Duke | Robert J. Margolis, MD Center *for* Health Policy

Ninth Annual Sentinel Initiative Public Workshop

Barbara Jordan Conference Center at the Kaiser Family Foundation
February 2, 2017

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

Welcome & Overview

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

Keynote Address

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

The Sentinel Initiative: Perspectives from FDA's Leadership

Join the conversation with **#sentinelinitiative**

Questions & Answers

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

Updates from the Sentinel Coordinating Center

Join the conversation with **#sentinelinitiative**

Sentinel in 2017

Richard Platt
for the Sentinel Investigators

February 2, 2017

Sentinel partner organizations

Lead – HPHC Institute

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

Data and scientific partners

HealthCore Anthem
VANDERBILT SCHOOL OF MEDICINE
health care systems research network
MASSACHUSETTS
HUMANA
HCA Hospital Corporation of America
OPTUM™
KAISER PERMANENTE
aetna℠

Scientific partners

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

Sentinel Common Data Model and Distributed Database

Enrollment
Person ID
Enrollment start & end dates
Drug coverage
Medical coverage
Medical record availability

Demographic
Person ID
Birth date
Sex
ZIP code
Etc.

Dispensing
Person ID
Dispensing date
National drug code (NDC)
Days supply
Amount dispensed

Encounter
Person ID
Service date(s)
Encounter ID
Encounter type & provider
Facility
Etc.

Diagnosis
Person ID
Service date(s)
Encounter ID
Encounter type & provider
Diagnosis code & type
Principal discharge diagnosis

Procedure
Person ID
Service date(s)
Encounter ID
Encounter type & provider
Procedure code & type
Etc.

Lab Result
Person ID
Result and specimen collection dates
Test type, immediacy & location
Logical Observation Identifiers Names and Codes (LOINC ®)
Test result & unit
Etc.

Vital Signs
Person ID
Measurement date and time
Height and weight
Diastolic & systolic BP
Tobacco use & type
Etc.

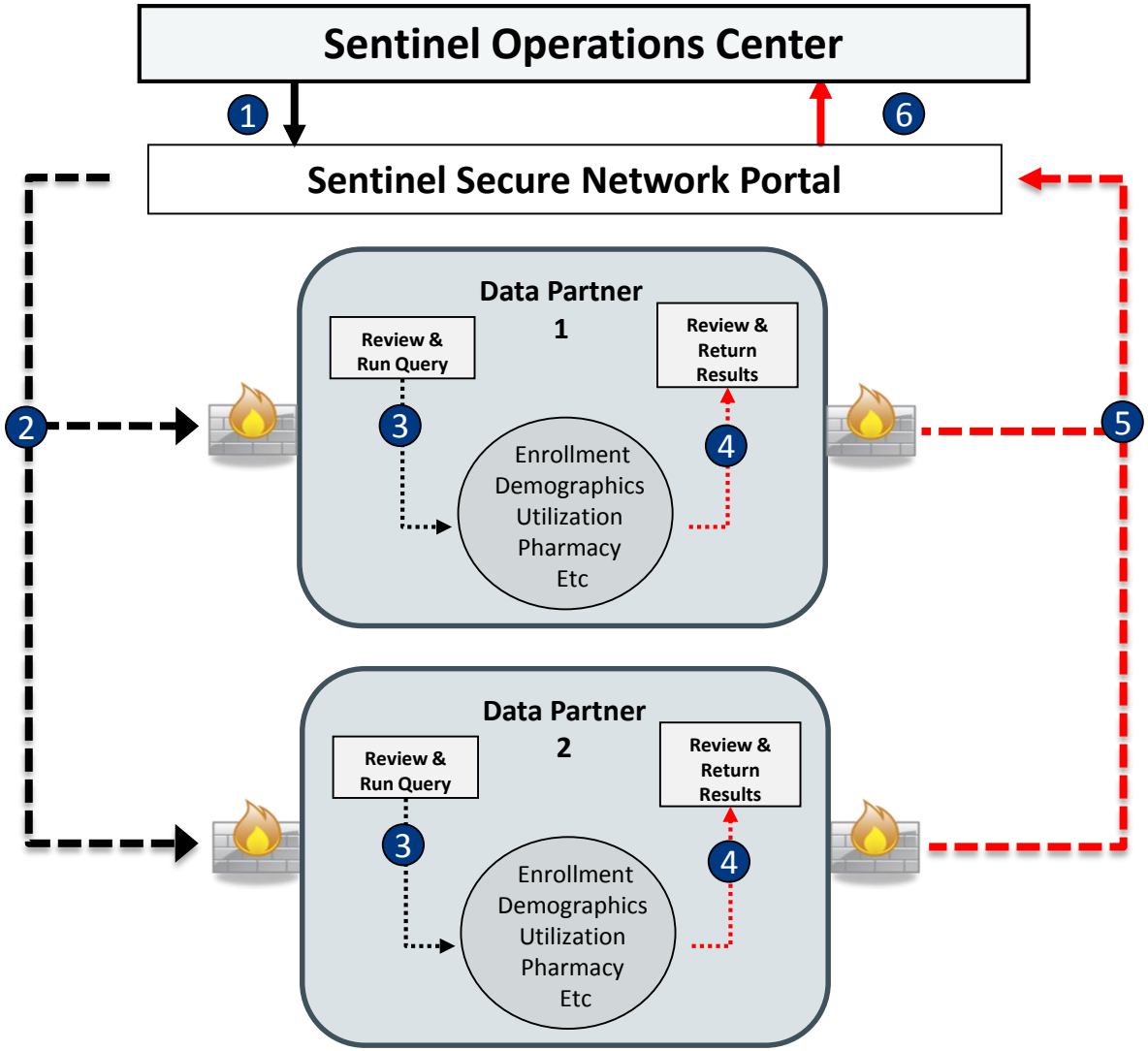
Inpatient Pharmacy
Person ID
Administration date and time
Encounter ID
National Drug Code (NDC)
Route
Dose
Etc.

Inpatient Transfusion
Person ID
Blood product code and type
Encounter ID
Blood type
Administration start and end dates and times
Etc.

Death
Person ID
Death date
Source
Confidence
Etc.

Cause of Death
Person ID
Cause of death
Source
Confidence
Etc.

Sentinel distributed analysis



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

Sentinel distributed database*

- Populations with well-defined person-time for which most medically-attended events are known
- 223 million unique member IDs
- 425 million person-years of observation time
- 43 million people currently accruing new data
- 5.9 billion dispensings
- 7.2 billion unique encounters
- 42 million people with ≥1 laboratory test result

* As of January 2017

Sentinel Initiative

Sentinel Infrastructure

Sentinel System

- ARIA
- PRISM (vaccines)
- BloodSCAN (blood products)

FDA-Catalyst

Sentinel in 2016

- Janet Woodcock, Director of Center for Drug Evaluation and Research (CDER) at 8th Annual Sentinel Initiative Public Workshop:
  - Sentinel is now an "*integral part of routine safety surveillance*“
- Two classes of activity
  - Production
    - New FDA requesters
    - Requests for new routine capabilities
  - Development

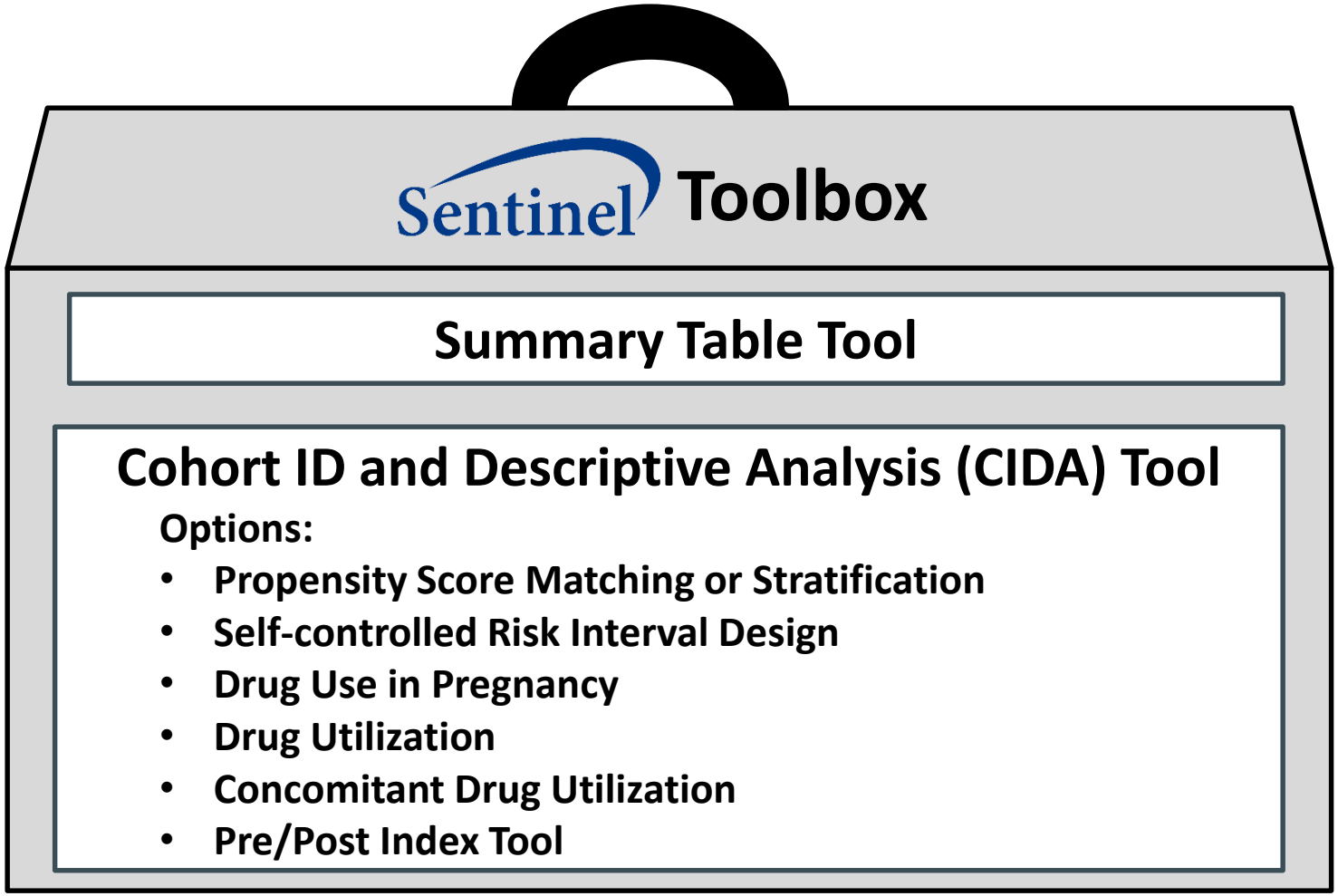
Protocol based analyses – Custom programs

- New programs to answer questions not addressable with existing tools
- Requires extensive planning, implementation, and testing

Production

- Routine Analytic Framework
  reusable programs that support ARIA:
  Active Risk Identification and Analysis

Sentinel's Tools



Rapid querying via reusable programs

Three ways to address questions

Routine Analytic Framework (RAF)

- Off-the-shelf query "templates"
- Standard inputs, standard output
- Quick execution

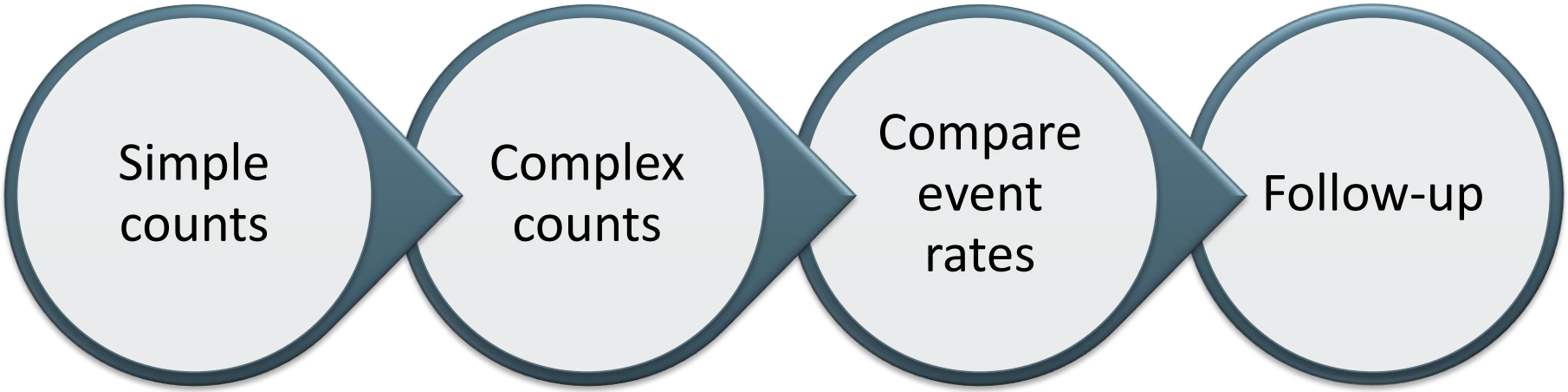
RADaR: Rapid Analytic Development and Response: RAF + custom code

- Hybrid approach: custom code leveraging RAF
- Standard inputs, custom output

Custom Programs

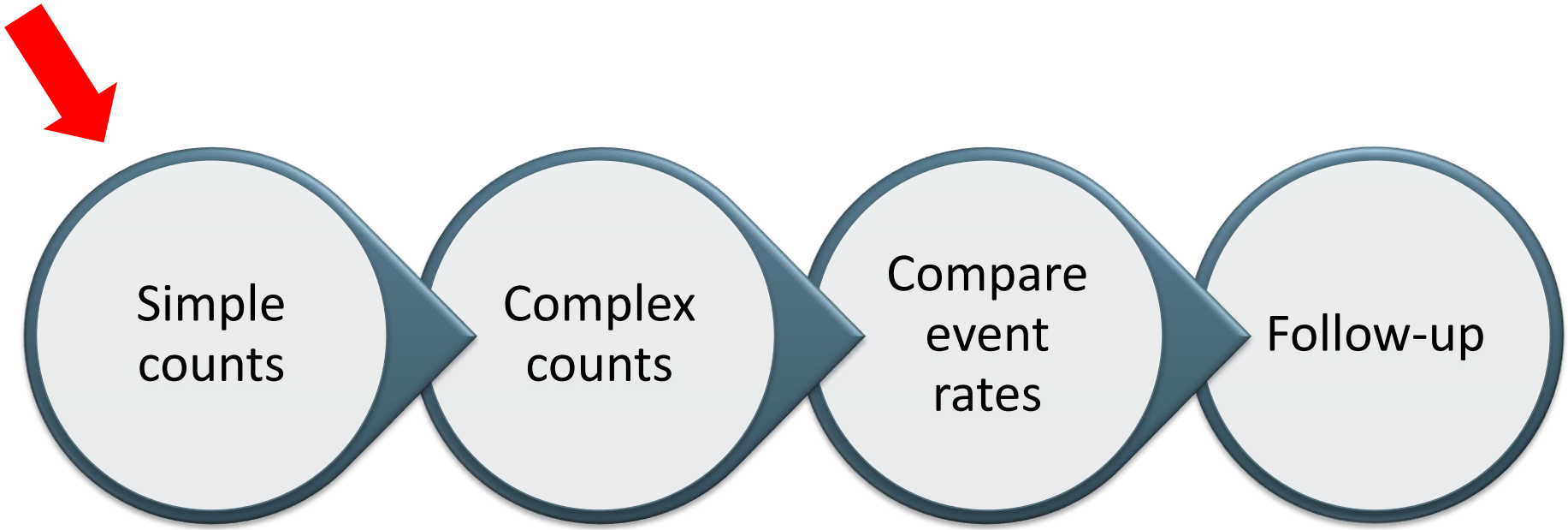
- Analysis as specified
- Custom inputs, custom output
- Longer execution

Querying Sequence



Determine use and frequency	Identify/ describe population	Comparative assessment	New queries; Line Lists; Chart Review

Querying Sequence



Determine use and frequency

Identify/ describe population

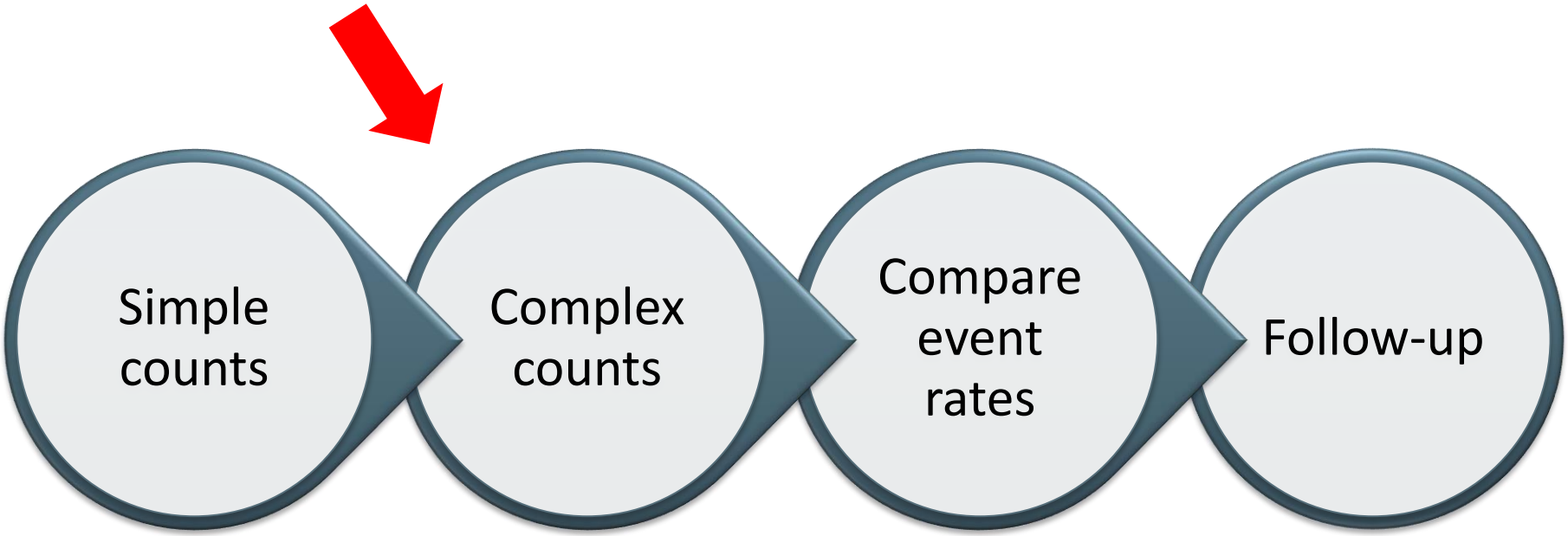
Comparative assessment

New queries; Line Lists; Chart Review

Simple counts (summary table queries)

- Counts of individuals with exposure or condition
- 49 queries / 291 scenarios in 2016

Querying Sequence



Determine use and frequency

Identify/ describe population

Comparative assessment

New queries; Line Lists; Chart Review

Complex count queries (Level 1 / 1+)

- Counts and rates of events within user specified times, among populations identified using complex "and/or/not" relationships.
  - Example: Rates of first diagnosis of heart failure or cardiomyopathy among new users of different drugs used to treat ADHD, by age and duration of exposure
- 53 queries, 800+ scenarios in 2016

You can observe a lot by just watching

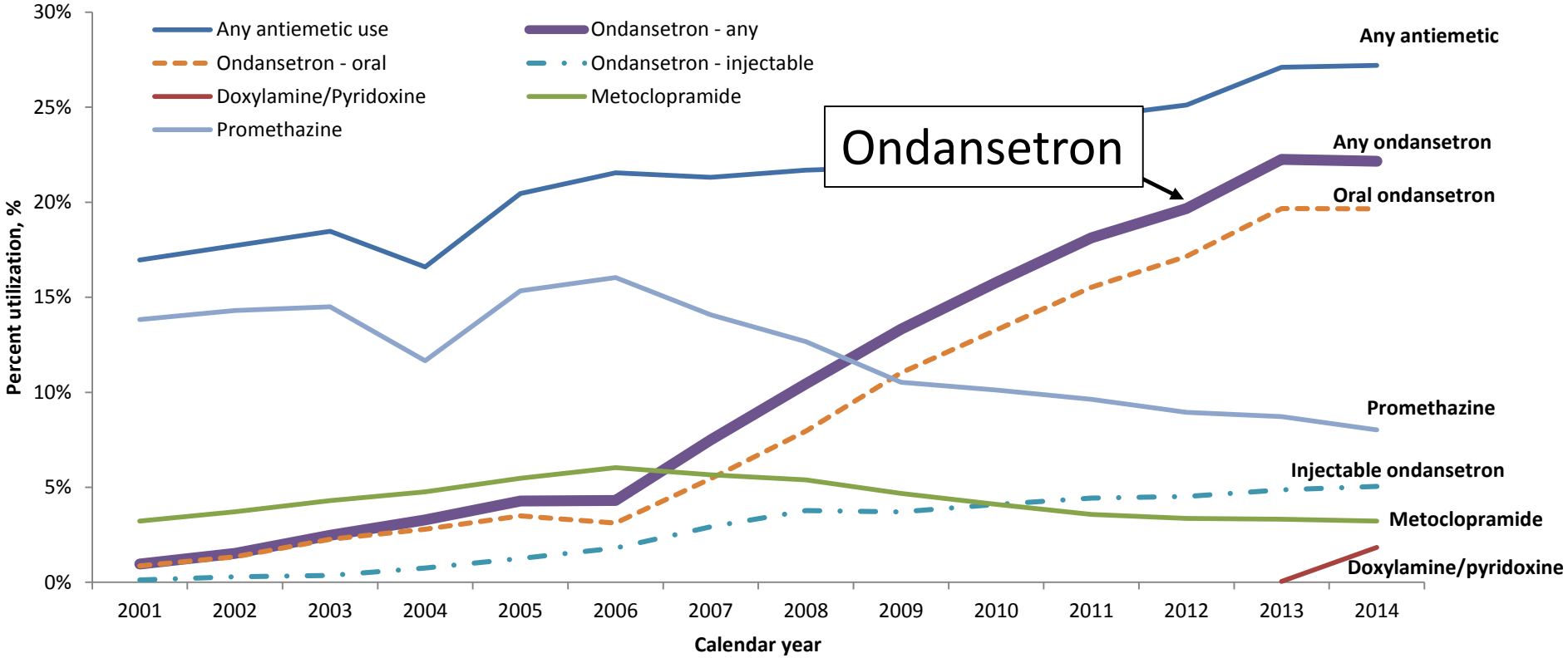
Yogi Berra

www.brainyquote.com/quotes/quotes/y/yogiberra125285.html

Background

- Ondansetron is … approved for prevention of nausea and vomiting (NV) with chemotherapy, radiotherapy, and post-operatively
  - Not approved for NV in pregnancy (NVP) but prescribed off-label
  - Only doxylamine/pyridoxine(Diclegis™, approved 2013) approved for NVP
- Several recent studies suggest an increase in congenital malformations with ondansetron use in early pregnancy; however evidence is inconclusive
- Needed to better understand antiemetic use in a cohort of pregnant women

Use of antiemetic drugs among live birth pregnancies in the Sentinel Distributed Database, 2001-2014[a,b]



[a] Dashed lines for oral and injection ondansetron form represent a portion of all total ondansetron use as shown by the solid purple line. Summation of oral and injection utilization sums to greater than total ondansetron use since some women received both products.

[b] Not all Mini-Sentinel data partners contributed data for the entire study period

Lockwood G. Taylor, PhD, MPH, ICPE Aug 26, 2016

Conclusion

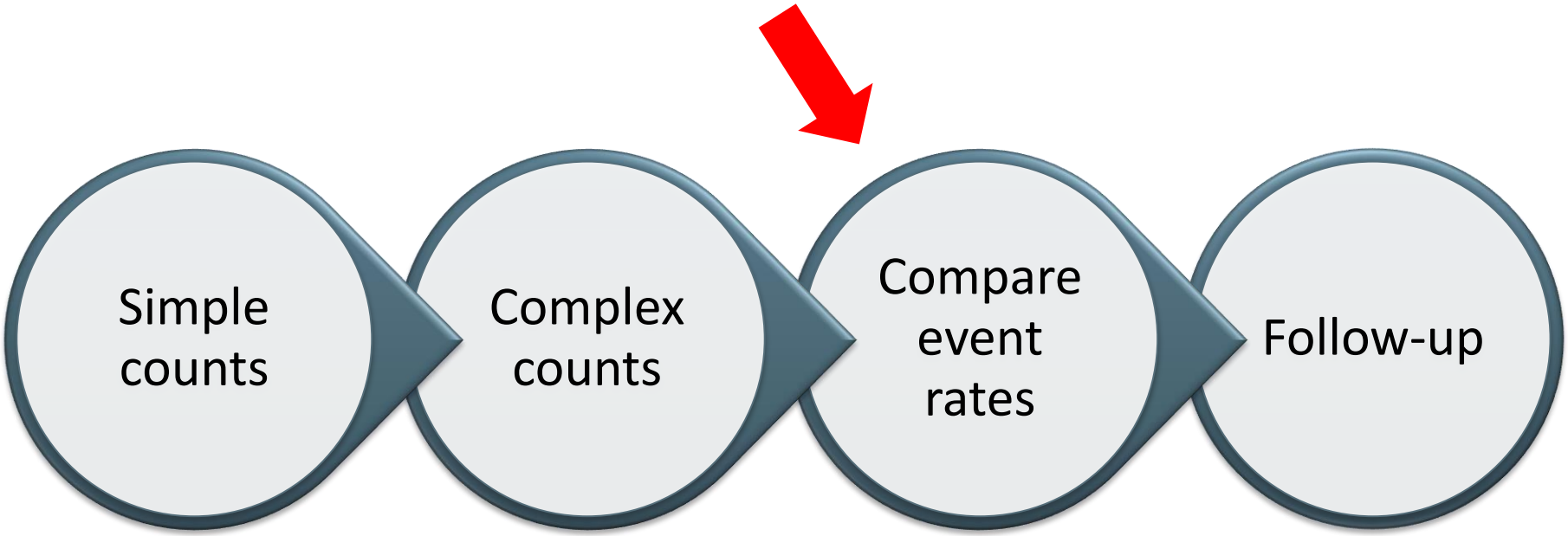
- Given the widespread use of ondansetron in pregnancy, a great need exists for data establishing its efficacy as well as methodologically rigorous post-marketing assessments to evaluate its safety in pregnant women.

Blood transfusion during pregnancy

- Need for rapid assessment of frequency of transfusion during pregnancy
- Sentinel Distributed Dataset identified 1,946,032 deliveries with coverage during entire pregnancy from 2008-2015 (~8% of U.S. deliveries)
- 21,048 (1.1%) pregnancies had blood transfusion
- Report with integrated data from 15 data partners returned to FDA within 3 working days of final specification

www.sentinelinitiative.org/vaccines-blood-biologics/assessments/blood-transfusions

Querying Sequence



Determine use and frequency → Identify/ describe population → Comparative assessment → New queries; Line Lists; Chart Review

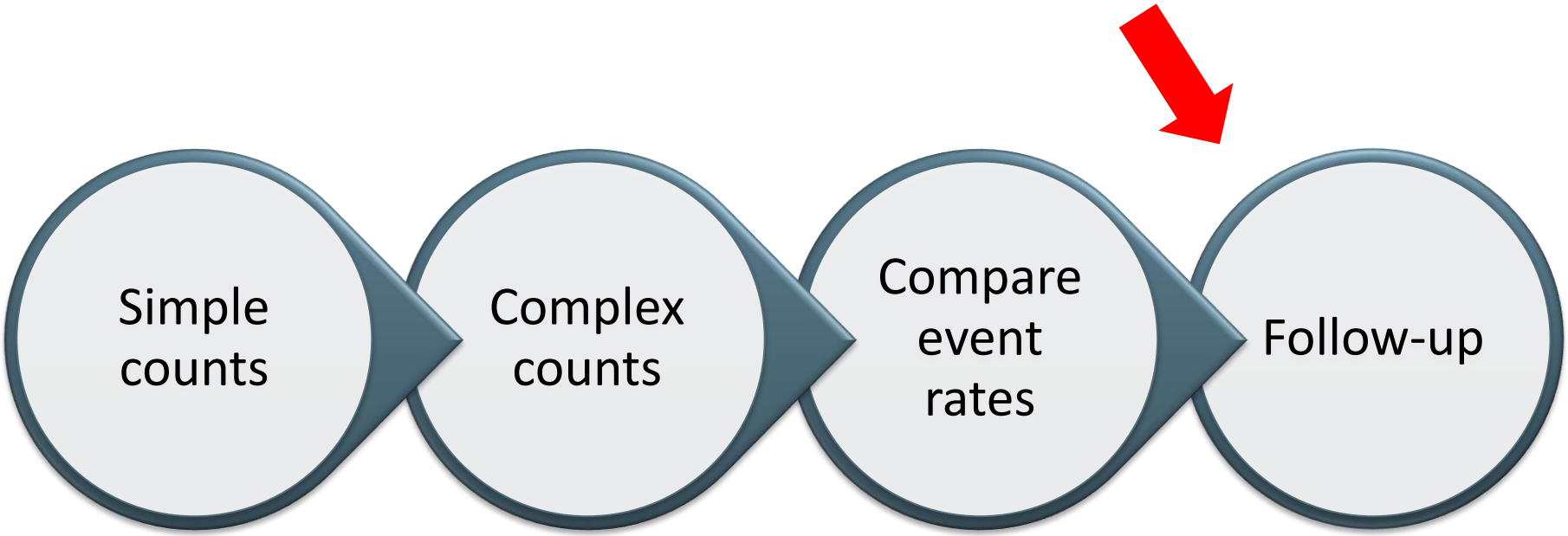
Comparison of rates (Level 2 / 2+)

- Adjusted relative rates or hazard ratios comparing outcomes among two cohorts identified by complex count program

  or

- Adjusted self-controlled risk interval analysis
  - Example: Risk of seizures associated with new use of ranolazine
- 11 queries / 100+ scenarios in 2016

Querying Sequence



Determine use and frequency → Identify/ describe population → Comparative assessment → New queries; Line Lists; Chart Review

Patient Episode Profile Retrieval (PEPR)

Day 0, office visit
Routine health check
Immunization

Day 4, office visit
Gastroenteritis

Day 7, hospitalized
Vomiting / cough
Dehydration
Gastroenteritis

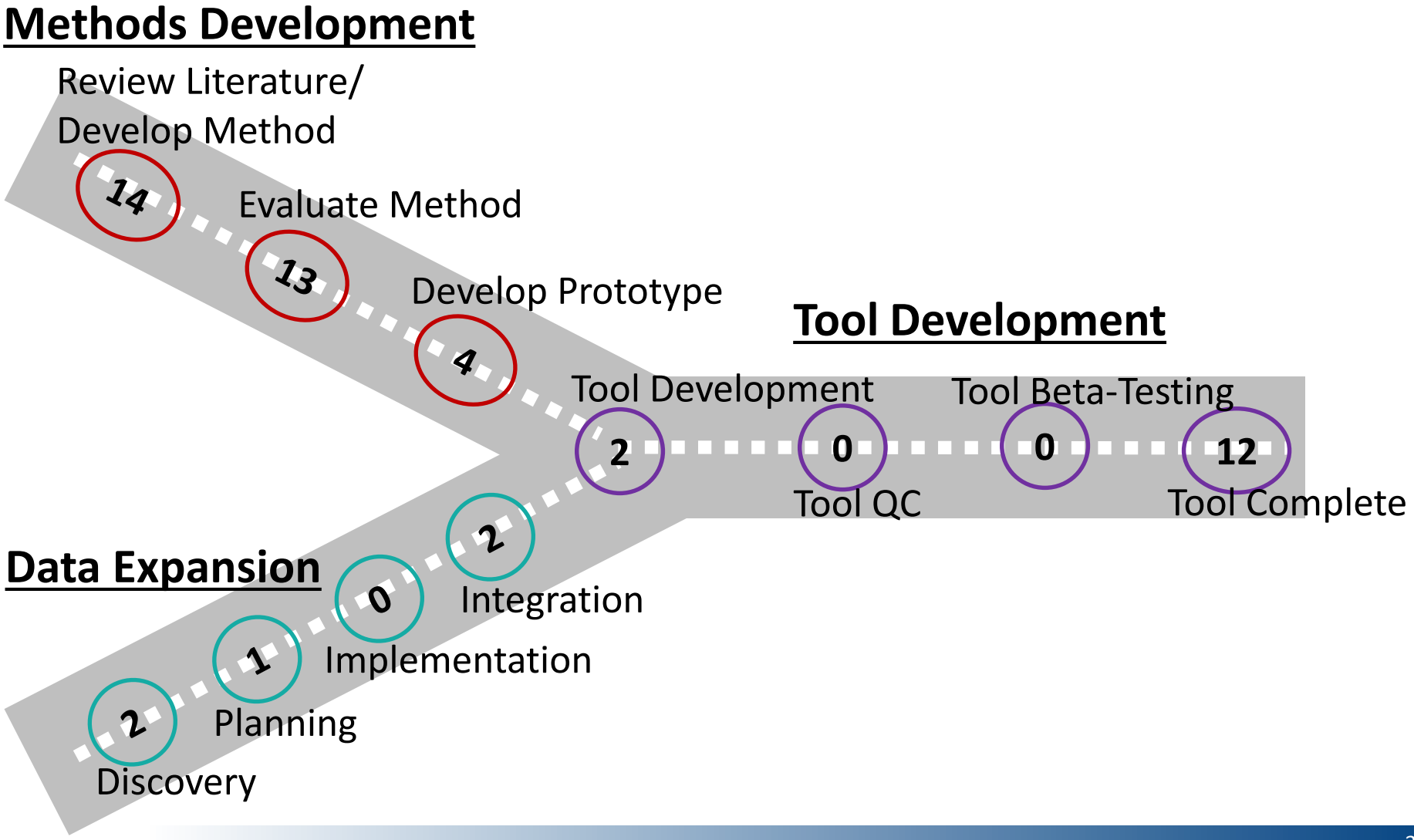
Episode Detail						^ Incidence: F = first observed; I = incident; blank = prevalent # Primary Dx: P = primary; S = secondary; X = N/A ~ Med enroll segment containing the admission date of the encounter or the drug enroll segment containing the dispensing date									
Days from expos	Enc type	LOS	Clinical code			Code description	Incidence^	P Dx#	Node (Y/N)	Main expos (Y/N)	Any vacc (Y/N)	Rx days supp	Rx amt	Cov start~	Cov end~
			Cat	Type	Code										
0	AV		DX	09	V0382	Need Proph Vacc Agnst Strep Pne					1			-386	1260
0	AV		DX	09	V068	Need Proph Vacc Against Oth Comb Dz	F				1			-386	1260
0	AV		DX	09	V202	Routine Infant/Child Health Check								-386	1260
0	AV		PX	C4	90471	Immunization Admin	F				1			-386	1260
0	AV		PX	C4	90472	Immunization Admin Each Add	F				1			-386	1260
0	AV		PX	C4	90669	PCV7 Vaccine Im					1			-386	1260
0	AV		PX	C4	90710	MMRV Vaccine Sc	F			1	1			-386	1260
0	AV		PX	C4	99392	Prev Visit Est Age 1-4	F							-386	1260
4	AV		DX	09	0090	Inf Colitis Enterit & Gastroenterit	F							-386	1260
4	AV		PX	C4	99213	Office/Outpatient Visit Est	F							-386	1260
7	IP	1	DX	09	27651	Dehydration	I	P						-386	1260
7	IP	1	DX	09	53550	Uns Gastrit & Gastroduodit No Hemorr	I	X						-386	1260
7	IP	1	DX	09	7862	Cough	I	X						-386	1260
7	IP	1	DX	09	78703	Vomiting Alone	I	S	1					-386	1260
7	IP	1	PX	C4	71020	Chest X-Ray 2Vw Frontal & Latl	F							-386	1260
7	IP	1	PX	C4	74000	X-Ray Exam Of Abdomen	F							-386	1260

www.sentinelinitiative.org/sites/default/files/Methods/Mini-Sentinel_PRISM_Data-Mining-Infrastructure_Report_0.pdf

New Types of Queries for Other Uses

- Medications errors
  - Name confusion medication errors
  - Dosing errors
- Geographic location stratification

Development Projects in 2016



Data expansion projects

Project name	Description	Status and timeline
Centers for Medicare and Medicaid Services (CMS) fee for service beneficiary on-boarding	• Initial extract, 2010-2015, covers ~35 million with prescription drug coverage	2nd quarter 2017 for quality-checked, queryable data
Inpatient data expansion	• Three sites exploring populating inpatient pharmacy + inpatient transfusion tables	Go / no-go decision expected 2nd quarter 2017.
Rapid surveillance / refresh-on-demand	• Plan and build a 'refresh on-demand' system using freshest-feasible data extracts	Go / no-go decision expected 1st quarter 2017
Diagnosis date and procedure date/time expansion	• Inpatient records will add actual diagnosis date and procedure date and time	Approx. 12 months

Methods development active in 2016 (selected)

ICD10 preparedness
Disease risk score exploratory methods
Optimal propensity score matching strategies for subgroup analyses
Analyzing Laboratory data for routine surveillance
Evaluating performance of analytic modules using simulation (Big Sim)
Quantitative Bias Analysis (QBA)
TreeScan Bias / Power Calculation / Evaluation / Propensity scores
Outcome-based TreeScan (aka DrugScan)

Sentinel

Type here to search...

Sentinel | Drugs | Vaccines, Blood & Biologics | Communications | FDA-Catalyst | Report Finder

Sentinel is a National Medical Product Monitoring System

LEARN MORE

ABOUT

- Background
- Coordinating Center
- Privacy and Security

SAFETY ASSESSMENTS

- Active Risk Identification and Analysis System
- Assessments of Drugs
- Assessments of Vaccines, Blood, & Biologics

DATA & SURVEILLANCE TOOLS

- Distributed Database and Common Data Model
- Complementary Data Sources
- Routine Querying Tools
- Validations and Literature Reviews

COMMUNICATIONS

- FDA Safety Communications
- Publications and Presentations
- Sentinel Initiative Events
- Report Finder

Latest Postings

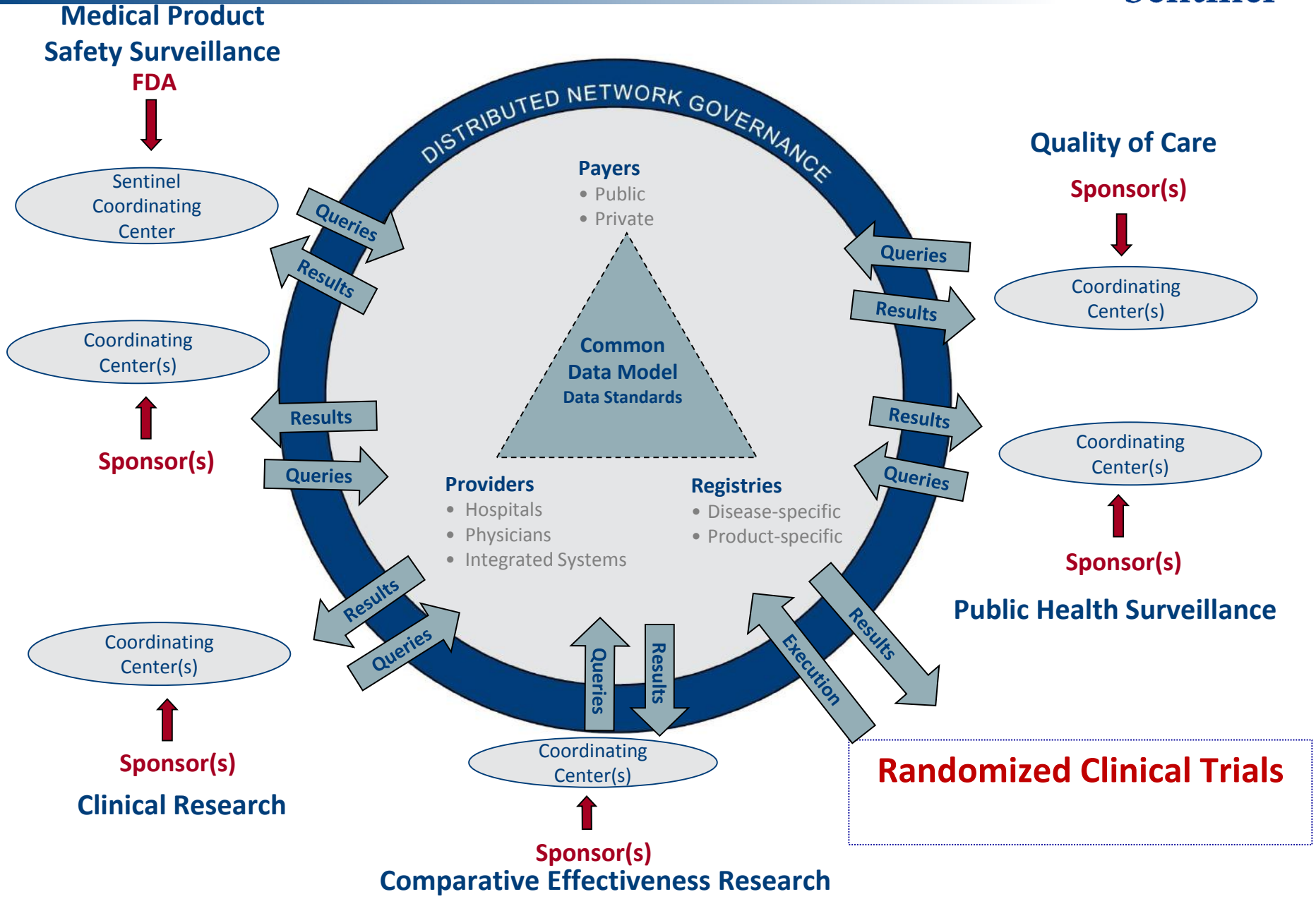
SPOTLIGHT

- Public Workshop: The Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System
  Tue, 11/15/2016
- Sentinel Initiative Public Workshop - Ninth Annual
  Tue, 11/08/2016

STUDY PROTOCOLS & SURVEILLANCE PLANS

- Influenza Vaccines and Birth Outcomes Protocol (PRISM)
  Fri, 01/20/2017
- Identify and Evaluate Manufacturer-Level Drug Utilization and Switching Patterns in Sentinel
  Mon, 12/12/2016

MODULAR PROGRAMS


Medical Product Safety Surveillance
FDA
Sentinel Coordinating Center
Coordinating Center(s)
Sponsor(s)
Clinical Research
Coordinating Center(s)
Sponsor(s)
Comparative Effectiveness Research
Coordinating Center(s)
Sponsor(s)
Public Health Surveillance
Quality of Care
Sponsor(s)
Coordinating Center(s)
Randomized Clinical Trials
DISTRIBUTED NETWORK GOVERNANCE
Payers
• Public
• Private
Common Data Model
Data Standards
Providers
• Hospitals
• Physicians
• Integrated Systems
Registries
• Disease-specific
• Product-specific
Queries
Results
Queries
Results
Queries
Results
Queries
Results
Queries
Results
Queries
Results
Execution
Queries
Results

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Science & Research

Home > Science & Research > Science and Research Special Topics > National Medical Evidence Generation Collaborative (EvGen Collaborative)

National Medical Evidence Generation Collaborative (EvGen Collaborative)

Resources for You

- Office of Medical Products and Tobacco

National Medical Evidence Generation Collaborative (EvGen Collaborative)

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

www.fda.gov/ScienceResearch/SpecialTopics/EvGenSystem

Medical Product Safety Surveillance

FDA

Sentinel Coordinating Center

Innovation in Medical Evidence Development and Surveillance

Biologics & Biosimilars Collective Intelligence Consortium

Queries

Results

Results

Queries

Results

Queries

Results

Queries

Results

Execution

DISTRIBUTED NETWORK GOVERNANCE

Payers
- Public
- Private

Common Data Model
Data Standards

Providers
- Hospitals
- Physicians
- Integrated Systems

Registries
- Disease-specific
- Product-specific

Quality of Care

Sponsor(s)

Coordinating Center(s)

CDC

Public Health Surveillance

NIH Collaboratory Rethinking Clinical Trials®
Health Care Systems Research Collaboratory
NIH Collaboratory About Us Demonstration Projects Cores News Collaboration Distributed Research Network
NIH Collaboratory › NIH Collaboratory Distributed Research Network
NIH Collaboratory Distributed Research Network

NIH

Clinical Research

pcornet The National Patient-Centered Clinical Research Network

Comparative Effectiveness Research

IMPACT-AFib

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Reagan-Udall Foundation
FOR THE FOOD AND DRUG ADMINISTRATION

Innovation in Medical Evidence Development and Surveillance

- The Reagan-Udall Foundation for the FDA is a not-for-profit organization established by the United States Congress to advance regulatory science

- The Innovation in Medical Evidence Development and Surveillance (IMEDS) program provides an entry point for private and public sector stakeholders that would like to use Sentinel data, tools, and methods

Introducing IMEDS, a Public-Private Resource for Evidence Generation

Posted on **January 17, 2017** by **FDA Voice**

By: Robert M. Califf, M.D.

FDA has been working to establish a national resource for FDA-approved medical products that can be used by public and private-sector entities, including regulated industry, to conduct large scale evaluations of safety issues in an environment that is secure and protects patient privacy. These evaluations include epidemiologic studies of medical products in collaboration with multiple healthcare data partners and the analytic center utilized by FDA through the agency's Sentinel System. This new resource is called the Innovation in Medical Evidence Development and Surveillance System, or IMEDS.

One of the unique aspects and advantages of IMEDS is that it was launched on January 1, 2017 as a public-private partnership by the *Reagan-Udall Foundation for the Food and Drug Administration*, a not-for-profit organization created by Congress in 2007 to advance regulatory science. The IMEDS framework specifically provides governance that allows private-sector entities to gain access to the system with appropriate oversight. As a result, the FDA Sentinel System's distributed data as well as scientific methods and tools will now be available for

Insights from Phase II of the IMEDS Evaluation Pilot – Lessons Learned and Future Needs

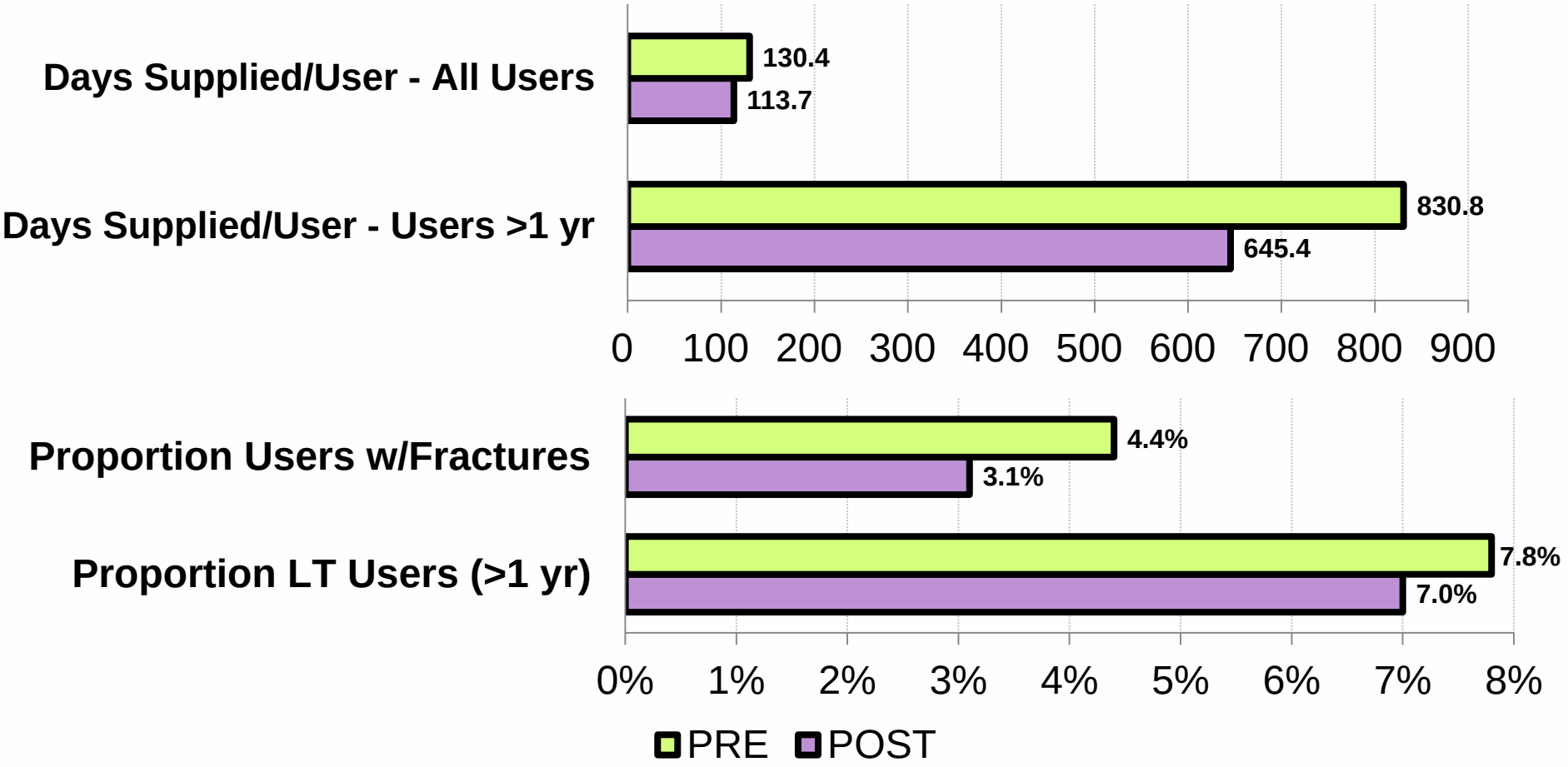
PPIs Usage Patterns before/after 2010 Label Change

Rachel Sobel

January 4, 2017

Pfizer
WORLDWIDE SAFETY & REGULATORY
Worldwide Research & Development

Results – PPI Use Patterns and Incident Fractures



Results similar for prevalent users (data not shown)

NIH Collaboratory *Rethinking Clinical Trials®*

Health Care Systems Research Collaboratory

NIH Collaboratory | About Us | Demonstration Projects | Cores | News | Collaboration

NIH Collaboratory ▸ NIH Collaboratory Distributed Research Network

NIH Collaboratory Distributed Research Network

Millions of people. Strong collaborations. Privacy first.

The NIH Collaboratory Distributed Research Network enables investigators to collaborate with each other in the use of electronic health dat multisite research programs.

The Network's querying capabilities reduce the need to share confidential or proprietary data by enabling authorized researchers to send qu partners). In some cases, queries can take the form of computer programs that a data partner can execute on a preexisting dataset. The d aggregated (count) data, rather than the data itself. This form of remote querying reduces legal, regulatory, privacy, proprietary, and techr research.

The network seeks to build strong and trusted collaborations to support the research that will lead to improved health for millions of people

What does the NIH Collaboratory Distributed Research Network do?

- Provides infrastructure and mechanisms to facilitate multicenter studies using electronic clinical, administrative, and research data
- Allows searchable discovery of available data resources, health systems, researchers, and re-usable analytic tools
- Enables authorized investigators to identify clinical, administrative, and research datasets of interest
- Facilitates multisite distributed querying of data resources, while allowing the data to remain in the control of the data owners
- Serves as a repository of tools to leverage EHRs to support clinical research across multiple health systems

www.nihcollaboratory.org/Pages/distributed-research-network.aspx

NIH Collaboratory Is Soliciting Users

NIH Collaboratory *Rethinking Clinical Trials®*
Health Care Systems Research Collaboratory

NIH Collaboratory | About Us | Demonstration Projects | Cores | News | Collaboration Spaces | The Living Textbook | Distributed Research Network

News ▸ NIH Collaboratory Invites Requests to Query the Distributed Research Network

NIH Collaboratory Invites Requests to Query the Distributed Research Network

Do you have a question about the rates of medical conditions or the frequency of use of medical and surgical treatments? ' data that can answer these questions. The Collaboratory invites prep-to-research questions.

Download the guidance document (Word) for full details on the application process.

pcornet | The National Patient-Centered Clinical Research Network

www.pcornet.org

PCORnet: The National Patient-Centered Clinical Research Network

The Patient-Centered Outcomes Research Institute (PCORI) is supporting the development of PCORnet, the National Patient-Centered Clinical Research Network, to create a large, highly representative, national network for conducting clinical outcomes research.

PCORnet will transform clinical research by engaging patients, care providers, and health systems in collaborative partnerships to improve healthcare and advance medical knowledge. By bringing research and patient care together, this innovative health data network will be able to explore the questions that matter most to patients and their families. Read more ….

Resource Center

Contact Us

Office Hours

Questions?

(844) 275-6276 / 844-ASK-NCRN
Local: (919) 668-2286

Member Log-in [Central Desktop]

Resources

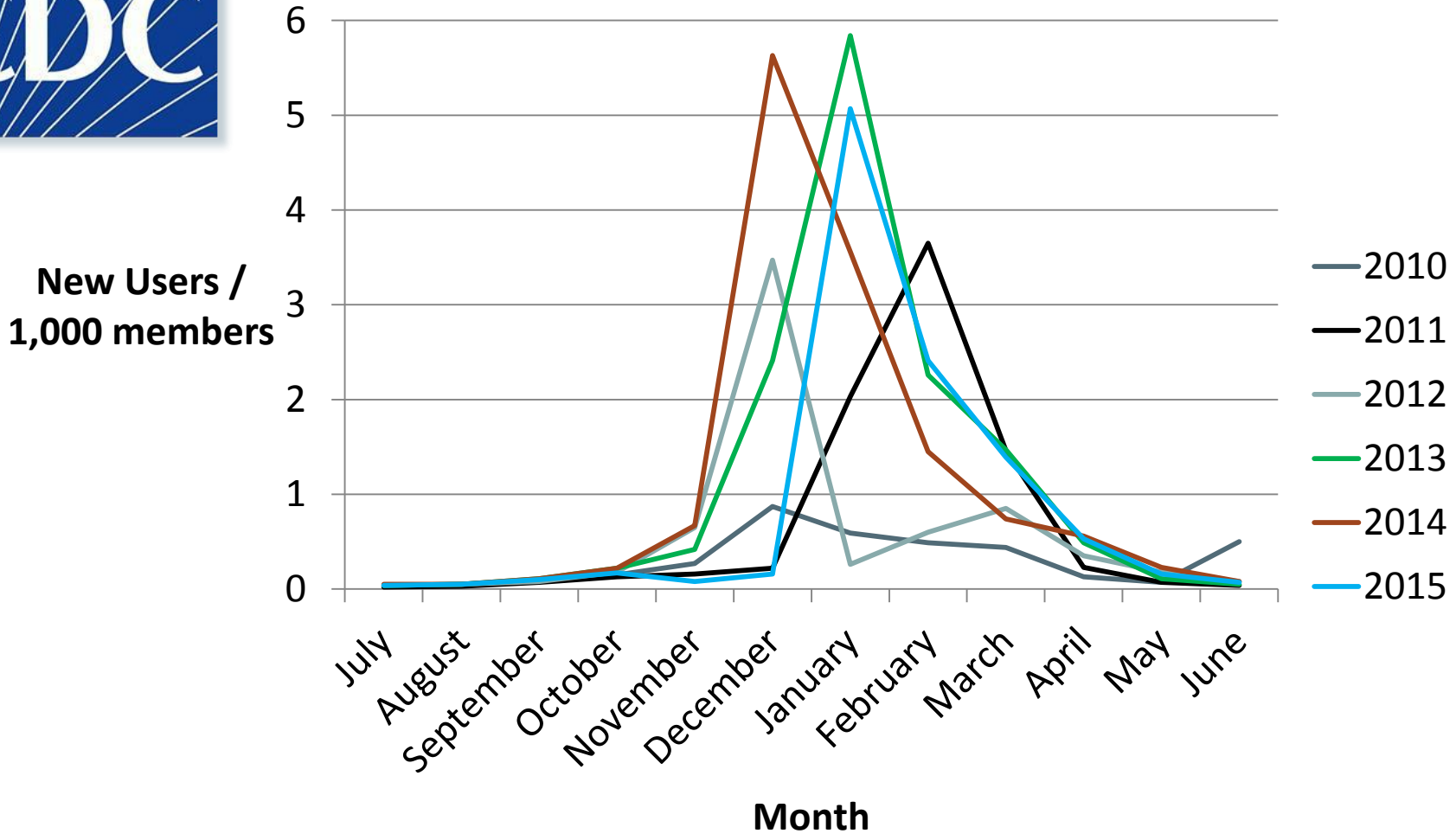
FAQs

FDA Mini-Sentinel Assessments

PCORnet-Sentinel Collaborations (Genesis) with CDC

- Surveillance methods for congenital Zika syndrome
- Inpatient antibiotic utilization

Oseltamivir dispensing: Influenza proxy



www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Sentinel_Modular-Program-Report_cder_mpl1r_wp030_nsdp_v01.1.pdf, p. 30-31

Sentinel Initiative

Sentinel Infrastructure

Sentinel System

- ARIA
- PRISM (vaccines)
- BloodSCAN (blood products)

FDA-Catalyst

FDA-Catalyst: IMPACT-AFib Randomized Trial

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

- Randomized controlled trial of direct mail to health plan members with AFib and to their providers to encourage consideration of oral anticoagulation
- Proof of concept multicenter randomized trial using Sentinel Initiative infrastructure

IMPACT-AFib Workgroup

aetna℠

Duke Clinical Research Institute

Harvard Pilgrim Health Care

Patient representative

HealthCore® Anthem®

FDA U.S. FOOD & DRUG ADMINISTRATION

HUMANA®

OPTUM™

CLINICAL TRIALS TRANSFORMATION INITIATIVE

IMPACT-AFib

[HEALTH PLAN LOGO]

IMPACT AFib address
IMPACT AFib address

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

Dear [Member Name],

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.

According to our records, you may have been diagnosed w ion. We know your health can be a challenge, and hope this information about w to lowe risk for stro will help.

People who have the heart at irregula y kno n as "atrial fibrillation" are at an inc ased risk o aving e.

*Please visit **www.IMPACT-AFib.org**, to learn more a t atrial fibril n, strok k, and a agular medications. More information about t IMPACT- initiative i ailable by calling [XXX-XXX-XXXX] or ema duke/healthpl 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]

Facts about atrial fibrillation, anticoagulant medication, and stroke

- Atrial fibrillation is an abnormal heartbeat in the top chambers of the heart that causes the ch nt This allows blood clots to form in the non-beating ch ers.
- At ibrillation increases the ri f a stroke because a blood clot may form in the heart, th avel to the brain causing roke.
- An so known as b d thinners, are a type of medication that reduces the bo ability to form blood clo d decreases the chance of a clot forming in the top ch ers of the heart.
- As is NOT effective in decr g the risk of stroke.

M people with atrial fibrillatio hould take an anticoagulant medication to reduce their risk of a stroke.

This packet and the packet sent to your doctor are funded by the IMPACT-AFib Initiative. This U.S. Food and Drug Administration-sponsored research study is being conducted by [Health Plan], in collaboration with researchers at Harvard Pilgrim Health Care Institute and the Duke Clinical Research Institute. The goal of this initiative is to improve the use of oral anticoagulant medications for stroke prevention in patients with atrial fibrillation.

Disclaimer: Lorem ipsum dolor sit amet, est donec semper pharetra orci, mus ac nec ultricies id, dictum condimentum massa non dapibus. In viteae vestibulum purus facilisis, amet ornare nec quis nec.

IMPACT-AFib

Patient Information

You may have atrial fibrillation and may be at risk of a stroke.

Taking an anticoagulant medication may prevent a stroke.

Atrial fibrillation (AFib) is a heartbeat irregularity. If you hav Fib your blood can pool, which increases the risk of a blood clo rming in your heart. The blood clot can travel to your brain, causin stroke.

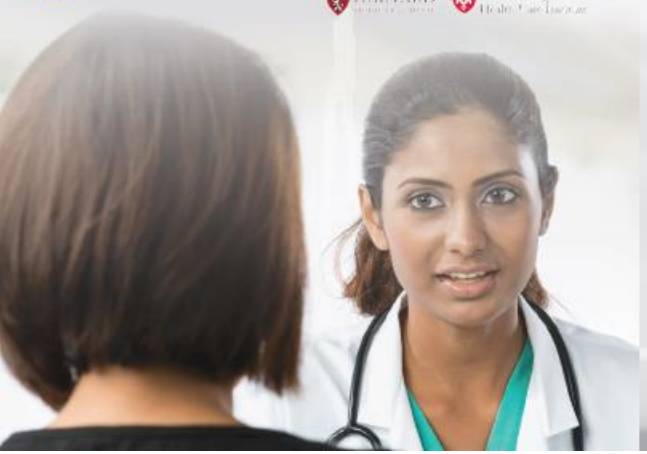
Anticoagulant medications, also called blood thinners, can vent most strokes in patients with AFib. If you are not taking an ant gulant medication, you may suffer a stroke that could have been pr nted.

Please review this information and talk with your doct to find out if you should be on an anticoagulant medication to prevent a stroke.

Duke Clinical Research Institute

DEPARTMENT OF POPULATION MEDICINE

HARVARD



How do I know if I'm at a high risk for stroke?
If you have AFib, you are at a higher risk of stroke. You are at additional risk if you:

- Have high blood pressure
- Have high blood sugar
- Have weak heart function
- a stroke or m troke
- ave had eart atta or blocked ssel in ur leg
- re ov 4 years
- re a wo n

I have AFib only sometimes. Am I still at risk for a stroke?

Yes, the risk is similar whether your AFib is all the time, often, or only occasionally.

What is an anticoagulant?
Anticoagulants are medications that:

- Prevent blood clots
- Keep existing clots from moving

Examples include: Coumadin, Eliquis, Pradaxa, Savaysa, warfarin, and Xarelto.*

**The information in this mailing is NOT sponsored by any drug company.*

For more information, please visit impact-afib.org

If my doctor prescribes an anticoagulant, how should I take it?

- Take your medication exactly as directed by your doctor
- Take it at the same time each day
- If you forget to take your medication one day, take a dose as soon as possible on the same day
- Do not take a double dose the following day to "catch up"

Tell ur doctor if you are pregnant or plan to become preg nt, are breastfeeding or plan to breastfeed, if you ve liver or kidney problems, or are planning to have urgery.

Will anticoagulant medications prevent strokes?

- Anticoagulant medications reduce the risk of stroke by 70% in patients with atrial fibrillation.

What about aspirin?

- Aspirin is **not** an effective medication for decreasing the risk of stroke caused by atrial fibrillation.

Intervention Materials for Providers

- Provider letter – sent from health plan Chief Medical Officer, describes call to action
- Provider enclosure – myths and facts on use of OACs
- Response mailer – way for providers to share feedback

Font Size

Mini-Sentinel

Search

Home | Assessments | Methods | Data | Communications | All Reports

Home

About Mini-Sentinel

- Background
- Distributed Database
- Collaborators
- Coordinating Center
- Principles & Policies
- Privacy
- Standard Operating Procedures

Contact Mini-Sentinel

info@mini-sentinel.org

Welcome to Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products. Mini-Sentinel uses pre-existing electronic healthcare data from multiple sources. Collaborating Institutions provide access to data as well as scientific and organizational expertise. Mini-Sentinel is part of the FDA's Sentinel Initiative, which is exploring a variety of approaches for improving the Agency's ability to quickly identify and assess safety issues.

Most Mini-Sentinel activities focus on assessments, methods, or data. Visit the following links to learn more about each type of activity:

- Assessments - Medical product exposures, health outcomes, and links between them
- Methods - Techniques for identifying, validating, and linking medical product exposures and health outcomes
- Data - Mini-Sentinel Distributed Dataset and tools used to access the data

The information contained on this website is provided as part of FDA's commitment to place knowledge acquired from the Mini-Sentinel Pilot in the public domain as soon as possible. **FDA will continue to communicate information about the safe use of medical products using existing channels, such as FDA's press announcements, MedWatch Alerts, Drug Safety Communications, and Safety**

Spotlight

- Sentinel Program Interim Report
- FDA Sentinel Contract Awarded to Harvard Pilgrim Health Care Institute

Latest Postings

Common Data Model

- Common Data Model v5.0.1

Data Quality Review Programs

- Data Quality Review and Characterization Programs v3.3.2

Ongoing Projects

- Validating Type 1 and Type 2 Diabetes Mellitus in the Mini-Sentinel Distributed Database using the Surveillance PREvention, and ManagEment of Diabetes Mellitus (SUPREME-DM) DataLink
- Metabolic Effects of Second Generation

HugeDomains.com
Shop for over 200,000 Premium Domains

Questions? We're here to help! Call today:
1-303-893-0552

Home | Categories | FAQs | About Us | Contact Us | Shopping Cart

Get your domain name today, we make it easy

Search: Enter Keyword or Phrase [Search]

MiniSentinel.com is for sale (Mini Sentinel)

Click here to buy MiniSentinel.com for **$1,995**

Create a blog, promote your business, or build a site for your personal use.
Your web address is memorable and uniquely your own.

Buy Now

Only $1,995
Call us for more information: 1-303-893-0552

Shop with confidence - return any domain within 30 days

30 Day Satisfaction Guarantee! Learn More

Sentinel

Type here to search...

Sentinel | Drugs | Vaccines, Blood & Biologics | Communications | FDA-Catalyst | Report Finder

Sentinel is a National Medical Product Monitoring System

LEARN MORE

ABOUT

- Background
- Coordinating Center
- Privacy and Security

SAFETY ASSESSMENTS

- Active Risk Identification and Analysis System
- Assessments of Drugs
- Assessments of Vaccines, Blood, & Biologics

DATA & SURVEILLANCE TOOLS

- Distributed Database and Common Data Model
- Complementary Data Sources
- Routine Querying Tools
- Validations and Literature Reviews

COMMUNICATIONS

- FDA Safety Communications
- Publications and Presentations
- Sentinel Initiative Events
- Report Finder

Latest Postings

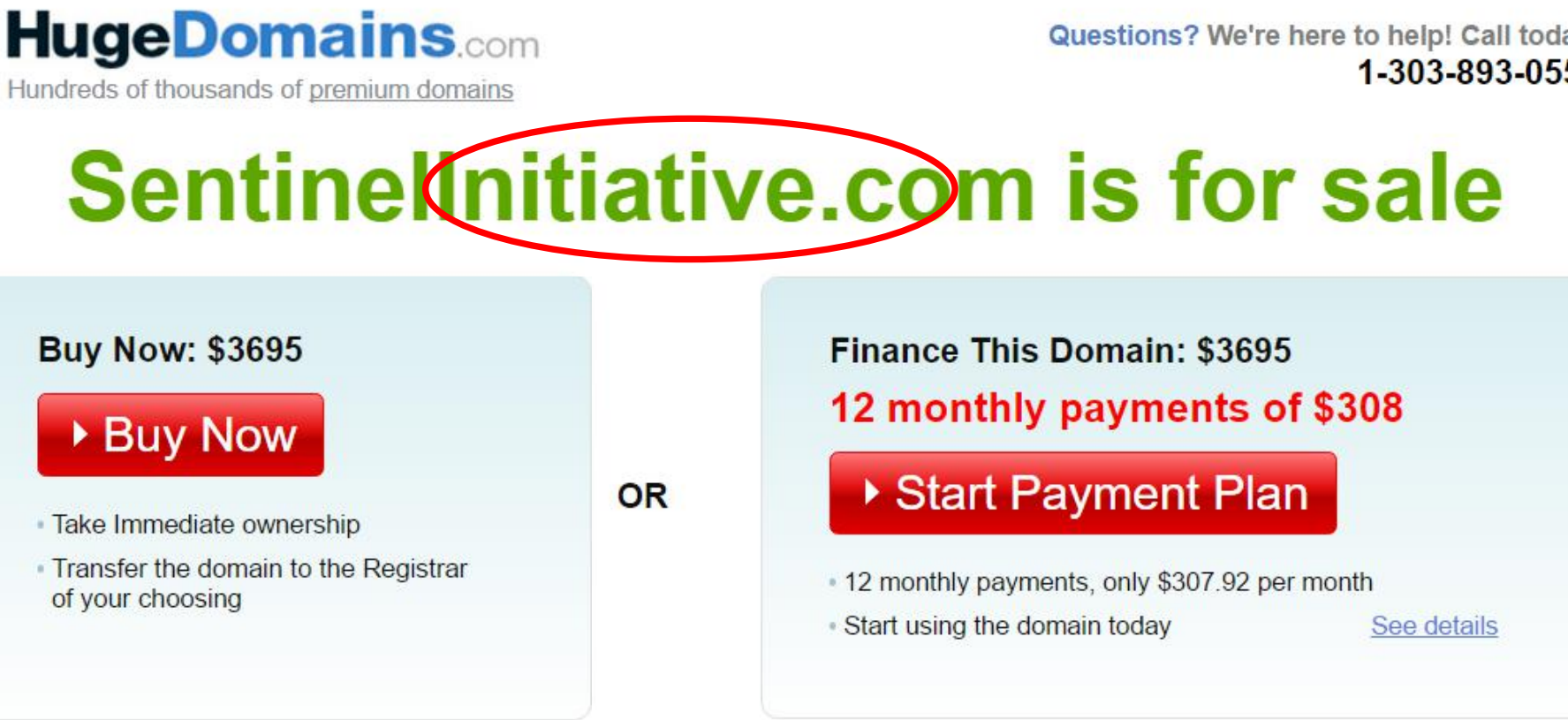
SPOTLIGHT

- Public Workshop: The Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System
  Tue, 11/15/2016
- Sentinel Initiative Public Workshop - Ninth Annual
  Tue, 11/08/2016

STUDY PROTOCOLS & SURVEILLANCE PLANS

- Influenza Vaccines and Birth Outcomes Protocol (PRISM)
  Fri, 01/20/2017
- Identify and Evaluate Manufacturer-Level Drug Utilization and Switching Patterns in Sentinel
  Mon, 12/12/2016

MODULAR PROGRAMS


HugeDomains.com
Hundreds of thousands of premium domains
Questions? We're here to help! Call today:
1-303-893-0552
SentinelInitiative.com is for sale
Buy Now: $3695
Buy Now
Take Immediate ownership
Transfer the domain to the Registrar of your choosing
OR
Finance This Domain: $3695
12 monthly payments of $308
Start Payment Plan
12 monthly payments, only $307.92 per month
Start using the domain today
See details
Talk to a domain expert: 1-303-893-0552
Hurry - once it's sold this opportunity will be gone!


Sentinel

Aetna

Annemarie Kline

Alan Bauck

Yihai Liu

Kaiser Permanente Data Coordinating Center

Duke Clinical Research Institute

Meyers Primary Care Institute

Harvard Pilgrim Health Care Institute

Robert Greenlee

Susan Andrade

Jerry Gurwitz

University of Illinois at Chicago

Grace Lee

Weill Cornell Medical

University of Iowa

Kaiser Permanente Colorado

Vanderbilt University School of Medicine

Kaiser Permanente Mid-Atlantic

Marie R Griffin

Kaiser Permanente Northwest

Northern California

Christine Whitmore

Dave Smith

Lisa Herrinton

Tony Morrow

[illegible]

Rohan Das

Gwyn Saylor

Smita Bhatia

Saloni Bhatia

Carolyn Neff

Sonal Singh

Nandakumar Nagaraja

Jennifer Robinson

Laura Shockro

Jim Nordin

Tiffany Woodworth

Lucas Ovans

William Cooper

Brian Owens

Peter Taylor

Judy Dudley

Tracy Lieu

Shannon Stratton

Susan Gruber

[illegible]

Leah Sanzaro

Tamara Lischka

Claire Spettell

Kathe Fox

Cheryl McMahill-Walraven

Yanhua Zhou

Jen Goldsack

Michael A. Mueller

Kim Lane

Laurie Van Arman

Fang Zhang

Gaby VazquezBenitez

Zilu Zhang

Carlos Grijalva

Lauren Zichittella

Kecia Carroll

Bruce Fireman

Rebecca Mohr

[illegible]

Duke | Robert J. Margolis, MD Center *for* Health Policy

Updates from the Sentinel Coordinating Center

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

State of Sentinel Safety Surveillance Activities

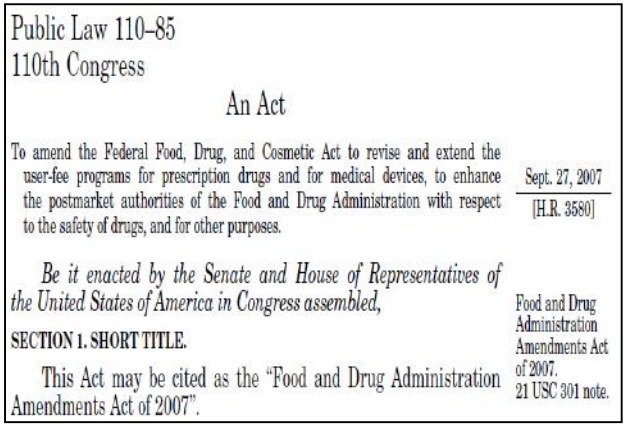
Join the conversation with **#sentinelinitiative**

FDA's Active Risk Identification and Analysis (ARIA) System

Robert Ball, MD, MPH, ScM
Deputy Director
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research
February 2, 2017

2007 FDA Amendments Act (FDAAA)

- Post Marketing Requirements
- Safety Labeling Changes
- Risk Evaluation and Mitigation Strategies (REMS)
- Required Safety Reviews (“915” and “921”)
- **Active post-market Risk Identification and Analysis system**
  - **FDA Sentinel Initiative**



Public Law 110–85
110th Congress

An Act

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

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

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

SECTION 1. SHORT TITLE.

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

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

Active Risk Identification and Analysis (ARIA) System

- Mandated creation in Section 905 of FDAAA 2007
- Linked to PMR in Section 901(3)(D)(i):
  - "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)."

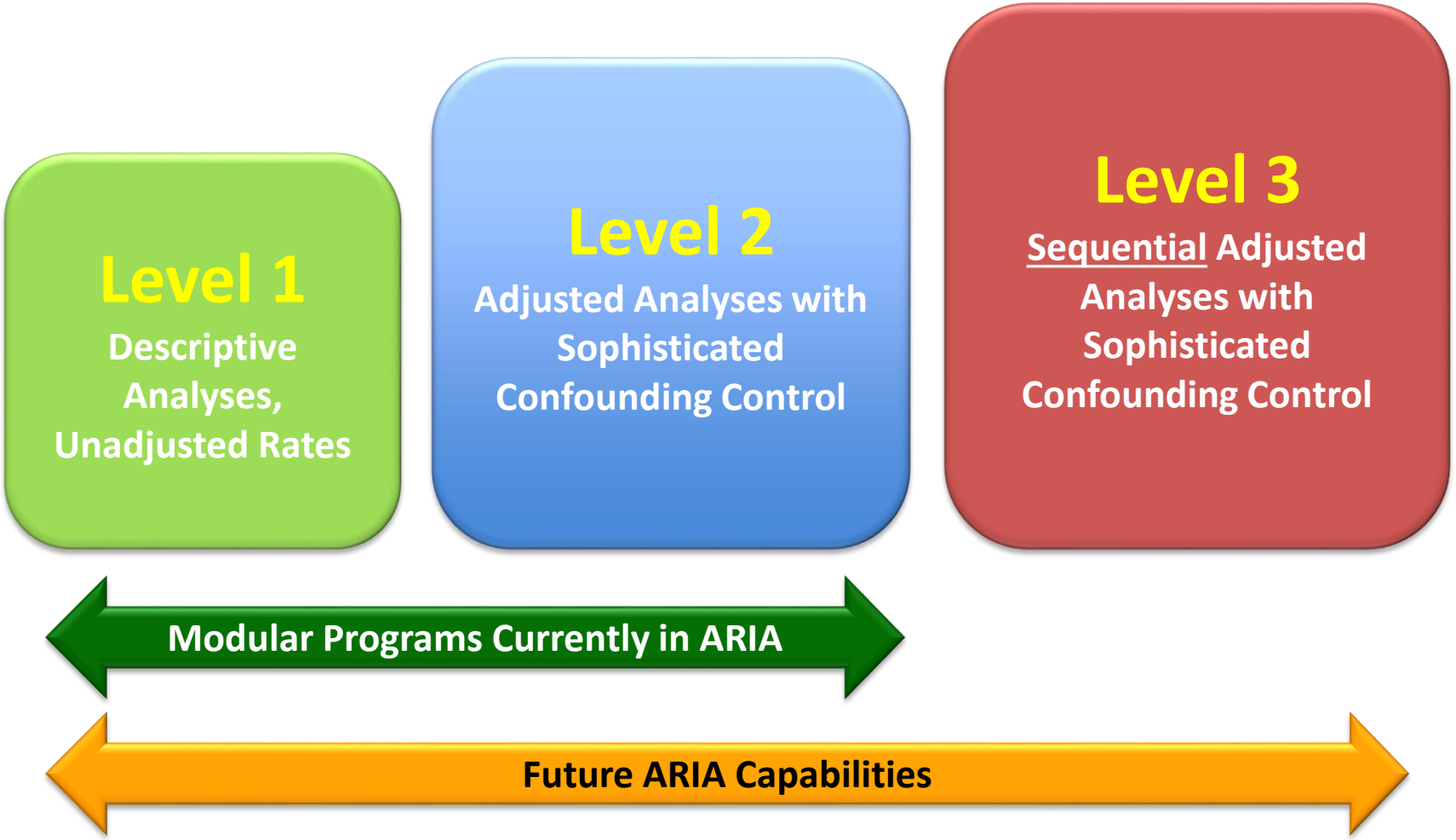
Defining ARIA

ARIA uses a subset of Sentinel System's full capabilities to fulfill the FDAAA mandate to conduct active safety surveillance

* Pre-defined, parameterized, and re-usable to enable faster safety surveillance in Sentinel (in contrast to protocol based assessments with customized programming)

† Electronic claims data, without manual medical record review

ARIA is Comprised of Distributed Querying Approach using Modular Programs



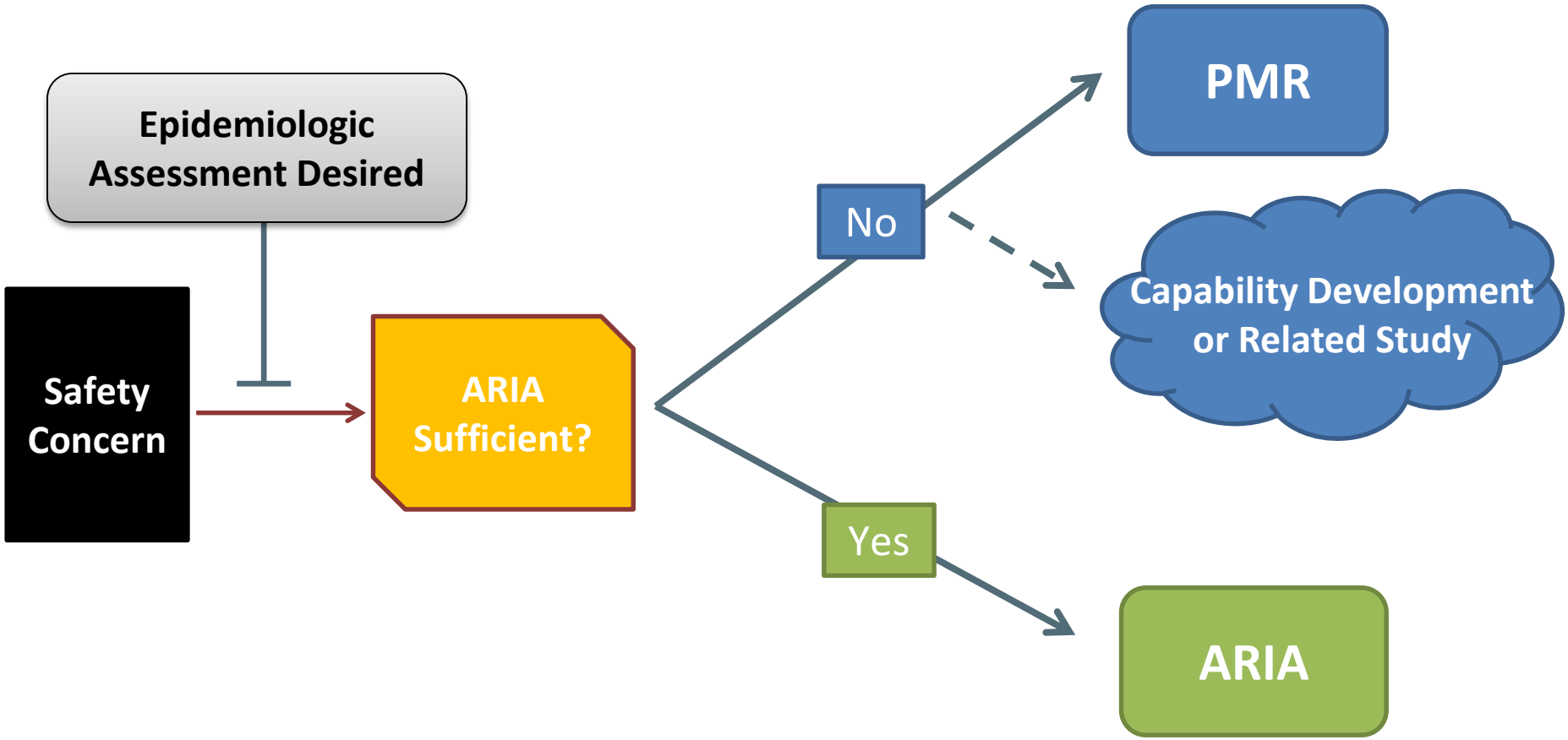
What is Sufficiency?

- Adequate data
  - Drug
  - Health Outcomes of Interest
  - Confounders
- Appropriate method
- To answer the question of interest*
- To a satisfactory level of precision

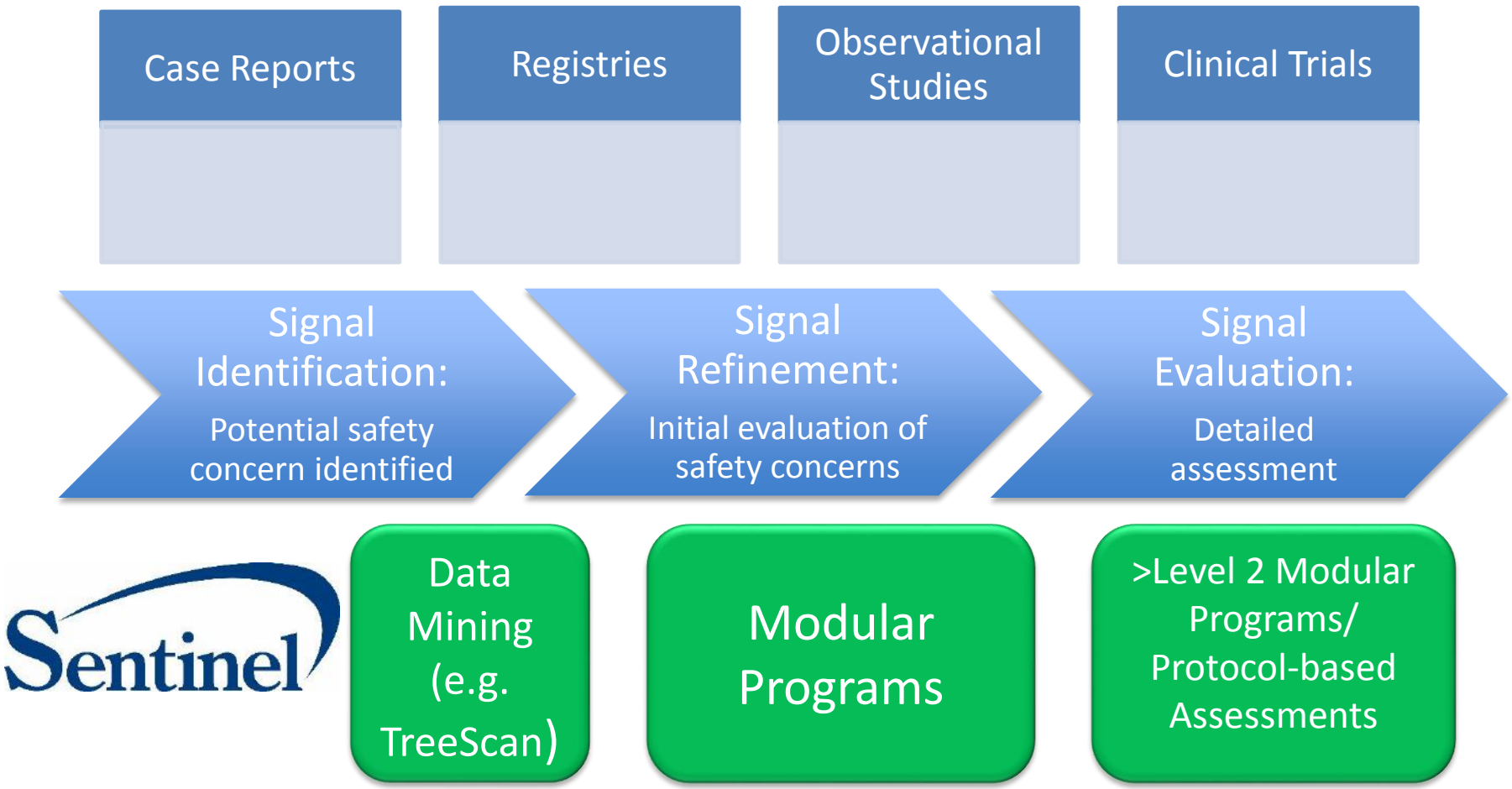
*FDAAA study purpose is one of the following:

- assess a known serious risk related to the use of the drug
- assess signals of serious risk related to the use of the drug
- identify an unexpected serious risk when available data indicate the potential for a serious risk

Sufficiency: A Regulatory Decision Point



Post-Market Safety Assessment



Thank you

Duke | Robert J. Margolis, MD Center *for* Health Policy

State of Sentinel Safety Surveillance Activities

Join the conversation with **#sentinelinitiative**

Integrating Sentinel Activities into the Drug Review Process: A CDER Perspective

Ninth Annual Sentinel Initiative Public Workshop

February 2, 2017

Mwango Kashoki, MD MPH

Associate Director for Safety

Office of New Drugs (OND)

FDA/Center for Drug Evaluation and Research (CDER)

Highlights from CDER Activities

Widespread Adoption & Integration ARIA

- Implementation of new processes for routine integration of ARIA into CDER review activities
- Routine use of ARIA in majority of therapeutic areas regulated by CDER

New Tools

- Evaluating confounding control tools and methods and developing new tools for generic drug switching, REMS evaluation, and medication errors

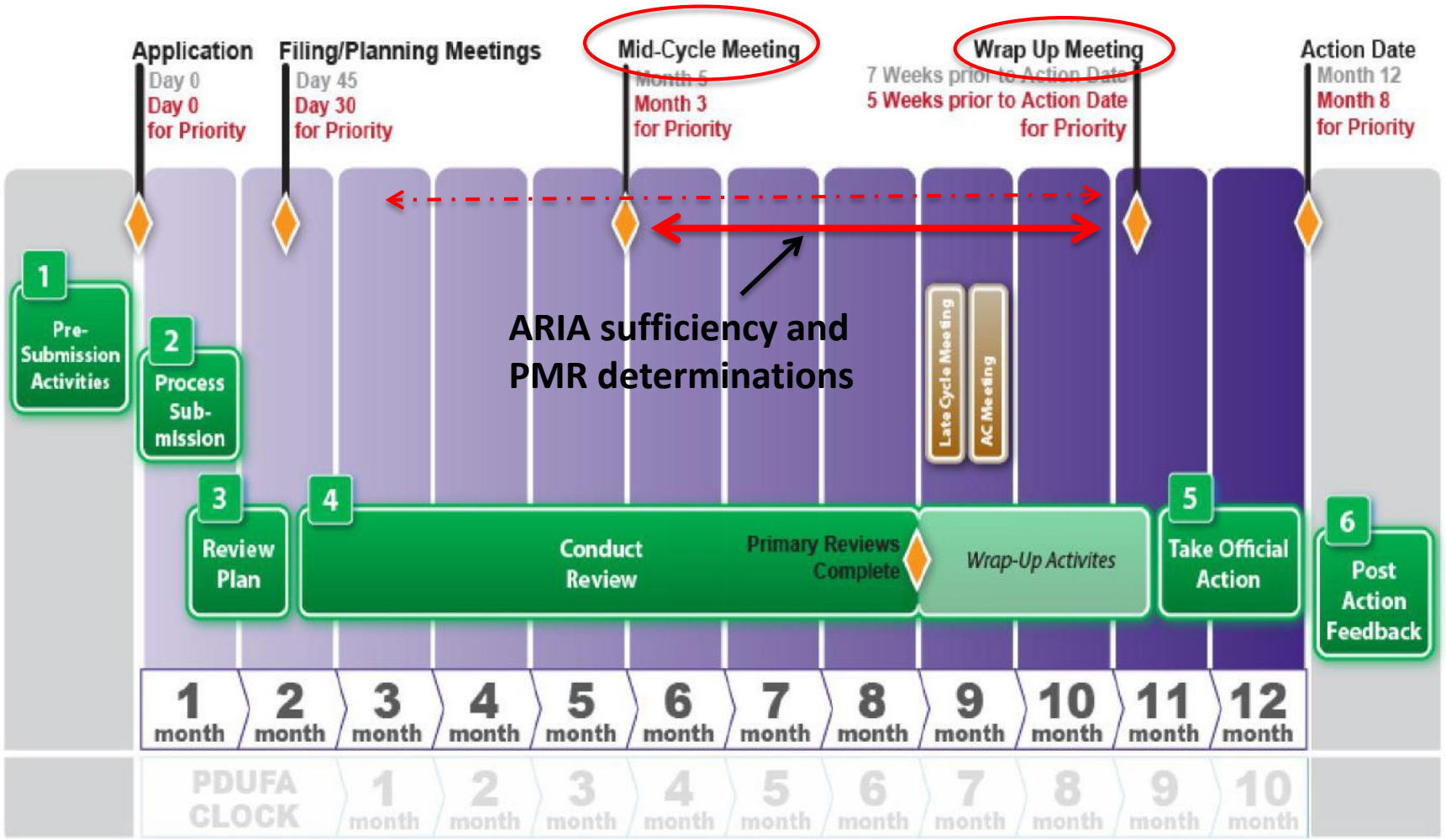
New Data Sources, Tough Outcomes

- Continuing to add new data partners
  - Expanding the CDM to capture Hospital Corporation of America's EMR data elements
  - Add Medicare Virtual Research Data Center
- Assess new approaches for detecting health outcomes of interest

Opportunities for Integration of Sentinel Analyses into Drug Review

- Review of new and supplemental marketing applications (NDAs/BLAs)
  - Determination of whether ARIA is sufficient for the purposes under section 505(o)(3) of the FDCA, or if a PMR is necessary
  - To supplement information about drug use and/or drug effects
- Postmarket surveillance
  - Signal identification
- Assessment of known or potential safety signals
  - Signal refinement
  - Signal evaluation

Integrating Sentinel Into NDA/BLA Review



Integrating Sentinel Into NDA/BLA Review Processes (contd.)

- Scientific considerations
  - What characteristics indicate sufficiency of ARIA for assessment of a particular safety signal
- Defining roles and responsibilities in Sentinel analyses
  - Office of Surveillance and Epidemiology (OSE)
  - Office of New Drugs (OND)
  - Office of Biostatistics (OB)
  - Other CDER offices
- Establishing processes for internal communication and documentation
  - Timeframes for assessment of ARIA sufficiency
  - Review team discussions about purpose of the signal evaluation and sufficiency of ARIA for this purpose
  - Documenting ARIA sufficiency determination

Results of Sentinel Analyses and Regulatory Decision Making

Works in progress…

- Process for communicating results of Sentinel analyses with review teams
- Interpretation of Sentinel analysis output
- Consideration of Sentinel analysis results in context of other available information
  - Strengths, limitations of Sentinel as a data source
  - Strengths, limitations of Sentinel analytic method(s)

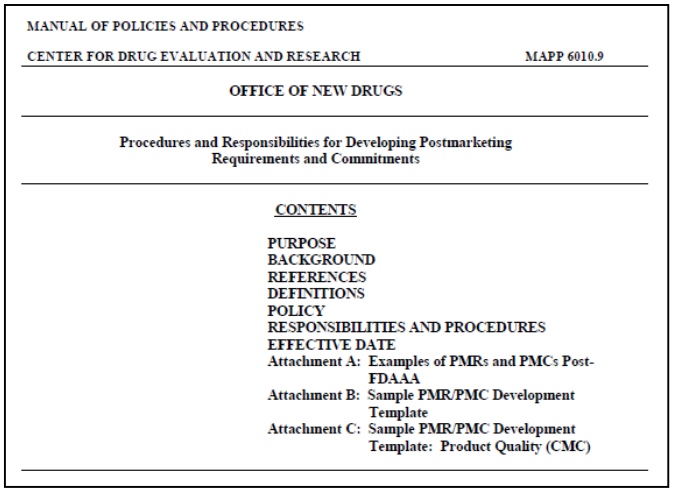
Communicating about Sentinel

- Public communication about sentinel analyses and related work products
  - Completed Sentinel analyses
    www.sentinelinitiative.org
  - Posters, abstracts, manuscripts

- *In progress* - Policies and procedures for informing sponsors about:
  - Planned use of Sentinel to evaluate a safety signal involving their respective products
  - Results from completed Sentinel analyses

PDUFA VI Commitment Letter:

"By the end of FY 2020, FDA will facilitate integration of Sentinel into the human drug review program in a systematic, efficient, and consistent way through staff development and by updating existing SOPPs and MAPPs, as needed."



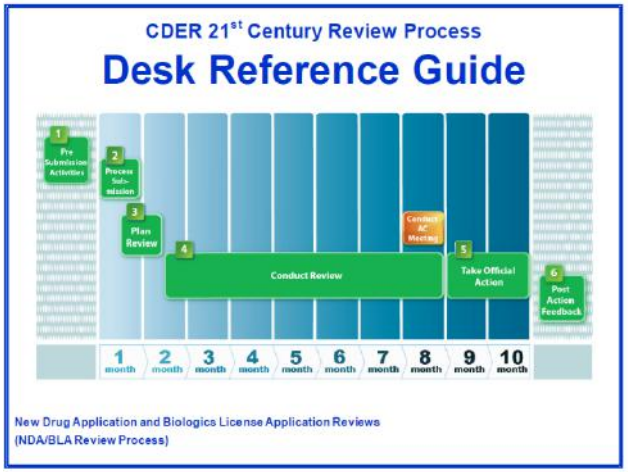
MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH — MAPP 6010.9

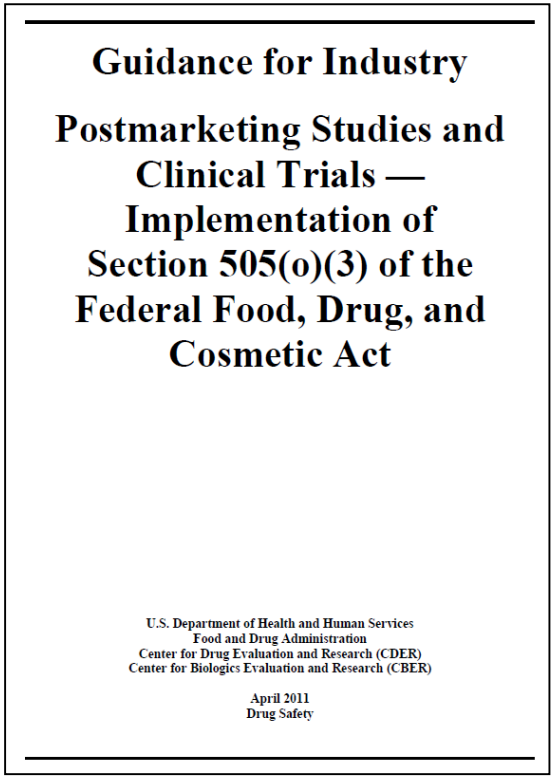
OFFICE OF NEW DRUGS

Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments

CONTENTS



Other existing (or new) MAPP or guidance?



Guidance for Industry

Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2011
Drug Safety


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Duke | Robert J. Margolis, MD Center *for* Health Policy

State of Sentinel Safety Surveillance Activities

Join the conversation with **#sentinelinitiative**

U.S. FOOD & DRUG ADMINISTRATION

Integrating Sentinel Activities into the Regulatory Process: A CBER Perspective

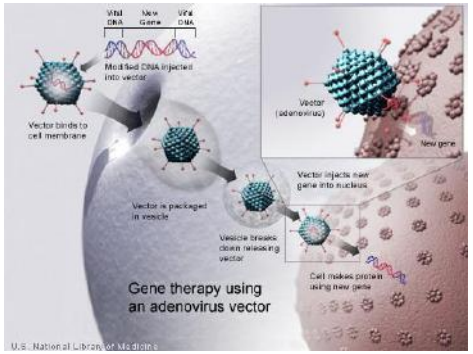
Scott Proestel, M.D.
Director, Division of Epidemiology
FDA Center for Biologics Evaluation and Research
Ninth Annual Sentinel Initiative Public Workshop
February 2, 2017

CBER Safety Surveillance Data Sources

- Premarket safety data
- Postmarket spontaneous AE surveillance (FAERS/VAERS)
- Medical literature
- Other national regulatory authorities
- Signal detection in claims data (Sentinel/TreeScan)
- Pharmacoepidemiologic studies
  - Centers for Medicare and Medicaid Services data
  - Vaccine Safety Datalink (VSD)
  - Sentinel

CBER Use of Sentinel

- Historically, CBER has used PBAs in all 3 product offices
- ARIA tools have become more sophisticated
- Transitioned to more use of ARIA
- Continue with some PBAs and methods development



CBER Sentinel Case Study - Blood Safety Continuous Active Surveillance Network (BloodScan)

- Safety surveillance for blood/blood products
- Uses all 18 data partners
- Claims data and electronic health records
- Inpatient blood transfusion data has improved surveillance
- Immune globulin (IVIG) and thromboembolic events (TEE) case study

CBER Sentinel Case Study

IVIG

- Purified plasma fraction of polyclonal immunoglobulin G
- Derived from pooled donor plasma
- Used for immune deficiency diseases, autoimmune disorders, and inflammatory disorders

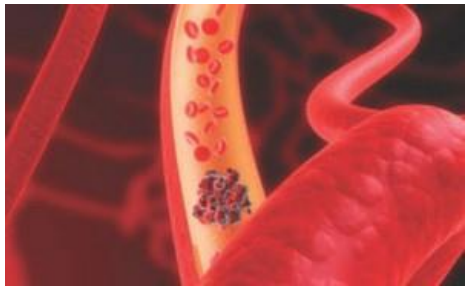
CBER Sentinel Case Study

IVIG and TEE

- Case series first reported in 1986
- Spontaneous case reports
- Laboratory evaluations – thrombogenicity
- Warning labeling in 2002
- Pharmacoepi study of IVIG-associated same day TEE (HealthCore claims data)
- Box warning in 2013
- Magnitude of risk and risk factors?

CBER Sentinel Case Study

"Evaluation of the Risk of Thromboembolic Events After Immunoglobulin Administration"



- Protocol-based assessment
- Retrospective, self-controlled risk-interval design
- Initiated IVIG use between 2006-2012
- 14 data partners, medical record confirmation
- Physician-adjudicators confirm exposures, outcomes, and timing
- Goal: estimate RR of IVIG for TEE, identify potential risk factors
- Results: to be posted on Sentinel Website soon!

Regulatory Decisions

- Continued monitoring
- Further study
- Public communication
- Label/PV plan revisions
- PMC/PMR/REMS
- Market withdrawal

Acknowledgments

IVIG and TEE Sentinel Assessment Workgroup:

- Eric M. Ammann, MS, PhD, Elizabeth A. Chrischilles, MS, PhD, Ryan M. Carnahan, PharmD, MS, BCPP, Bruce Fireman, MA, Candace C. Fuller, PhD, MPH, Marin L. Schweizer, PhD, Crystal Garcia, MPH, Madelyn Pimentel, BA, Charles E. Leonard, PharmD, MSCE, Meghan A. Baker, MD, ScD, Adam Cuker, MD, MS, Enrique C. Leira, MD, MS, Jennifer G. Robinson, MD, MPH, Scott K. Winiecki, MD, Sudeepta Dandapat, MD, Jayasheel Eshcol, MD, Saket Girotra, MD, MS, Sherry Grund, RN, Cole Haskins, BS, Rami Kafa, MD, David Martin, MD, MPH, Nandakumar Nagaraja, MD, MS, Michael Nguyen, MD, Adela Niedermann, RN, Angela M. Overton MSN, RN, CNRN, SCRN, Lois Pedelty, RN, Usha Perepu, MBBS, MRCP, Victoria Polich, RN, Kim Price, RN, CCM, Erin Rindels, MSN, RN, CNRN, SCRN, NVRN-BC, Nicholas Rudzianski, BS, Darren Toh, ScD, James C. Torner, PhD

Slide reviewers:

- Azadeh Shoaibi
- Richard Forshee


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Duke | Robert J. Margolis, MD Center *for* Health Policy

State of Sentinel Safety Surveillance Activities

Join the conversation with **#sentinelinitiative**

Questions & Answers

Join the conversation with **#sentinelinitiative**

Break

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CBER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

CBER Sentinel Program

Azadeh Shoaibi, PhD, MHS
CBER Sentinel Lead
On behalf of CBER Sentinel Team

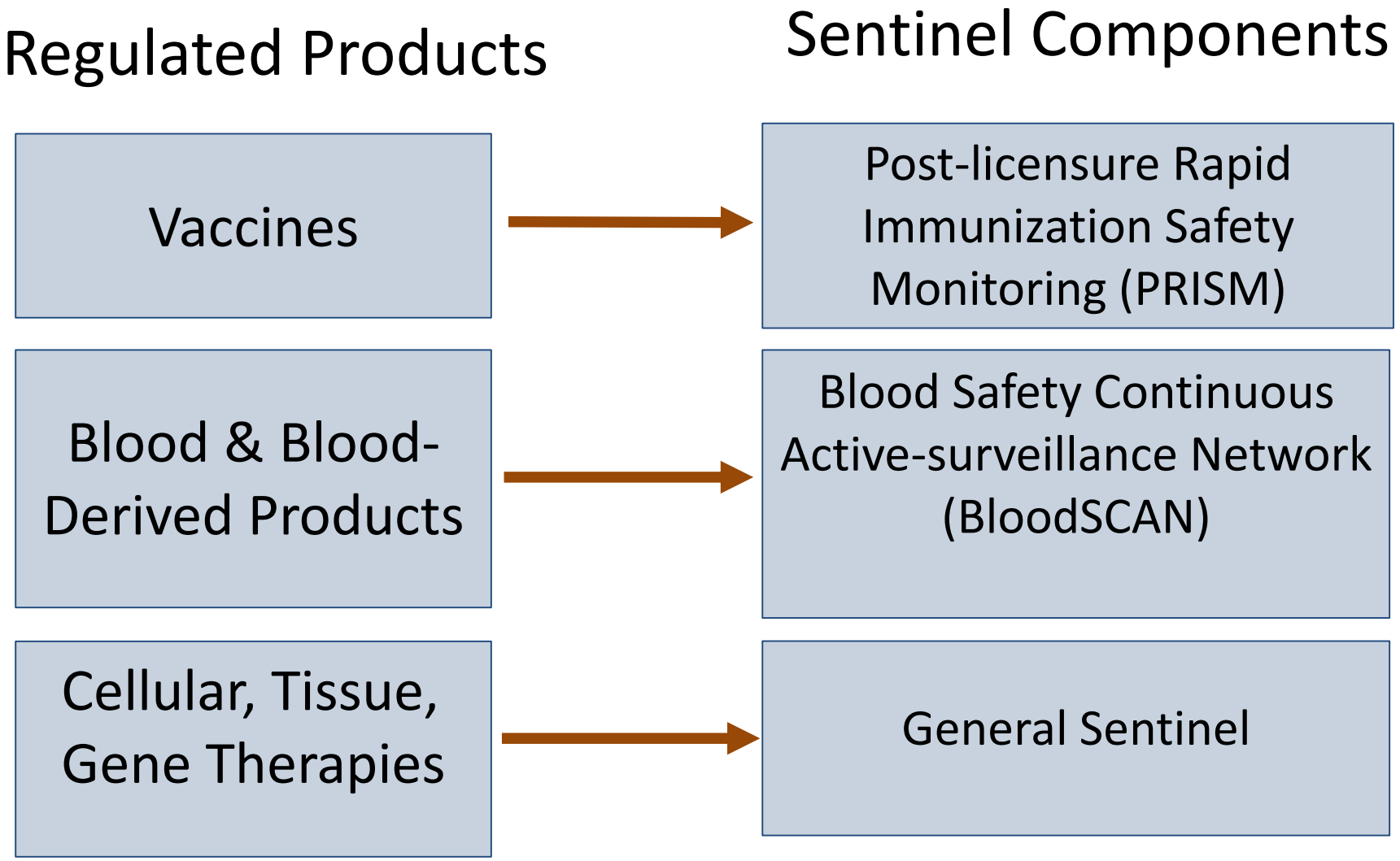
Office of Biostatistics and Epidemiology
FDA Center for Biologics Evaluation and Research

February 2, 2017

Outline

1. Current priority areas
2. Update on recent activities
3. Major accomplishments
4. Future direction

CBER Sentinel

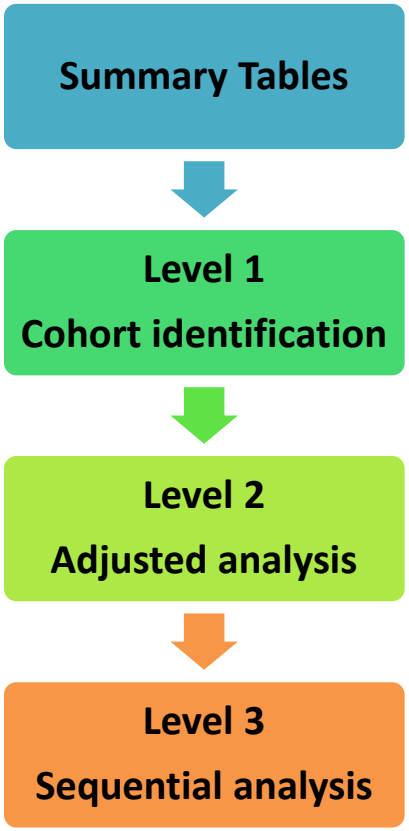


CBER Sentinel Program
Current Priority Areas

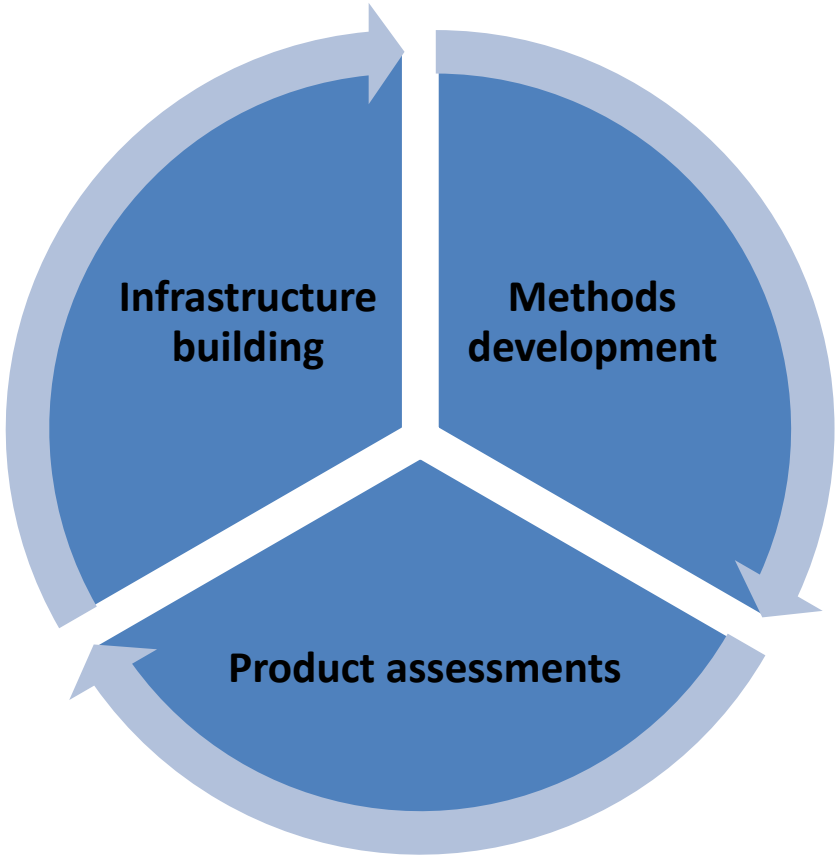
1. Expansion of hemovigilance capabilities
2. Signal refinement/evaluation of vaccines & blood through use of claims data, EHR such as HCA
3. Safety of vaccines in pregnancy
4. Signal identification of vaccines using TreeScan
5. Vaccine effectiveness activities

Current Instruments

Rapid Query Tools (ARIA)



Protocol-Based Activities



Update on recent activities

Rapid Queries (ARIA) 2016

Query Type	Frequency
Summary Tables	4
Level 1	10
Level 2	1
Level 3	1
Total	**16**

Protocol-Based Activities (Completed)

Methods Development Infrastructure Building	Product Assessments
Data mining infrastructure	Influenza vaccine and birth outcomes
Birth certificate linkage	Intravenous immunoglobulins and thromboembolic events
Scan statistics	
Self-controlled risk interval tool pilot	
Vaccine effectiveness pilot	

Protocol-Based Activities (Ongoing)

Methods Development Infrastructure Building	Product Assessments
Quantitative bias analysis	Pneumococcal conjugated 13-valent (PCV13) vaccine and Kawasaki Disease
TreeScan power calculation	Influenza vaccine 2 seasons and febrile seizure in children
TreeScan bias	Human papilloma virus 9-valent (HPV9) vaccine TreeScan analysis
Influenza vaccine and birth defects	
Transfusion-Related Acute Lung Injury in HCA database	

Vaccine Safety in Pregnancy

- Protocol-based activity with medical chart review
- Test case
  - Exposure: inactivated influenza vaccine
  - Outcome: spontaneous abortion vs. live birth, oral cleft in newborns

Objectives

- Build infrastructure and develop methods to examine pregnancy outcomes (PRISM priority area) and birth defects following vaccination
- Examine positive predictive value of claims-based algorithms for spontaneous abortion (SAB), gestational age, and oral cleft

Current Status

- Pregnancy outcomes: SAB and gestational age
  - Project almost completed
- Birth defects: oral cleft in newborns
  - Medical chart review close to completion

Signal Identification: TreeScan

- Human papilloma virus 4-valent (HPV4) vaccine analysis as a pilot completed
- HPV9 vaccine analysis underway
- Expanding TreeScan capabilities
  - Longer term and variable follow-up period
  - Power calculation

BloodSCAN

- Data sources:
  - Claims and administrative data
  - Inpatient electronic health records (EHR): Hospital Corporation of America (HCA) database
- Access to inpatient blood transfusion data broadens capabilities for blood safety surveillance

BloodSCAN

- Intravenous immunoglobulins (IVIg) and thromboembolic events (TEE)
- Transfusion-Related Acute Lung Injury (TRALI)

Intravenous Immunoglobulins and Thromboembolic Events

- Data source
  - Claims and administrative data
- Objective
  - Evaluate risk of TEE following IVIg exposure
- Study design
  - Self-controlled risk-interval
- Current status
  - Project almost completed

Transfusion-Related Acute Lung Injury (TRALI)

- Data source: HCA inpatient EHR
- Infrastructure building: become familiar with HCA database
- Test case: TRALI assessment
- Objective: to evaluate incidence rate of TRALI after plasma, platelet, packed RBC administration
- Protocol posted Sept. 2016
- Current status:
  - TRALI cases identified electronically
  - Medical chart retrieval and adjudication underway

Vaccine Effectiveness

- Assessing use of Sentinel capabilities for effectiveness evaluation in a limited capacity for specific situations
  - Pilot project almost completed

CBER Sentinel Program
Major Accomplishments

1. Use of rapid query tools (ARIA)
2. Integration of Sentinel into regulatory process and participation of product offices
3. Transition from development to production mode
4. Initiation of vaccine effectiveness activities

Future

- Less focus on protocol-based activities, more focus on rapid query tools (ARIA) for product safety assessments
- Continue to expand infrastructure and capacity
- In collaboration with the Sentinel Operations Center and CBER product offices
  - Work toward making Sentinel more efficient
  - Areas of improvement:
    - Reduce data lag
    - Explore alternative data sources, such as EHR, due to limitations in claims-administrative data

Summary

1. Significant accomplishments for CBER Sentinel Program over the past year
2. Availability and utilization of more sophisticated rapid query tools (ARIA) to interrogate database
3. Incorporation of biologics effectiveness activities
4. Integration of Sentinel into regulatory process
5. Transition from development to production mode
6. Contribution of Sentinel to medical product safety and to public health

Acknowledgements

- Sentinel Operations Center at Harvard Pilgrim
- Data Partners
- CBER Sentinel Central Team, OBE and other CBER investigators
- Sentinel investigators and collaborators across many institutions

Thank you!

azadeh.shoaibi@fda.hhs.gov

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CBER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

Conducting Vaccine Effectiveness Surveillance in Sentinel's PRISM Program

Maria Said, MD, MHS
FDA/CBER/OBE
Sentinel Annual Meeting
February 2, 2017

Project Rationale

- PRISM, which is part of Sentinel and uses a subset of Sentinel data partners, is a valuable and rich resource.
  - Large number of members from geographically diverse areas
  - Multiple potentially useful data elements (e.g. demographics, outpatient pharmacy dispensing, outcome data etc.)
- PRISM had been used for successful vaccine safety studies; why not also for vaccine effectiveness?
- PRISM's observational data might be able to supplement data from randomized clinical trials (RCTs) under certain circumstances.

What Gaps Could PRISM Fill?

- In certain situations, for confirmation of effectiveness for vaccines approved under accelerated approval or the animal rule
- Evaluation of effectiveness in specific populations
- Evaluation of effectiveness to prevent rare conditions
- Situations in which an RCT is not ethical and/or feasible
- Supplement/confirm what has already been learned in an RCT

Biologics Licensure Pathways: Some Key Aspects

- "Traditional" Approval
  - Provides direct pre-licensure evidence of effectiveness by demonstrating protection against disease or, in some cases, through use of a scientifically well-established correlate that predicts protection against disease
- Accelerated Approval
  - Demonstrates effectiveness using a surrogate endpoint that is reasonably likely to predict clinical benefit
- "Animal Rule" Approval
  - Demonstrates effectiveness in animal model(s) and applies to products that would ameliorate or prevent serious or life-threatening conditions

What Gaps Could PRISM Fill?

- In certain situations, for confirmation of effectiveness for vaccines approved under accelerated approval or the animal rule
- Evaluation of effectiveness in specific populations
- Evaluation of effectiveness to prevent rare conditions
- Situations in which an RCT is not ethical and/or feasible
- Supplement/confirm what has already been learned in an RCT

What Gaps Could PRISM Fill?

- In certain situations, for confirmation of effectiveness for vaccines approved under accelerated approval or the animal rule
- Evaluation of effectiveness in specific populations
- Evaluation of effectiveness to prevent rare conditions or a more specific endpoint
- Situations in which an RCT is not ethical and/or feasible
- Supplement/confirm what has already been learned in an RCT

What Gaps Could PRISM Fill?

- In certain situations, for confirmation of effectiveness for vaccines approved under accelerated approval or the animal rule
- Evaluation of effectiveness in specific populations
- Evaluation of effectiveness to prevent rare conditions or a more specific endpoint
- Situations in which an RCT is not ethical and/or feasible
- Supplement/confirm what has already been learned in an RCT

What Gaps Could PRISM Fill?

- In certain situations, for confirmation of effectiveness for vaccines approved under accelerated approval or the animal rule
- Evaluation of effectiveness in specific populations
- Evaluation of effectiveness to prevent rare conditions or a more specific endpoint
- Situations in which an RCT is not ethical and/or feasible
- Supplement/confirm what has already been learned in an RCT

Project Overview

- Objective: To address the suitability of using PRISM to estimate vaccine effectiveness
- Project Components
  - Overview of study designs and methods used in vaccine effectiveness studies, particularly observational studies using administrative databases
  - Exploration of the PRISM database through a use case

Project Approach

- Data Elements (Study Population, Exposures, Outcomes, Covariates)
- Methods (Study Designs and Statistical Adjustment)
- Assessments: Existing Sentinel/PRISM Tools and Protocol Based Assessments
- A Descriptive Use Case (would not link the exposure to the outcome)

Use Case

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas MaCurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman*

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.

Lancet Infect Dis 2015; 15: 293–300

Published Online
February 9, 2015
http://dx.doi.org/10.1016/S1473-3099(14)71087-4

Use Case

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas MaCurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman*

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.

Lancet Infect Dis 2015; 15: 293–300

Published Online February 9, 2015 http://dx.doi.org/10.1016/S1473-3099(14)71087-4

Could we do the same study, but using the PRISM Database?

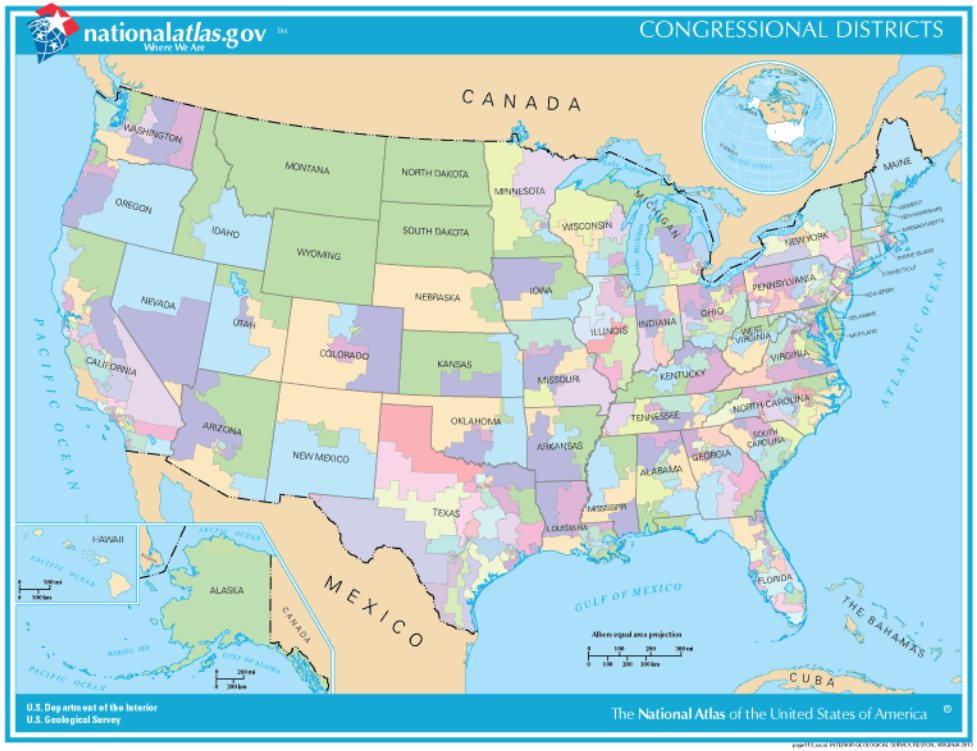
Use Case

Table 1: Baseline characteristics of high-dose and standard-dose cohorts from 24 501 matched pharmacies

	High-dose cohort (n=929730)	Standard-dose cohort (n=1 615 545)	Standardised mean difference
Sex			
Female participants	538 380 (57·91%)	959 072 (59·37%)	0·03
Male participants	391 350 (42·09%)	656 473 (40·63%)	0·03
Race			
White	867 552 (93·31%)	1 512 633 (93·63%)	0·01
Black	25 463 (2·74%)	41 714 (2·58%)	0·01
Other race/unknown	16 235 (1·75%)	27 571 (1·71%)	<0·01
Asian	12 973 (1·40%)	21 178 (1·31%)	0·01
Hispanic	6112 (0·66%)	10 328 (0·64%)	<0·01
Native North American	1395 (0·15%)	2121 (0·13%)	0·01
Dual enrolled	45 186 (4·86%)	79 750 (4·94%)	<0·01
Age (years)	75·74 (7·19)	75·35 (7·27)	0·05
65–74	461 260 (49·61%)	841 789 (52·11%)	0·05
75–85	340 728 (36·65%)	561 385 (34·75%)	0·04
85 and older	127 742 (13·74%)	212 371 (13·15%)	0·02

Izurieta et al. Lancet Infect Dis 2015;15:293-300.

(1) Data Elements

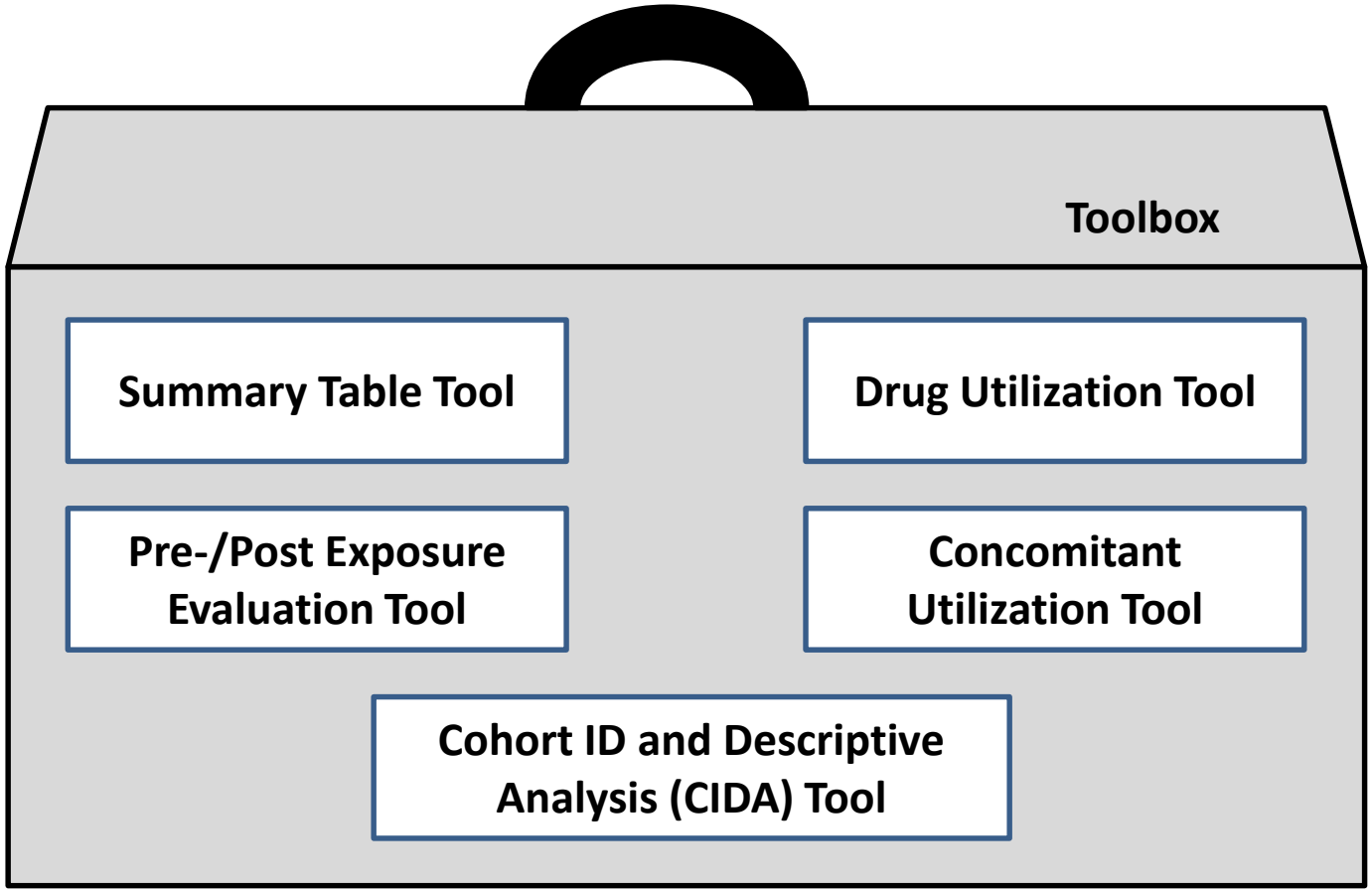


- Data Elements - Study Population
  - Size
  - Geographic coverage
  - Age distribution
  - Representativeness

(2) Methods (Study Designs)

Study Design	Description	Applicability to Sentinel	Recommended /Viable for Sentinel?	Example(s) from Literature
Cohort Study	Group of vaccinated and unvaccinated health plan members identified and followed up to ascertain vaccine-preventable disease events	<u>Strength</u> - Large captive population with longitudinal information <u>Limitation</u> - Difficult to identify unvaccinated people	Yes	Izurieta HS, et al. Lancet Infect Dis 2015;15(3):293-300. Panozzo CA, et al. Am J Epidemiol 2014;179(7):895-909
Case Control Study etc…	…	…	…	…

(3) Assessments/Tools



(4) Use Case Output

- Numbers of patients receiving high-dose vs. standard-dose influenza vaccination
- Numbers of episodes and patients with influenza diagnosis or pneumonia diagnosis
- Patient characteristics including age, sex, and medical history

Project Status

- Draft White Paper completed and revisions ongoing
- White Paper to be posted on the website

Acknowledgments

Harvard SOC

- Meghan Baker
- Libby Cavagnaro
- Sandra Feibelmann
- Hana Lipowicz
- Cathy Panozzo

FDA

- Deepa Arya
- Rich Forshee
- Hector Izurieta
- Yun Lu
- David Menschik
- Douglas Pratt
- Azadeh Shoaibi

Work Group Members

- Roger Baxter
- Kevin Fahey
- Bruce Fireman
- Lisa Jackson
- Nicola Klein
- James Nordin
- Carla V. Rodriguez
- Nandini Selvam


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CBER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

Using Sentinel Data for Benefit-Risk Assessments

Richard Forshee, Ph.D.
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

Sentinel Annual Meeting

Washington, DC

February 2, 2017

FDA U.S. FOOD & DRUG ADMINISTRATION

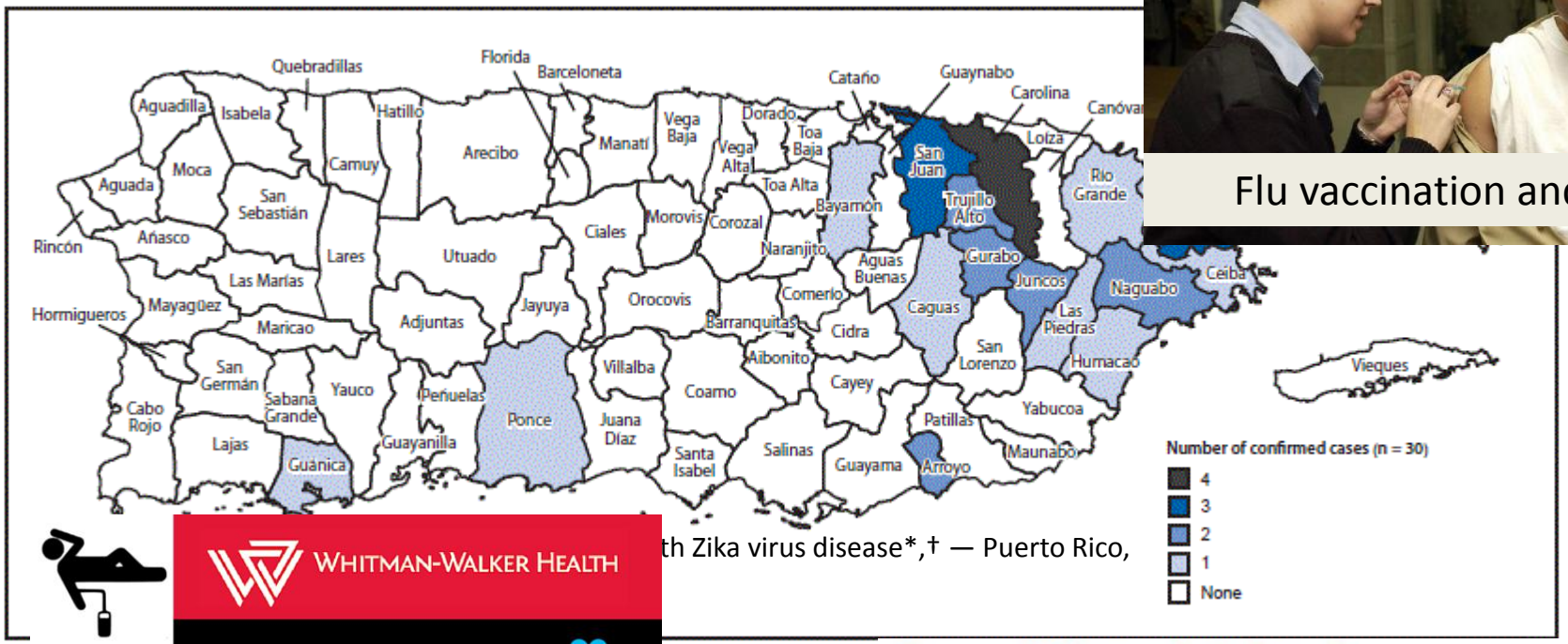
CBER is responsible for regulating vaccines, blood and blood products, and cellular, tissue, and gene therapies with diverse benefits and risks

Consider three examples

Zika infections increasing rapidly in Puerto Rico

Widespread Zika infections warrant urgent action to protect pregnant women

Flu vaccination and GBS

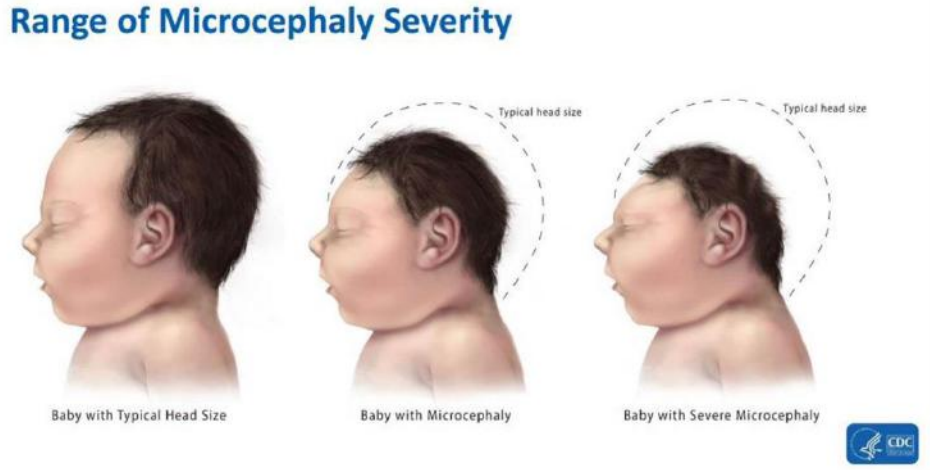


th Zika virus disease*,† — Puerto Rico,

FDA 1985

FDA 2015 Draft Proposal

2015 Proposal



Sentinel Data Can Help CBER Accomplish Our Public Health Mission

- Timely Data to support benefit-risk assessment
- Assessments support decision-making by FDA and stakeholders

- Will discuss two transfusion B-R assessments
  - Transfusion-transmission of Zika
  - Testing strategies of US blood supply for Babesia

Blood donation is common and provides multiple life-saving products

"U.S. Army Cpl. Christopher LeRoy, of the 932nd Blood Support Detachment, monitors the progress of Sgt. Jennifer Skebong, of the 583rd Medlog Company, as she gives blood at Bagram Airfield, Afghanistan, July 4, 2007. For the first time blood platelets are being collected in country for treatment of critically injured patients. (U.S. Air Force photo by Senior Airman Dilia DeGrego) www.army.mil "
Public Domain: https://commons.wikimedia.org/wiki/File:Bagram_blood_donation_-a.jpg

Blood and Blood Products

- Blood Donations and Transfusions
  - About 14.2 M RBC Units collected
  - About 13.2 M RBC Units were transfused
- Blood donations are the source for other blood products
  - Clotting Factor Products
  - Immune Globulin Products
  - Others

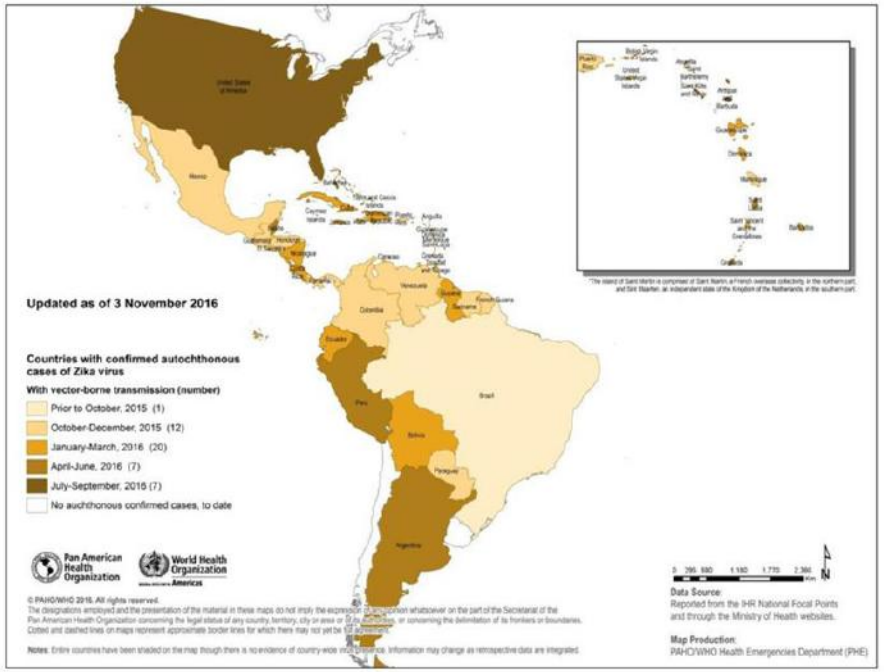
FDA U.S. FOOD & DRUG ADMINISTRATION

Sentinel can provide timely data to support benefit-risk assessment:

Zika Virus in Puerto Rico Example

Background: Zika Virus

- Local transmission of Zika virus (ZIKV) in more than 59 countries and territories
- Microcephaly associated with infection during pregnancy
- Known risk of transmission through blood
- FDA recommended travel-based donor deferral and testing of blood collected in areas with active local transmission in Feb. 2016



Background: Zika Virus Outbreak in Puerto Rico

- 34,577 laboratory-confirmed Zika cases had been confirmed in Puerto Rico as of January 25, 2017 (CDC, https://www.cdc.gov/zika/intheus/maps-zika-us.html)
- Blood collection in Puerto Rico was temporarily suspended
- Nucleic acid test (NAT) under IND for testing of whole blood and components became available in March 30, 2016
- Local blood collection has been resumed and tested with NAT since April 3, 2016

Objectives of CBER TTZIKV Risk Assessment

- To develop a tool for rapid assessment of risk of transfusion-transmission of ZIKA Virus (TTZIKV)

- To estimate risk after blood screening using individual nucleic acid testing (ID NAT) for blood units collected in Puerto Rico

- To estimate the risk for pregnant women

Some of the Major Model Inputs

Input Parameters	References
Window period (days) Triangular (0, 0.5, 3)	AABB Zika Virus Symposium O'Connor et al. 2016
Transfused units for pregnant women Normal (0.48%, 6.6×10^{-5})	Sentinel Database (Not Puerto Rico specific)
Transfusion transmission rate Triangular (37.5%, 37.5%,100%)	Minimum and most likely values- Sabino et al. 2016 Maximum value- assumption

Some of the Major Model Inputs

Input Parameters	References
Transfused units for pregnant women Normal (0.48%, 6.6×10^{-5})	Sentinel Database (Not Puerto Rico specific)
Transfusion transmission rate Triangular (37.5%, 37.5%,100%)	Minimum and most likely values- Sabino et al. 2016 Maximum value- assumption

Sentinel was able to quickly provide a key input for a risk assessment with important public health implications

Partial Results- Model predicted cumulative risk, period April 3rd - November 17th, 2016

(33,227 total reported clinical cases)

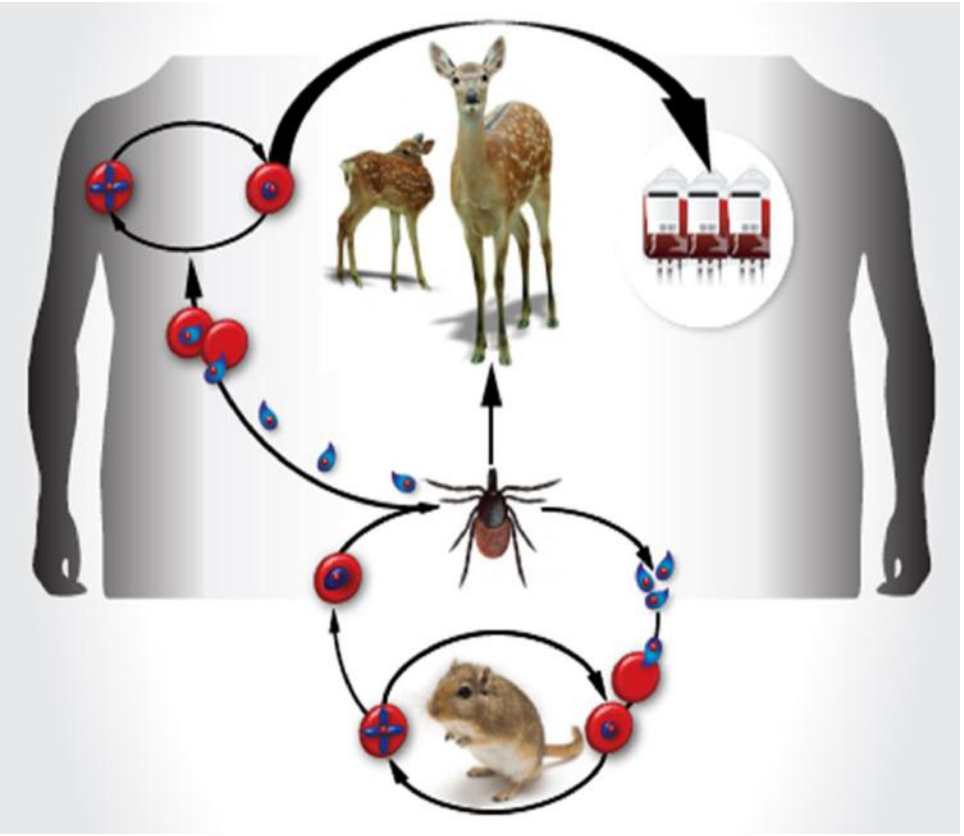
	Mean Cumulative Risk (2.5-97.5th%ile)	
	Without blood testing	**With blood testing**
Infectious RBC units	1936	262
TTZIKV	1128 (159-3751)	153 (13-565)
TTZIKV in pregnant women	5.4 (0.8-18)	0.7 (0.06-2.7)
TTZIKV in immunocompromised	393 (56-1309)	53 (4-196)

ID NAT reduces TTZIKV risk by ~86%

U.S. FOOD & DRUG ADMINISTRATION

Geographic data to support benefit-risk assessment: Transfusion-Transmitted Babesiosis

Babesia microti and Blood Safety



- Tick-borne disease
- Chronically infected asymptomatic individuals cause Transfusion Transmitted Babesiosis (TTB)
- Discussed at 2015 Blood Products Advisory Committee Meeting

Slide courtesy of Dr. Sanjai Kumar, FDA/CBER

Why this Issue is Important

- No licensed donor testing is available
- *B. microti* is among the most frequently transfusion-transmitted infections
- Cases of Babesia in the U.S. are regionally located but risk of transfusion-transmitted infection is nationwide
- Recent investigational testing of blood donations for *Babesia microti* infections provides data on the potential utility of testing

Slide courtesy of Dr. Sanjai Kumar, FDA/CBER

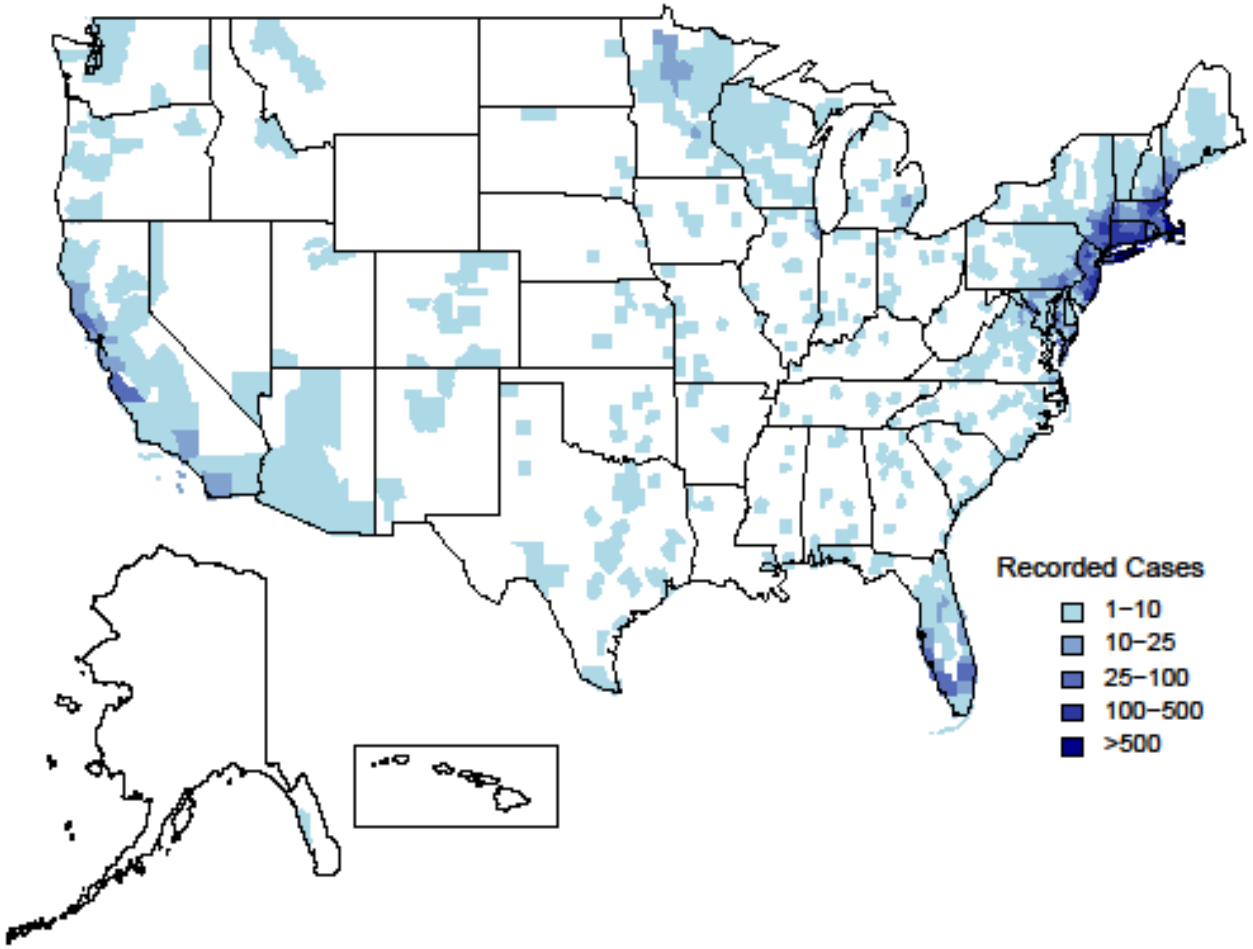
Clinical Symptoms and Pathogenesis

- Ranges from asymptomatic to mild to life-threatening severe disease
- Neonates, immuno-compromised, asplenic, and elderly are at the highest risk of severe disease
- Fatality rates of 6 - 9% in the hospitalized cases and 21% in immuno-compromised cases

Slide courtesy of Dr. Sanjai Kumar, FDA/CBER

Geographic Distribution of Babesiosis (CMS)

- 2006-2013
  - 10,301 unique diagnoses of babesiosis
- Cases reported from all states and Washington D.C., except Wyoming



Slide courtesy of Dr. Sanjai Kumar, FDA/CBER

Summary of TTB Benefit-Risk Assessment

- **TTB B-R Assessment presented at and used to inform discussion/decisions at FDA Blood Products Advisory Committee Meeting in 2015**
- **Used Center for Medicare & Medicaid Services (CMS) data to evaluate possible Testing Scenarios**

Scenarios overview

No Testing | Serology Only | Serology + NAT

S: 5 States*

S+N: 5

S: 9

S+N: 9

S: 15 + DC

S+N: 15 + DC

S: 15 + DC,
N: 5

S: 50 + DC

S: 50 +DC,
N: 5

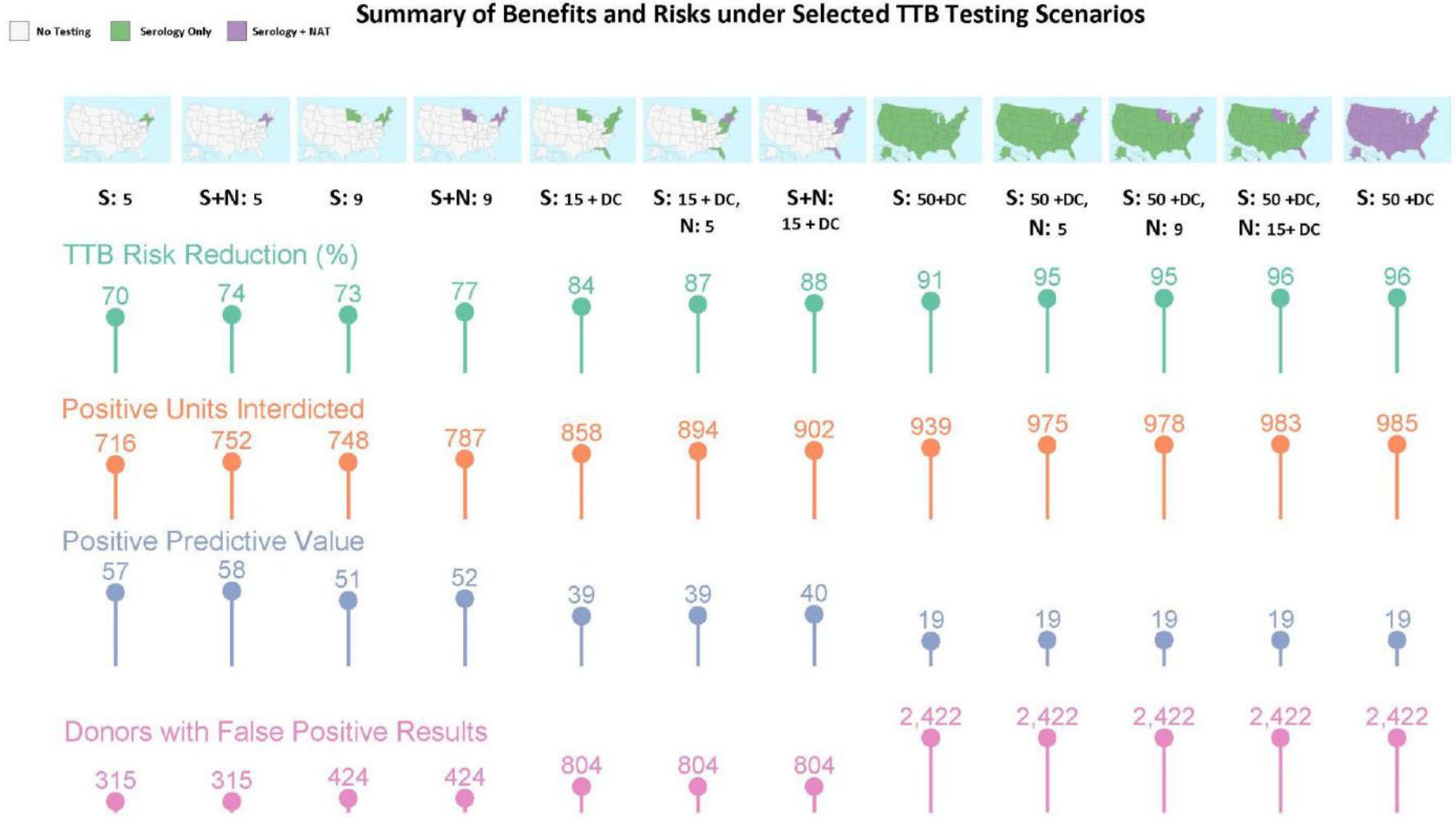
S: 50 +DC,
N: 9

S: 50 + DC,
N: 15 + DC

S+N: 50 + DC

*Number of States Using Testing

Summary of Benefits and Risks under Selected TTB Testing Scenarios



Blood Products Advisory Committee Meeting, May 13, 2015

Geographic Distribution

- Data on the geographic distribution of emerging infectious diseases (and other conditions) can inform important regulatory decisions
- We have successful examples using CMS data
- Most CMS participants are 65+ years old
- For certain projects, Sentinel data with geographic data would be very helpful
- CBER recognizes the need to aggregate to appropriate geographic levels, such as 3-digit ZIP code

Conclusion

- Sentinel data has already been used as inputs in CBER benefit-risk assessments
- CBER continues to explore other ways that Sentinel data can help us accomplish our public health mission

Acknowledgments

- Zika
  - Hong Yang
  - Kinnera Chada
  - Yin Huang
  - Steve Anderson
  - Office of Blood Research and Review
- Previously presented at Society for Risk Analysis 2016
- Babesiosis
  - Arianna Simonetti
  - Mikhail Menis
  - Sanjai Kumar
  - Office of Blood Research and Review
- Previously presented at Blood Products Advisory Committee 2015


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Thank you!

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CBER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

Questions & Answers

Join the conversation with **#sentinelinitiative**

Lunch Break

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CDER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

Sentinel

FDA U.S. FOOD & DRUG ADMINISTRATION

Ninth Annual Sentinel Initiative
Public Workshop, February 2, 2017

Incidence of heart failure and cardiomyopathy following initiation of medications for attention deficit hyperactivity disorder

COLLABORATORS

FDA Center for Drug Evaluation and Research

Division of Epidemiology 1: Andrew D. Mosholder, Lockwood Taylor

Division of Psychiatry Products: Glenn Mannheim

Harvard Pilgrim Health Care Institute

Lisa Ortendahl, Tiffany Woodworth, Darren Toh

Background

- Stimulants used to treat Attention Deficit Hyperactivity Disorder (ADHD) may be administered for long durations, often well into adulthood
- Illicit stimulant use is associated with cardiomyopathy (Diercks et al., Am J Cardiol 2008; Jafari Giv, Cardiovasc Toxicol 2016)
- Case reports of cardiomyopathy with therapeutic stimulant use exist (Marks et al., Am J Ther 2008; Nymark et al., Vasc Health Risk Manag 2008), but few available population-based data evaluate the risk

- Hypothesis: If cardiomyopathy is a long-term adverse effect of stimulant treatment, may observe an increase in the incidence with longer duration of use

- Purpose: To assess the incidence of heart failure & cardiomyopathy, among adult and pediatric ADHD medication users with no history of heart failure, by duration of ADHD medication use.

Methods

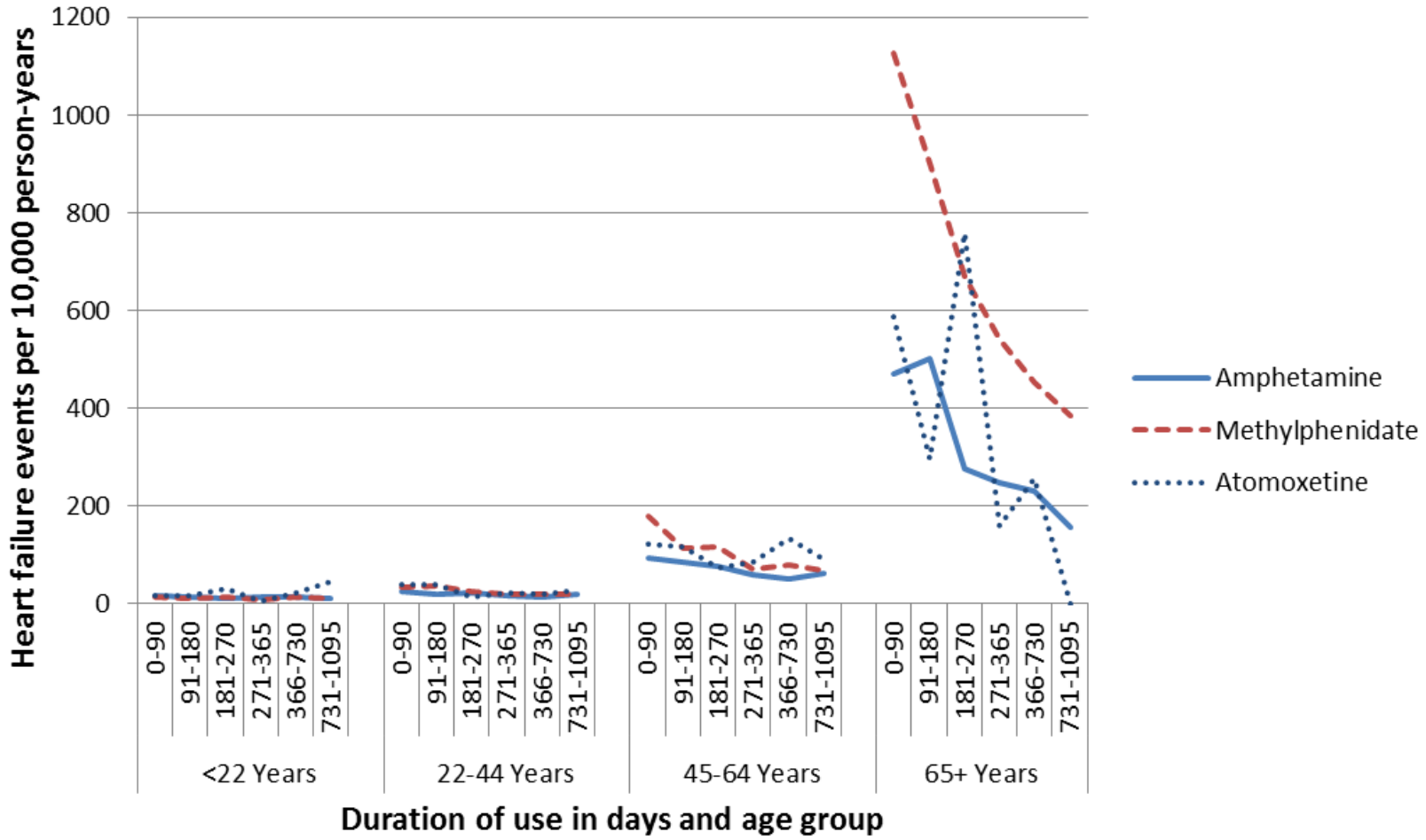
- Modified L1 descriptive analysis
- 15 Sentinel Data Partners contributed data
- Time period: January 1, 2000-March 3, 2016
- Patients: Users of amphetamine products (including lisdexamfetamine), methylphenidate, or atomoxetine
- No ADHD medication or outcome within the preceding 183 days
- Age groups: <22, 22-44, 45-64, and 65+ years
- Exposure episodes allowed gaps in days supply up to 90 days (to allow for variability in patterns of use).
- Only each patient's first treatment episode analyzed

Methods (2)

- Outcome (modified from Allen et al., 2014):
  - Heart failure or cardiomyopathy ICD-9-CM diagnosis codes (398.91, 402.x1, 402.x3, 404.x1, 404.x3, 422.90, 425.4, 425.9, 428.xx)
  - Principal diagnosis if inpatient/institutional
- Durations of use analyzed, in days
  - 0-90
  - 91-180
  - 181-270
  - 271-365
  - 366-730
  - 731-1,095 (=3 yrs)

Results

Figure 1. Rate of heart failure events (per 10,000 person years) by age group, medication, and duration of use



Limitations

- Did not assess risk relative to non use
- Could not account for potential confounding
- Combining heart failure with cardiomyopathy might have obscured a trend for cardiomyopathy alone

Conclusions

- No consistent increases in heart failure/cardiomyopathy over 3 years of ADHD medication use, in any age category.
- Hypothesis of a higher incidence emerging with longer duration of treatment not supported
- In older age groups, trend for higher incidence of heart failure earlier in the course of treatment
- 1.7% of patients 65+ years initiating ADHD medication developed heart failure/cardiomyopathy within 90 days

Conclusions

- Trend suggests depletion of susceptibles, to the extent that patients at risk of developing heart failure while receiving the medication tend to do so earlier in the course of treatment
- Biological plausibility?
  - Older literature suggests adrenergic agonists harmful in heart failure (Carbonin and Zuccala, 1996)
  - Beta blockers are used therapeutically in heart failure

Sentinel's Role in Safety Assessment

- Hypothesis that cardiomyopathy could be associated with long term stimulant use based on
  - Case reports
  - Known association with stimulant abuse
- Sentinel analysis
  - Did not support hypothesis
  - Identified a new signal for heart failure with short term use in patients 65+
- Possible next steps to address this new signal
  - Explore risk factors among older patients who develop heart failure/cardiomyopathy with ADHD medication
  - Conduct meta-analysis of heart failure & cardiovascular outcomes in randomized, controlled trials of ADHD medications in adults

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CDER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

Prospective Surveillance of AMI Events in New Users of Saxagliptin

Ninth Annual Sentinel Initiative Public Workshop
Washington, D.C.
February 2, 2017

Christian Hampp, Ph.D., B.S. Pharm
Senior Epidemiologist, Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration

Acknowledgments

Mini-Sentinel

Darren Toh (co-lead)

Bruce Fireman (co-lead)

Melissa Butler

Jack Hamilton

Samuel Lendle

Gwyn Saylor

SOC

Aarthi Iyer

Madelyn Pimentel

Malcolm Rucker

Neesha Nathwani

Amanda McNeill

FDA

Marsha Reichman (FDA lead)

David Graham

Christian Hampp

Rongmei Zhang

Mary Ross Southworth

Jennifer Pippins

Mark Levenson

Amy Egan

Data Partners

Aetna

Group Health

Harvard Pilgrim

HealthCore

HealthPartners

Henry Ford

Humana

KP Colorado

KP Hawaii

KP Mid-Atlantic

KP N California

KP Northwest

KP Southeast

Lovelace

Marshfield

Meyers

Optum

Vanderbilt

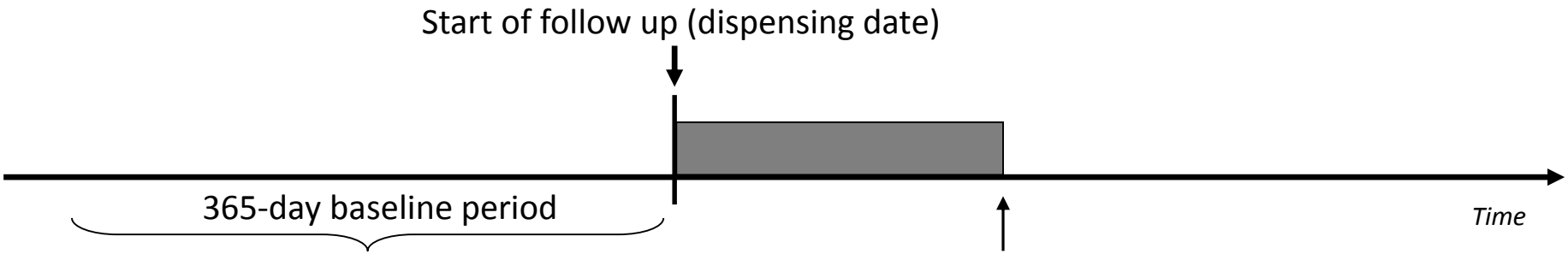
Motivation

- Need for infrastructure to prospectively monitor the safety of new drugs
- Saxagliptin, a DPP-4 inhibitor, is an oral anti-hyperglycemic agent approved in 2009
- Saxagliptin was chosen by FDA as the first NME to be prospectively monitored in the Mini-Sentinel pilot
  - Results from Mini-Sentinel would complement results from a post-market CV outcomes trial (SAVOR-TIMI 53)
  - Mini-Sentinel could provide interim safety info about saxagliptin while FDA awaited final results from the trial
  - Prospective surveillance could help identify safety issues more quickly than conventional observational studies

Surveillance design

- Protocol-based analysis: Protocol was published, subsequent revisions publicly posted
- New-user cohort design
- Four head-to-head comparisons
  - Saxagliptin
    - vs. sitagliptin
    - vs. pioglitazone
    - vs. second-generation sulfonylureas
    - vs. long-acting insulin products

Surveillance design



- Application of inclusion/exclusion criteria
- Assessment of covariates

- **Outcome: AMI**
- Death
- Health plan disenrollment
- Discontinuation of initial treatment
- Initiation of another drug in the pair
- End of surveillance period

Contributing person-times

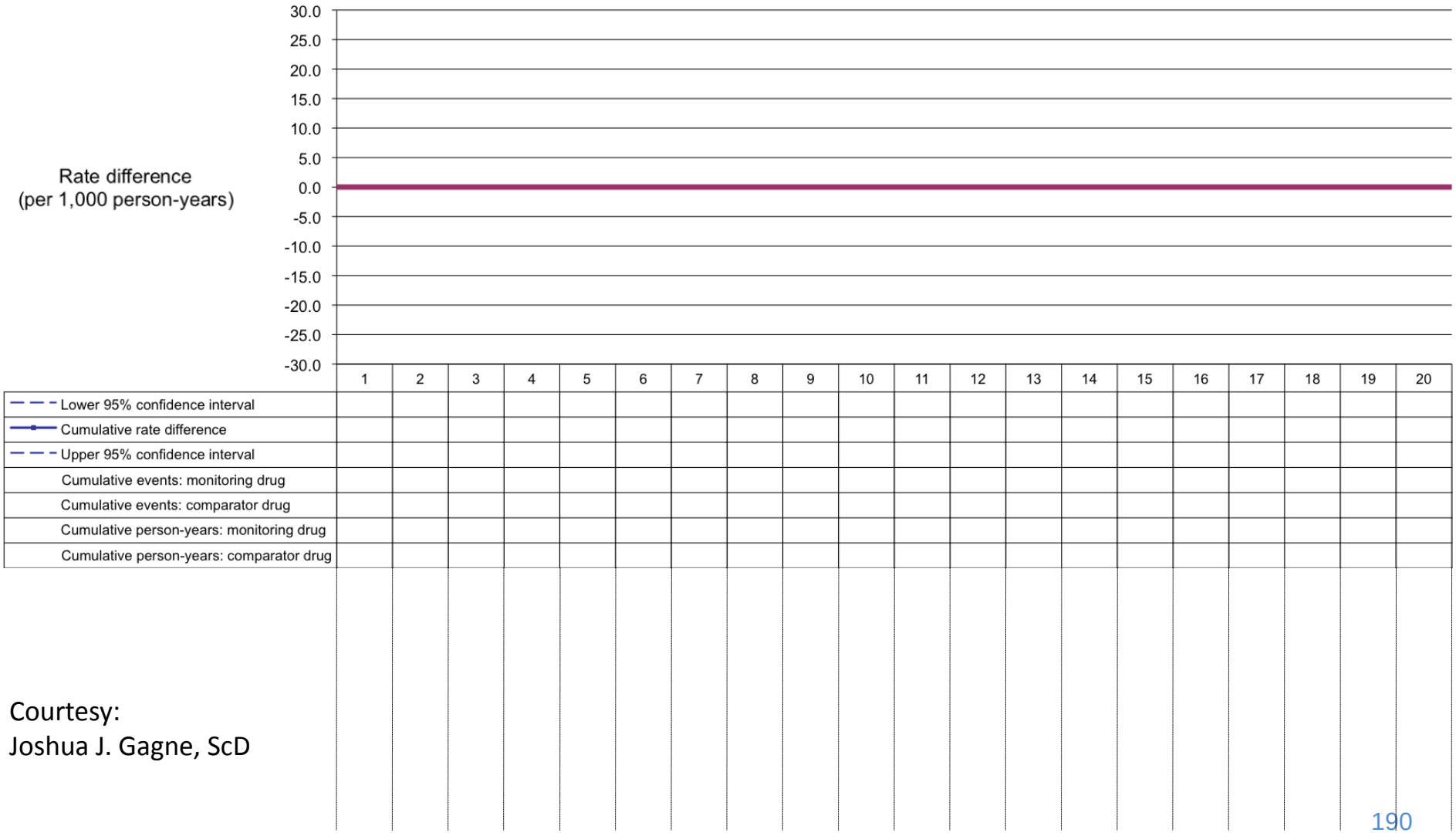
Statistical analysis

- Covariate adjustment:
  - Propensity score matching (1:1)
  - Disease risk score stratification (by decile)
- Covariates:
  - Patient demographics
  - Medical history
  - Medication use
  - Cardiovascular risk factors
  - Other antihyperglycemic treatments
  - Health services utilization measures

Statistical analysis

- Cox regression model to estimate hazard ratios and 95% confidence intervals
- Three patient groups
  - All patients
  - Patients with prior CVD history
  - Patients without prior CVD history

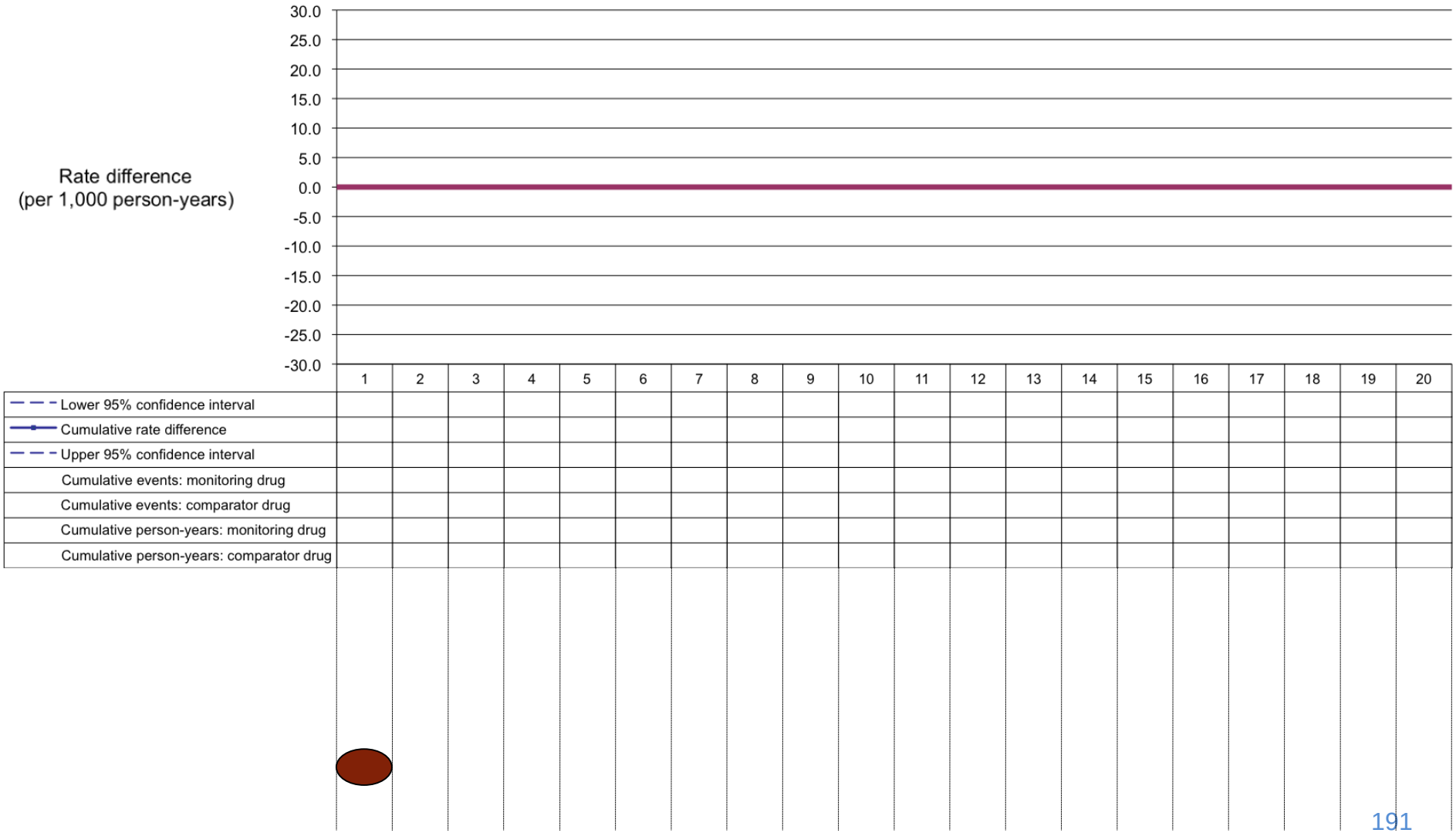
What prospective surveillance looks like



Courtesy:
Joshua J. Gagne, ScD

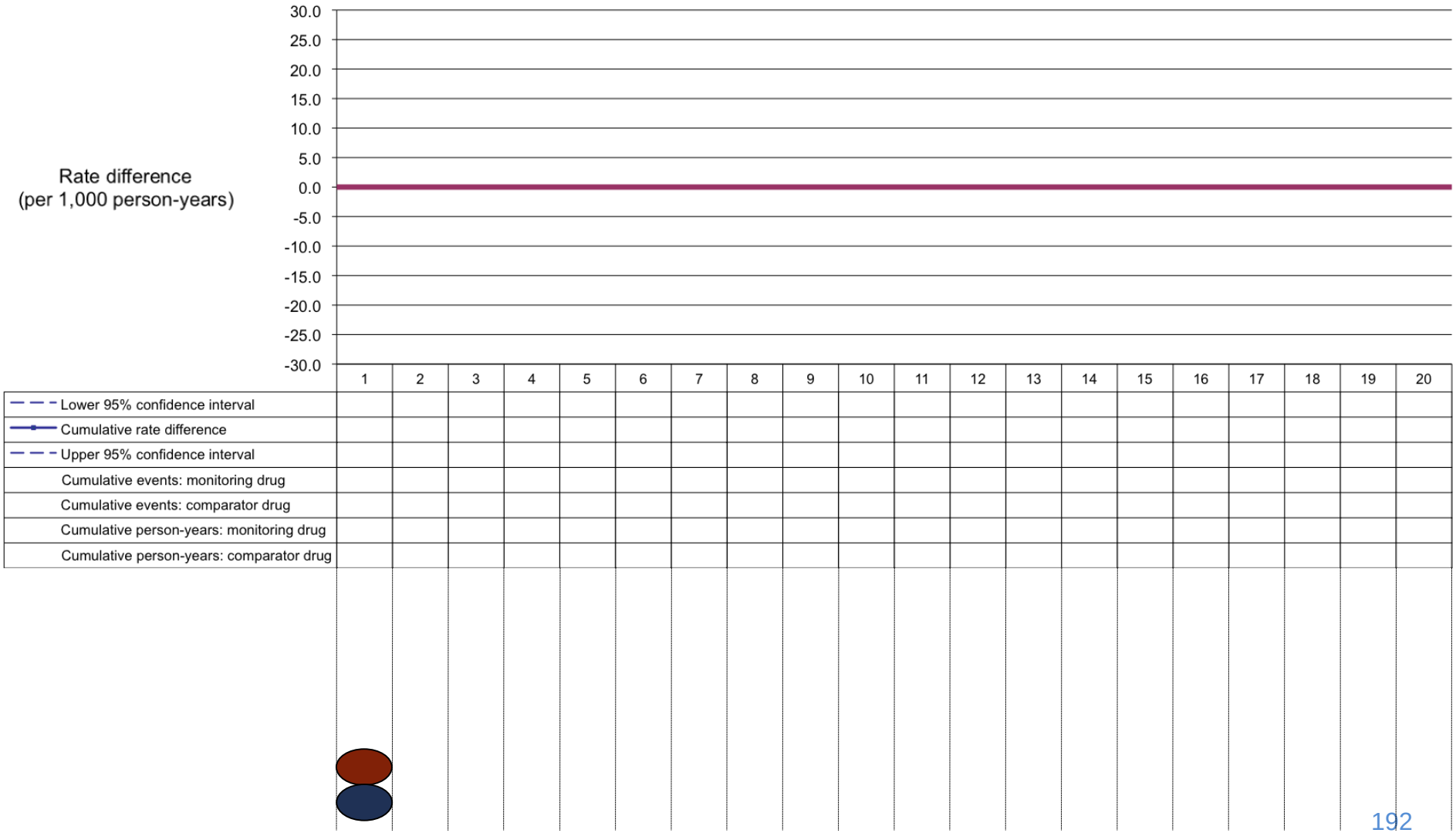
* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like



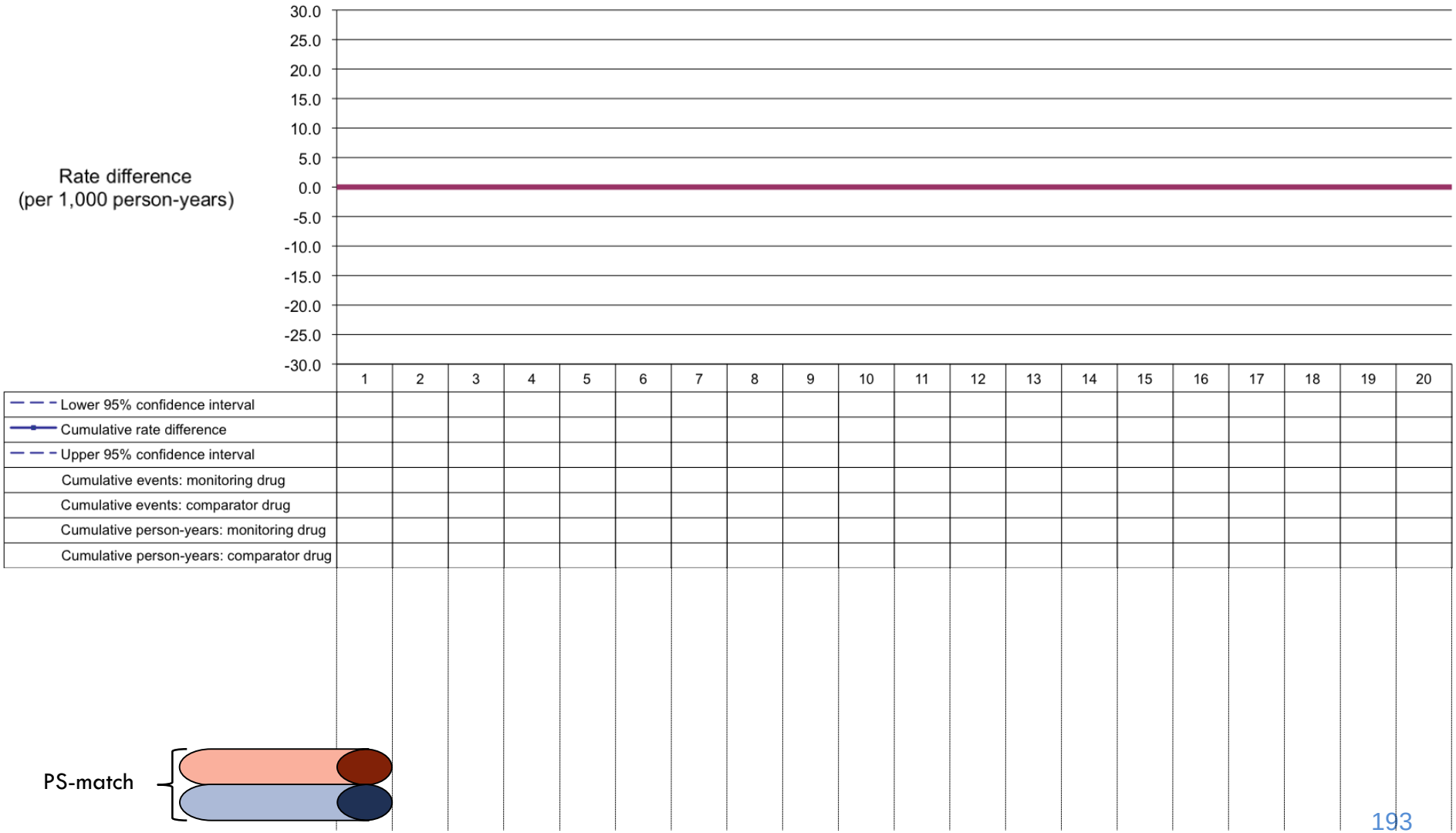
* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like



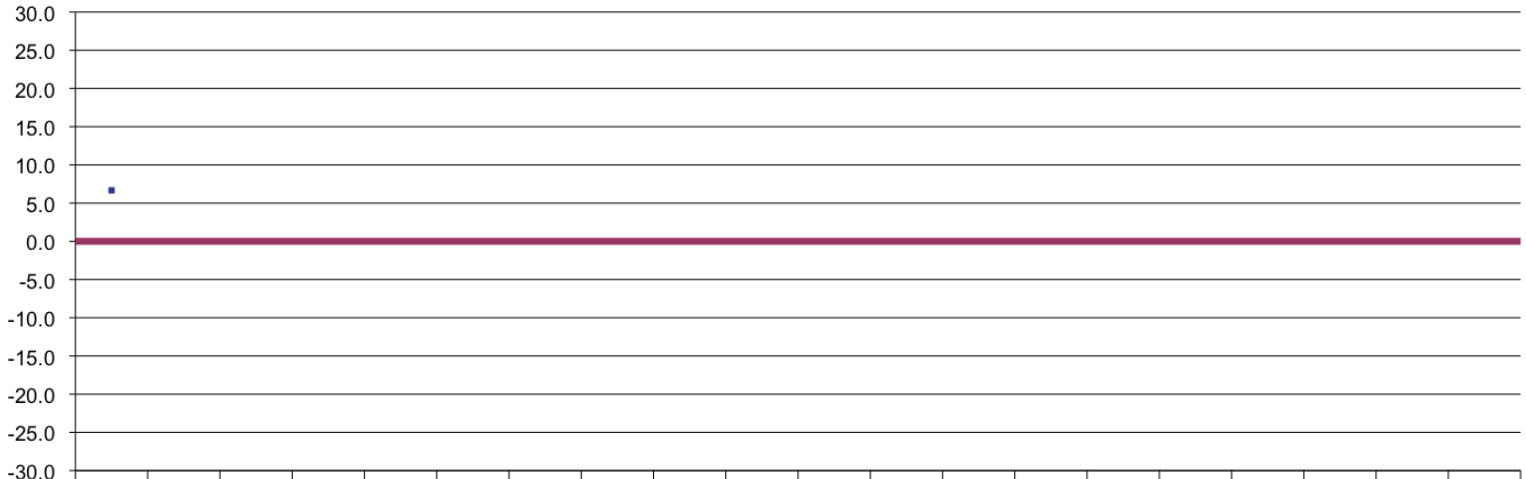
* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like



* Data are not from Mini-Sentinel and are shown for illustrative purposes only

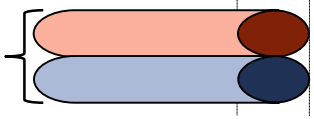
What prospective surveillance looks like



Rate difference
(per 1,000 person-years)

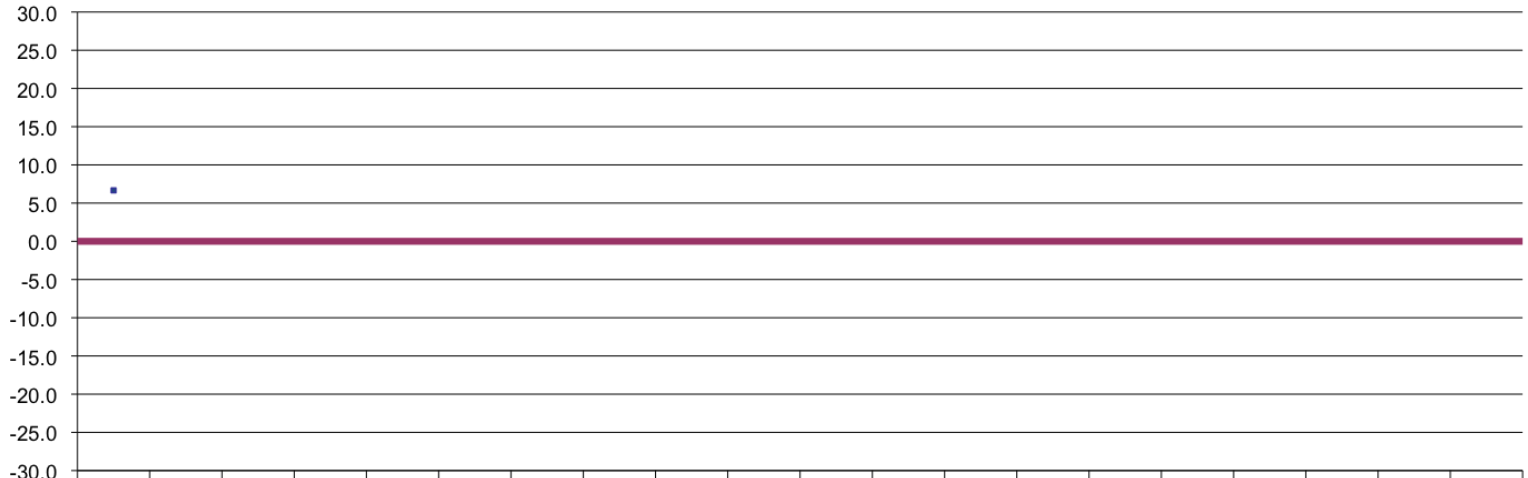
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50																			
Cumulative rate difference	6.67																			
Upper 95% confidence interval	35.88																			
Cumulative events: monitoring drug	3																			
Cumulative events: comparator drug	2																			
Cumulative person-years: monitoring drug	150																			
Cumulative person-years: comparator drug	150																			

PS-match



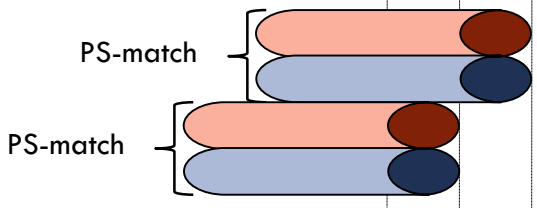
* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like



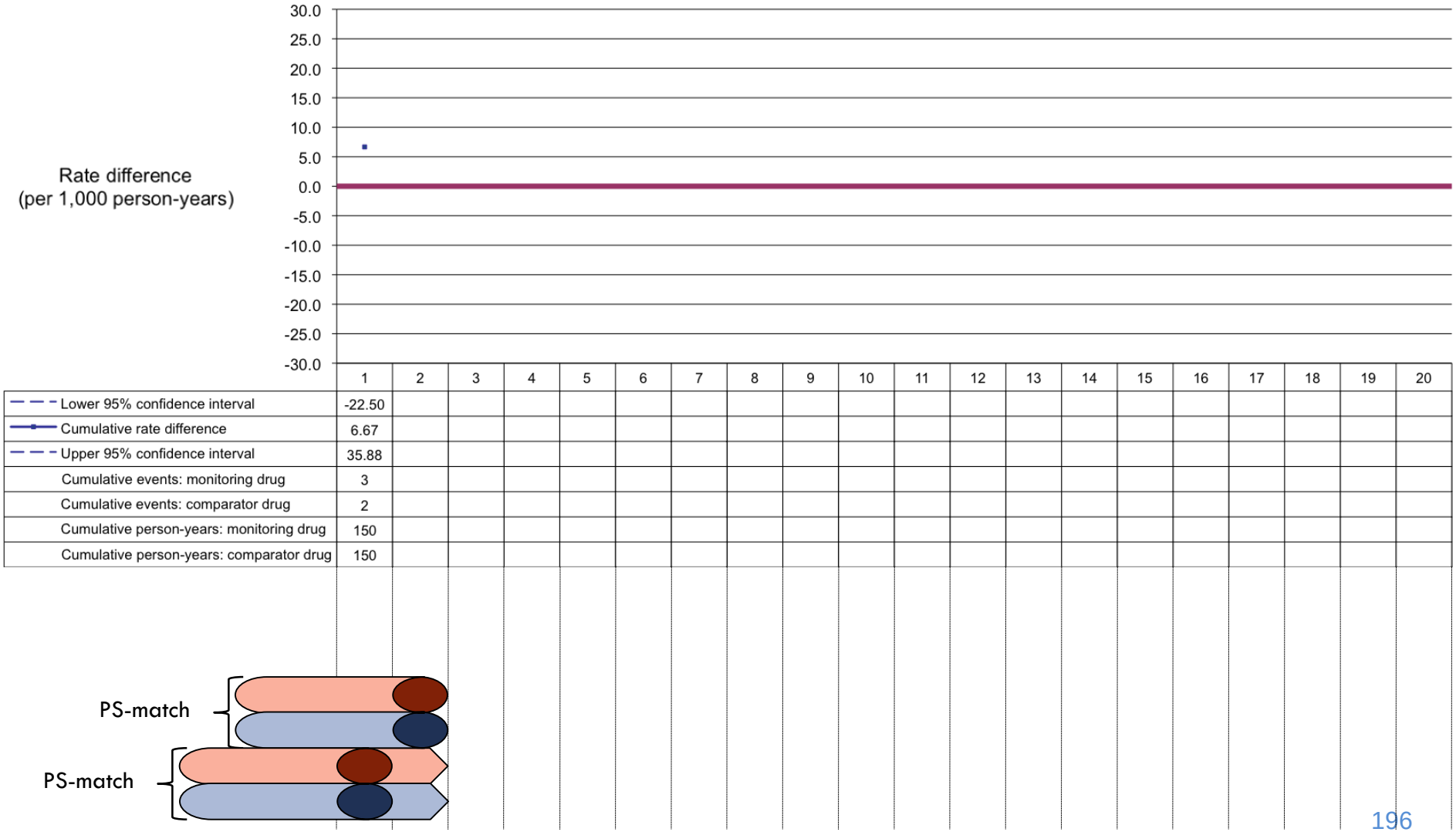
Rate difference
(per 1,000 person-years)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50																			
Cumulative rate difference	6.67																			
Upper 95% confidence interval	35.88																			
Cumulative events: monitoring drug	3																			
Cumulative events: comparator drug	2																			
Cumulative person-years: monitoring drug	150																			
Cumulative person-years: comparator drug	150																			



* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like

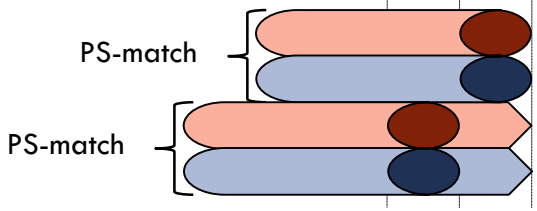


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50																			
Cumulative rate difference	6.67																			
Upper 95% confidence interval	35.88																			
Cumulative events: monitoring drug	3																			
Cumulative events: comparator drug	2																			
Cumulative person-years: monitoring drug	150																			
Cumulative person-years: comparator drug	150																			

* Data are not from Mini-Sentinel and are shown for illustrative purposes only

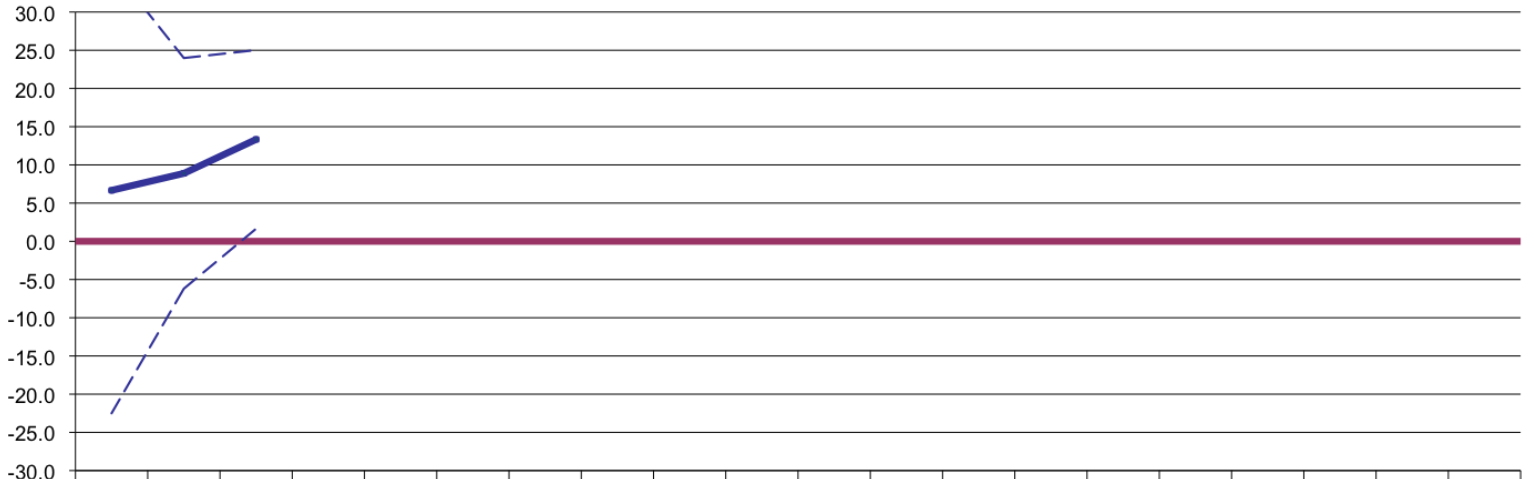
What prospective surveillance looks like

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20																		
Cumulative rate difference	6.67	8.89																		
Upper 95% confidence interval	35.88	23.98																		
Cumulative events: monitoring drug	3	8																		
Cumulative events: comparator drug	2	4																		
Cumulative person-years: monitoring drug	150	450																		
Cumulative person-years: comparator drug	150	450																		

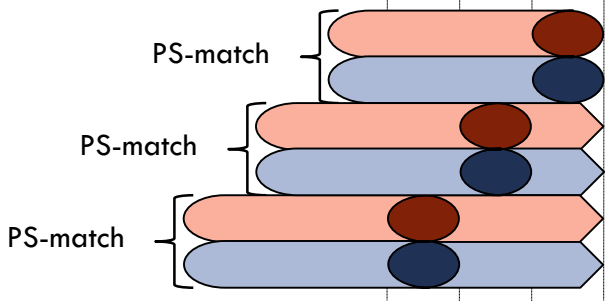


* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like

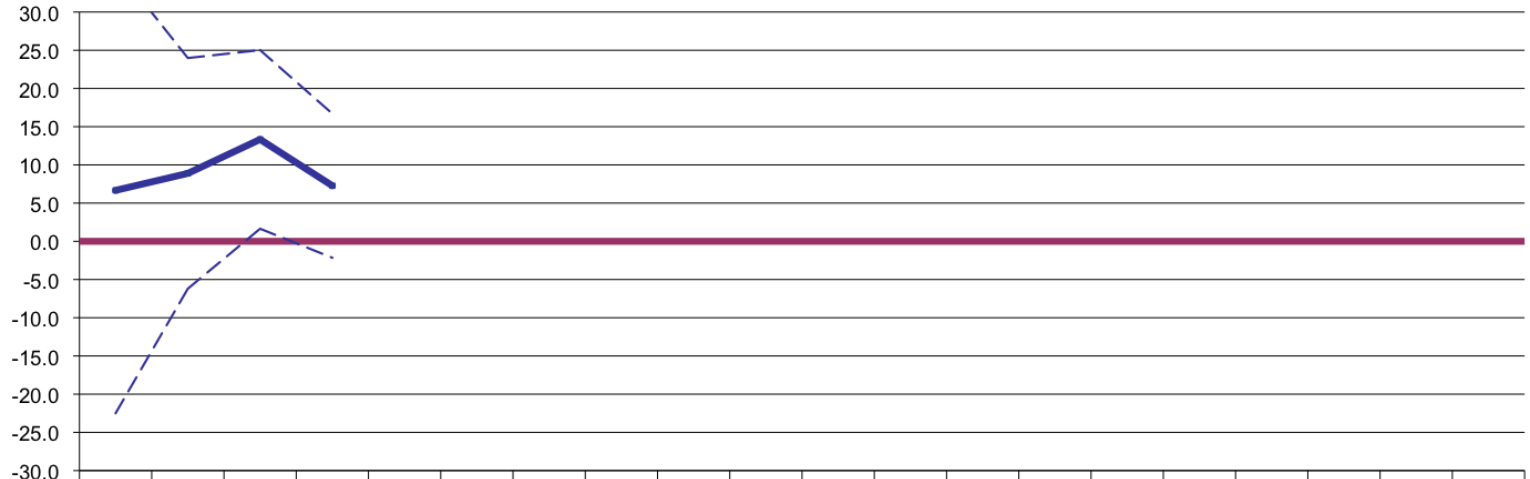


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65																	
Cumulative rate difference	6.67	8.89	13.33																	
Upper 95% confidence interval	35.88	23.98	25.02																	
Cumulative events: monitoring drug	3	8	15																	
Cumulative events: comparator drug	2	4	5																	
Cumulative person-years: monitoring drug	150	450	750																	
Cumulative person-years: comparator drug	150	450	750																	

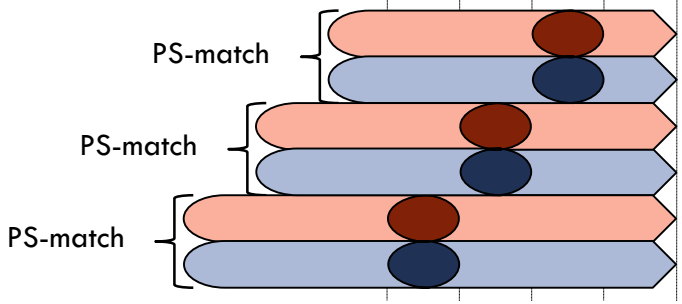


* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like



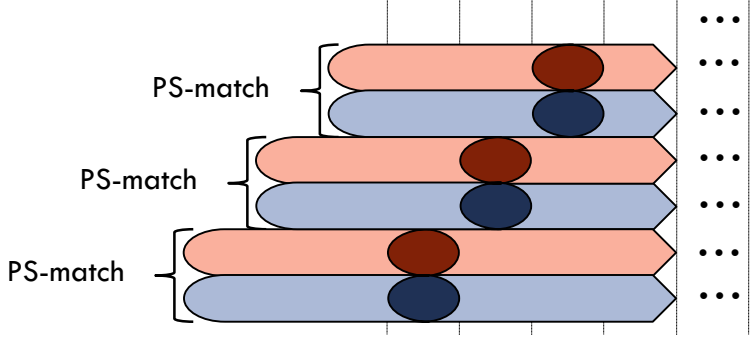
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65	-2.16																
Cumulative rate difference	6.67	8.89	13.33	7.27																
Upper 95% confidence interval	35.88	23.98	25.02	16.70																
Cumulative events: monitoring drug	3	8	15	18																
Cumulative events: comparator drug	2	4	5	10																
Cumulative person-years: monitoring drug	150	450	750	1100																
Cumulative person-years: comparator drug	150	450	750	1100																



* Data are not from Mini-Sentinel and are shown for illustrative purposes only

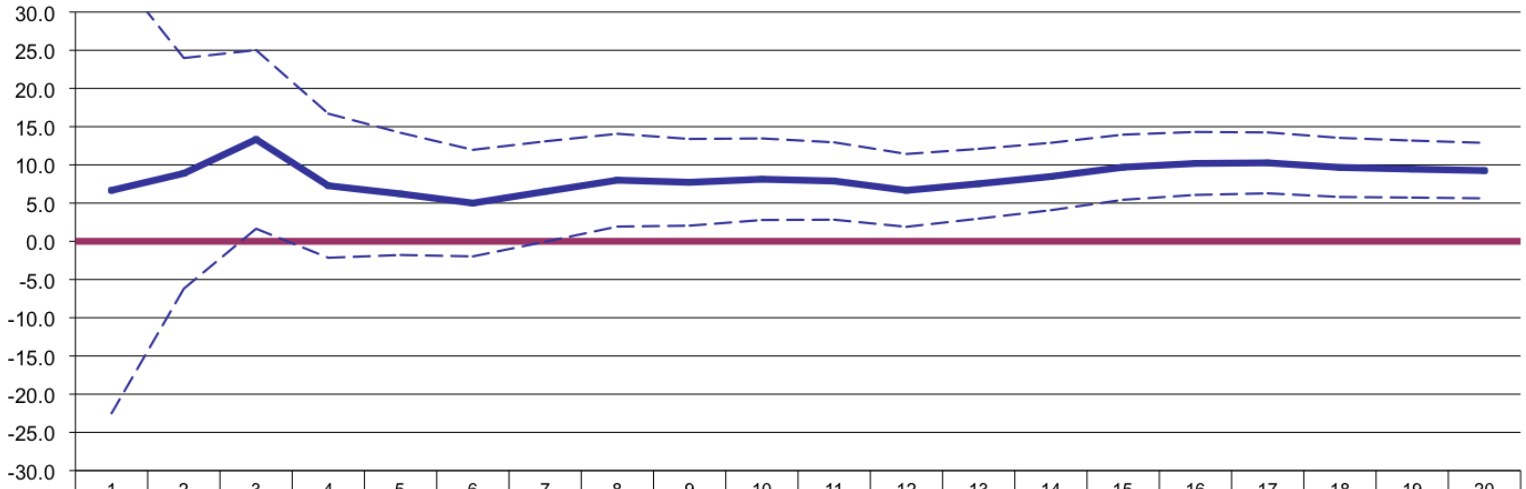
What prospective surveillance looks like

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65	-2.16	-1.79															
Cumulative rate difference	6.67	8.89	13.33	7.27	6.21															
Upper 95% confidence interval	35.88	23.98	25.02	16.70	14.20															
Cumulative events: monitoring drug	3	8	15	18	22															
Cumulative events: comparator drug	2	4	5	10	13															
Cumulative person-years: monitoring drug	150	450	750	1100	1450															
Cumulative person-years: comparator drug	150	450	750	1100	1450															

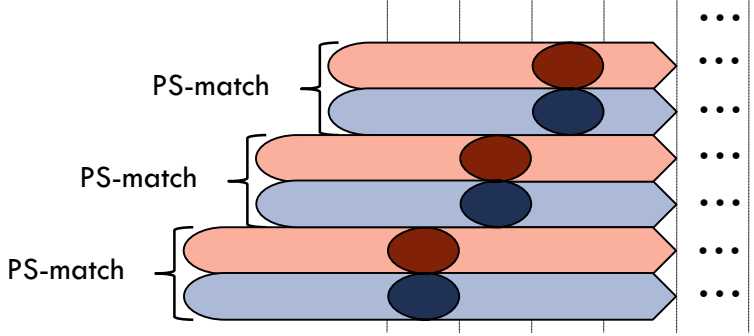


* Data are not from Mini-Sentinel and are shown for illustrative purposes only

What prospective surveillance looks like



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65	-2.16	-1.79	-1.97	-0.06	1.93	2.05	2.79	2.83	1.90	2.96	4.07	5.43	6.07	6.28	5.80	5.72	5.62
Cumulative rate difference	6.67	8.89	13.33	7.27	6.21	5.00	6.51	8.00	7.72	8.13	7.89	6.67	7.53	8.48	9.70	10.19	10.27	9.67	9.45	9.25
Upper 95% confidence interval	35.88	23.98	25.02	16.70	14.20	11.97	13.08	14.07	13.39	13.46	12.95	11.43	12.09	12.89	13.96	14.31	14.25	13.53	13.18	12.88
Cumulative events: monitoring drug	3	8	15	18	22	25	33	40	45	51	56	58	65	73	82	89	95	99	103	108
Cumulative events: comparator drug	2	4	5	10	13	16	19	20	23	25	28	32	33	34	34	35	37	41	43	46
Cumulative person-years: monitoring drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700
Cumulative person-years: comparator drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700



* Data are not from Mini-Sentinel and are shown for illustrative purposes only

Sequential surveillance

- Prospective surveillance: **7** sequential analyses
- Overall chance of false positive signal kept below 0.05 (one-sided)
- At each sequential analysis step: **2** methods of covariate adjustment x **4** comparisons x **3** CVD strata = **24** analyses

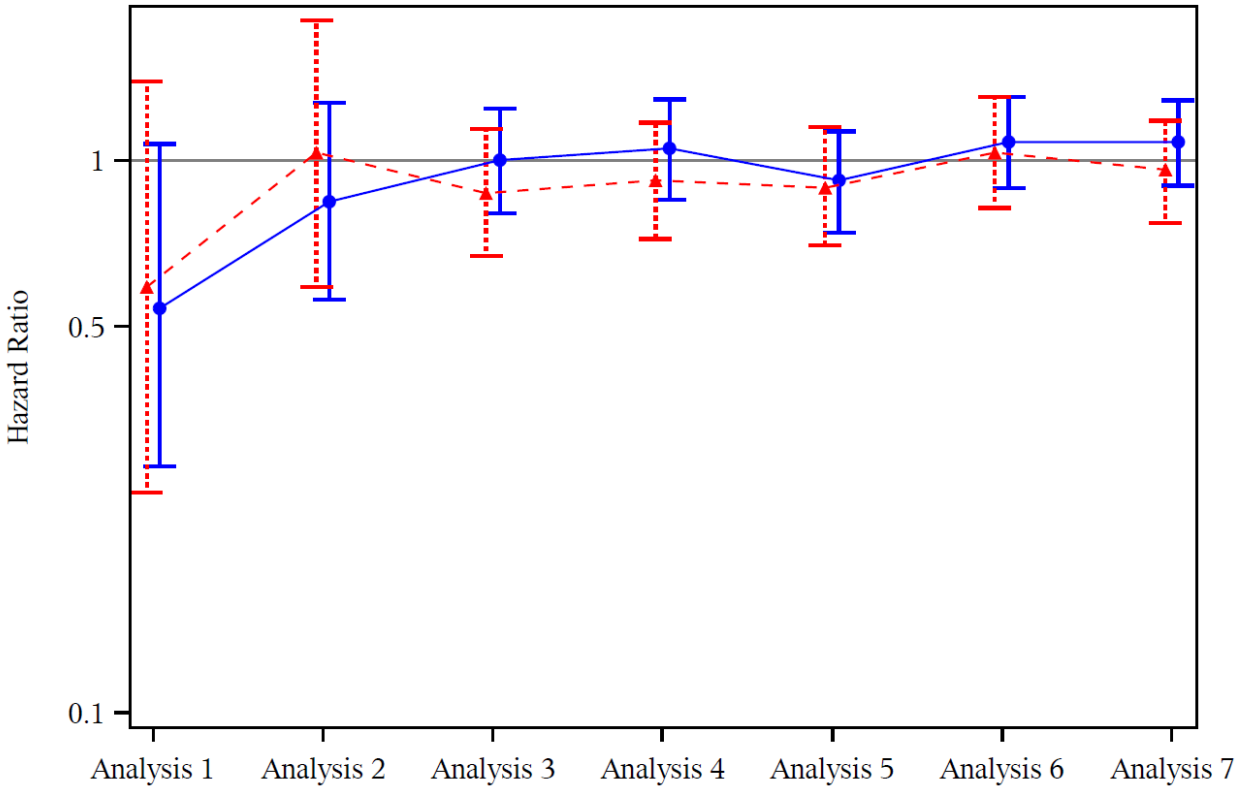
Selected baseline characteristics

Covariate	Saxagliptin*	Sitagliptin	Pioglitazone	2nd-generation sulfonylureas	Long-acting insulin
Total N	82,264	220,912	146,045	452,969	262,117
Patient demographic					
Mean age	57.3	59.1	58.4	59.0	59.5
Male sex	56.1%	54.9%	58.1%	55.2%	54.0%
Comorbid condition	%	%	%	%	%
Asthma	6.6	7.2	6.6	8.0	9.3
Cancer	6.4	7.4	6.2	7.3	9.1
COPD	6.2	7.7	6.3	8.6	11.0
Chronic kidney disease	5.8	7.6	7.6	9.1	13.8
Dementia	1.4	2.5	1.9	2.7	3.9
Depression	9.0	10.1	9.2	11.1	14.0
ESRD	0.5	0.9	0.8	1.1	2.0
Fracture	2.8	3.4	3.1	3.3	4.3
Heart failure	5.3	7.5	4.5	7.8	11.8
HIV / AIDS	0.2	0.2	0.2	0.2	0.3
Hyperlipidemia	79.2	77.5	76.7	71.5	76.4
Hypertension	78.0	78.0	76.0	74.2	79.4
Hypoglycemia	4.2	5.2	5.4	6.4	10.6
Obesity or weight gain	18.8	19.3	16.9	20.1	24.0
Osteoporosis	4.3	4.8	4.2	4.4	4.6
Peripheral neuropathy	14.4	15.9	15.6	15.0	22.9
Tobacco use	7.2	7.6	7.1	10.4	12.4

* Included saxagliptin users who contributed to one or more pairwise comparisons

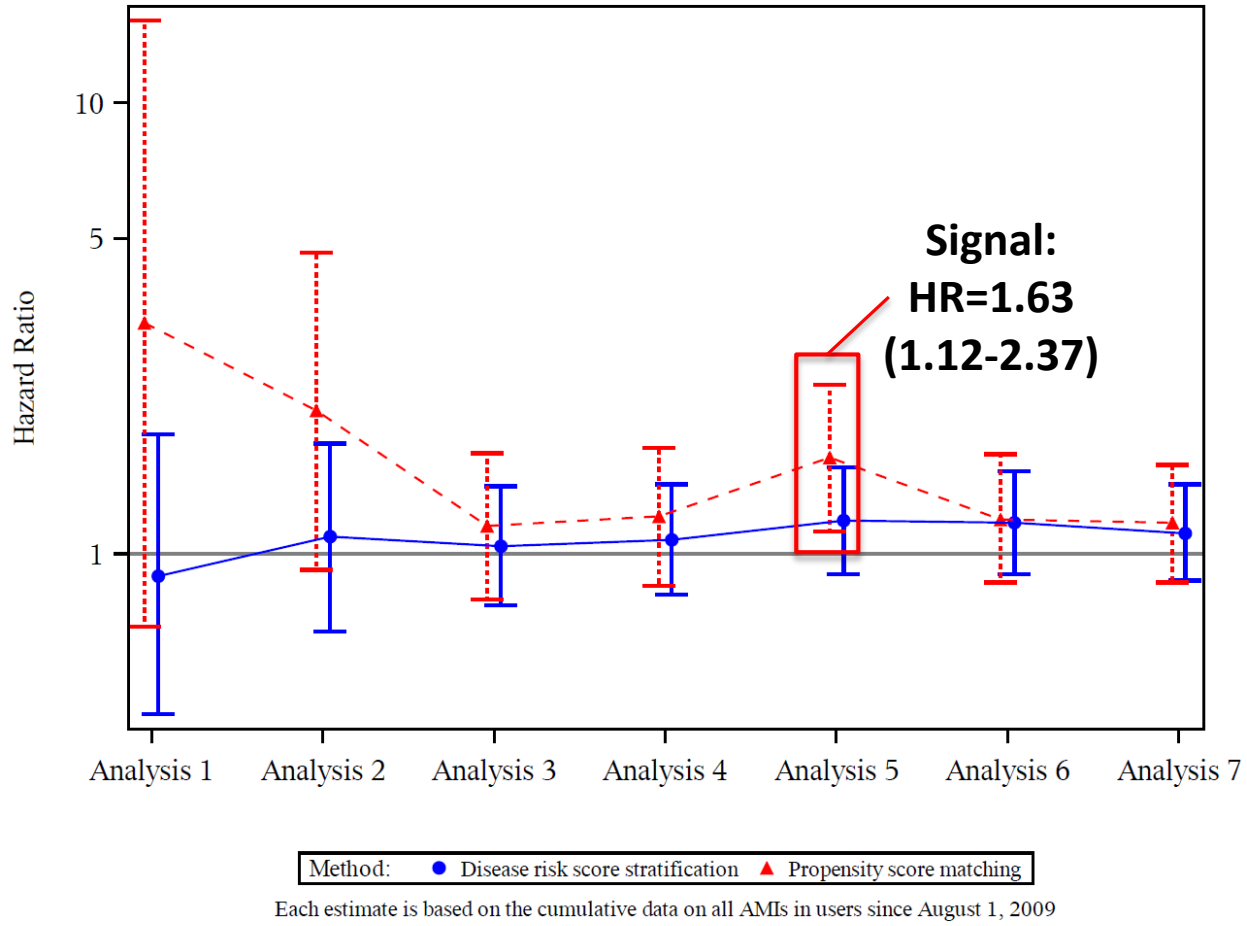
AMI: Saxagliptin vs. sitagliptin

	Look 1	Look 2	Look 3*	Look 4	Look 5	Look 6	Look 7
Data from 8/1/09 through	*6/30/11*	*12/31/11*	*12/31/11*	*6/30/12*	*3/31/13*	*12/31/13*	*8/31/14*

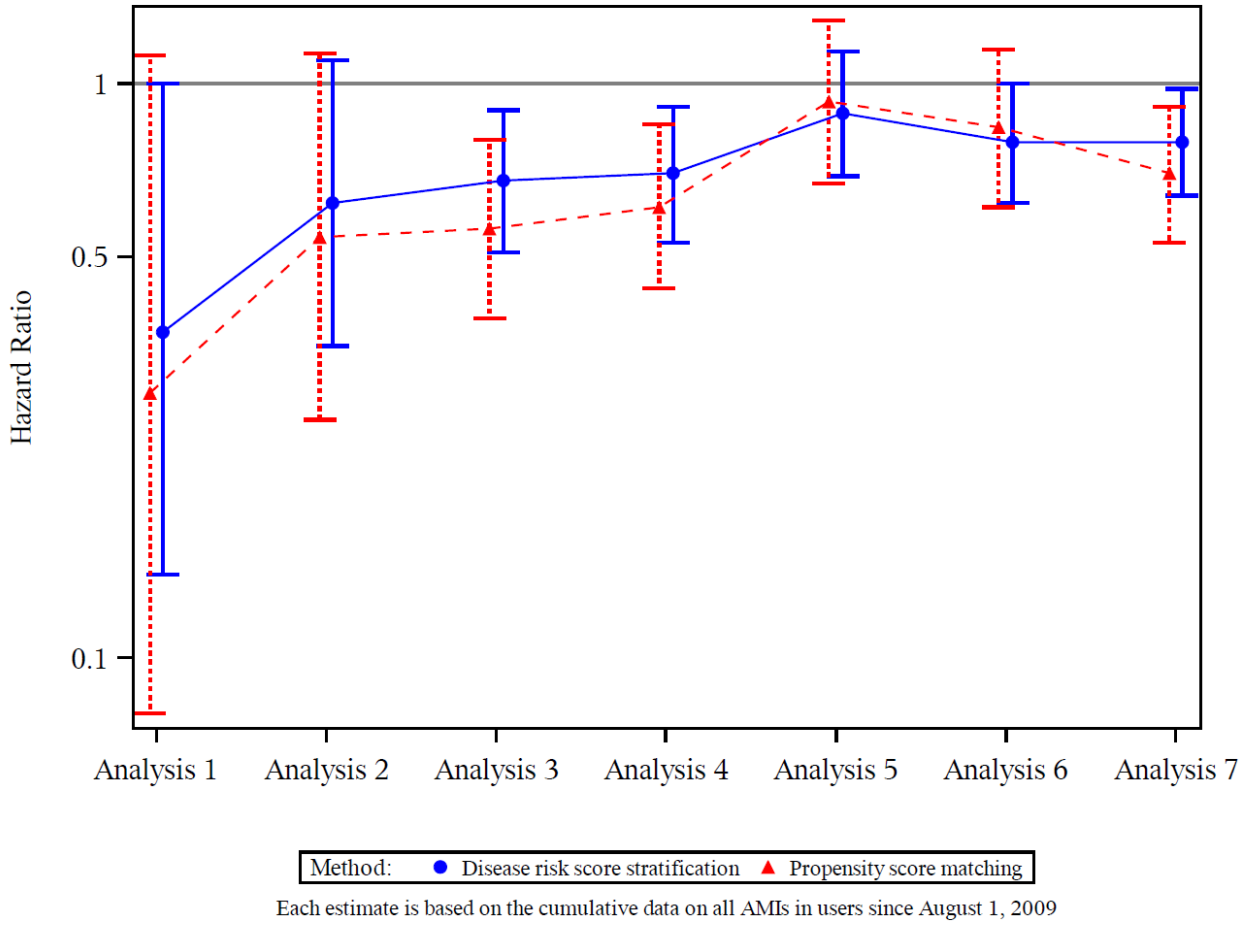


Each estimate is based on the cumulative data on all AMIs in users since August 1, 2009

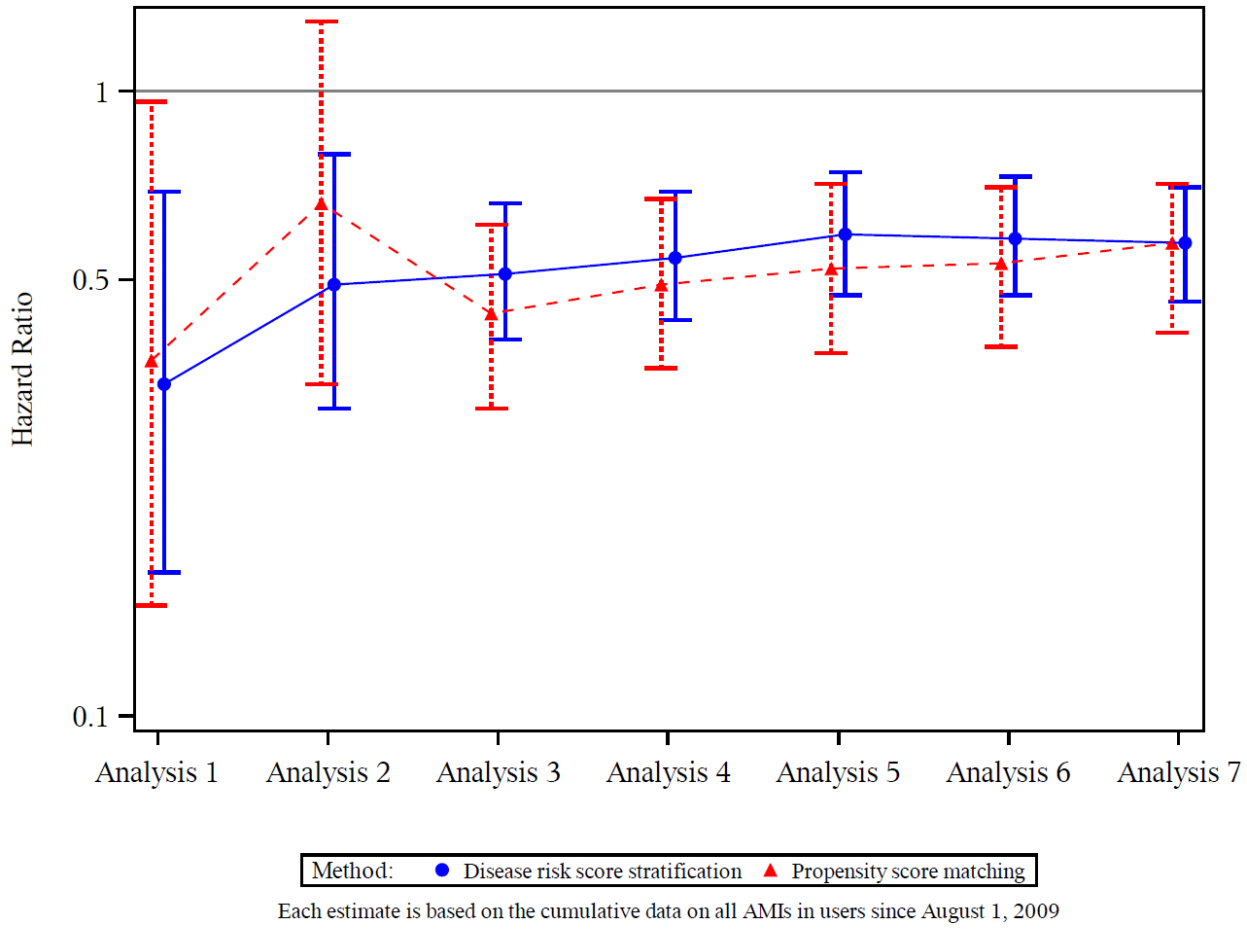
AMI: Saxagliptin vs. pioglitazone



AMI: Saxagliptin vs. sulfonylureas



AMI: Saxagliptin vs. long-acting insulin



For the one analysis that signaled

- PS-matched analysis
  - Fifth look: HR 1.63 (1.12, 2.37)
  - Sixth look: HR 1.19 (0.86, 1.66)
  - Seventh look: HR 1.17 (0.86, 1.57)

- Corresponding DRS-stratified analysis
  - Fifth look: HR 1.18 (0.90, 1.55)
  - Sixth look: HR 1.17 (0.90, 1.52)
  - Seventh look: HR 1.11 (0.87, 1.42)

Possible reasons for the signal

- Risk of AMI was higher with saxagliptin vs. pioglitazone
- Residual or unmeasured confounding
- Errors in data or analytic code
- Chance finding

Study Conclusion

We found no strong evidence to suggest a higher risk of AMI in saxagliptin users compared to users of sitagliptin, pioglitazone, second-generation sulfonylureas, or long-acting insulin

SAVOR-TIMI 53 trial

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

N Engl J Med 2013;369:1317-26.

Comparisons with SAVOR-TIMI 53 trial

Characteristics	SAVOR-TIMI 53 Trial	Mini-Sentinel surveillance*
Comparator	Placebo	Select anti-hyperglycemics
No. saxagliptin users	8,280	82,264
No. comparator users	8,212	146,045 to 452,969
Length of follow-up	2.1 years (median)	4 to 8 months (mean)
No. AMI in saxagliptin	265	94 to 171
No. AMI in comparator	278	75 to 1,085
Statistical analysis	Intention-to-treat	As-treated
Hazard ratio for AMI	0.95 (95% CI: 0.80, 1.12)	0.54 to 1.17

* From end-of-surveillance analysis that included all patients

Regulatory Importance

- Results from first “looks” were available before SAVOR-TIMI 53
- Real-life, head-to-head comparisons
- First prospective surveillance in (Mini-) Sentinel: established infrastructure for future studies

Thank you

Christian Hampp, PhD

christian.hampp@fda.hhs.gov

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CDER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

Sentinel

FDA U.S. FOOD & DRUG ADMINISTRATION

Ninth Annual Sentinel Initiative
Public Workshop, February 2, 2017

Risk of seizures associated with Ranolazine (Ranexa)

COLLABORATORS

FDA Center for Drug Evaluation and Research

Division of Epidemiology 1: Efe Eworuke, Margie Goulding, David Moeny, Michael Nguyen

Division of Cardio-Renal Products: MaryRoss Southworth

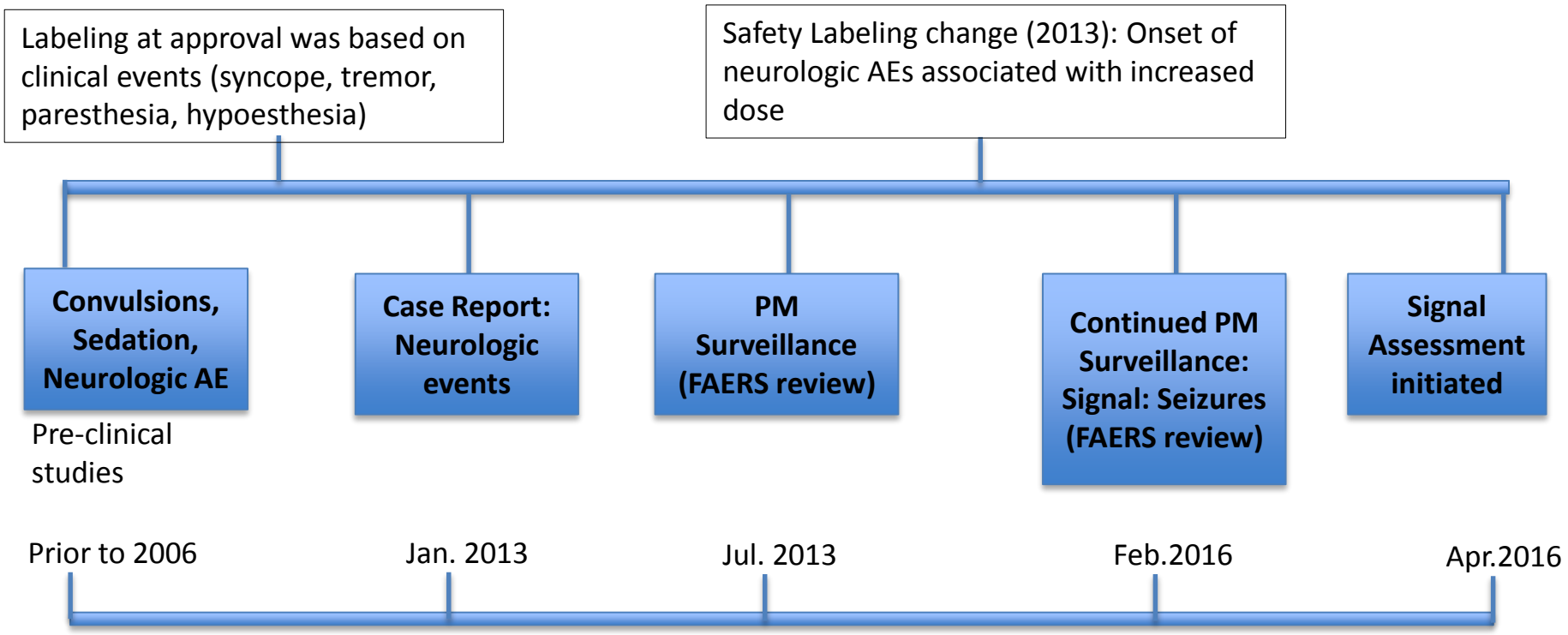
Harvard Pilgrim Health Care Institute

Emily Welch, Judith Maro

Background

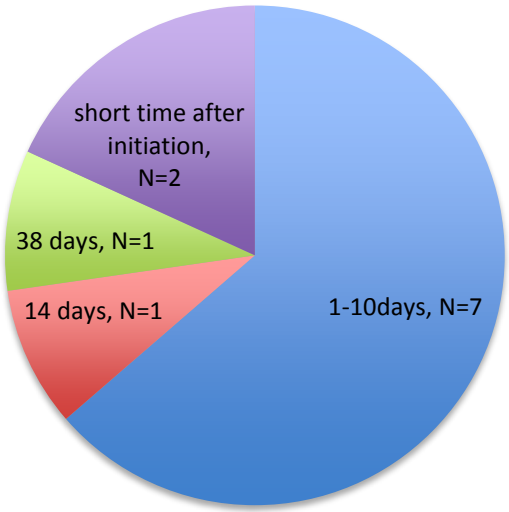
- Ranexa is an oral drug given twice daily for angina
- Angina is chest pain caused by insufficient blood flow to the heart (myocardial ischemia)
  - Possible pharmacological activity:
    - Demonstrated effects on sodium channels which are present in the cardiac, central and peripheral nervous systems

Safety Issue Timeline



Description of FAERS Case Reports

FAERS Reports
Time to Seizure Onset Following Ranexa Exposure
(N=11)



Median Age: 78 years

Outcome: Hospitalization (63.6%);

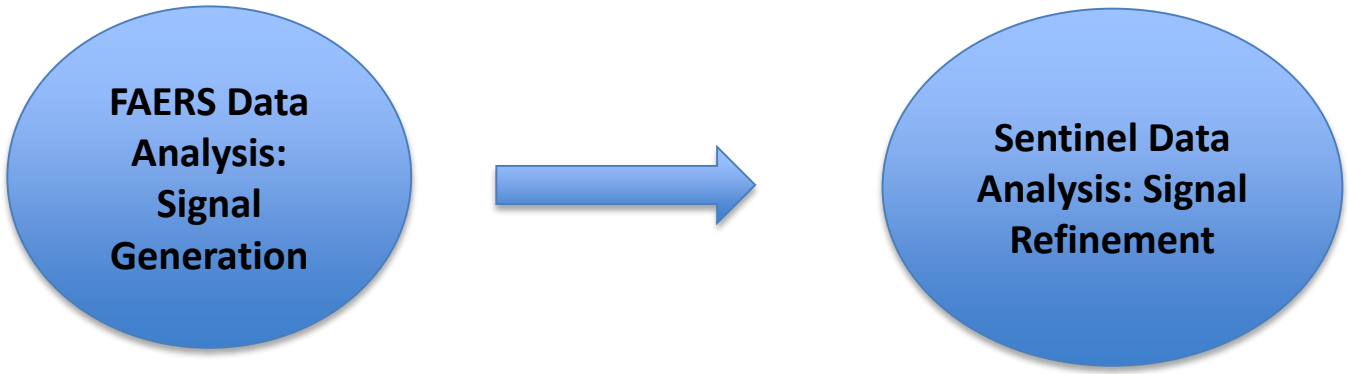
Dechallenge: Positive (72.7%)

Renal status: Chronic renal failure (36.3%); not reported (63.6%)

Temporality/Dechallenge: indicators for possible causality

Sentinel Objective

- To investigate whether Ranexa use is associated with an increased risk of seizures



Isolated Reports

Are seizures temporally associated with initiation of Ranexa?

Study Design Considerations

- Absence of an appropriate comparator
  - AHA* recommends Ranexa in circumstances in which beta blockers, calcium channel blockers, and nitrates are not adequately effective or are not tolerated.

- Self-controlled risk interval design (SCRI)-Level 2 Sentinel modular program
  - FAERS data reveal onset of seizures within a short period after exposure (7 out of 9 cases* occurred within 10 days)
  - SCRI design best suited for acute outcome, time-invariant confounders are controlled

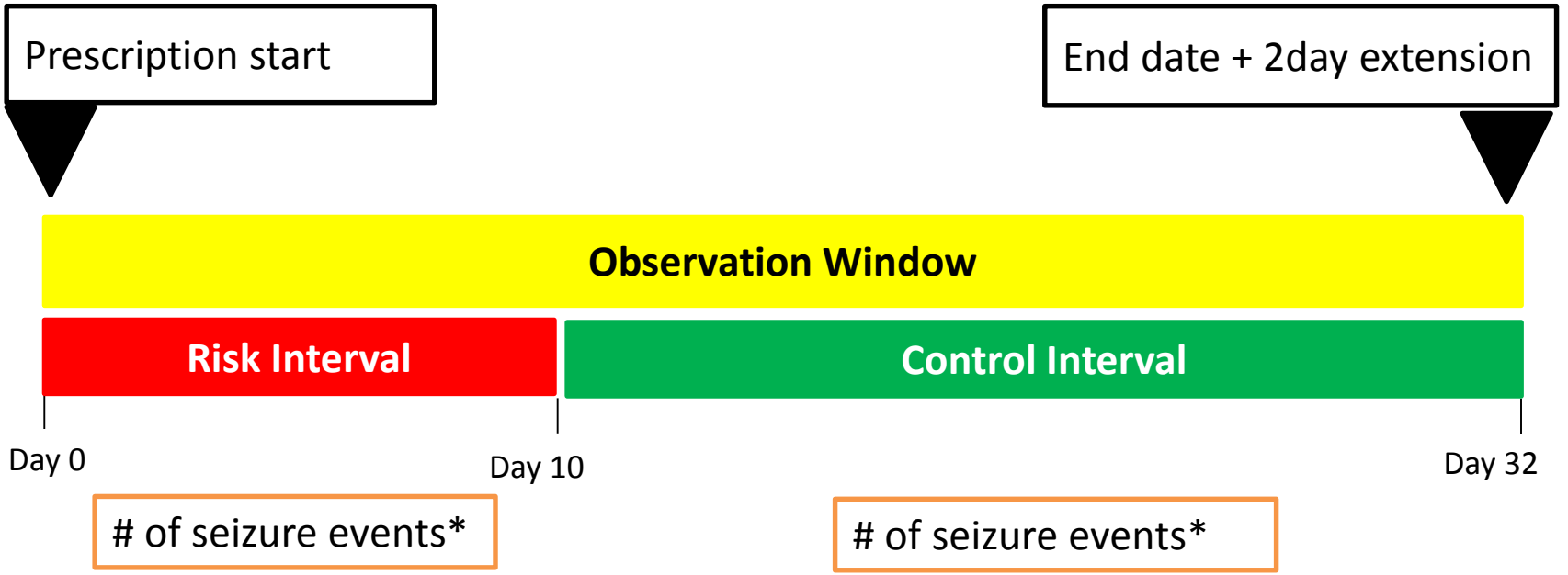
*AHA: American Heart Association

* Cases for which onset of seizure was reported

Methods

- Data: 01/01/2006 – 09/30/2015 from 12 health plans
- Cohort Definition: Patients ≥18 years old with at least 183 days medical and drug coverage
- Eligibility Criteria:
  - New use of Ranexa (no Ranexa during 183 day period (baseline) before use) and No epilepsy or seizure diagnosis and/or no anti-epileptic drug (AED) during baseline period – Ranexa cohort
  - New use of Ranexa (no Ranexa during 183 day period (baseline) before use) and No epilepsy or seizure diagnosis **but use of AED** during baseline period – Ranexa with AED cohort
- First valid 30-day prescription plus a 2-day extension period (observation window)

Self-Controlled Risk Interval Design



*Seizure event: ICD-9 codes for Epilepsy (345.X), convulsions (780.3X) or myoclonus (333.2) in Inpatient or Emergency Department discharge (PPV: 84% - Kee et al. 2012)

Populations of Interest

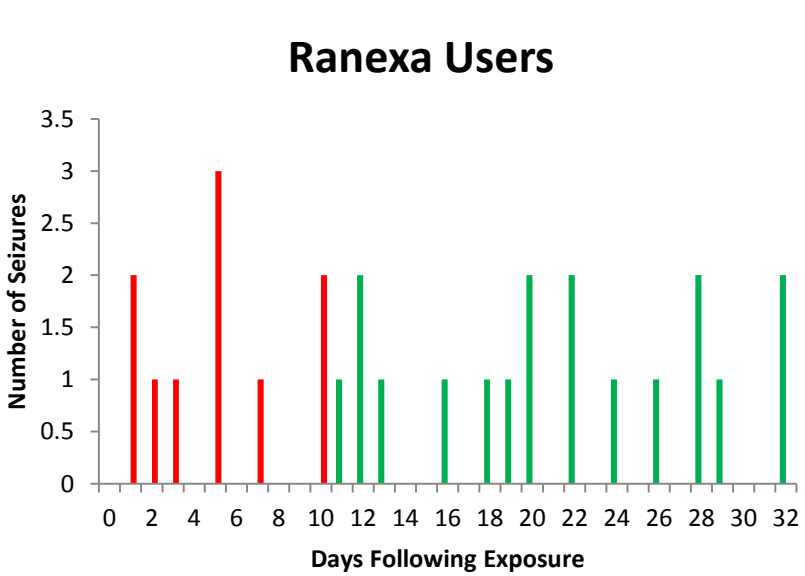
Population of interest	Description
Ranexa Users	Ranexa users with no epilepsy and no use of AED at baseline
Ranexa Users with AED	Ranexa Users with no epilepsy at baseline but used AED at baseline
Age categories	55-64 years, 65-74 years, 75+
Pre-existing renal disease	Presence of a diagnosis code for renal conditions including dialysis at baseline
Pre-existing liver disease	Presence of diagnosis code for liver conditions at baseline

Cases Characteristics Summary

Variables	FAERS cases	Sentinel Cases[a]	
		Ranexa users	Ranexa with AED[b]
Number of patients	11	28	11
Age, 55-64	0	5	1
Age, 65-74	2	5	4
Age, 75+	5	16	5
Gender, Female	50%	42.9%	72.7%
Renal Condition	36.3%	64.3%	NR
Liver Condition	NR	17.9%	NR

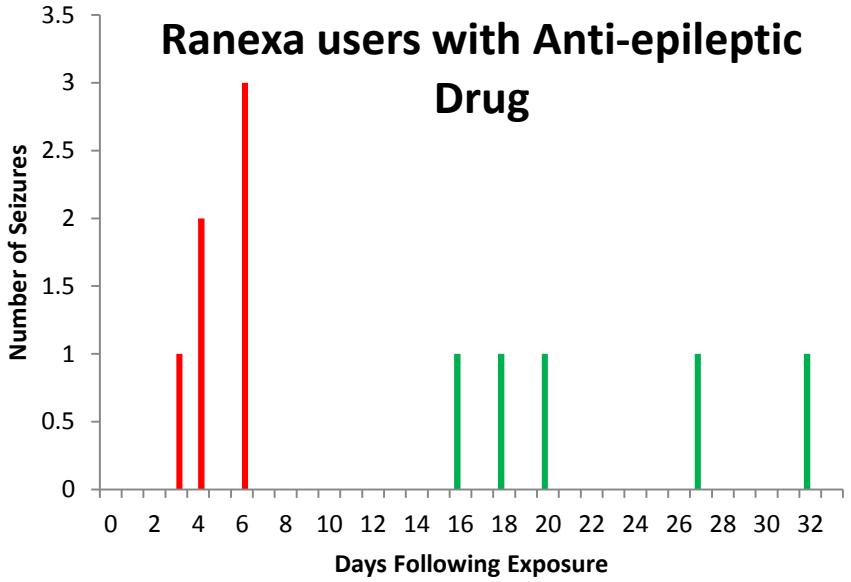
[a]Among 58,285 Ranexa users included in the study
[b]AED: Anti-epileptic Drug
NR: Not Reported

Seizure risk in risk window compared to control window



# Events in risk window	# Events in control window
10	18

Relative Risk: 1.1 (CI: 0.5-2.6)



# Events in risk window	# Events in control window
6	5

Relative Risk: 2.4 (CI: 0.7-7.9)

Seizure risk stratified by population of interest

Population of interest	Number of Events in Risk Window	Number of Events in Control Window	Relative Risk	95% Confidence Interval
Age: 55-64	2	3	1.3	0.2, 8.5
Age: 65-74	3	2	3.0	0.5, 24.1
Age: 75+	5	11	1.0	0.3, 3.0
Pre-existing renal disease	7	11	1.3	0.5, 3.7
Pre-existing liver impairment	1	4	0.5	0.1, 3.8

Result Summary

- Seizure rate within 10 days of Ranexa initiation is rare, and does not appear to be higher than in days 11-30
- For Ranexa users with history of AED, there is a non-significant 2.5 fold increase in seizure risk
  - AED population is a mix of epilepsy patients and those who use AED for other conditions such as pain
    - Role of epilepsy
    - Role of polypharmacy
- Slight increased risk (not significant) for renal impairment patients as well as older patients

Sentinel's Role in Safety Assessment

- **FAERS data:** Identified seizure signal among Ranexa users
  - Severity of signal, temporality, dechallenge heightened need for further investigation
- **Sentinel:** Signal refinement
  - Quantify seizure risk among Ranexa users
  - Identified populations for future evaluation– older patients, renal disease condition and use of anti-epilepsy drugs
- Further signal refinement in Medicare underway
  - Better representation of cases in an older population


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Duke | Robert J. Margolis, MD Center *for* Health Policy

Overview of CDER's Current Sentinel System Activities

Join the conversation with **#sentinelinitiative**

Questions & Answers

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

Engagement in the Sentinel System

Join the conversation with **#sentinelinitiative**

SENTINEL ENGAGEMENT PARTNERS WORKGROUP

J. Stephen Mikita
Sentinel Planning Board Member
Patient Advocate

February 2, 2017

SENTINEL ENGAGEMENT PARTNERS WORKGROUP

Issue: Critical Stakeholders are largely unaware of the Sentinel System, its commitment to health, safety, and protection of patient privacy.

- Public
- Health Advocacy Groups
- Providers
- Health Plan Members

WORKGROUP CHARTER

"Create a Plan of Action to Increase Awareness and Tell the Sentinel System's Story, Successes, and Value"

"Develop Messages and Tools to Increase Awareness of the Sentinel System's Public Health Value and Commitment to Privacy"

WORKGROUP

Patient Representatives
- Stephen Mikita
- Bray Patrick-Lake
- Sharon Terry

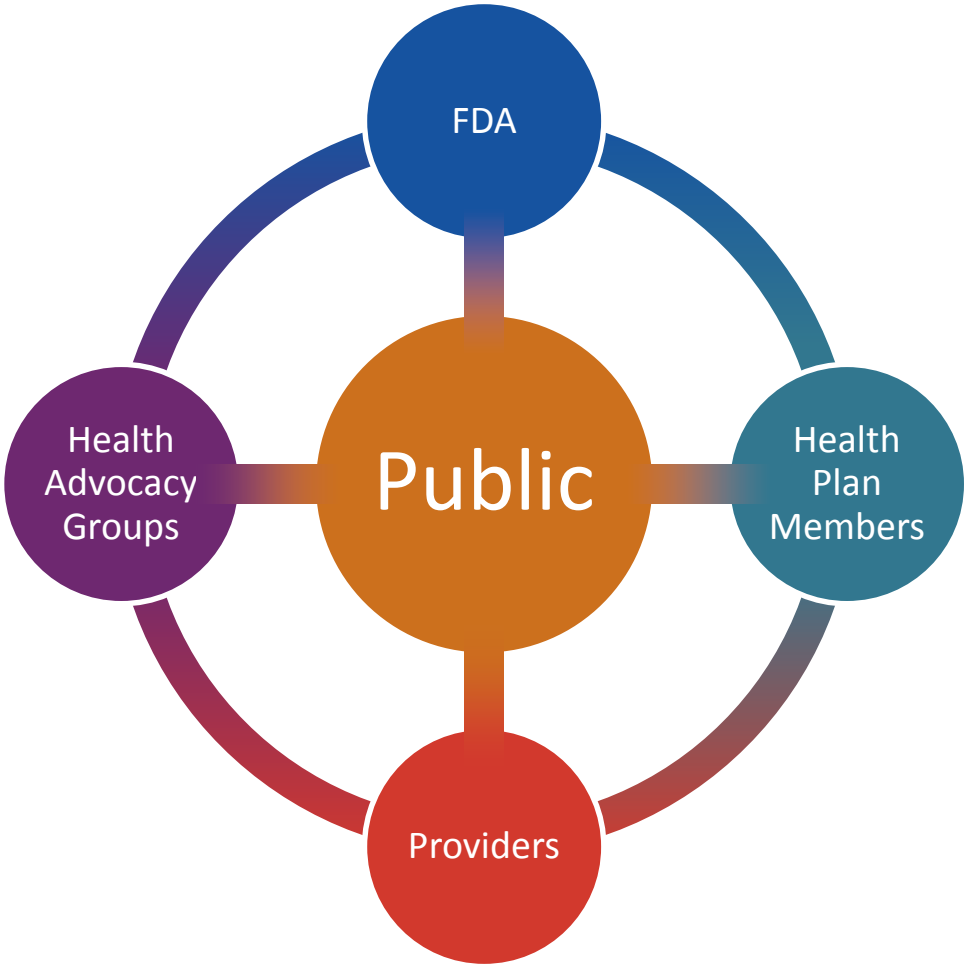
FDA
- Carlos Bell
- David Martin
- Anna Staton

Health Plan Members
- Jamie Brocki
- Nancy Falk

Providers
- Barry Dickinson
- Consuelo Wilkins

Sentinel System
- Barbara Evans
- Susan Forrow
- Richard Platt

The Engagement Partners Workgroup



WORKGROUP OBJECTIVES

Foundational Principles

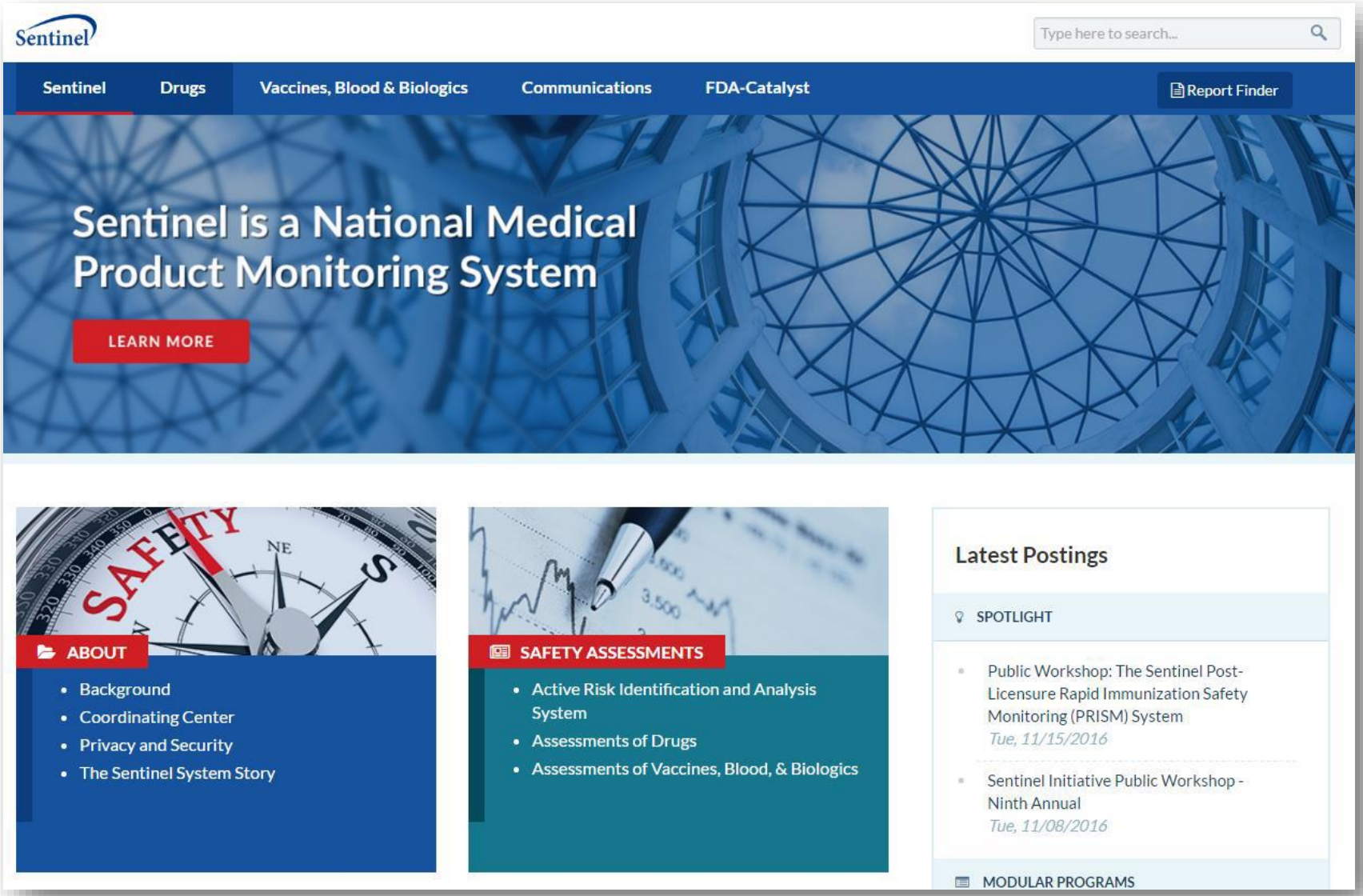
- Transparency
- Relevance
- Effective Communication

STRATEGIES FOR ENGAGEMENT

- **Coordinated Communication Strategy**—Key Elements of the Sentinel System.
- **Targeted Messages**—Tailored to Each Engagement Partner's Critical Role.

WHAT IS SENTINEL SYSTEM'S STORY?

- FDA's Safety Mission/Another Tool
- Critical Components
- Operation
- Sentinel System in Action
- Privacy


Sentinel
Type here to search...
Sentinel
Drugs
Vaccines, Blood & Biologics
Communications
FDA-Catalyst
Report Finder
Sentinel is a National Medical Product Monitoring System
LEARN MORE
ABOUT
Background
Coordinating Center
Privacy and Security
The Sentinel System Story
SAFETY ASSESSMENTS
Active Risk Identification and Analysis System
Assessments of Drugs
Assessments of Vaccines, Blood, & Biologics
Latest Postings
SPOTLIGHT
Public Workshop: The Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System
Tue, 11/15/2016
Sentinel Initiative Public Workshop - Ninth Annual
Tue, 11/08/2016
MODULAR PROGRAMS


SAFETY
NE
S
ABOUT
Background
Coordinating Center
Privacy and Security
The Sentinel System Story

HOW IT WORKS?

For the Public

Sentinel System's Story

How does the Sentinel System work?

The Sentinel System answers questions like these: *How many people are taking the same drug or getting the same vaccine? How many are having bad side-effects? How many are men and women? How many are young, old, pregnant, or take other drugs?*

For Providers

Sentinel System's Story

Sentinel System's Current Capabilities

The Sentinel System's data infrastructure involves a distributed data network that can ask questions of data held by participating health plans, insurers, and hospital networks.1 These organizations maintain physical and operational control over their respective electronic data in their existing environments. To facilitate analysis, they each transform a copy of their data into a common data model that contains standardized administrative and clinical information.

HOW DOES FDA USE IT?

For the Public

Sentinel System's Story

What does the FDA do with all the information?

The FDA gets important answers from the Sentinel System about bad side effects in certain drugs or vaccines. The FDA studies this new information along with other information it gets from doctors and drug companies. The FDA decides the best way to make doctors and patients aware of side effects. The FDA can send out a warning to doctors and patients. Or the FDA can issue a safety communication to warn the public about taking a medicine or getting a vaccine.

For Providers

Sentinel System's Story

Sentinel System's Current Capabilities

Currently, the Sentinel System can analyze over 300 million person-years of high quality, unduplicated, curated data, working with a broad group of scientific collaborators who regularly provide technical support in evaluating this information for FDA review. When data from Sentinel System queries are evaluated and a potential problem is identified, FDA may require additional study, or initiate specific actions, such as revised labeling requirements, restricted use, issuance of a MedWatch alert, or even removal of a product from the market.

SENTINEL IN ACTION

For the Public

Sentinel System's Story

Sentinel in action

Example 1

In 2012, the FDA got reports from doctors about patients taking a new medicine to help prevent blood clots. The reports were about patients bleeding too much when they took the new medicine. The Sentinel System looked at a big group of patients on the new medicine. Then, it looked at a big group of patients on an older medicine. This information did not suggest the new medicine was less safe than the older medicine. Patients could continue taking the new medicine while additional studies were performed.

For Providers

Sentinel System's Story

Sentinel System's Outcome Assessments

The Sentinel System has been used to ascertain valuable information about new prescription medications and vaccines. As an example, the bleeding rates of two anticoagulants. The Sentinel System's preliminary analysis did not identify excess risk associated with a certain anticoagulant; a more detailed follow up study is nearing completion. In another instance, the Sentinel System found that the administration of a first dose of a rotavirus vaccine led to an increased risk of intussusception, which was not detected during clinical trials before FDA approved the new vaccine. A final illustration of the Sentinel System's usefulness involved demonstrating that children vaccinated with a particular influenza vaccine were not at an increased risk of seizures.

PRIVACY

For the Public

Sentinel System's Story

Protecting your privacy

No one at the FDA looks at your personal information. They do not look at your Name, Address, Phone Number, etc. The Sentinel System learns about big groups of patients taking the same medicine or getting the same vaccine.

For Providers

Sentinel System's Story

The Sentinel Sytem Protects Patient Privacy

The Sentinel System aggregates data and produces summary information from large patient cohorts treated with the same drug or vaccine, whenever possible. When individual level data are needed, patients' identifiers are removed.

NEXT STEPS

Dissemination/Roll Out

- **Public** → Going Live!
- **Health Advocacy Groups** → Organizations & Presentations
- **Providers** → AMA Collaboration
- **Health Plan Members** → Data Partners

THANK YOU!

Special Thanks:

- Susan Forrow, Senior Project Manager
- Katherine Freitas, Research Assistant

Duke | Robert J. Margolis, MD Center *for* Health Policy

Engagement in the Sentinel System

Join the conversation with **#sentinelinitiative**

Questions & Answers

Join the conversation with **#sentinelinitiative**

Break

Join the conversation with **#sentinelinitiative**

Duke | Robert J. Margolis, MD Center *for* Health Policy

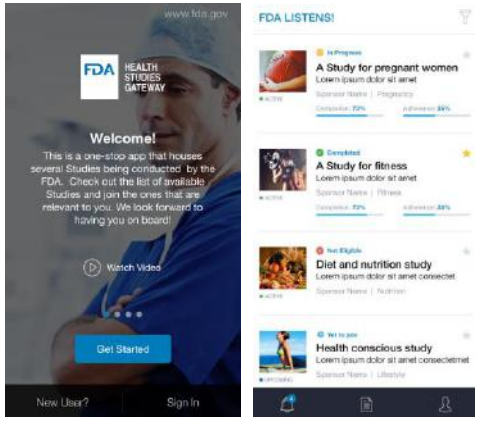
Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

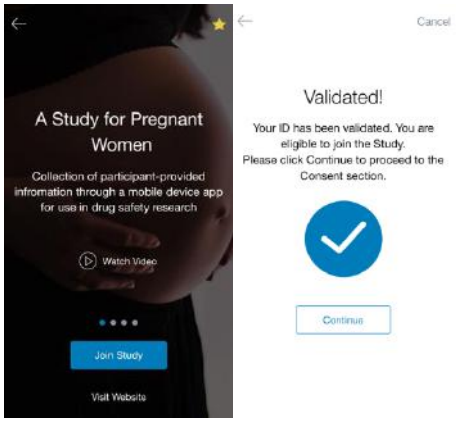
Join the conversation with **#sentinelinitiative**

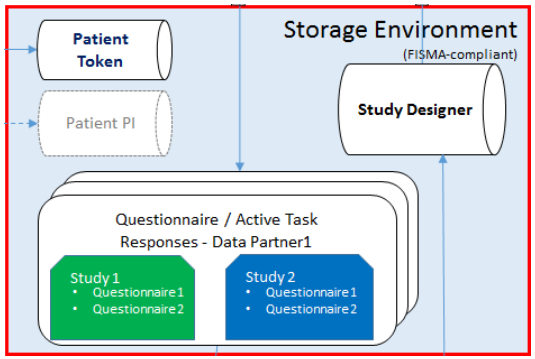
FDA Catalyst Mobile App and IMEDS

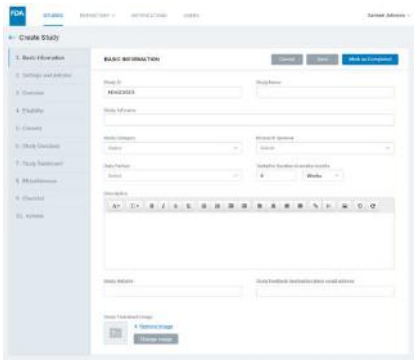
David Martin, MD, MPH
Captain, US Public Health Service
Center for Drug Evaluation and Research

FDA Catalyst Mobile App



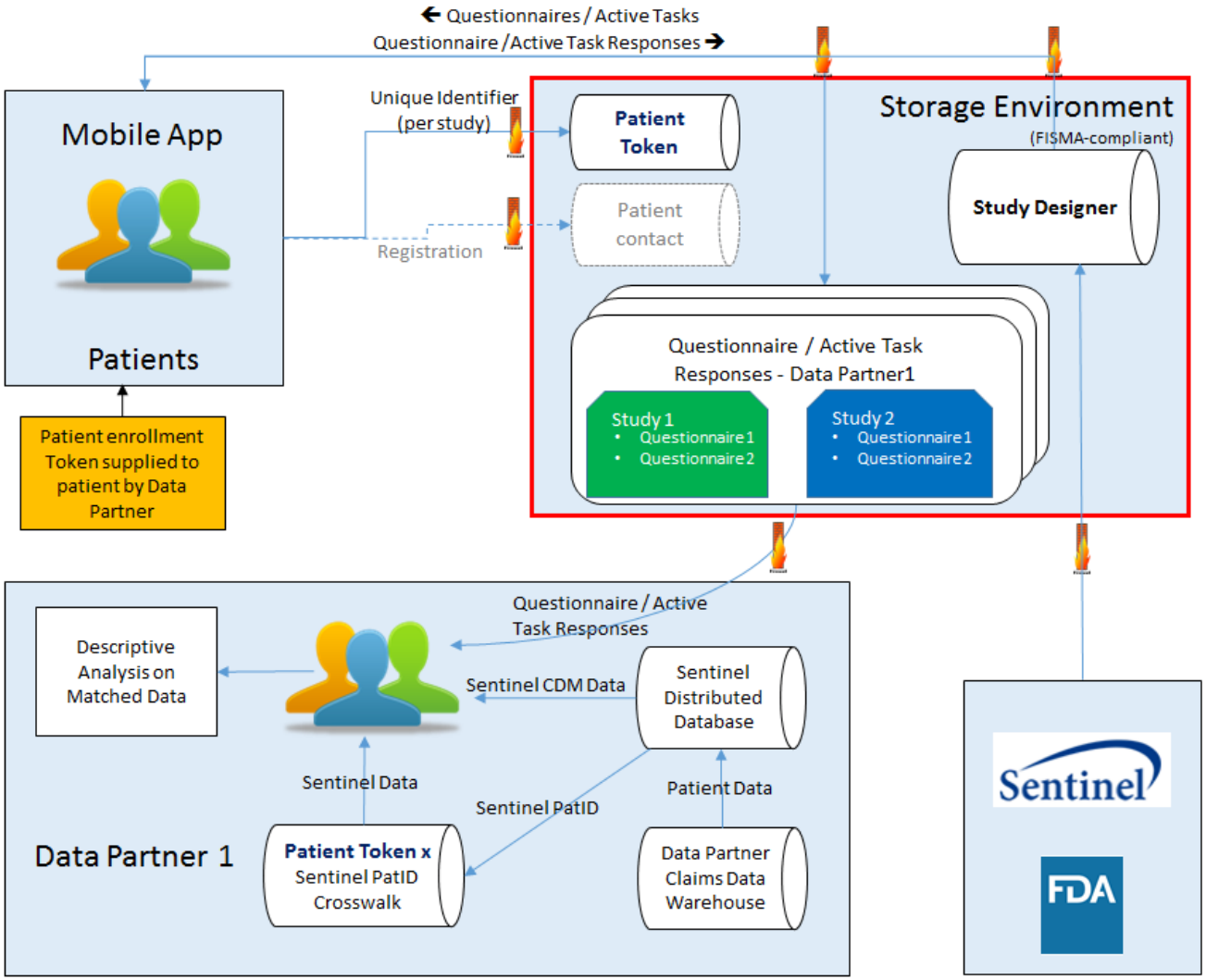






Wireframes are samples only and are subject to change as development continues

Linking Primary and Secondary Data



Reagan-Udall Foundation
FOR THE FOOD AND DRUG ADMINISTRATION

FDA

IMEDS

- Enables sponsors to use modular programs, customized studies, or a blended approach that complements the FDA Active Risk Identification and Analysis system

- Organizations interested in partnering with IMEDS should email IMEDS@reaganudall.org

Duke | Robert J. Margolis, MD Center *for* Health Policy

Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

Join the conversation with **#sentinelinitiative**

From Vision to Reality
PCORnet Opens for Business

Rachael Fleurence, PhD, Program Director PCORnet

Patient-Centered Outcomes Research Institute (PCORI)

February, 2017

pcornet℠ | The National Patient-Centered Clinical Research Network

PCORnet: the National Patient-Centered Clinical Research Network

PCORnet is **a large, highly representative, national patient-centered clinical research network**.

Our **vision** is to support a learning U.S. healthcare system and to enable **large-scale clinical research** conducted with **enhanced quality and efficiency**.

Our **mission** is to enable people to make informed healthcare decisions by efficiently conducting clinical research relevant to their needs.

With PCORnet, we have developed a nationwide functional research network that…

- **Engages** people, clinicians, and health system leaders throughout
- **Creates** infrastructure, tools, and policies to support rapid, efficient clinical research
- **Utilizes** multiple data sources including electronic health records, insurance claims data, data reported directly by people, and other data sources

pcornet®

PCORnet embodies a “community of research” by uniting people, clinicians & systems

20
Patient-Powered Research Networks (**PPRNs**)

+

13
Clinical Data Research Networks (**CDRNs**)

=

PCORnet
A national infrastructure for people-centered clinical research

pcornet®

PPRNs

American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network (ABOUT Network)
University of South Florida

ARthritis patient Partnership with comparative Effectiveness Researchers (AR-PoWER PPRN)
Global Healthy Living Foundation

CCFA Partners Patient Powered Research Network
Crohn's and Colitis Foundation of America

Collaborative Patient-Centered Rare Epilepsy Network (REN)
Epilepsy Foundation

Community and Patient-Partnered Centers of Excellence for Behavioral Health
University of California Los Angeles

Community-Engaged Network for All (CENA)
Genetic Alliance, Inc.

COPD Patient Powered Research Network
COPD Foundation

DuchenneConnect Registry Network
Parent Project Muscular Dystrophy

Health eHeart Alliance
University of California, San Francisco (UCSF)

ImproveCareNow: A Learning Health System for Children with Crohn's Disease and Ulcerative Colitis
Cincinnati Children's Hospital Medical Center

Interactive Autism Network
Kennedy Krieger Institute

Mood Patient-Powered Research Network
Massachusetts General Hospital

Multiple Sclerosis Patient-Powered Research Network
Accelerated Cure Project for Multiple Sclerosis

National Alzheimer's and Dementia Patient and Caregiver-Powered Research Network
Mayo Clinic

NephCure Kidney International
Arbor Research Collaborative for Health

Patients, Advocates and Rheumatology Teams Network for Research and Service (PARTNERS) Consortium
Duke University

Phelan-McDermid Syndrome Data Network
Phelan-McDermid Syndrome Foundation

PI Patient Research Connection: PI-CONNECT
Immune Deficiency Foundation

Population Research in Identity and Disparities for Equality Patient-Powered Research Network (PRIDEnet)
University of California San Francisco

Vasculitis Patient Powered Research Network
University of Pennsylvania

pcornet®

CDRNs

Accelerating Data Value Across a National Community Health Center Network (ADVANCE)
Oregon Community Health Information Network (OCHIN)

Chicago Area Patient Centered Outcomes Research Network (CAPriCORN)
The Chicago Community Trust

Greater Plains Collaborative (GPC)
University of Kansas Medical Center

Kaiser Permanente & Strategic Partners Patient Outcomes Research To Advance Learning (PORTAL) Network
Kaiser Foundation Research Institute

Research Action for Health Network (REACHnet)
Louisiana Public Health Institute (LPHI)

Mid-South CDRN
Vanderbilt University

National PEDSnet: A Pediatric Learning Health System
The Children's Hospital of Philadelphia

New York City Clinical Data Research Network (NYC-CDRN)
Weill Medical College of Cornell University

OneFlorida Clinical Data Research Network
University of Florida

Patient-Centered Network of Learning Health Systems (LHSNet)
Mayo Clinic

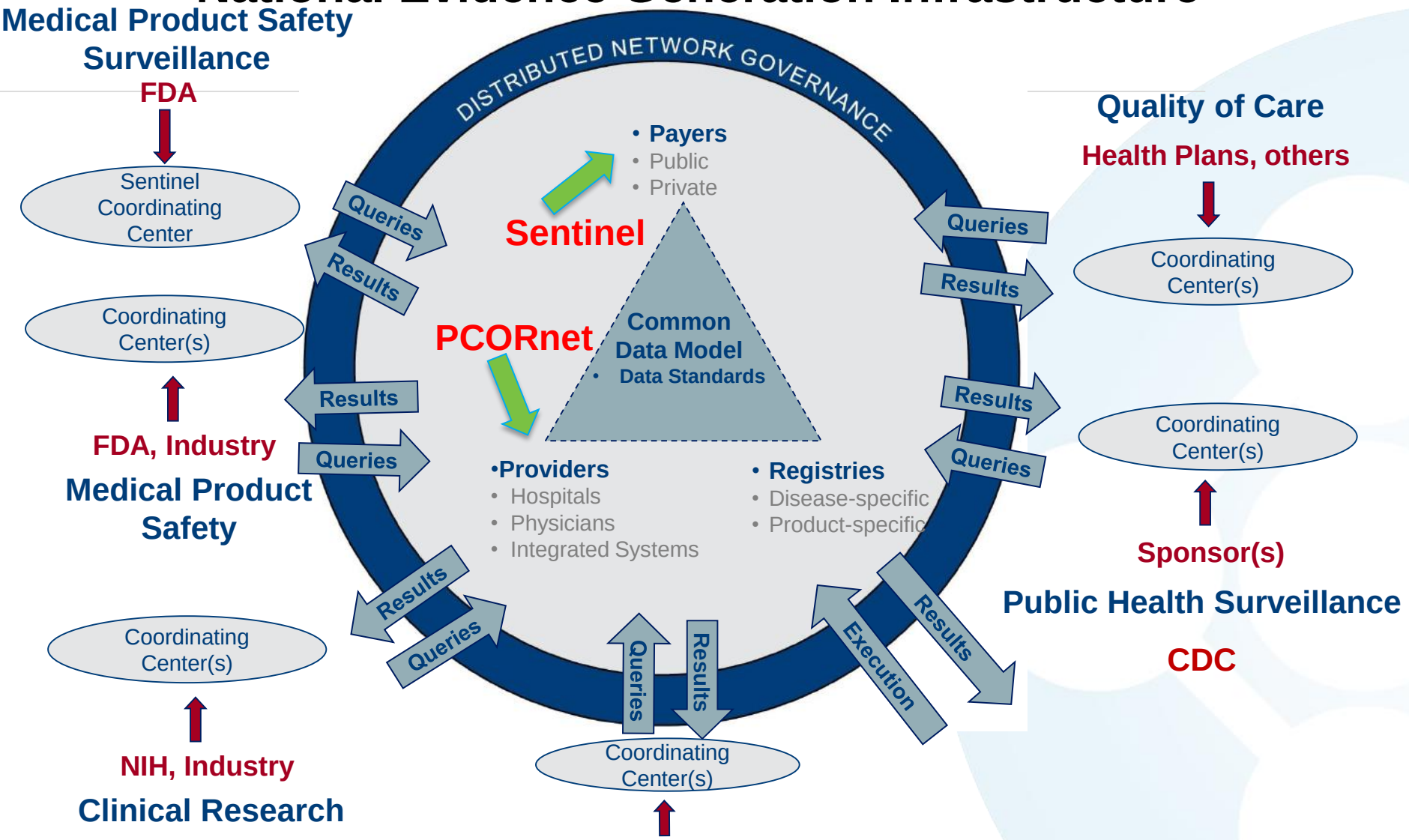
Patient-oriented SCAlable National Network for Effectiveness Research (pSCANNER)
University of California, San Diego (UCSD)

PaTH: Towards a Learning Health System
University of Pittsburgh

Scalable Collaborative Infrastructure for a Learning Healthcare System (SCILHS)
Harvard University

pcornet®

PCORnet as Part of a National Evidence Generation Infrastructure



pcornet®

PCORnet – Based on Common Data Model

Encounter

SITE 1
Social Work Visit
Allied Health
Office Visit
Nurse Visit
Procedure Visit
Employee Health
Vascular Lab
Sleep Study Visit
Social Work Visit

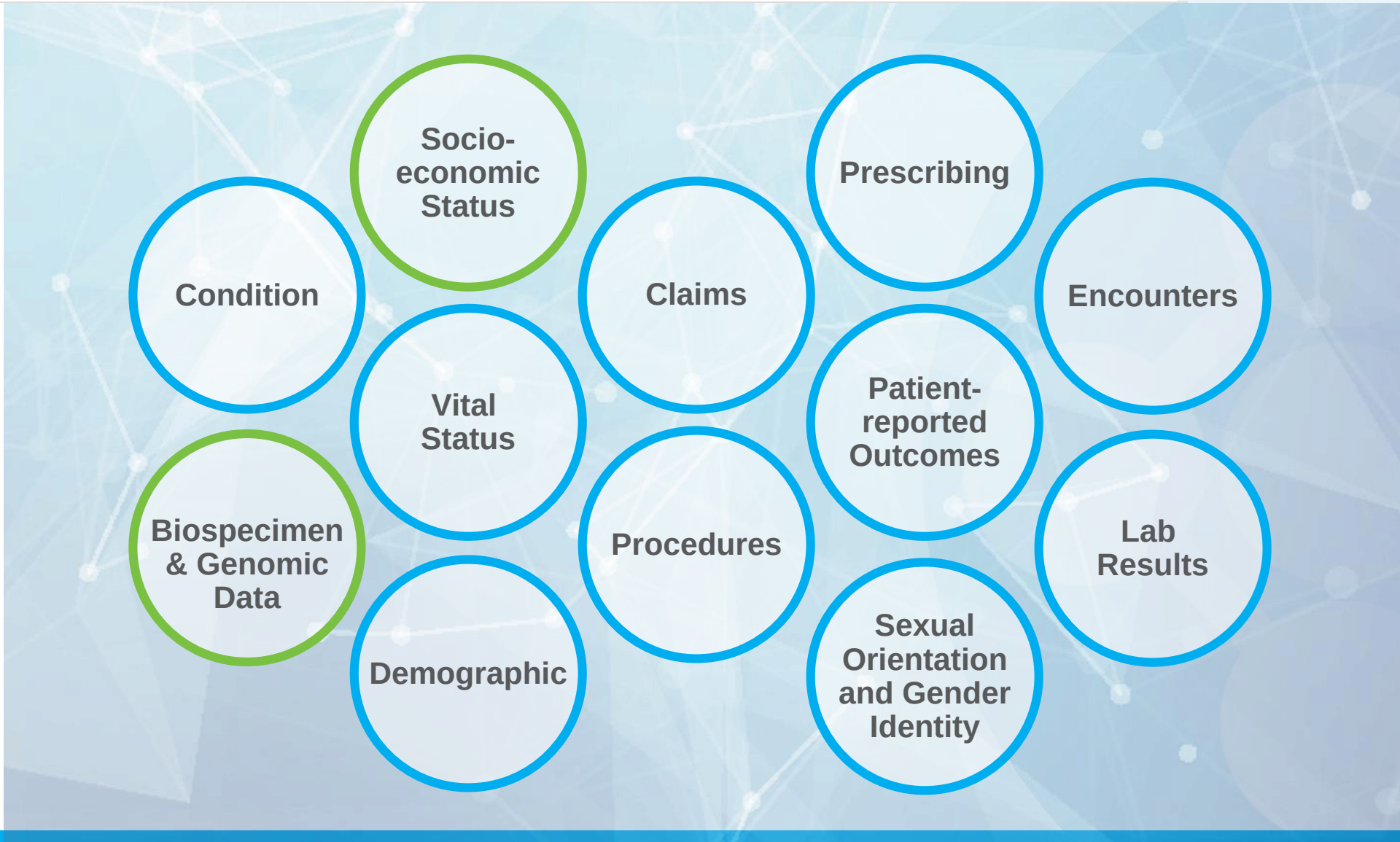
SITE 2
Office Visit
Specimen
Postpartum Visit
Clinical Support
Initial Prenatal

SITE 3
Home Care Visit
Office Visit
Therapy Visit
Orders Only
Cardiology Testing
Hospital Encounter

Common Data Model
Ambulatory Visit (AV)
Emergency Department (ED)
ED Admit to Inpatient (EI)
Inpatient Hospital (IP)
Non-Acute Inst. Stay (IS)
Other Ambulatory (OA)
Other (OT)
Unknown (UN)
No Information (NI)

In order to be able to trust results of an analysis, we need to have consistent representations

Common Data Model



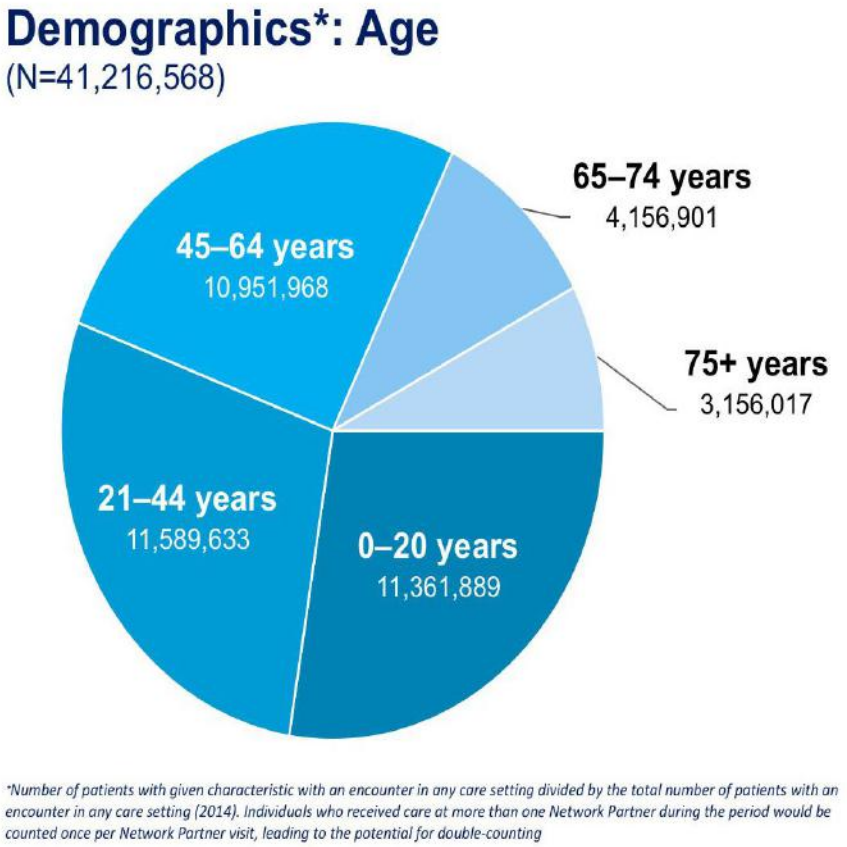
Data Characterization: Cycle 1

- 82 DataMarts across 13 CDRNs
- Cycle 1 of Data Characterization
- Characterized 7 tables
  - Demographic
  - Enrollment
  - Encounter
  - Diagnosis
  - Procedures
  - Vital
  - Harvest
- Run on CDM v3.0

pcornet®

Approximately…

- 90 million patients with a medical encounter in past 5 years
- 42 million records to support clinical trials
- 83 million records to support observational studies



pcornet®

Conditions

Condition	PCORnet
Respiratory conditions	2,837,803
Selected malignancies	1,294,158
Myocardial infarction	354,929
Stroke	420,802
Rheumatoid arthritis	254,803
Ulcerative colitis	88,029
Hypertension	5,902,641
Renal disease	1,018,729
Influenza/pneumonia	869,306

pcornet®

Data Characterization: Cycle 2

- Added 4 tables
  - Prescribing
  - Dispensing
  - Laboratory Results
  - Death
- Ended January 6th 2017

pcornet®

Early Results

- Number of patients
  - ~94 million patients available for observational studies (with AV, IP or ED visit in the past 5 years)
  - ~46 million patients available for clinical trials (with AV, IP or ED visit in the past year)
- Query run times
  - 57% took < 3 hours
  - 18% took > 10 hours
  - Strongly correlated with size of the DataMart but not correlated with use of SAS views (25% of DataMarts)

pcornet®

Lab Results

Lab	Records
Total	2.3 billion
A1C	72 million
CK	17 million
CK_MB	8 million
CK_MBI	3 million
Creatinine	288 million
HGB	298 million
INR	78 million
LDL	89 million
TROP_I	21 million
TROP_T_QL	273K
TROP_T_QN	4 million
Other	1.4 billion (~12 DataMarts)

pcornet®

Medications

	Dispensings (39 DataMarts)	Orders (72 DataMarts)	Dispensings/Orders in DataMarts with both tables (30 DataMarts)
Total	1.9 billion	4.0 billion	
10 concepts of interest*	744 million	1 billion	439 million/586 million
ACE inhibitors	63 million	47 million	38 million/24 million
Antidepressants	99 million	78 million	53 million/41 million
Antidiabetics	60 million	64 million	29 million/32 million
Antiepileptics	52 million	55 million	56 million/120 million
Antirheumatics	94 million	205 million	41 million/36 million
Antiulcerants	70 million	75 million	25 million/30 million
Beta-blockers	41 million	61 million	55 million/111 million
Narcotic analgesics	88 million	183 million	60 million /145 million
Respiratory agents	93 million	283 million	51 million /31 million
Statins	84 million	57 million	

pcornet®

*Required identifying the drug names in each class and the RXCUI (orders) and NDCs (dispensings) for each drug.

PCORnet supports many kinds of research

Pre-research

- Feasibility queries
- Engagement
- Match-making

Observational studies

- Cross-sectional
- Epidemiology
- Health services
- Comparative effectiveness or safety

Interventional studies

- Clinical trials
- Pragmatic randomized clinical trials
  - e-Identification
  - e-Consent
  - e-Randomization
  - e-Data Collection
  - e-Follow-up
- Cluster randomization

pcornet®

Pragmatic Clinical Trials: Enabling Pragmatic Research: eScreening, eEnrollment and eFollowup

ADAPTABLE Enrollee

Baseline Data

OR

Adaptable
The Aspirin Study

Call FOLLOW-UP
- *Patient Reported Outcomes*
- *Medication use*
- *Health outcomes*

Portal FOLLOW-UP
- *Patient Reported Outcomes*
- *Medication use*
- *Health outcomes*

4 8 12 16 20 …. 30

PCORNet Coordinating Center FOLLOW-UP
- *Via Common Data Model*
- *Longitudinal health outcomes*

CMS & Payer Virtual Data Warehouse FOLLOW-UP
- *Longitudinal health outcomes*

http://adaptablepatient.com

pcornet®

ADAPTABLE: Site Enrollment Rates (as of 1/8)

CDRN	Site	Site Activated	Started Enrollment	Total Enrolled	Enrollment Rate/Month
MidSouth	Vanderbilt	4/18/2016	April	307	30.7
OneFlorida	U of Florida	11/1/2016	November	62	20.66
REACHnet	Ochsner	4/18/2016	April	132	13.2
PaTH	UPMC	7/18/2016	August	68	11.33
PaTH	Penn State	9/23/2016	October	45	11.25
pScanner	UCLA	11/7/2016	November	33	11
PaTH	Utah	9/23/2016	October	38	9.5
GPC	KUMC	11/1/2016	November	27	9
NYC_CDRN	Montefiore	11/9/2016	November	17	5.66
GPC	Iowa	7/18/2016	August	32	5.33
Capricorn	Northwestern	8/30/2016	September	26	5.2
Mid-South	Duke	11/9/2016	November	12	4
REACHnet	BSW	9/19/2016	October	10	2.5
NYC_CDRN	NYU	11/1/2016	November	5	1.66
PaTH	Temple	9/23/2016	October	5	1.25
REACHnet	Tulane	8/30/2016	October	2	0.5

pcornet®

Front Door now open to the PCORnet community, and will be open in April to the outside

Through PCORnet Front Door, we invite PCORnet researchers and other investigators, patient groups, healthcare organizations, clinicians or clinician groups, government and industry scientists, and sponsors to collaborate on important patient-centered clinical research studies.

Faster answers to pre-research queries

SUBMIT
Data Network Request

Valuable expertise via network collaboration

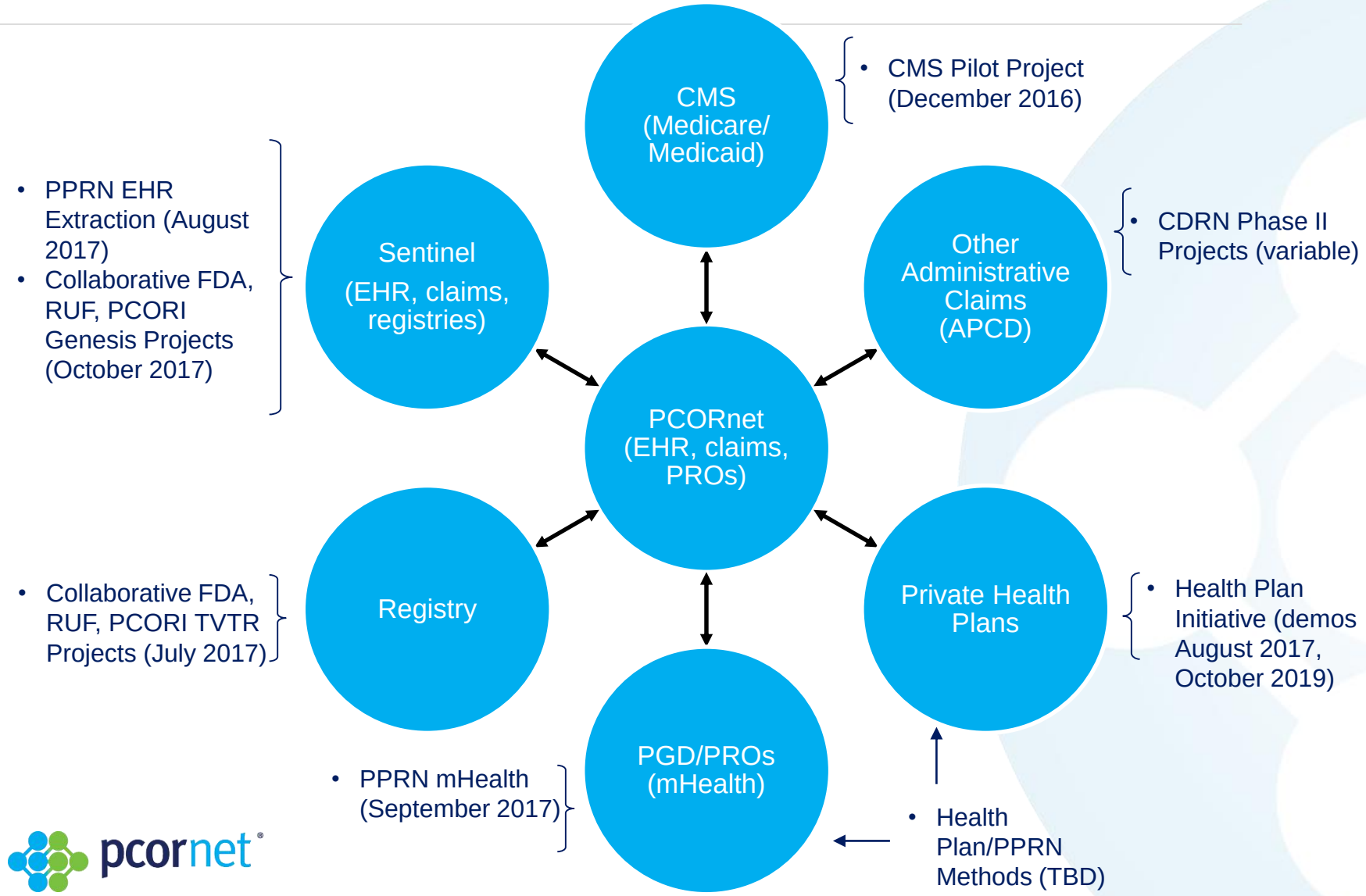
SUBMIT
Request for Network Collaboration

Enhanced credibility via PCORnet study designation

SUBMIT
Request for PCORnet Study Designation

pcornet®

Data Linkage/Collaboration Projects: Data Sources



pcornet®

Genesis Pilot Projects

Public Health Focus Area	Genesis Project Title	Institute/Affiliation	Principal Investigator
Congenital Zika syndrome surveillance	Planning for Congenital Zika Syndrome Surveillance in PCORnet and Sentinel	University of Florida	Dr. William Hogan
Monitoring and reporting antimicrobial utilization	Data Model for Initiatives to Monitor Exposure to Antimicrobials in PCORNet and Sentinel (DataMIME)	Medical Research Analytics and Informatics Alliance (MRAIA)	Dr. William Trick

pcornet®

Planning for Congenital Zika Syndrome Surveillance in PCORnet and Sentinel

- Purpose: Begin understanding and utilizing the surveillance potential using the EHR and administrative data infrastructure of PCORnet and the Food and Drug Administration's (FDA's) Sentinel Initiative

- Study Goals:
  - Identify and characterize subpopulations of infants of interest and test within the OneFlorida CDRN data infrastructure
  - Leverage PCORnet and Sentinel capabilities to enhance Zika syndrome detection and reporting
  - Contribute to knowledge of the natural history and outcomes of infants with congenital Zika syndrome

pcornet®

Initiatives to Monitor Exposure to Antimicrobials in PCORnet and Sentinel (DataMIME)

- Purpose: Develop and pilot a PCORnet technical infrastructure for the generation of unit-level Antimicrobials (AU) measures critical to antimicrobial utilization and monitoring national public health priorities

- Study Goals:
  - Plan, develop and pilot an open source methodology using the PCORnet CDM as a model
  - Generate AU reports that can be submitted to CDC's Natural Healthcare Safety Network (NHSN) and enable surveillance requirements for FDA's Sentinel CDM
  - Develop ancillary tables to augment the existing PCORnet and Sentinel data models that will allow hospitals to generate comparable AU reports for hospital inpatients

pcornet®

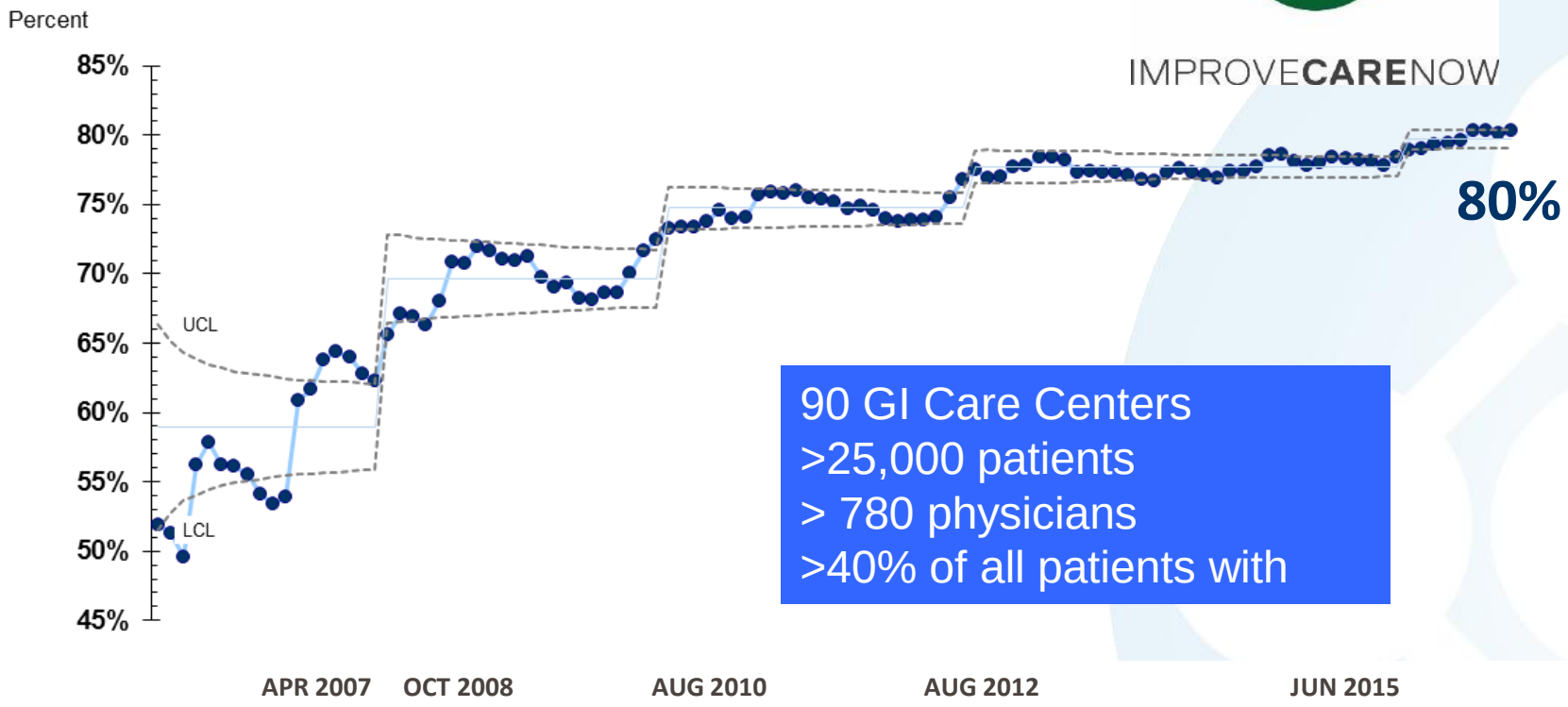
Patient-Powered Research Networks

- 20 Patient-Powered Research Networks, 220,000 patients across diseases and conditions consented to participate in research

- Future areas to watch:
  - First large pragmatic clinical trial in mindfulness
  - Use of mHealth data for research
  - Patient owned EHR share-able with researchers
  - Learning Network Pilots starting in Spring 2017

pcornet®

ICN PPRN is changing patients' health outcomes



IMPROVECARENOW

90 GI Care Centers
>25,000 patients
> 780 physicians
>40% of all patients with

Centers >75% registered

pcornet®

Percent of patients in clinical remission
Crohn's Disease and Ulcerative Colitis

Duke | Robert J. Margolis, MD Center *for* Health Policy

Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

Join the conversation with **#sentinelinitiative**

U.S. Department of Health & Human Services • National Institutes of Health

National Center for Complementary and Integrative Health

Perspectives from the NIH Healthcare Systems Research Collaboratory

Sentinel Initiative Public Workshop - February 2, 2017
Moving Beyond Surveillance

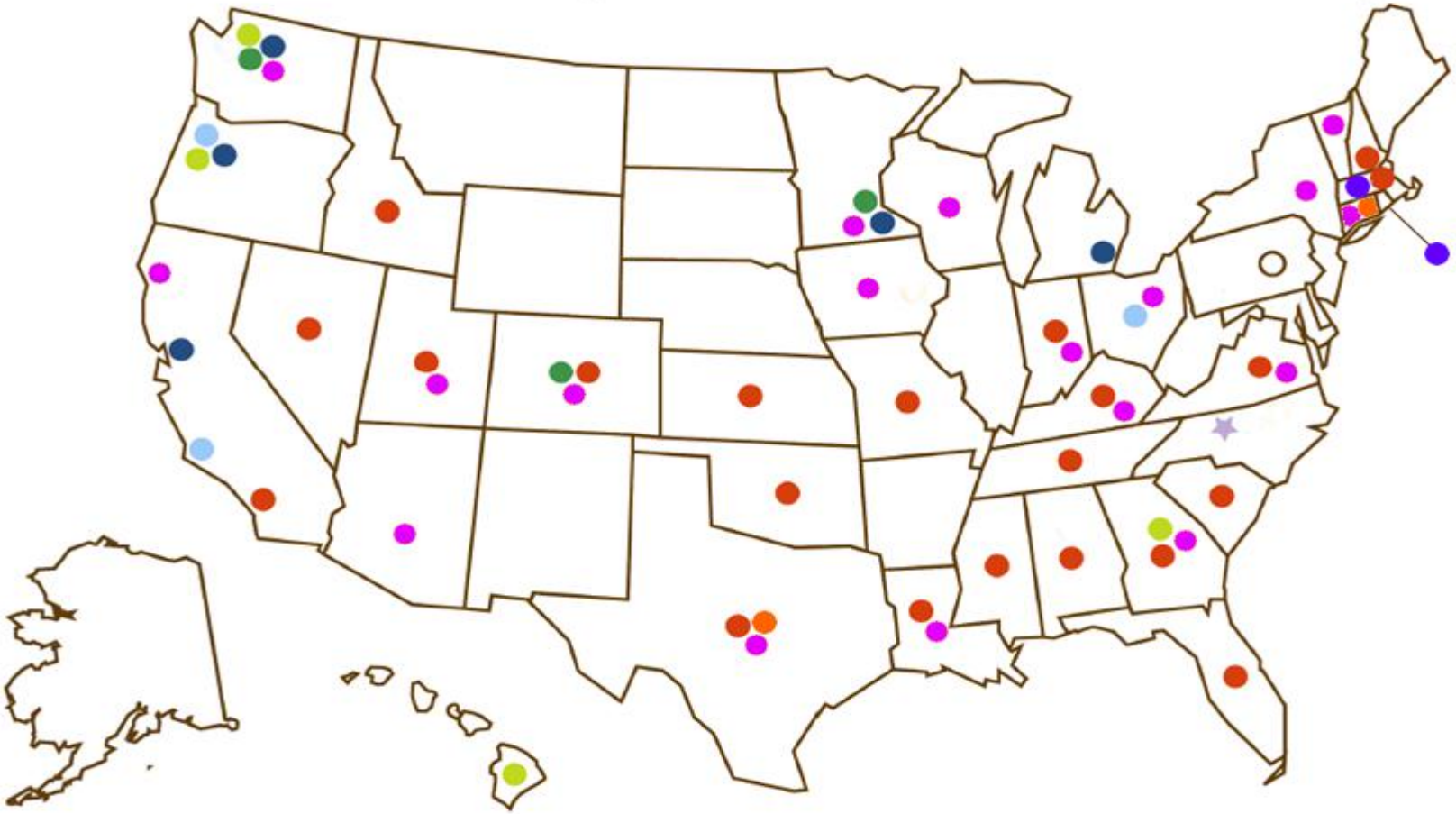
Catherine M. Meyers, MD
NIH/NCCIH
Director, Office of Clinical & Regulatory Affairs

NIH Health Care Systems Research Collaboratory

- **Goal: To strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations as research partners.**

- **Aim: To provide a framework of implementation methods and best practices that will enable the participation of many health care systems in clinical research. Research conducted in partnership with health care systems is essential to strengthen the relevance of research results to health practice.**

NIH Health Care Systems Research Collaboratory



- Collaboratory Coordinating Center
- Suicide Prevention Outreach Trial (SPOT)
- Time to Reduce Mortality in End-Stage Renal Disease (TiME) (sites in dialysis units across the US)
- Trauma Survivors Outcomes & Support (TSOS)
- Lumbar Image Reporting and Epidemiology
- Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC)
- Collaborative Care for Chronic Pain in Primary Care (PPACT)
- Active Bathing to Eliminate Infections (ABATE)
- Improving Chronic Disease Management with Pieces (ICD-Pieces)
- Pragmatic Trial of Video Education in Nursing Homes (PROVEN) (sites in nursing homes across the US)

NIH Collaboratory Pragmatic Trial HCS Partners

- Group Health Cooperative
- Kaiser Permanente
- Mayo Clinic
- Henry Ford Health System
- HealthPartners Institute
- Parkland Heath System
- Texas Health Resources
- ProHealth CT
- Fresenius and DaVita Dialysis Corporations
- Hospital Corporation of America
- US Level 1 Trauma Care Centers
- Genesis Healthcare
- UHS Pruitt Corporation
- Oregon Community Health Information Network (FQHCs)
- North Texas VA

NIH Collaboratory Coordinating Center

NIH Collaboratory › NIH Collaboratory Distributed Research Network

ome

NIH Collaboratory Distributed Research Network

Millions of people. Strong collaborations. Privacy first.

The NIH Collaboratory Distributed Research Network (DRN) enables investigators to collaborate with each other in the use of electronic health data, while also safeguarding protected health information and proprietary data. It supports both single- and multisite research programs.

The Network's querying capabilities reduce the need to share confidential or proprietary data by enabling authorized researchers to send queries to collaborators holding data (i.e., data partners). In some cases, queries can take the form of computer programs that a data partner can execute on a pre-existing dataset. The data partner can return the query result, typically aggregated (count) data, rather than the data itself. This form of remote querying reduces legal, regulatory, privacy, proprietary, and technical barriers associated with data sharing for research.

The network seeks to build strong and trusted collaborations to support the research that will lead to improved health for millions of people around the world.

On this page

Drs. Jeff Brown and Lesley Curtis explain the NIH Collaboratory Distributed Research Network.

Documents

NIH Collaboratory Distributed Research Network User's Guide

NIH Collaboratory DRN Request Form

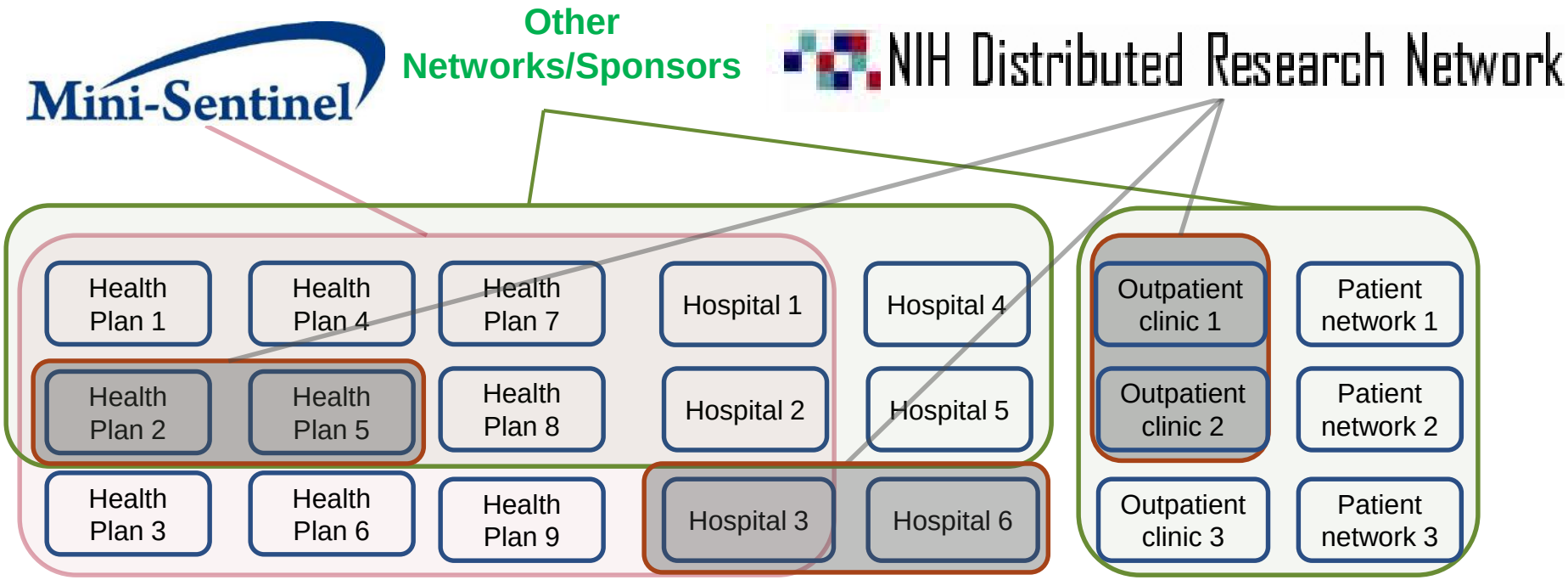
DRN Governance

Recent Presentations

6/5/2015: Grand Rounds Presentation: NIH Collaboratory Distributed Research Network (Video; Slides)

11/14/2014: Grand Rounds Presentation: Using the NIH

Sharing of Infrastructure



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

NIH Collaboratory DRN Data Partners

- Aetna
- Group Health Research Institutes
- Harvard Pilgrim Health Care Institute
- HealthCore, Inc.
- HealthPartners Institute for Education and Research
- Humana: Comprehensive Health Insights, Inc.
- Meyers Primary Care Institute
- The MURDOCK Study
- OptumInsight, Inc.
- Ochsner Health Systems

NIH Collaboratory DRN

2014-2016 **Pilot project of 3 Queries from NIH**

2017 **Broader outreach to the research community**

Duke | Robert J. Margolis, MD Center *for* Health Policy

Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

Join the conversation with **#sentinelinitiative**

Questions & Answers

Join the conversation with **#sentinelinitiative**

Closing Remarks

Join the conversation with **#sentinelinitiative**

Adjournment

Join the conversation with **#sentinelinitiative**