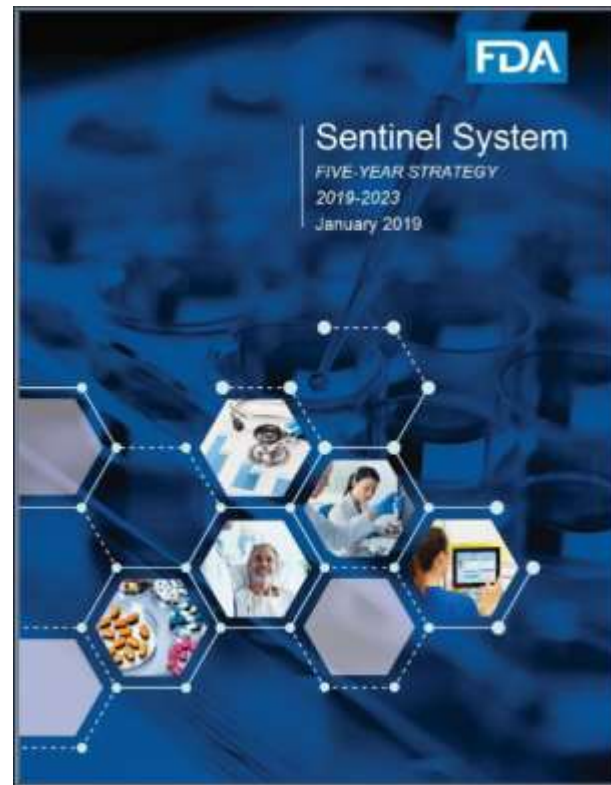


1. How long do patients starting use of drug A remain using it?
2. How often is drug A used in conjunction with drug B?
3. What indications are associated with use of drug A?
4. How often does a patient using brand drug A switch to generic drug B?
Of those, how many switch back to brand drug A?
5. How frequently does outcome B occur among users of drug A?
6. Is there an association between use of drug A during pregnancy and outcome C in infants?

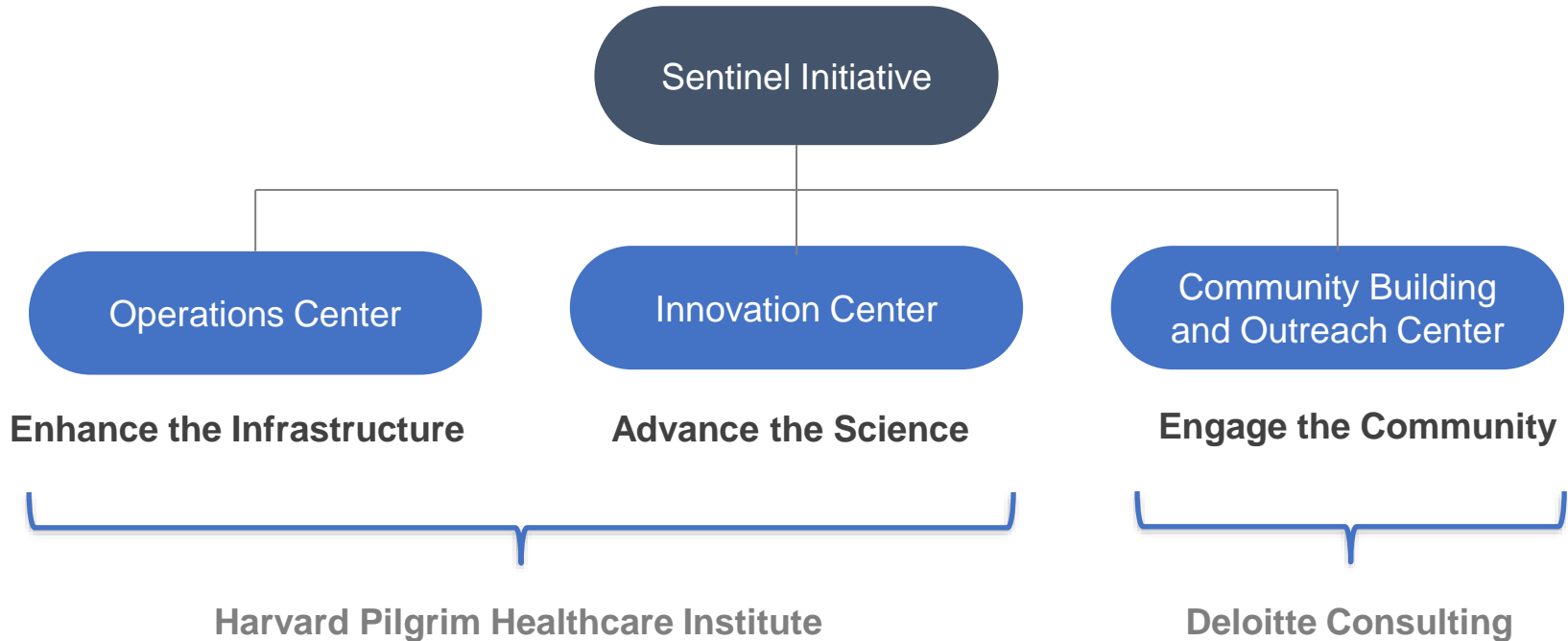
SENTINEL'S THREE CENTERS

Sentinel's Strategic Plan

- Maintain and enhance the Sentinel System's foundation, preserving FDA's long term investment in Sentinel's analysis tools and data infrastructure
- Diversify data sources, especially EHRs and claims linked to EHR
- Selectively incorporate advanced analytics
- Broaden touch points for participating in Sentinel's development
- Establish a Sentinel scientific community and disseminate knowledge to improve public health



New Sentinel Structure, 2019



Sentinel Operations Center (SOC)



- **Lead: Harvard Pilgrim Health Care Institute**
 - Includes >40 collaborating entities, data partners, scientific/methods expertise
- **Roles**
 - **ARIA system**
 - Maintain data partner network, Common Data Model, analysis tools
 - Conduct analyses to evaluate the safety and effectiveness of medical products
 - Post analytic packages, results, regulatory outcomes
 - **FDA Catalyst**
 - Lead studies involving interactions with providers and patients
 - Initiate RWE demonstration projects (e.g., pragmatic trials)
 - **Core infrastructure development**
 - Integrate new data sources into the query-ready distributed database
 - Create new analytic tools capable of operating in a distributed environment

Operations Center Collaborating Organizations



**Lead: Harvard Pilgrim
Health Care Institute**

DEPARTMENT OF POPULATION MEDICINE



HARVARD
MEDICAL SCHOOL



Harvard Pilgrim
Health Care Institute

Data & Scientific Partners



OPTUM[®]



TENNCARE



veradigm.



Penn
Medicine



Healthagen



aetna[™]



OPTUM Labs[®]



MASSACHUSETTS

BRIGHAM HEALTH



BRIGHAM AND
WOMEN'S HOSPITAL



KAISER PERMANENTE[®]

Colorado
Hawaii
Mid-Atlantic
Northern California
Northwest
Washington



RUTGERS



KAISER PERMANENTE[®]

Kaiser Permanente Washington
Health Research Institute



TriNetX⁷



HARVARD
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SCHOOL OF PUBLIC HEALTH

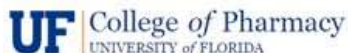


SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON



COLLEGE OF PUBLIC HEALTH

Booz | Allen | Hamilton



IBM Watson Health



HealthPartners[®] Institute



Duke Clinical Research Institute

Innovation Center (IC)



- **Lead: Harvard Pilgrim Health Care Institute**
 - Includes >50 collaborating entities
- **Innovation Cores:**
 1. **Novel Data Sources**
 2. **Randomized Trial and RWE Innovation**
 3. **Advanced Analytics**
 4. **Informatics**
- **Roles:**
 - Engage with academia and technology industry to develop innovative methods to further advance Sentinel, with a focus on early phases of methods development
 - Develop EHRs, signal detection, causal inference approaches, and advanced analytics
 - Host an Innovation Day public meeting

Innovation Center Collaborating Organizations: Leads



Innovation Center Lead



Novel Data Sources Core



Randomized Trial and Real-World Evidence Innovation



Advanced Analytics Core



Informatics Core



Innovation Center Collaborating Organizations: Data & Scientific Partners

FDA

HealthCore



Healthagen

aetna



OPTUM



KAISER PERMANENTE



HARVARD
T.H. CHAN

SCHOOL OF PUBLIC HEALTH

Humana



PRAcnet



MASSACHUSETTS
GENERAL HOSPITAL



OPTUM Labs



Penn
Medicine

PARTNERS
HEALTHCARE

Corrona
data to empower



veradigm

Colorado
Hawaii
Mid-Atlantic
Northern California
Northwest
Washington



amazon

HEALTH SCIENCES SOUTH CAROLINA

AETION



College of Pharmacy
UNIVERSITY of FLORIDA



PennState

RUTGERS



Stakeholders, Technology
and Research CRN

Epic

patientslikeme



Concerto
HealthAI



Pitt

School of Medicine

THE
UNIVERSITY
OF UTAH



Stanford
University



HealthPartners Institute



Berkeley
UNIVERSITY OF CALIFORNIA



ILLINOIS



AMIA



doc.ai

HCA
Healthcare

OAK RIDGE
National Laboratory

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES INITIATIVE

MUSC
Medical University
of South Carolina

COLUMBIA
UNIVERSITY



Putnam Data Sciences, LLC



evidation



Boston Children's Hospital



Microsoft

MDxHealth

UAB

THE UNIVERSITY OF TEXAS
COLLEGE OF PUBLIC HEALTH



Department of Population Health Sciences
Duke University School of Medicine



TriNetX

Microsoft

Research

Duke

Robert J. Margolis, MD
Center for Health Policy

Community Building and Outreach Center (CBOC)



- **Lead: Deloitte Consulting**
 - Co-lead: IQVIA
 - Collaborator: NOVA Research
- **Potential Roles**
 - Transform Sentinel into a vigorous scientific community
 - Modernize the Sentinel website and develop novel public portals to enhance usability, search, information management, and community engagement around Sentinel projects, tools, and results
 - Host scientific competitions to catalyze breakthrough ideas
 - Increase adoption and use of the Sentinel CDM and tools through external training, direct support, and stakeholder engagement

Knowledge check #2



Which of the following is NOT one of the three centers comprising Sentinel? Select one:

- A. Sentinel Operations Center (SOC)
- B. Innovation Center (IC)
- C. Center for Electronic Health Records (CEHR)
- D. Community Building and Outreach Center (CBOC)

Summary



- Sentinel is FDA's medical product active safety surveillance system
- 310.8 million cumulative patient identifiers, 2000-2018
- Uses a common data model and a distributed database
- Generates evidence to inform clinical decision-making
- Multiple ways to stay informed and active
 - Sentinel website
 - 5-year strategic plan

Resources



- Sentinel website: <https://www.sentinelinitiative.org/>
- Guidance for Industry: Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-studies-and-clinical-trials-implementation-section-505o3-federal-food-drug-and-0>
- Platt R, Brown JS, Robb M, McClellan M, Ball R, Nguyen MD, Sherman RE. The FDA Sentinel Initiative - An Evolving National Resource. N Engl J Med. 2018 Nov 29;379(22):2091-2093.
- Ball R, Robb M, Anderson SA, Dal Pan G. The FDA's sentinel initiative—A comprehensive approach to medical product surveillance. Clin Pharmacol Ther. 2016 Mar;99(3):265-8.

Resources

- Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System--a national resource for evidence development. N Engl J Med. 2011 Feb 10;364(6):498-9.
- Sentinel System Five-Year Strategy 2019-2023:
<https://www.fda.gov/media/120333/download>
- FDA in Brief: <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-announces-new-sentinel-system-contract-affirming-its-commitment-harnessing-real-world>

