ENGELBERG CENTER for Health Care Reform at BROOKINGS

Sentinel Initiative Public Workshop

The Brookings Institution
Marriott at Metro Center • Washington, DC
Tuesday, January 14, 2014

FDA's Mini-Sentinel Program to Evaluate the Safety of Marketed Medical Products

A Look Back, a Look Ahead

Richard Platt
Harvard Pilgrim Health Care Institute
Harvard Medical School
for the Mini-Sentinel Investigators

January 14, 2014

Sentinel Prototype

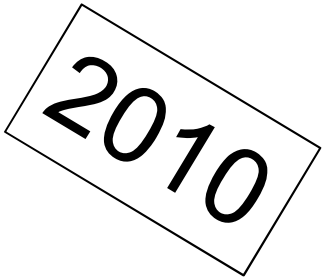
2010

- Develop a coordinating center for a distributed system
  - Access three or more health data environments with varied attributes to conduct analyses
  - Convene a Planning Board to develop governing documents and establish a Safety Science Committee charged with the day-to-day operations
  - Develop a means for secure communication with contracted data holders
- Evaluate emerging methods in safety science
  - Develop epidemiological and statistical methodologies for signal detection, signal strengthening, and signal validation
  - Test such methodologies in the evaluation of FDA-identified medical product-adverse event pairs of concern

Initial needs

- A workplan!
- Policies
  - Privacy
  - Governance
- Data model and method for querying the data
- Procedures at FDA, at Coordinating Center, at Partner sites
  - White papers
  - Standard operating procedures
- Infrastructure at FDA, at Coordinating Center, at Partner sites
  - Personnel
  - Hardware
  - Software

Everything!



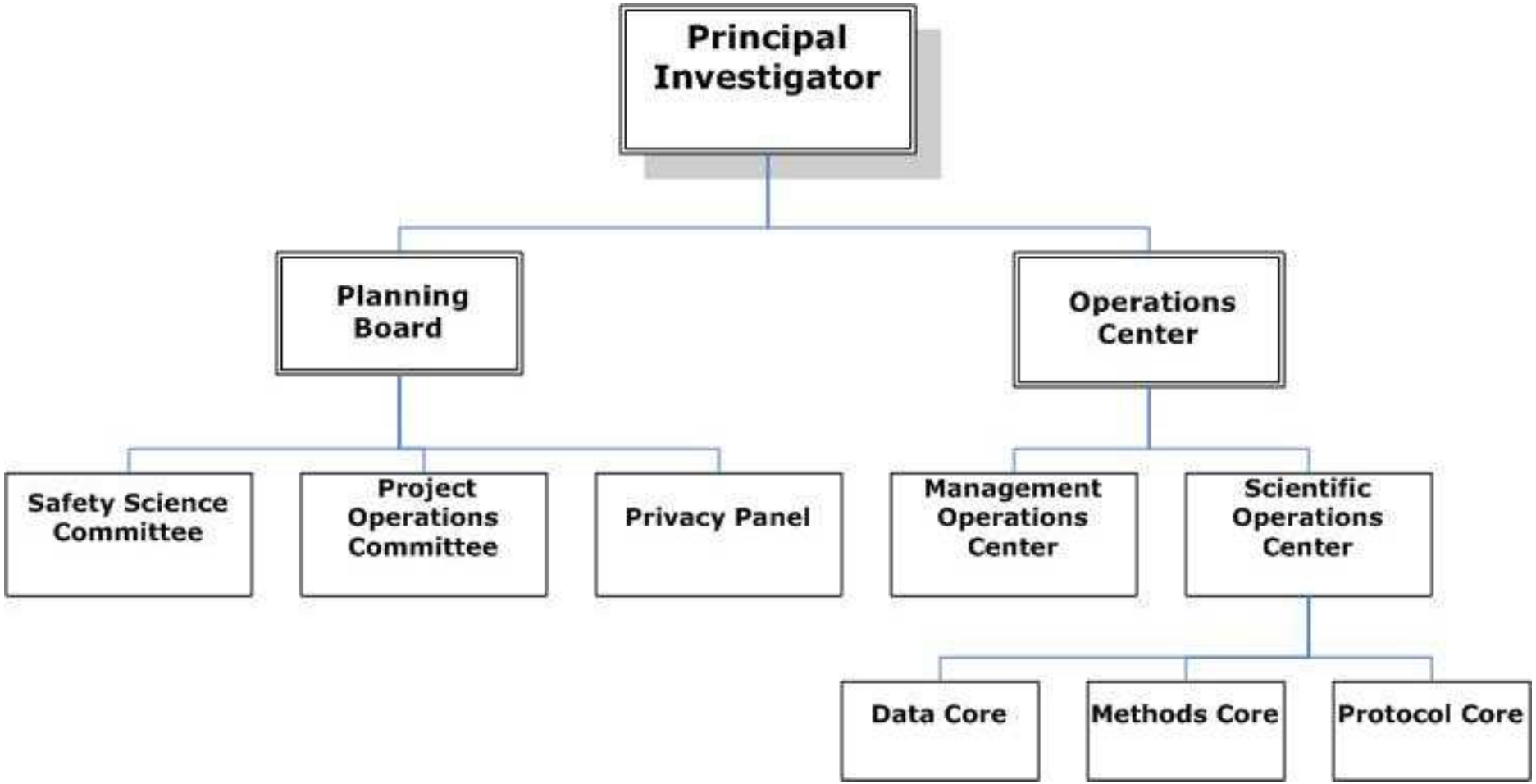
Coming soon

www.mini-sentinel.org

2011

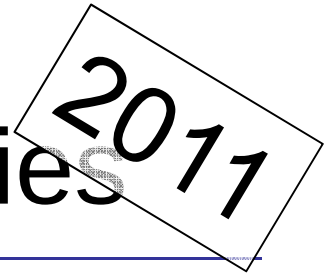
Coordinating Center

2011



Mini-Sentinel

Governance Principles/Policies

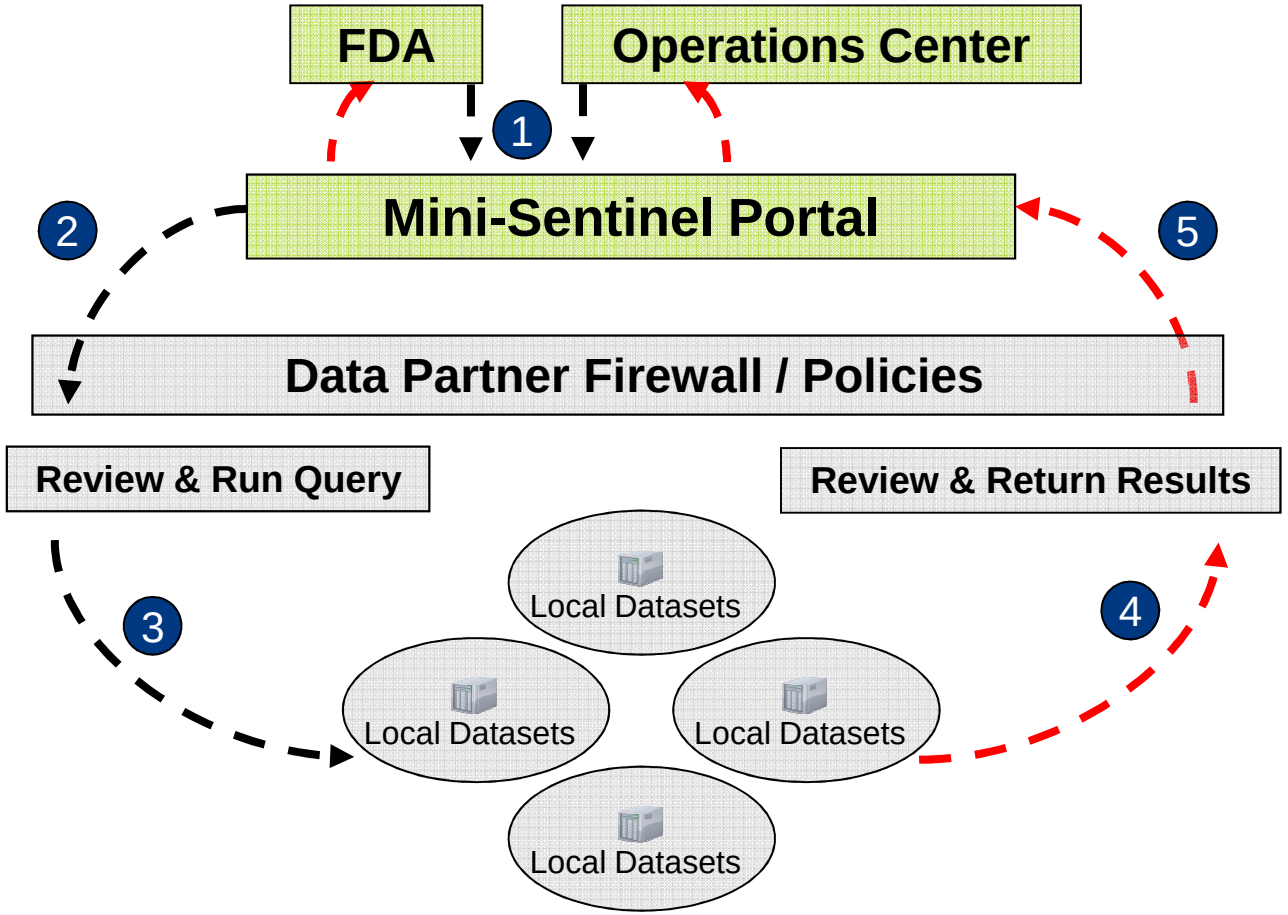


- Public health practice, not research
- Minimize transfer of protected health information and proprietary data
- Data partners participate voluntarily
- Public availability of “work product”
  - Tools, methods, protocols, computer programs
  - Findings
- Maximize transparency

Mini-Sentinel

Mini-Sentinel Distributed Analysis

2011



1- Query (an executable program) is submitted by FDA or Coordinating Center to the Portal
2- Data Partners retrieve the query
3- Data partners review query and perform analysis locally by executing the distributed program
4- Data partners review results
5- Data partners return results to the Portal

Mini-Sentinel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Welcome to Mini-Sentinel
Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products.
Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance.
Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise.
New Postings
December 16, 2010
Common Data Model v1.1
www.minisentinel.org
Additional Information
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2012

Mini-Sentinel Partner Organizations

HealthCore
WellPoint
Kaiser Permanente
hmo research network
Aetna
Humana Pharmacy Solutions®
Vanderbilt School of Medicine
OUTCOME™
Optum™
Penn Medicine
Cincinnati Children's change the outcome
DukeMedicine
Critical Path Institute Improving the Path for Innovative Therapies
UAB
Partners HealthCare
AHIP America's Health Insurance Plans
UIC
The University of Iowa College of Public Health
Rutgers Institute for Health

The Mini-Sentinel Distributed Database

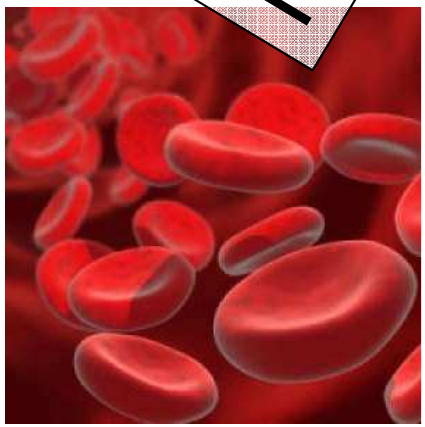
- Populations with well-defined person-time for which medically-attended events are known
- 126 million individuals*
  - 345 million person-years of observation time (2000-2011)
  - 44 million individuals currently enrolled, accumulating new data
  - 27 million individuals have over 3 years of data

*As of 12 December 2011. The potential for double-counting exists if individuals moved between data partner health plans.

Mini-Sentinel Modular Programs

1. Drug exposure for a specific period
2. Drug exposure with a specific condition
3. Outcomes following first drug exposure
4. Concomitant exposure to multiple drugs

Blood Safety Continuous Active-Surveillance Network (Blood-SCAN)



http://www.newsrx.com/images/sized/uploads/topics/blood1-300x300.jpg

- Strengthen FDA's hemovigilance capabilities
  - Initial focus on recipient safety
  - Emphasis on non-infectious complications
- Create and characterize a Blood-SCAN distributed database
  - Develop an active surveillance system for regulated blood and blood-derived product use
  - Harmonize Blood-SCAN with existing US biovigilance efforts

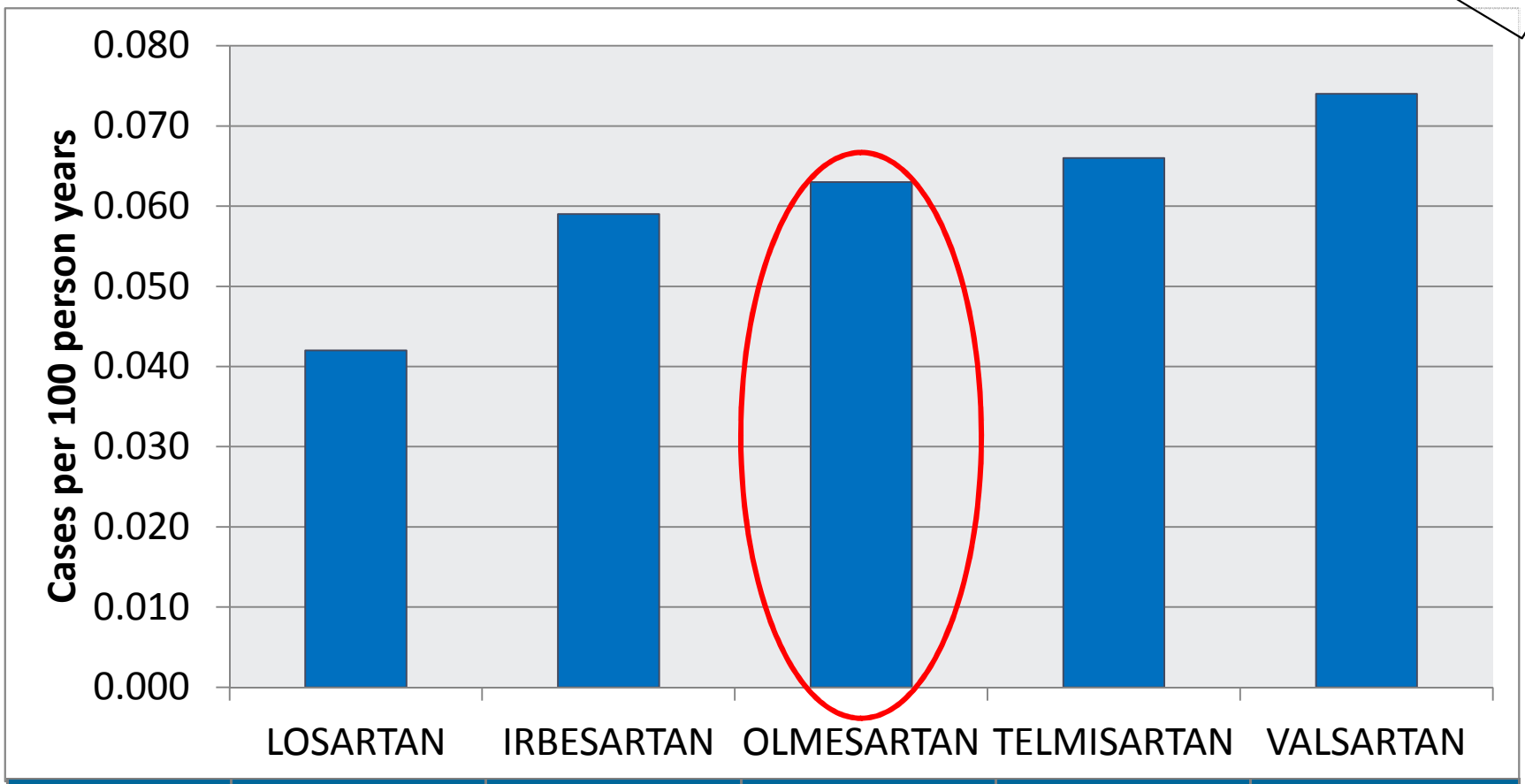
Taxonomy

Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

Monitoring scenario characteristics with implication for design choice[a]							Monitoring scenario characteristics with implication for analytic choice[a]		
	Characteristics of the (potential) exposure-HOI link								
			Strength of confounding						
Exposure persistence *(transient, sustained)*	**Onset of exposure risk window** *(Immediate, delayed)*	**Duration of exposure risk window** *(short, long)*	**Within-person** *(negligible, needs to be addressed)*	**Between-person** *(negligible, needs to be addressed)*	**HOI onset** *(abrupt, insidious)*	**Design choice[b]** *(self-controlled, cohort)*	**Background frequency of exposure** *(infrequent, rare)*	**Background frequency of HOI** *(infrequent, rare)*	**Analytic choice**
Transient (e.g. vaccine, *initiation* of a drug; including episodic drug use [e.g. triptans] to the extent that the question pertains to its transient nature)	Immediate	Short	Negligible	Needs to be addressed	Abrupt	3 self-controlled (or cohort)	Infrequent	Infrequent	9
								Rare	10
							Rare	Infrequent	11
								Rare	12
					Insidious	4 self-controlled or cohort	Infrequent	Infrequent	13
								Rare	14
							Rare	Infrequent	15
								Rare	16
			Needs to be addressed	Negligible	Abrupt	5	Infrequent	Infrequent	17

Exposure-outcome scenarios linked to design strategies

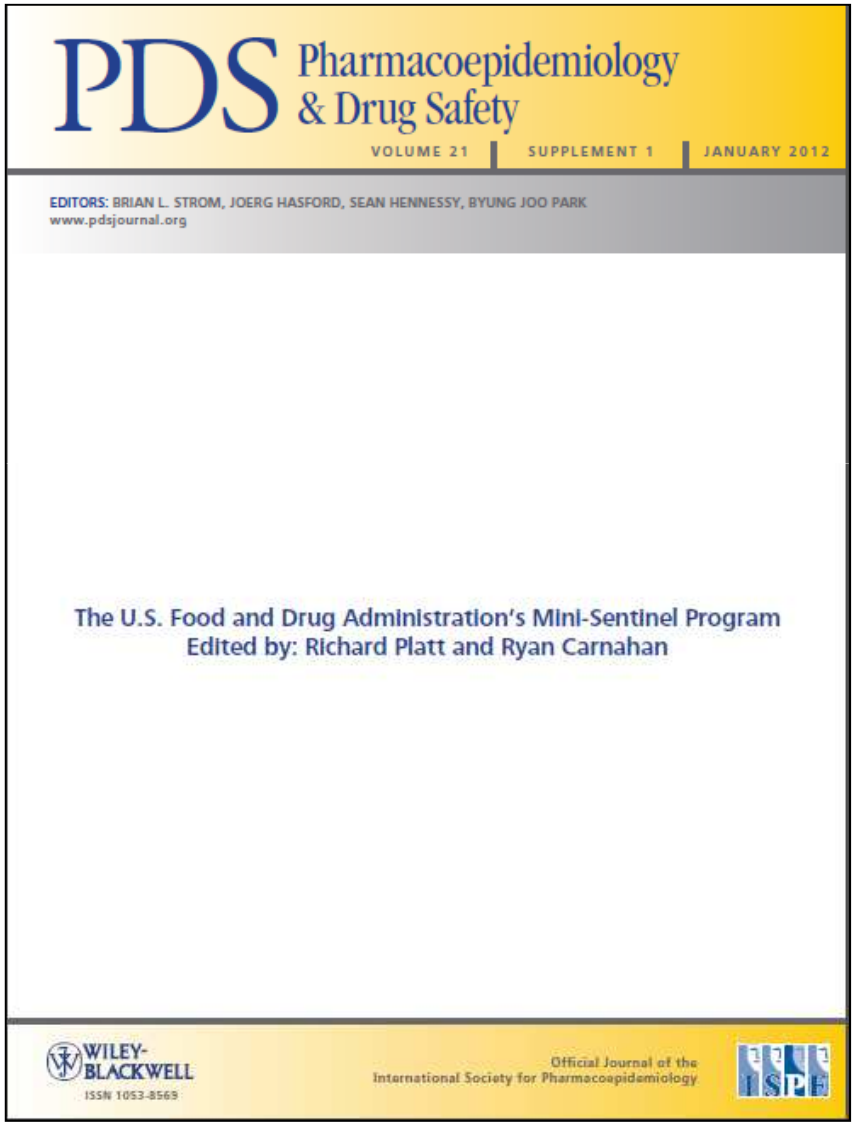
ARBs and celiac disease



Cases	63	10	17	5	50
New users	235,630	40,071	81,560	24,596	153,159

ARBs: New users after ≥365 day washout; Celiac Disease: 1st dx code after >365 day without diagnosis.

Mini-Sentinel Journal Supplement



- Supplement to Pharmacoepidemiology and Drug Safety
- 34 peer reviewed articles
- Goals, organization, privacy policy, data systems, systematic reviews, stats/epi methods, record retrieval and review, protocols for drug/vaccine studies...
- Open access!
- http://onlinelibrary.wiley.com/doi/10.1002/pds.v21.S1/issuetoc

2012

The NEW ENGLAND JOURNAL of MEDICINE

February 10, 2011. Volume 364: 498-9

Perspective

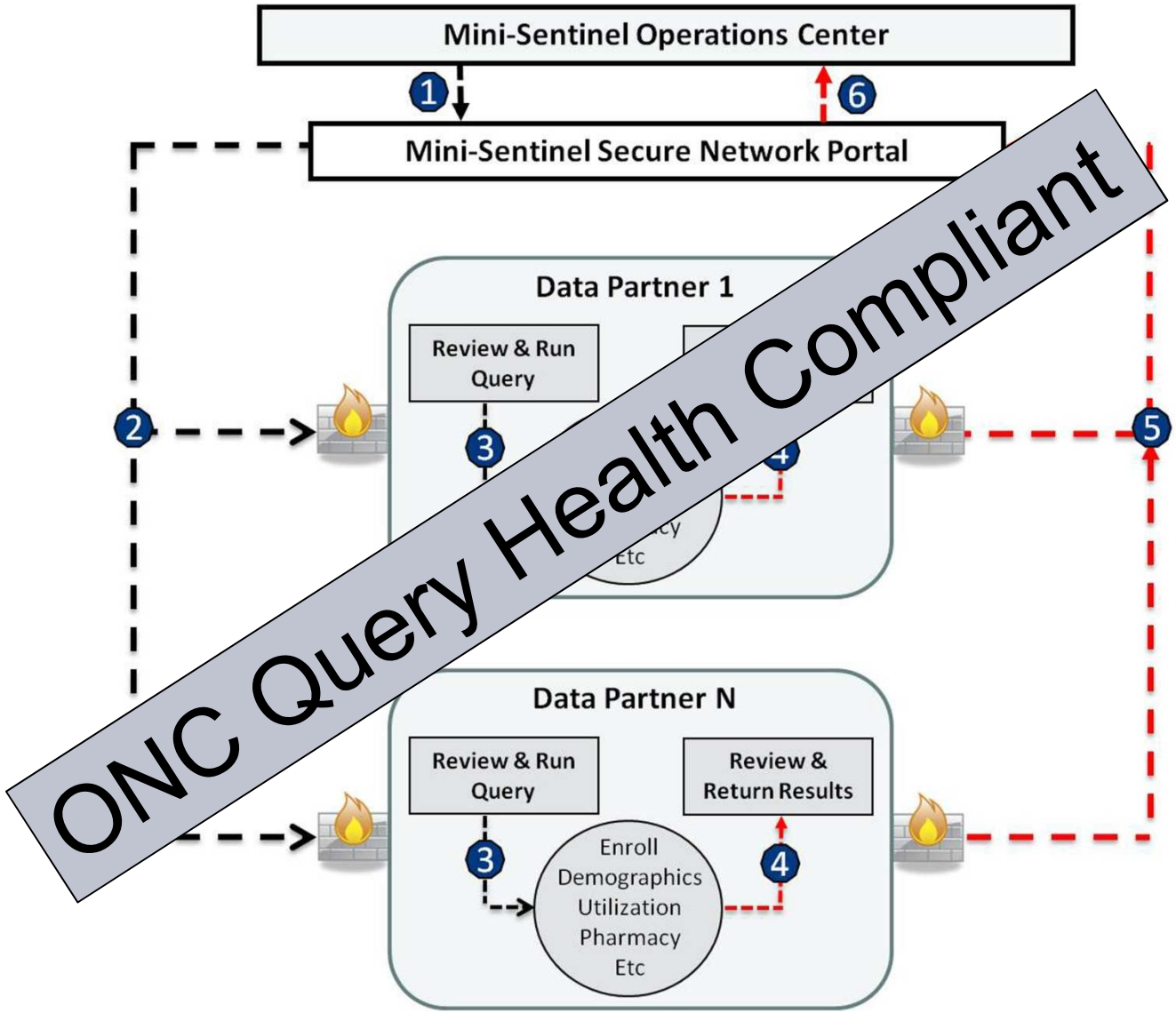
Developing the Sentinel System — A National Resource for Evidence Development

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

The Food and Drug Administration (FDA) now has the capacity to "query" the electronic health information of more than 60 million people, posing specific questions in order to monitor the safety of approved medical products. This information to answer additional convening an ongoing series of discussions among stakeholders to address the near- and long-term challenges inherent in implementing the Sentinel System.[3] In 2009, the FDA gave the Harvard Pilgrim Health Care Institute the lead role

2013

Mini-Sentinel Distributed Analysis



ONC Query Health Compliant

1- User creates and submits query (a computer program)

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

www.fda.gov/Drugs/DrugSafety/ucm326580.htm; Nov 2, 2012

The NEW ENGLAND JOURNAL of MEDICINE

2014

Perspective

Dabigatran and Postmarketing Reports of Bleeding

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

"In the months following the approval of the oral anticoagulant dabigatran ... in October, 2010, the FDA received through the FDA Adverse Event Reporting System many reports of serious and fatal bleeding events associated with use of the drug."

N Engl J Med 2013. DOI: 10.1056/NEJMp1302834

ORIGINAL INVESTIGATION

ONLINE FIRST

Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houstoun, PharmD; Mary Ross Southworth, PharmD; Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey, MD, MPH; Azadeh Shoaibi, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD

Toh Arch Intern Med.2012;172:1582-1589.

Mini-Sentinel

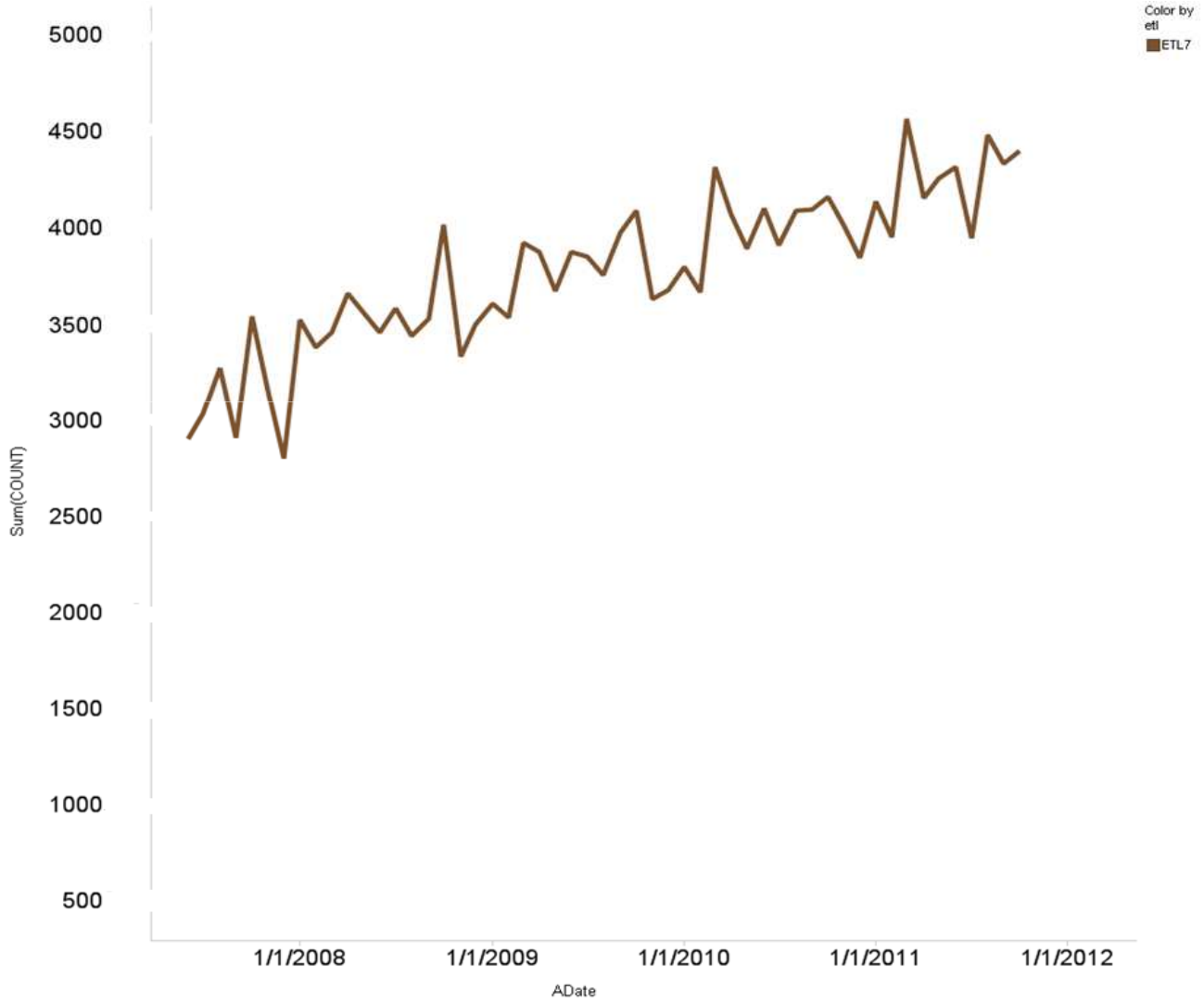
MINI-SENTINEL METHODS

FRAMEWORK FOR ASSESSMENT OF SIGNAL REFINEMENT POSITIVE RESULTS

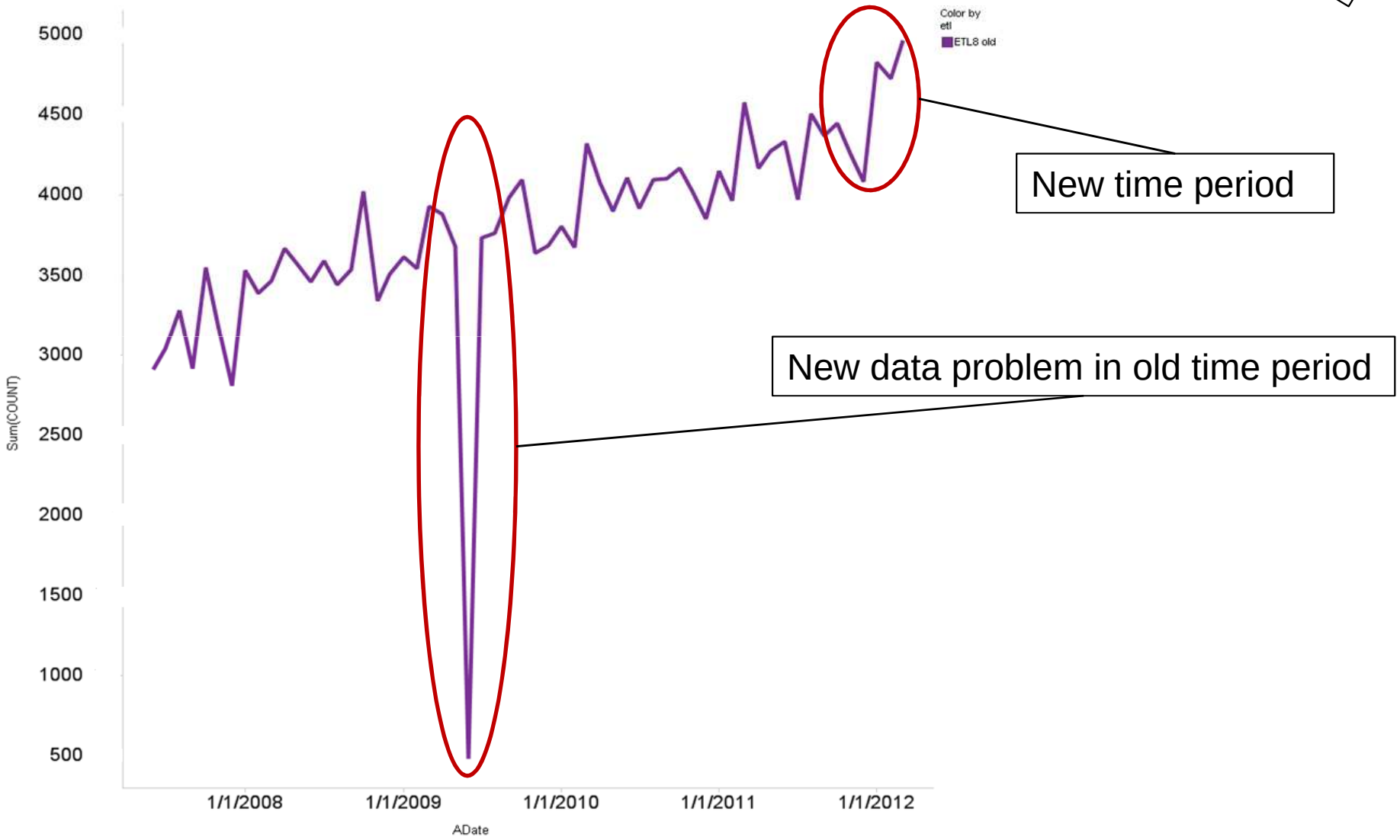
Prepared by: David L McClure, PhD[1], Marsha A Raebel, PharmD, BCPS, FCCP[2,3], W Katherine Yih, PhD, MPH[4], Azadeh Shoaibi, MS, MHS[5], Jerry Mullersman, MD, PhD, MPH[6], Colin Anderson-Smits, MPH[7], Rita Ouellet-Hellstrom, PhD[5], Aloka Chakravarty, PhD[5], Clara Kim, PhD[5], Jason M Glanz, PhD[2]

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Framework-for-Assessment-of-Signal-Refinement-Positive-Results.pdf

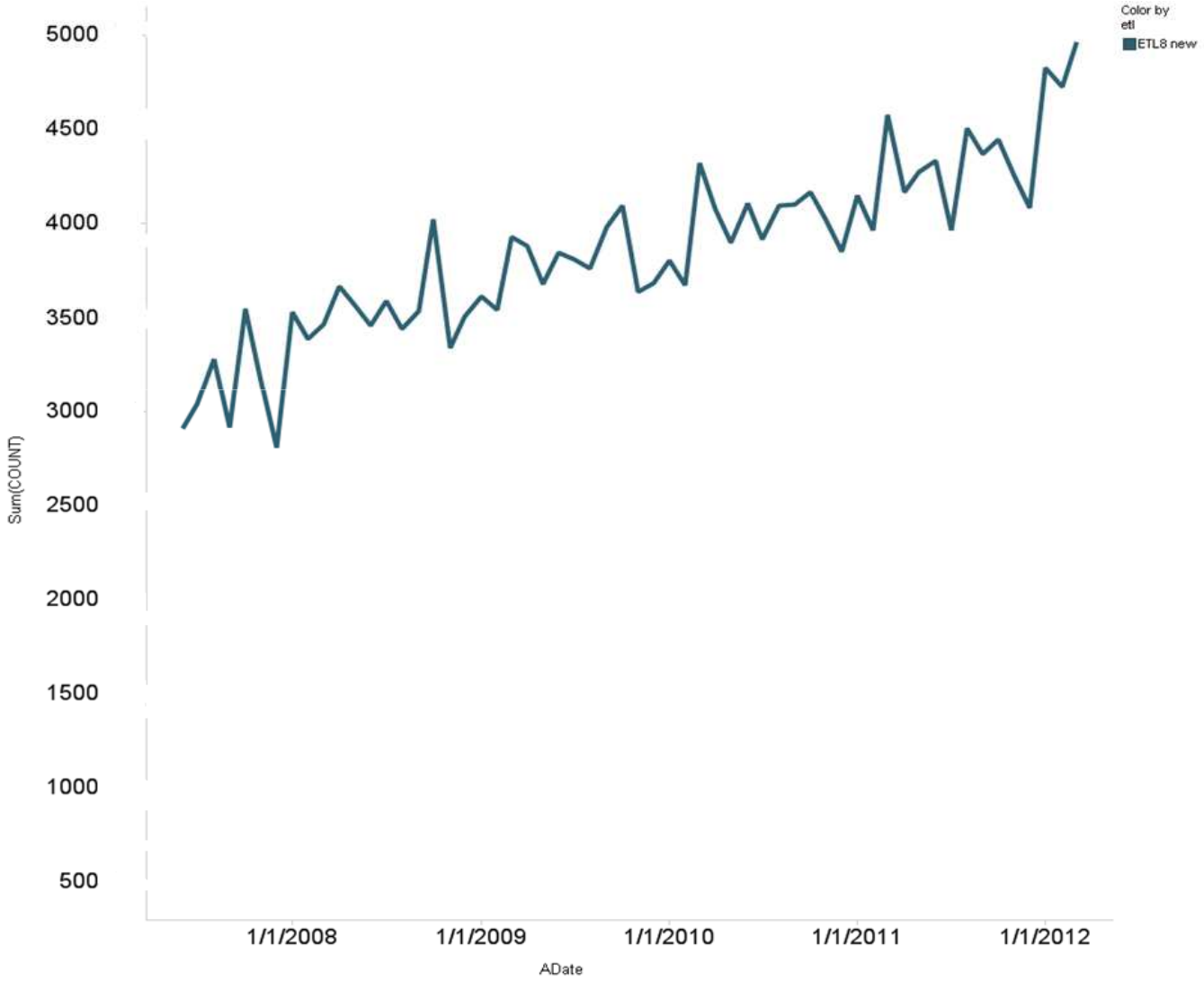
Data Visualization: After 7th refresh, partner A



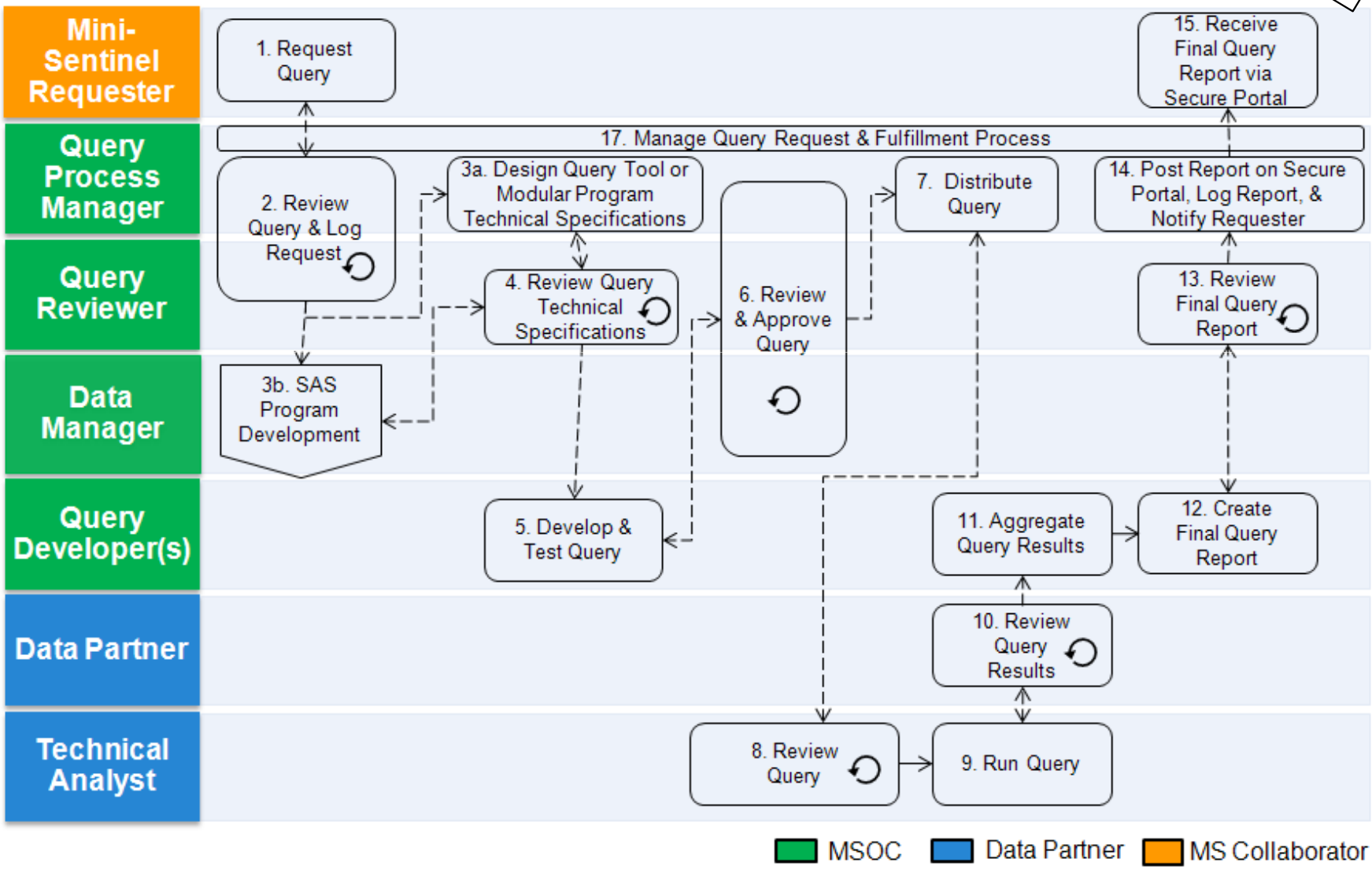
Data Visualization: After 8th refresh, partner A



Data Visualization: After 8th refresh fixed



Mini-Sentinel Query Fulfillment Process



Methods

- Improving confounder adjustment
- Validation of health outcomes of interest
- Data mining for vaccine adverse events
- **Implementing *Prospective Routine Observational Monitoring Program Tools (PROMPT)***

External engagements

- OMOP (now IMEDS)
- Clinical Trials Transformation Initiative
- ONC Standards & Interoperability Framework (Query Health)
- NIH Health Care System Collaboratory
- IOM Roundtable on Value and Science-Driven Health Care
- Academy Health EDM Forum
- Other new partners as opportunities present

Key contributors to Mini-Sentinel's progress 2013

- **Close, frequent, coordinated interactions between FDA, data partners, content experts, epidemiologists, and statisticians**
- Distributed data network
- Public health practice
- Focus on defined populations with sufficiently complete data
  - First: Claims and administrative data, plus access to full text records
  - Then: electronic medical records, registries, …
- Rapid cycle development of capabilities
- Ability to respond quickly to predefined needs

Costs and benefits

- Up to date distributed database + hundreds of rapid response queries
- Protocol based study
- Being prepared for pandemic or other crisis

2014

Mini-Sentinel PRISM Journal Supplement

- 2013 supplement to Vaccine
- 13 peer reviewed systematic reviews of algorithms for identifying health outcomes of interest for vaccine safety
- Open access!
- www.sciencedirect.com/science/journal/0264410X/31/supp/S10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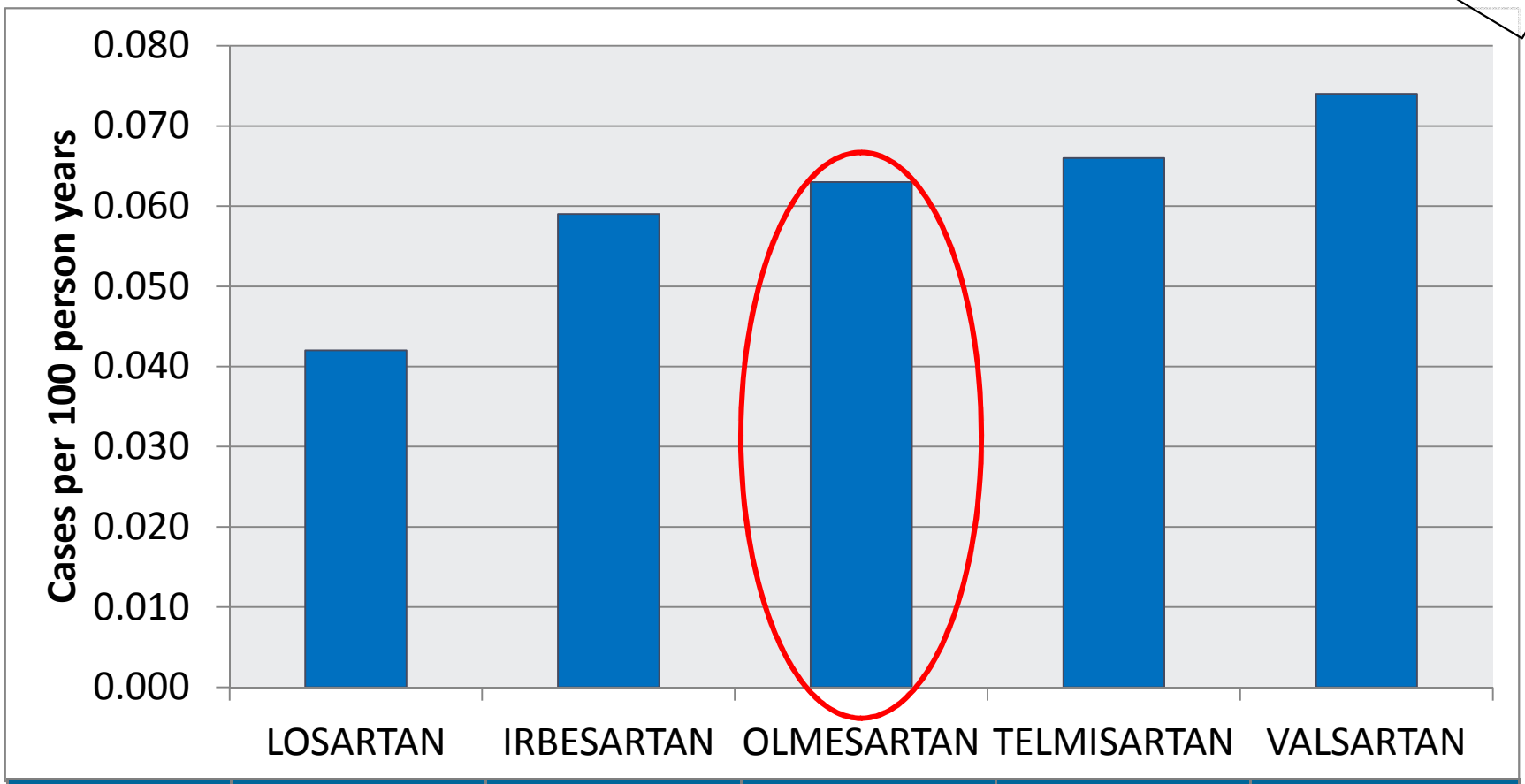
Drug Integrity and Supply Chain Security
Multistate outbreak of fungal meningitis and other infections
FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil
View and print full Drug Safety Communication (PDF - 54KB)
en Español
Safety Announcement
Facts about Olmesartan
Additional Information for Patients
Additional Information for Health Care Professionals
Data Summary
References
Safety Announcement
[7-3-2013] The U.S. Food and Drug Administration (FDA) is warning that the blood pressure drug
Olmesartan label change: sprue-like enteropathy
Discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.
Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of eight marketed ARB drugs. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.
FDA will continue to evaluate the safety of olmesartan-containing products and will communicate again if additional information becomes available.

ARBs and celiac disease



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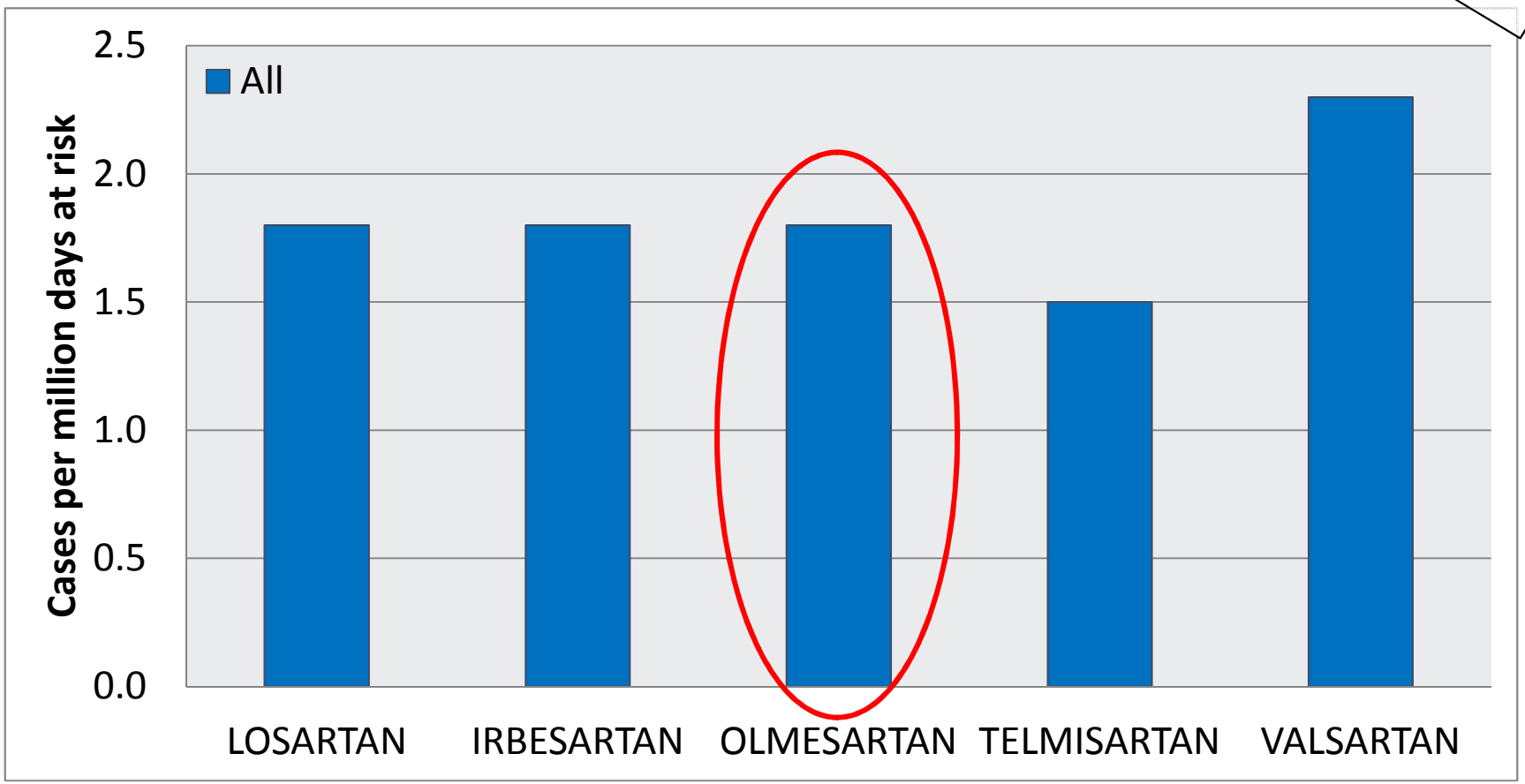
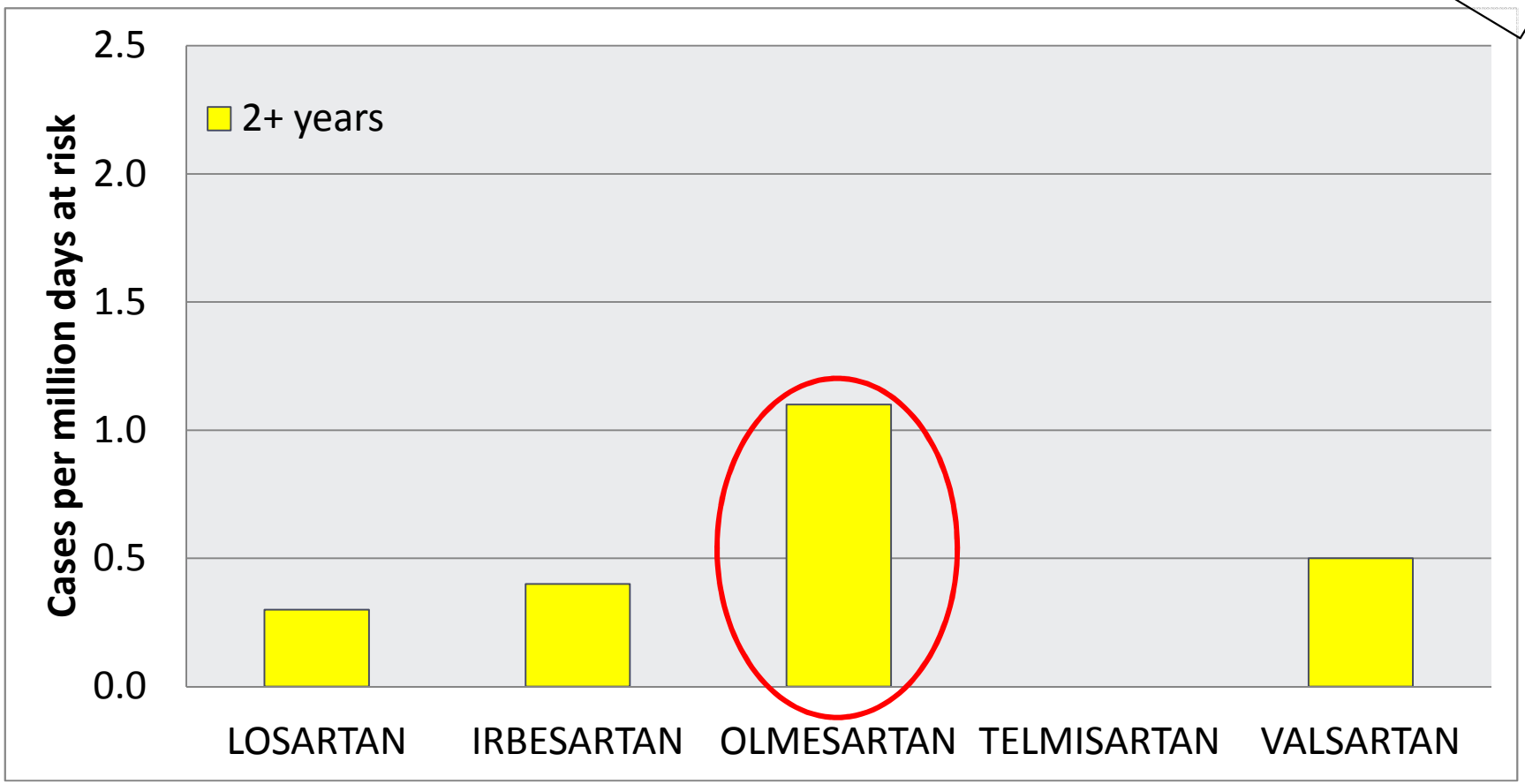


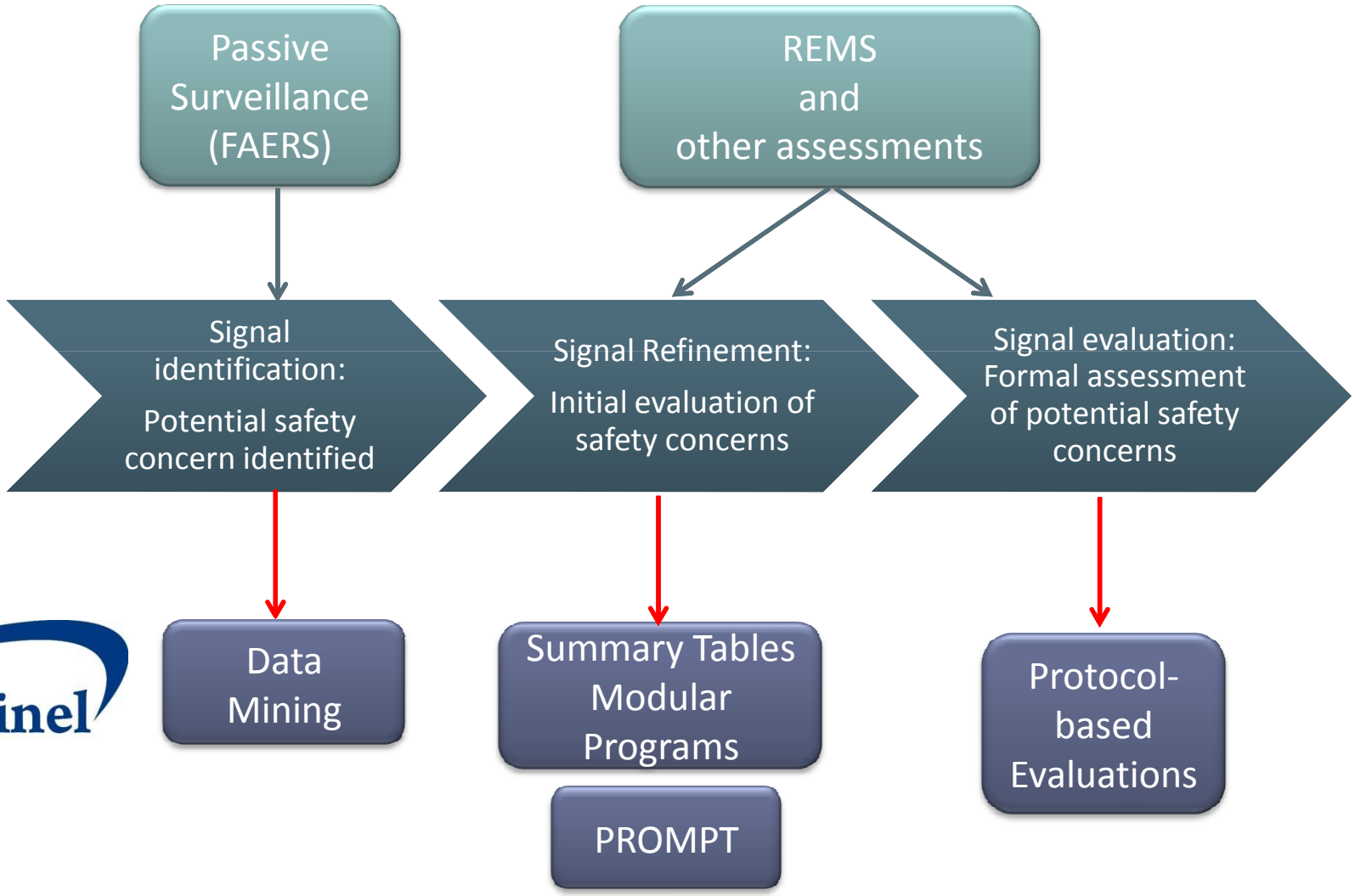
Cases	213	28	55	10	150
New users	535,045	69,868	171,630	44,770	346,618

ARBs and celiac disease: 2+ years



Cases	9	1	5	0	7
New users	25,045	2,721	4,419	1,124	13,925

Post-Market Safety Surveillance



Protocols under way or planned

- Anti-diabetic drugs and myocardial infarction
- Dabigatran and stroke / bleeding
- Influenza vaccine safety (same season)
- Metabolic effects of atypical antipsychotics in children and adolescents
- Influenza vaccine and febrile seizures
- IV iron products and anaphylactoid reactions
- Human papillomavirus vaccine and thromboembolic events.
- Influenza vaccine and birth defects, spontaneous abortion
- IV immune globulins and thromboembolic events
- Pneumococcal vaccine and Kawasaki disease

Vaccines, Blood & Biologics

Safety & Availability (Biologics)
- Biologics Product Shortages Q&A
- Recalls (Biologics)
- Biologic Product Shortages
- Report a Problem to the Center for Biologics Evaluation & Research
- Biologic Product Security
- Pandemics
- Blood Safety & Availability
- Tissue Safety & Availability
- Vaccine Safety & Availability
- HIV Home Test Kits

Resources for You

- 2013 Safety and Availability Communications

FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Safety Communication — June 13, 2013

FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Approves Required Revised Labeling for RotaTeq Based on the Study Results

Purpose: To inform the public and healthcare providers that FDA is releasing final study results from a Mini-Sentinel postlicensure observational study of intussusception (a form of bowel obstruction) after vaccination with RotaTeq (Merck and Co., Inc.) and Rotarix (GlaxoSmithKline Biologicals).

RotaTeq and Rotarix are vaccines for the prevention of rotavirus gastroenteritis in infants 6 weeks to 32 weeks of age (RotaTeq) and infants 6 weeks to 24 weeks of age (Rotarix). The study was conducted in Mini-Sentinel's Postlicensure Rapid Immunization Safety Monitoring (PRISM) program, the largest vaccine safety surveillance program in the United States.

FDA has approved required revisions to the Prescribing Information and Patient Information for RotaTeq as a result of the new safety data from this Mini-Sentinel PRISM study. New information was added to the Highlights, the existing intussuscep[illegible]ions section, and the Post-Marketing Experience section of the Full Pr[illegible]nt Information. The Mini-Sentinel PRISM study is the largest study c[illegible]date and identified an increased risk of intussusception in the 21 day time period after the first dose of RotaTeq, with most cases occurring in the first 7 days after vaccination. No increased risk was found after the second or third doses. These findings translate into 1 to 1.5 additional cases of intussusception per 100,000 first doses of RotaTeq.

Label change

The data from the Mini-Sentinel PRISM study regarding the risk of intussusception following the use of Rotarix were inconclusive. Based on this study, no changes were made to the Prescribing Information or to the Patient Information for Rotarix. However, based on data from an observational study previously conducted in Mexico, it is estimated that 1 to 3 additional cases of intussusception would occur per 100,000 vaccinated infants in the United States within 7 days following the first dose of Rotarix. In September 2012, FDA announced that it had approved revisions to the Prescribing Information and to the Patient Information for Rotarix to include these results from the study in Mexico.

2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

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

Major expansion activities in this year

- Operationalize prospective monitoring (PROMPT)
- Explore use of inpatient data
- Enhance querying capabilities and responsiveness to FDA's needs
- Develop the national resource for multiple users

Sentinel Prototype

2010

- Develop a coordinating center for a distributed system
  - Access three or more health data environments with varied attributes to conduct analyses
  - Convene a Planning Board to develop governing documents and establish a Safety Science Committee charged with the day-to-day operations
  - Develop a means for secure communication with contracted data holders
- Evaluate emerging methods in safety science
  - Develop epidemiological and statistical methodologies for signal detection, signal strengthening, and signal validation
  - Test such methodologies in the evaluation of FDA-identified medical product-adverse event pairs of concern

J. Woodcock, Dec 16, 2009

Mini-Sentinel met those goals

- Established access to 18 data environments
- Established the Planning Board and Safety Science Committee
- Developed a distributed data network with secure querying
  - PopMedNet has become national reference standard.
- Modified epidemiology and statistics methods for the distributed data network
  - Most assessments require no exchange of patient level data

And also

- Contributed to FDA's operations
  - Evaluated hundreds of medical product questions
  - 3 Drug Safety Communications
  - FDAAA Safety Label Change (rotavirus vaccine and intussusception)
  - FDA personnel have cited Mini-Sentinel in 26 presentations and publications
- Established a high level of transparency –
  - Protocols are posted for public comment before they are finalized

And also

- Demonstrated credibility through publication in the peer reviewed literature
  - Over 50 peer reviewed publications
- Established close, collegial collaboration between scientists and Mini-Sentinel scientists

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Perspective

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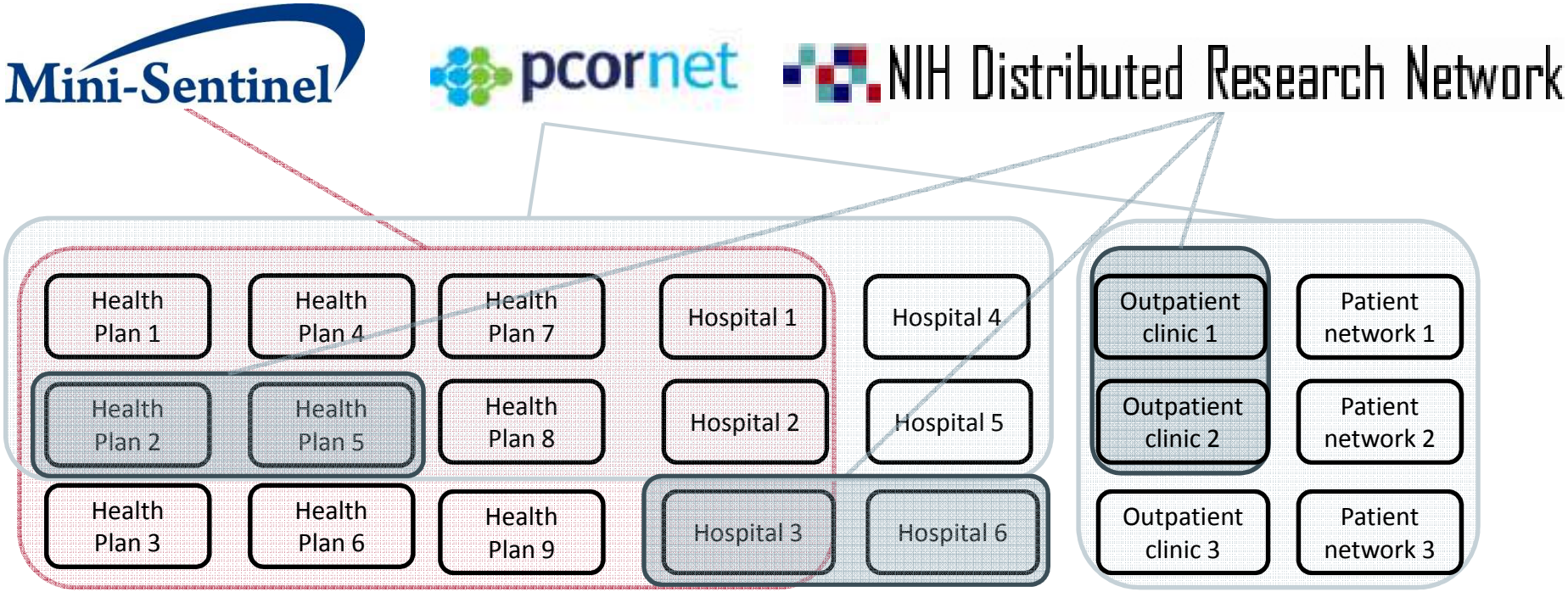
Multiple Networks Sharing Infrastructure



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

Thank you!