Biosimilar Collective Intelligence System: Utilizing Data Consortiums to Prove Safety and Effectiveness of Biosimilars

Reviewing current landscape of existing data consortiums: How they are being used, what they uncover, how they function—the Mini-Sentinel example

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November 12, 2013

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Harvard Pilgrim Health Care Institute/ Harvard Medical School

Outline

- Need for post marketing surveillance
- Why multisite studies
- Surveillance and sequential analysis
- Mini-Sentinel

At approval

- We know
  - Within a small, well-defined population in a controlled environment, and short-term exposure, the drug is
    - Relatively safe
    - More effective than placebo
- We don't know
  - Real-world safety
  - Real-world effectiveness
  - Comparative effectiveness
  - Cost-benefit

At approval: What's worse

We know that we don't have a **reliable system for actively monitoring and investigating** what we don't know

Benefits of a surveillance system

If we had a reliable system to generate post marketing evidence

- Change the risk-benefit calculation for stakeholders and the FDA
- Improve use of medications via evidenced-based medicine
- Encourage drug development

Surveillance goals

"A principal goal of our post approval drug-safety system should be to minimize the delay between approval and the discovery of these serious risks."

Sean Hennessy and Brian Strom, N Engl J Med, April 26, 2007

Sometimes multi-site studies are needed

- Rare exposures
- Rare outcomes
- Sample size (speed)
- Sub-group analyses
- Analytic flexibility

When multi-site studies are needed

Distributed networks aren't far behind

Some distributed networks

- CDC's Vaccine Safety Datalink (VSD)
- HMO Research Network
- FDA's post-market safety programs
- Meningococcal Vaccine Safety Study
- EU-ADR
- Scalable PArtnering Network for CER: Across Lifespan, Conditions, and Settings (SPAN)
- Post-licensure Rapid Immunization Safety Monitoring (PRISM)
- FDA Mini-Sentinel
- NIH Health Care Systems Collaboratory
- PCORI National Clinical Research Network

Distributed network approach

- Standardize data
- Data partners maintain physical control of their data
- Data partners control all uses of their data
- Data partners control all transfer of data
- Computer programs should run at multiple sites without modification

Distributed network key success factors and characteristics

- Engagement with data partners
- Coordinating center support
- Analytic tools
- Data, epidemiologic, and statistical expertise
- Type of data source (insurer, delivery system)
- Data refresh frequency
- Self-aware learning system
- Operational efficiency

Approaches to surveillance

- **Epidemiologic** study after specified time or exposures
  - Signal detection and hypothesis generation
  - Hypothesis testing
- **Sequential analysis of accumulating data**
  - Signal detection and hypothesis generation
- **Data mining**
  - Signal detection and hypothesis generation

Sequential surveillance

- Extract, manipulate, and summarize data as they accumulate
- Conduct periodic analysis
- Repeated statistical testing of the same data requires special methods
  - Sequential probability ratio test; Maximized SPRT
  - Group sequential methods

Active Surveillance of Vaccine Safety

A System to Detect Early Signs of Adverse Events

Robert L. Davis,[†] Margarette Kolczak,[‡] Edwin Lewis,[†] James Nordin,[§] Michael Goodman,[§] David K. Shay,[‡] Richard Platt,[¶] Steven Black,[†] Henry Shinefield,[†] and Robert T. Chen[‡]*

Background: There currently are no population-based systems in the United States to rapidly detect adverse events after newly introduced vaccines. To evaluate the feasibility of developing such systems, we used 5 years of data from 4 health maintenance organizations within the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink.

Methods: Within every year, each week's vaccinated children were followed for 4 weeks, and rates of adverse events were compared with rates among children of similar ages before the introduction of the new vaccine. We assessed risks for intussusception after rotavi-

Conclusions: We conclude that it is feasible to develop systems for rapid and routine population-based assessments of new vaccine safety.

(*Epidemiology* 2005;16: 336–341)

Recent events in the United States have underscored the need for surveillance systems that detect adverse events as soon as possible after the introduction of new vaccines (eg,

ORIGINAL ARTICLE

Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events

Tracy A. Lieu, MD, MPH,† Martin Kulldorff, PhD,* Robert L. Davis, MD, MPH,‡ Edwin M. Lewis, MPH,§ Eric Weintraub, MPH,‡ Katherine Yih, PhD, MPH,* Ruihua Yin, MS,* Jeffrey S. Brown, PhD,* and Richard Platt, MD, MSc,* for the Vaccine Safety Datalink Rapid Cycle Analysis Team*

Background: Rare but serious adverse events associated with vaccines or drugs are often nearly impossible to detect in prelicensure studies and require monitoring after introduction of the agent in large populations. Sequential testing procedures are needed to detect vaccine or drug safety problems as soon as possible after introduction.

Conclusions: Real-time surveillance combining dynamic data files, aggregation of data, and sequential analysis methods offers a useful and highly adaptable approach to early detection of adverse events after the introduction of new vaccines.

Key Words: vaccine safety, active surveillance, sequential analysis, meningococcal vaccine, drug safety

Basic implementation steps

- Choose exposure and outcome
- Choose the comparator and comparison (historical, concurrent)
- Collect and summarize data
- Conduct sequential analysis and testing
  - Observed > than expected?
  - …how about now?
  - …now?

Surveillance for adverse drug events

- Apply methods and lessons from Vaccine Safety Datalink
- Unique drug-specific issues
  - Patterns of drug use: New (incident), chronic, and intermittent use
  - Accommodate misclassification of exposure (e.g., non-adherence, prior drug use, concomitant drug use)
  - Adjust for co-morbidities

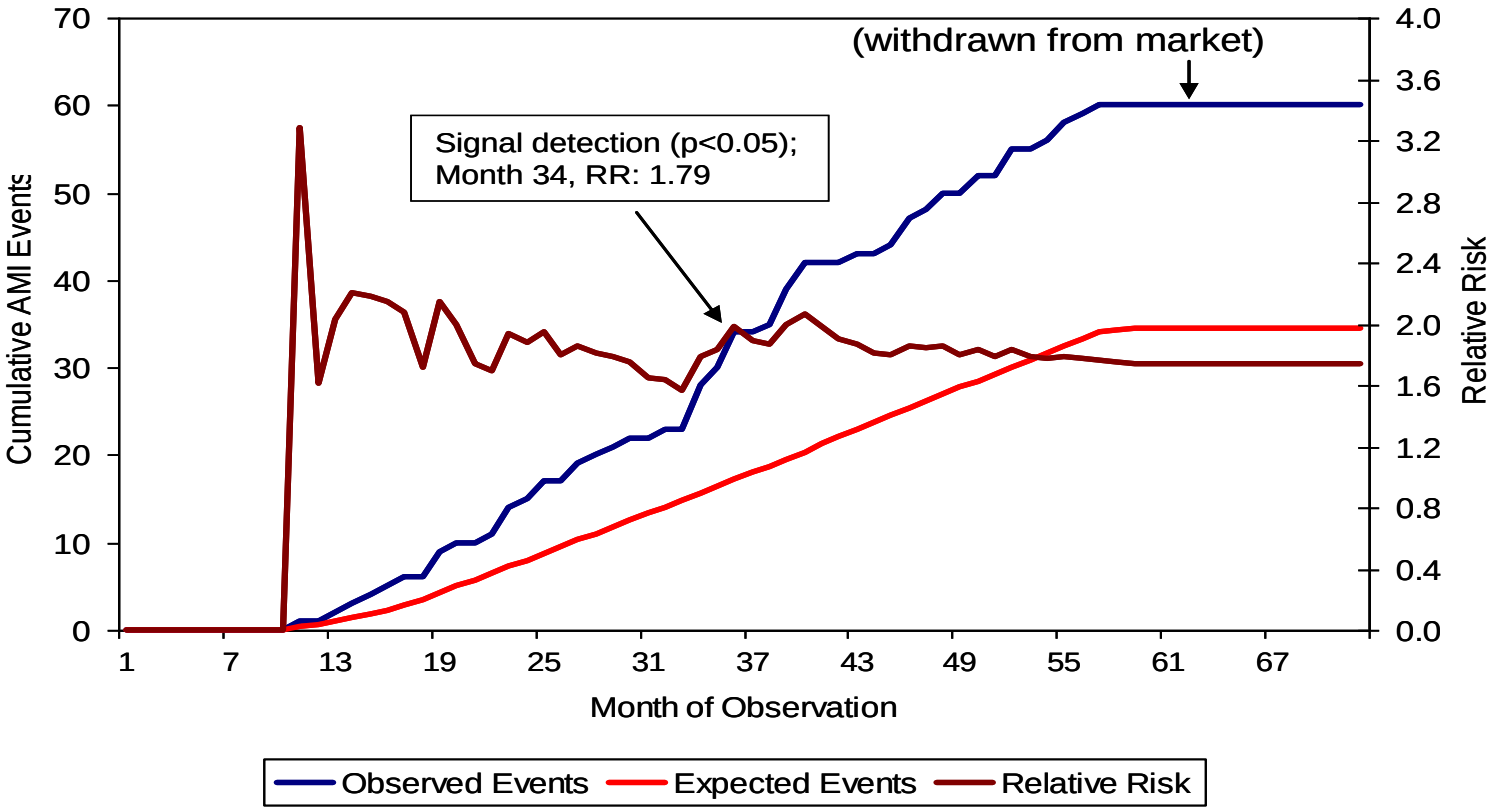
PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1275–1284
Published online 22 October 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1509

ORIGINAL REPORT

Early detection of adverse drug events within population-based health networks: application of sequential testing methods[†,‡]

Jeffrey S. Brown PhD[1,2*], Martin Kulldorff PhD[1], K. Arnold Chan MD, MPH, ScD[3,4], Robert L. Davis MD, MPH[5], David Graham MD[6], Parker T. Pettus MS[1,2], Susan E. Andrade ScD[2,7], Marsha A. Raebel PharmD[2,8], Lisa Herrinton PhD[2,9], Douglas Roblin PhD[2,10], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,7], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

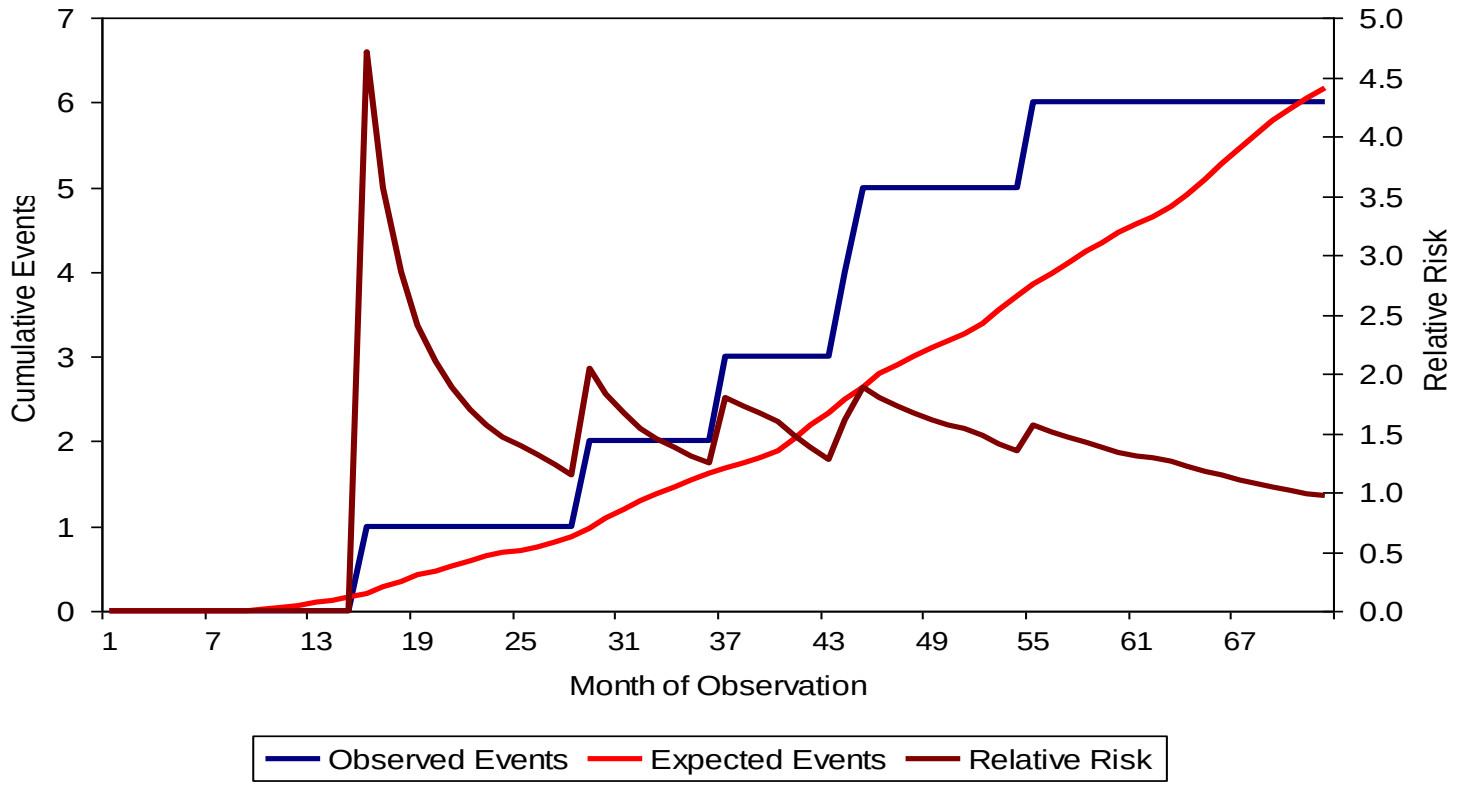
Observed and expected events for rofecoxib versus naproxen users: 2000-2005



Signal after 28 events (16 expected) among new users of drug

Brown *et al*. (2007) PDS; Adjusted for age, sex, health plan. Outcome: AMI.

Observed and expected events for cetirizine users versus non-users: 2000-2005



Negative control;6 observed and 6.1 expected. > 5 million exposed days.

Brown *et al*. (2007) PDS; Adjusted for age, sex, health plan. Outcome: Thrombocytopenia.

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2009; **18**: 226–234
Published online 15 January 2009 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1706

ORIGINAL REPORT

Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations†

Jeffrey S. Brown PhD[1,2*], Martin Kulldorff PhD[1], Kenneth R. Petronis PhD[3], Robert Reynolds ScD[3], K. Arnold Chan MD, MPH, ScD[4,5], Robert L. Davis MD, MPH[6], David Graham MD[7], Susan E Andrade ScD[2,8], Marsha A. Raebel PharmD[2,9], Lisa Herrinton PhD[2,10], Douglas Roblin PhD[2,6], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,8], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

…alternative specifications tend to result in earlier signal detection by 10–16 months, a likely consequence of more exposures and events entering the analysis.

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3412

ORIGINAL REPORT

Near real-time adverse drug reaction surveillance within population-based health networks: methodology considerations for data accrual†

Taliser R. Avery[1,2]*, Martin Kulldorff[1,2], Yury Vilk[1], Lingling Li[1], T. Craig Cheetham[2,3], Sascha Dublin[2,4], Robert L. Davis[2,6], Liyan Liu[2,5], Lisa Herrinton[2,5] and Jeffrey S. Brown[1,2]

Purpose: Practical considerations for implementation of real-time drug safety surveillance using safety of generic versus branded divalproex as use case

Methods: Near real time surveillance at 4 health plans; monthly data extracts

Results: Data quality review process for each extract at each site is crucial. Data lags exists but can be accounted for.

Conclusions: Near real-time sequential safety surveillance is feasible, but several barriers warrant attention. …differential accrual between exposure and outcomes could bias risk estimates towards the null, causing failure to detect a signal.

Sequential surveillance in distributed networks

- Sequential drug safety surveillance is possible
- Makes best use of routinely collected data
- Simple data requirements allow combining data from multiple sources
  - Dispensing, diagnoses, demographics, eligibility
  - Stratified counts for analysis
  - Distributed data model → no transfer of PHI
- Requires strong coordinating center
  - Data checking and coordination is complex
  - Range of expertise needed

2009

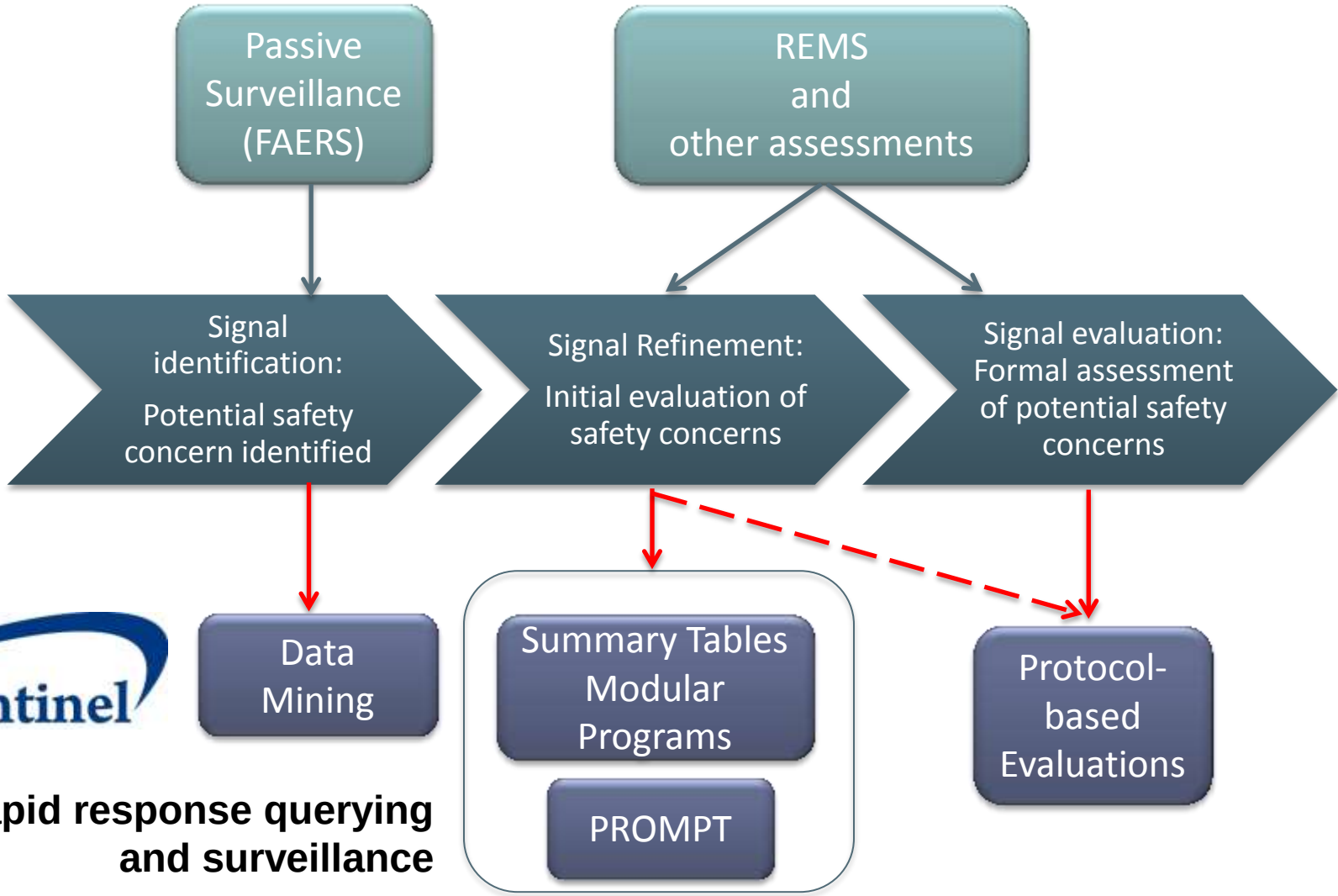
Mini-Sentinel

- Develop scientific operations for active medical product safety surveillance
- Create a coordinating center with continuous access to automated healthcare data systems, and the following capabilities:
  - Develop and evaluate scientific methods that might later be used in a fully-operational Sentinel System.
  - Evaluate safety issues
  - Identify and address barriers
- Operate under FDA's public health authority

Safety issues

- Exposure-outcome relationships
  - Retrospective
  - Prospective
- Medical product utilization
  - Age, sex, calendar time
- Disease burden
- Response to FDA's regulatory actions

Post-Market Safety Surveillance



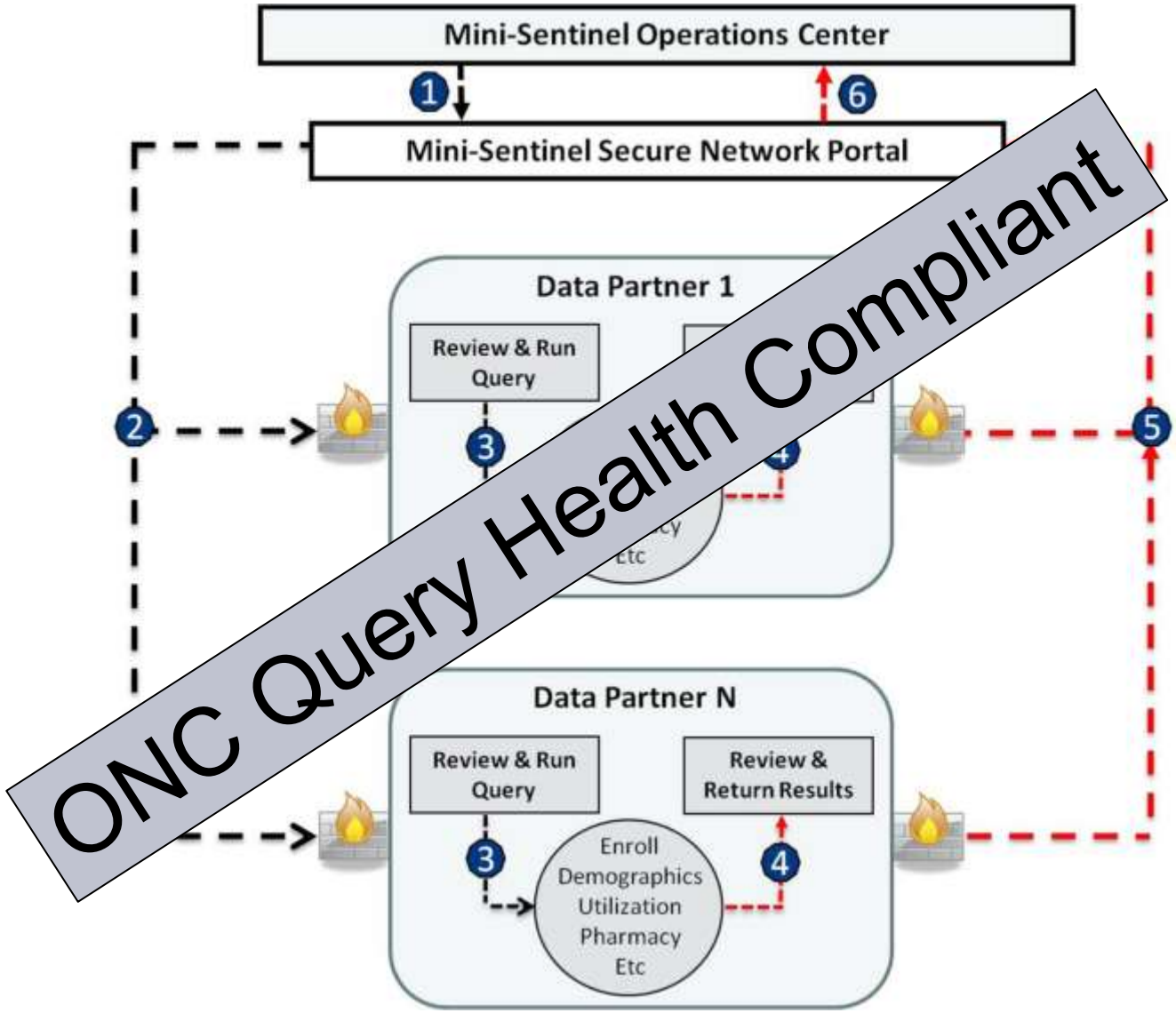
Mini-Sentinel Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners

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

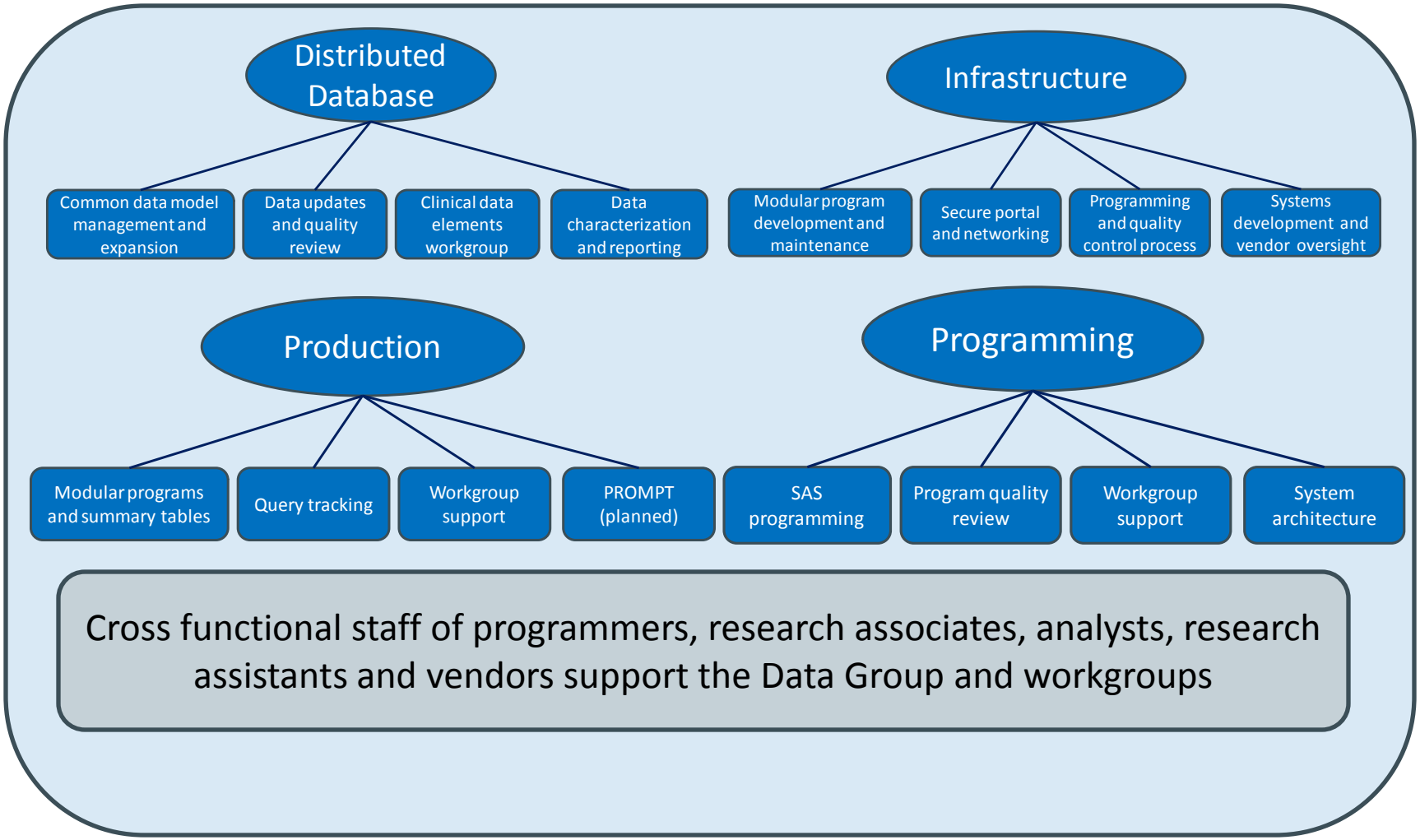
4- Data partners review results

5- Data partners return results via secure network

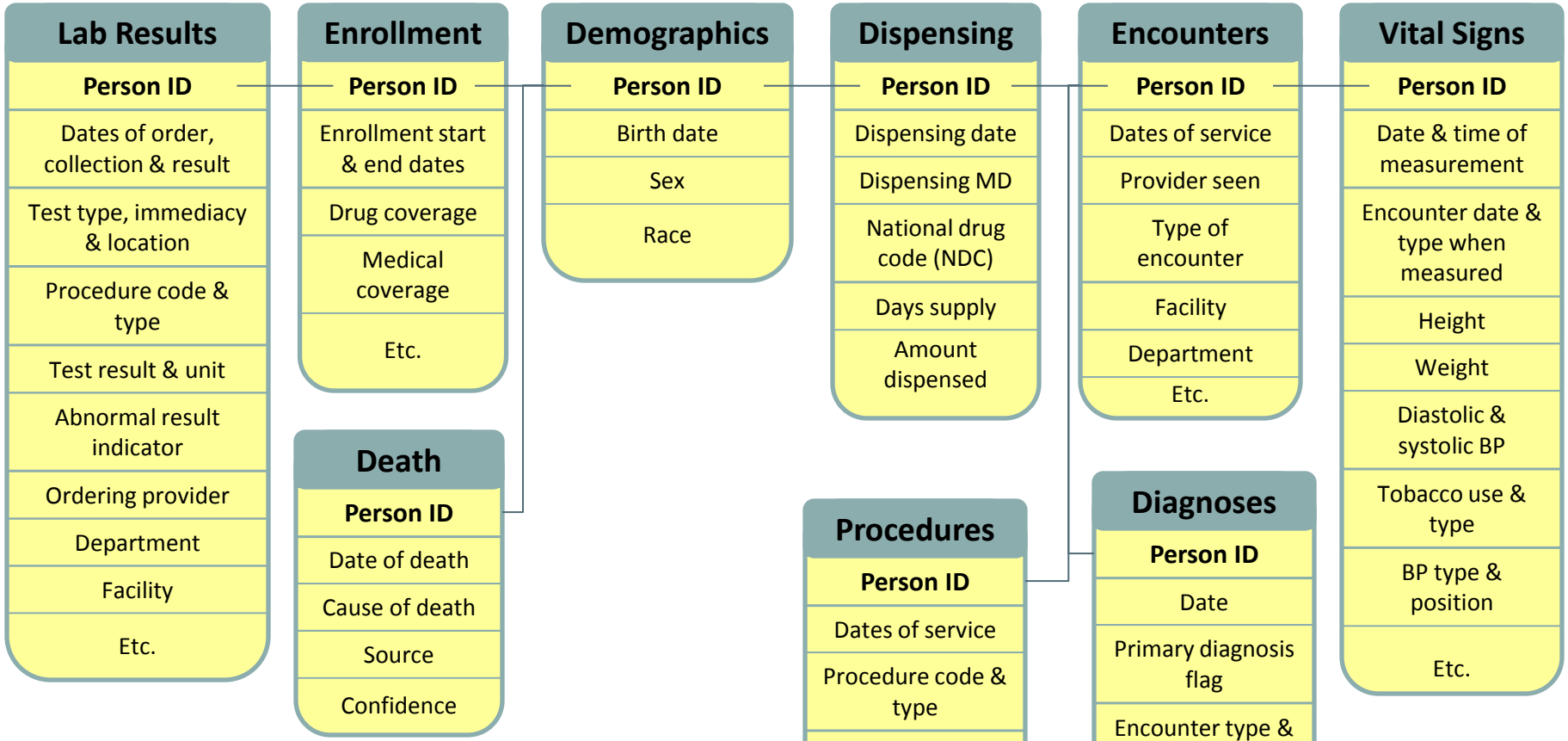
6 Results are aggregated

The Mini-Sentinel Coordinating Center Data Group

Structure of the data group



Mini-Sentinel Common Data Model

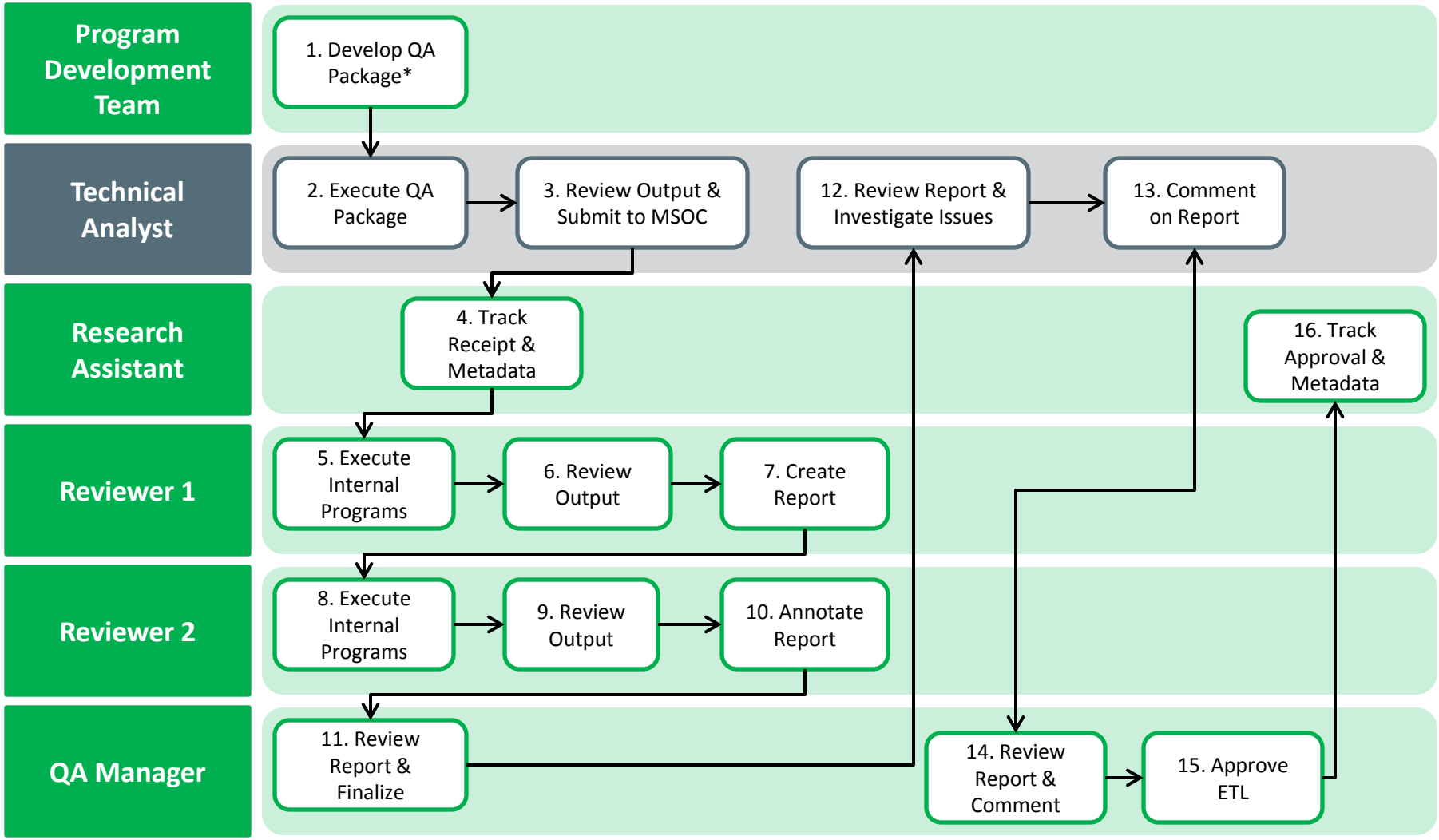


Immunization registries

Birth and fetal death registries

Inpatient data model

Data QA and characterization



*Program Development Team Follows MS SAS Program Development SOP to Create QA Package

Data checking and characterization

- Hundreds of tables per data partner per refresh
- 4 levels of data checks
- > 1400 checks

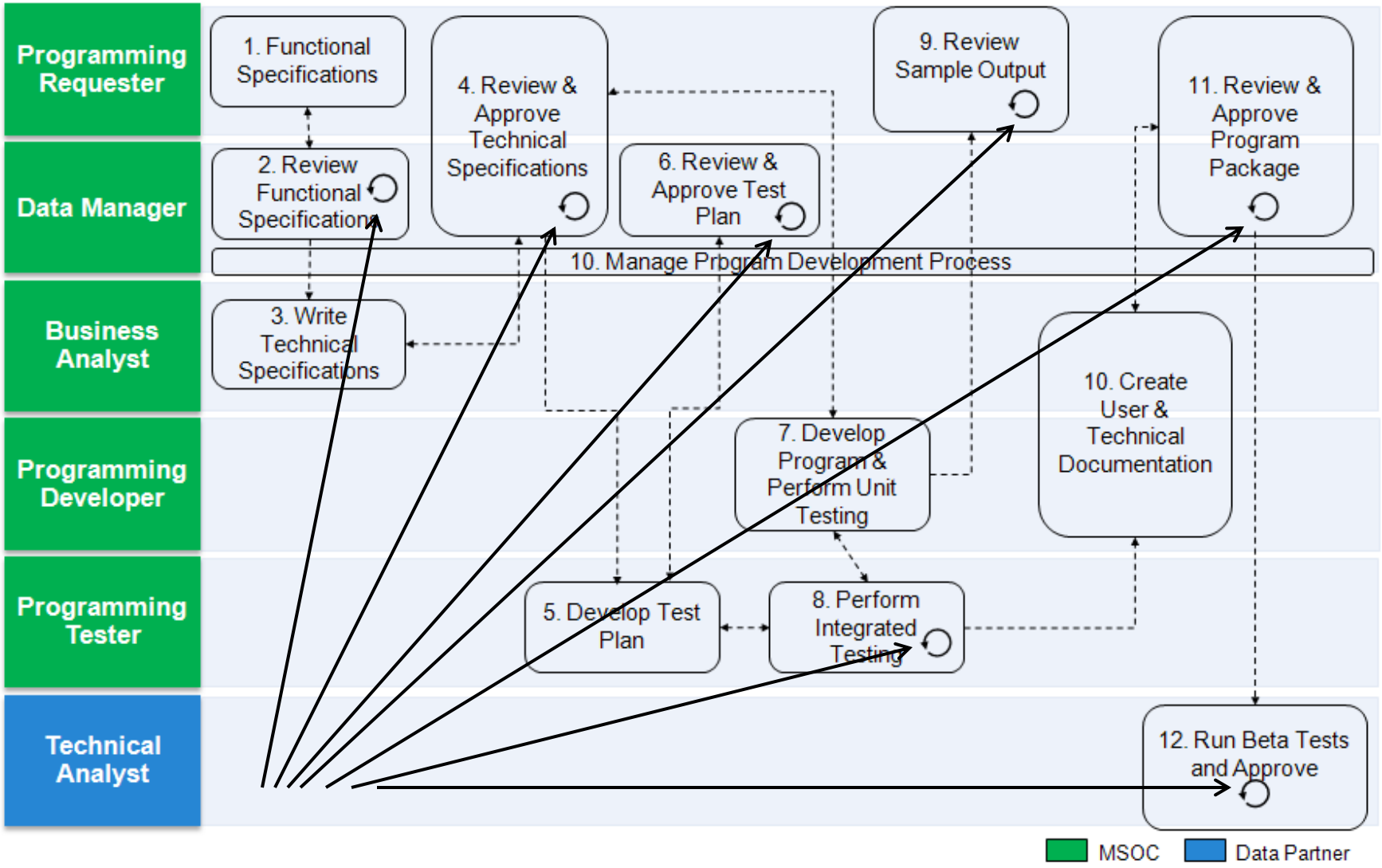
Obs	ENCTYPE	ADATE	COUNT	PERCENT
1	AV	2000	7030952	5.1370
2	AV	2001	7454699	5.4466
3	AV	2002	8014346	5.8555
4	AV	2003	8261199	6.0358
5	AV	2004	8251011	6.0284
6	AV	2005	8857635	6.4716
7	AV	2006	9576674	6.9969
8	AV	2007	10240959	7.4823
9	AV	2008	11831682	8.6445
10	AV	2009	13785025	10.0716
11	AV	2010	14499322	10.5935
12	AV	2011	14988289	10.9508
13	ED	2000	193108	0.1411
14	ED	2001	213180	0.1558
15	ED	2002	231296	0.1690
16	ED	2003	232122	0.1696
17	ED	2004	230756	0.1686
18	ED	2005	266406	0.1946
19	ED	2006	291381	0.2129
20	ED	2007	314060	0.2295
21	ED	2008	343936	0.2513
22	ED	2009	400500	0.2926
23	ED	2010	414312	0.3027
24	ED	2011	451881	0.3302
25	IP	2000	432504	0.3
26	IP	2001	477466	0.3
27	IP	2002	517710	0.3
28	IP	2003	543660	0.3
29	IP	2004	543692	0.3
30	IP	2005	587863	0.4

Obs	RXDATE	N
1	2000JAN	75816
2	2000FEB	68872
3	2000MAR	240058
4	2000APR	248527
5	2000MAY	261254
6	2000JUN	258289
7	2000JUL	241145
8	2000AUG	260316
9	2000SEP	252799
10	2000OCT	260813
11	2000NOV	254161
12	2000DEC	259611
13	2001JAN	275314
14	2001FEB	242270
15	2001MAR	278558
16	2001APR	260591
17	2001MAY	268647
18	2001JUN	267520
19	2001JUL	257699
20	2001AUG	279320
21	2001SEP	251170

Obs	Age_group	COUNT	PERCENT
1	0.1 0-1 Yrs	602059	1.4996
2	02. 2-4 Yrs	1376997	3.4298
3	03. 5-9 Yrs	2553188	6.3595
4	04. 10-14 Yrs	2638462	6.5719
5	05. 15-18 Yrs	2135457	5.3190
6	06. 19-21 Yrs	1670742	4.1615
7	07. 22-44 Yrs	14770481	36.7906
8	08. 45-64 Yrs	11221814	27.9515
9	09. 65-74 Yrs	1854092	4.6182
10	10. 75+ Yrs	1324163	3.2982

Obs	px_codetype	enctype	COUNT	PERCENT
1	09	AV	3891384	0.2061
2	09	ED	940211	0.0498
3	09	IP	7716848	0.4088
4	09	IS	168596	0.0089
5	09	OA	510196	0.0270
6	C2	AV	4906255	0.2599
7	C2	ED	325738	0.0173
8	C2	IP	392155	0.0208
9	C2	IS	18219	0.0010
10	C2	OA	222605	0.0118
11	C3	AV	212648	0.0113
12	C3	ED	5276	0.0003
13	C3	IP	7755	0.0004
14	C3	IS	269	0.0000
15	C3	OA	2030	0.0001
16	C4	AV	1364119936	72.2580
17	C4	ED	95271865	5.0466
18	C4	IP	50242438	2.6614
19	C4	IS	3914519	0.2074
20	C4	OA	27959691	1.4810
21	HC	AV	252901204	13.3963
22	HC	ED	14811325	0.7846
23	HC	IP	8125355	0.4304
24	HC	IS	1600478	0.0848
	HC	OA	31067795	1.6457
	ND	AV	16692216	0.8842
	ND	ED	639229	0.0339
	ND	IP	147970	0.0078
	ND	IS	12924	0.0007
	ND	OA	819916	0.0434
	OT	AV	194765	0.0103
	OT	ED	374	0.0000
	OT	IP	2607	0.0001
	OT	IS	1367	0.0001
	OT	OA	348	0.0000

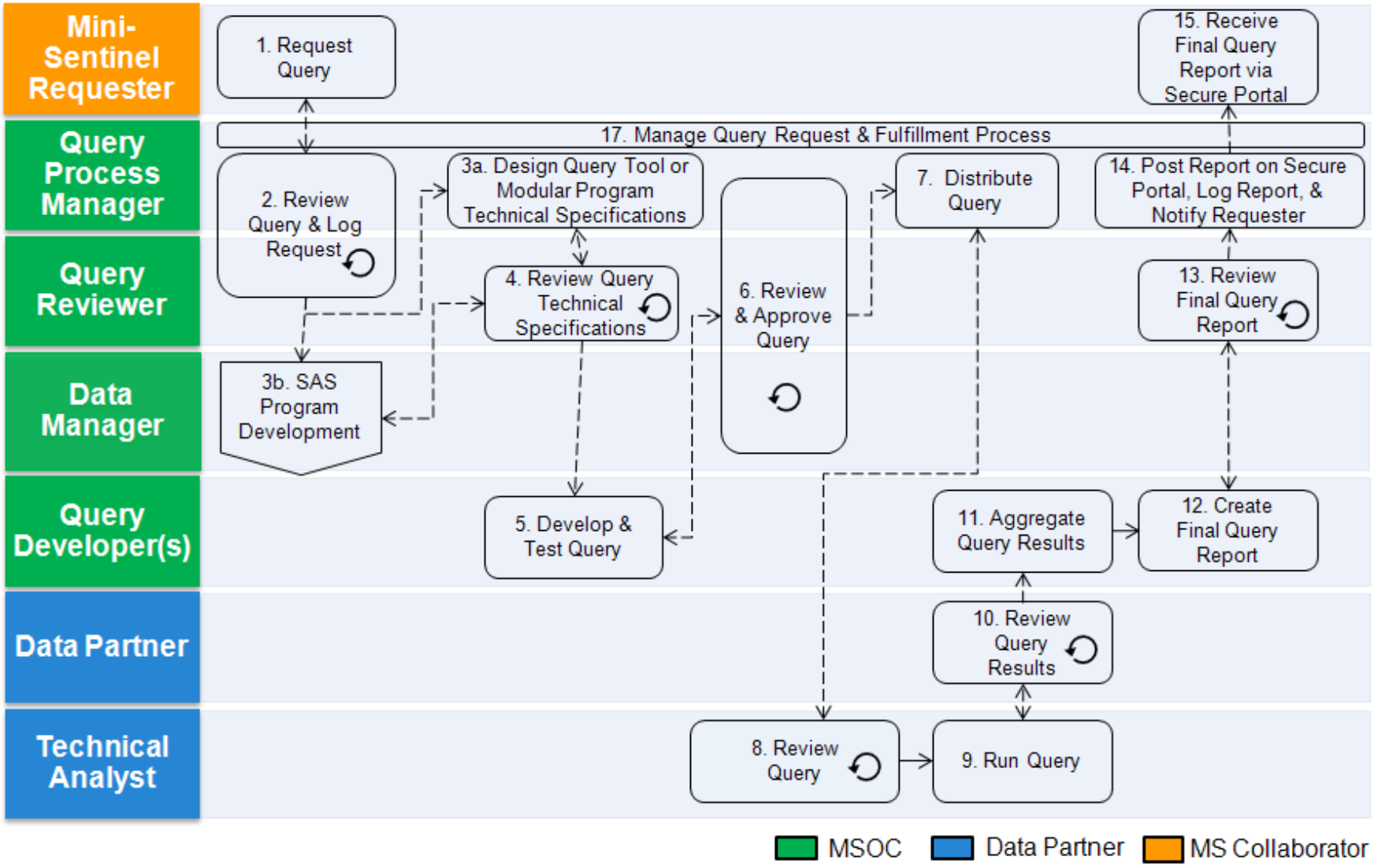
New program development



Testing process and environments

- Among the 18 data partners there are 10 different environments
  - SAS versions (9.2, 9.3, 9.4; different versions of each)
  - Computing environments (Windows, Unix, Linux)
- 18 unique local hardware settings and systems
- Each distributed program must run in all environments

Query fulfillment process



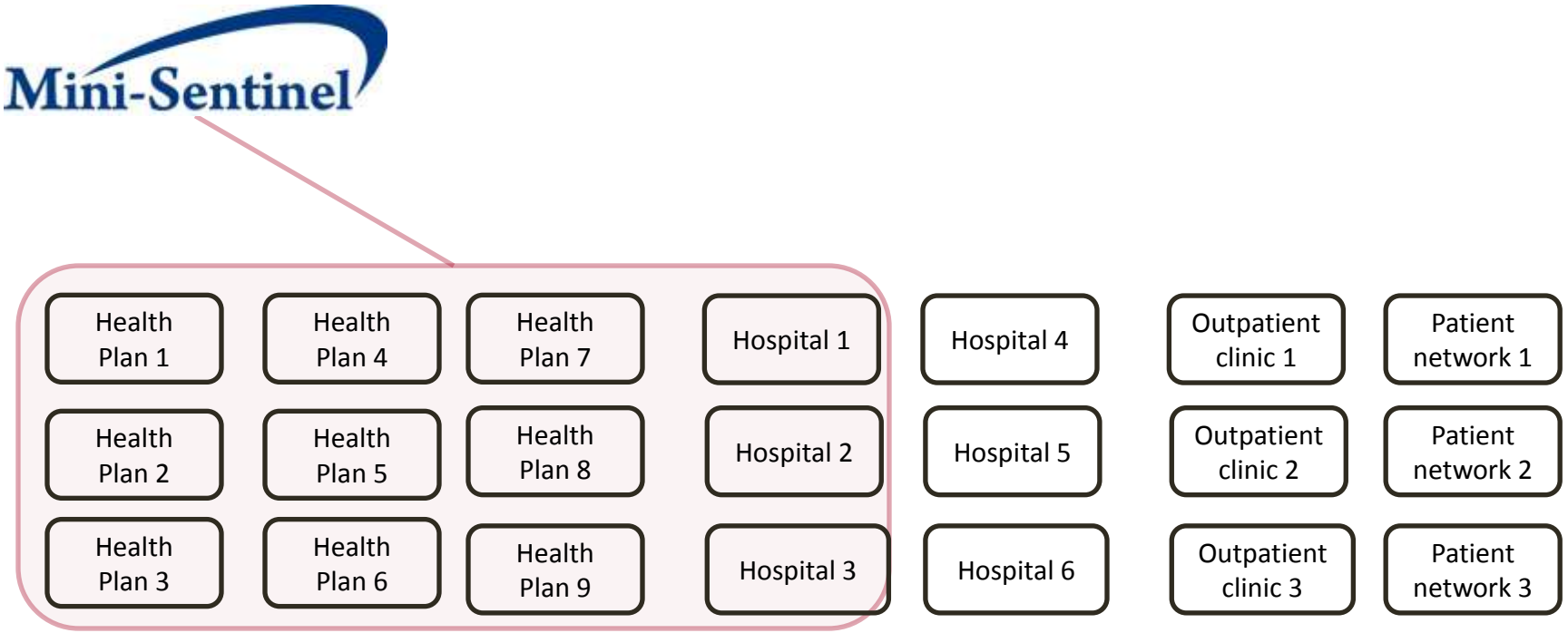
Mini-Sentinel infrastructure systems

- Operations are all based on SOPs
- Tools are treated like software
  - Bug tracking system for all changes to code and code development
- FISMA compliant secure portal
- Activity tracker
- Secure distributed query tool

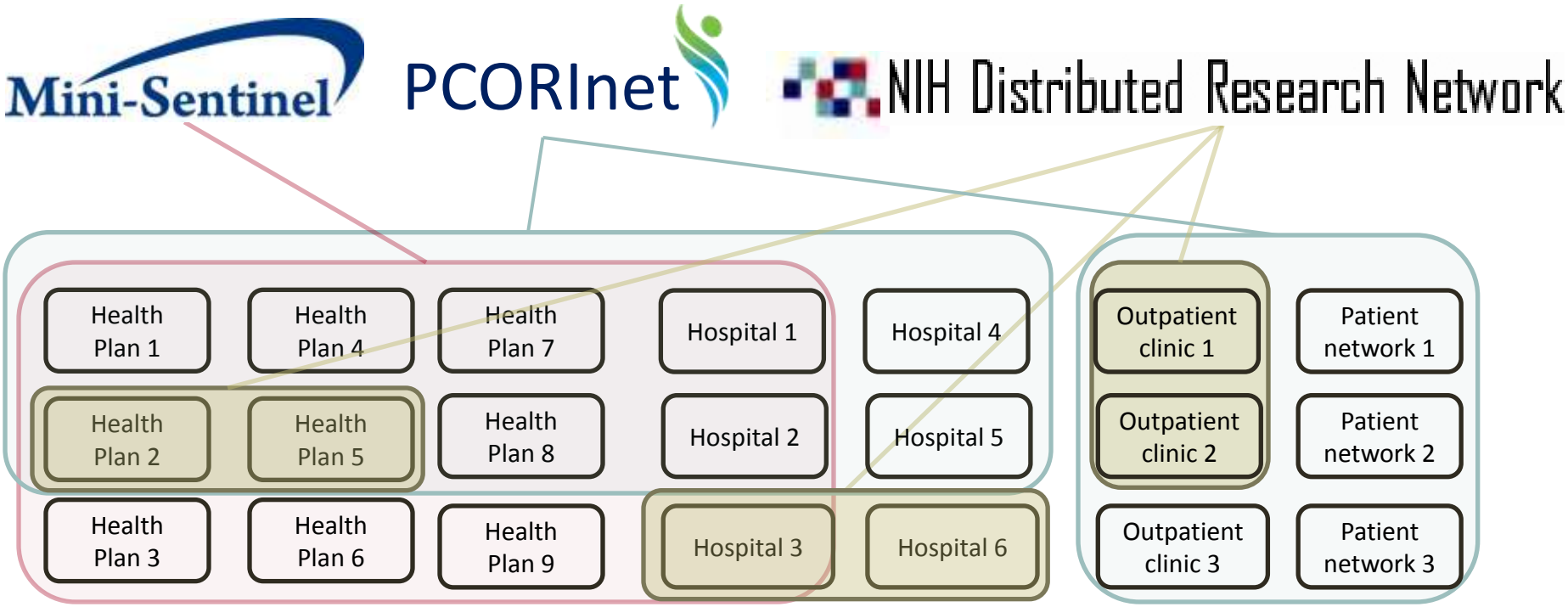
Mini-Sentinel querying tools

- Summary table queries
- Modular programs
  - Utilization patterns and cohort identification
  - Rate of adverse events following exposure
  - Background rates
- “macro” library
- Prospective Routine Observational Monitoring Program Tools (PROMPT)
  - Self-controlled design (exposure indexed)
  - Cohort design, with propensity score (exposure) matching
  - Cohort design, with regression adjustment (GEE)
  - Cohort design, with IPT weighted regression adjustment

Multiple networks sharing infrastructure



Multiple networks sharing 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

Thank you

Drugs

"This assessment […used…] FDA's Mini-Sentinel pilot..."

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

The NEW ENGLAND JOURNAL of MEDICINE

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

Drugs

Drug Safety and Availability

- Drug Alerts and Statements
- Importing Prescription Drugs
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors
- FDA Drug Safety Newsletter
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- 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 medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy. FDA has approved changes to the labels of these drugs to include [redacted]

Label change

Symptoms of sp[redacted] diarrhea with substantial weight loss. The enteropathy may [redacted]sartan, and sometimes requires hospitalization ([redacted]). If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started. 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.

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 ions section, and the Post-Marketing Experience section of the Full Pr nt Information. The Mini-Sentinel PRISM study is the largest study c date and identified an increased risk of intussusception in th otaTeq, 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.

ORIGINAL INVESTIGATION

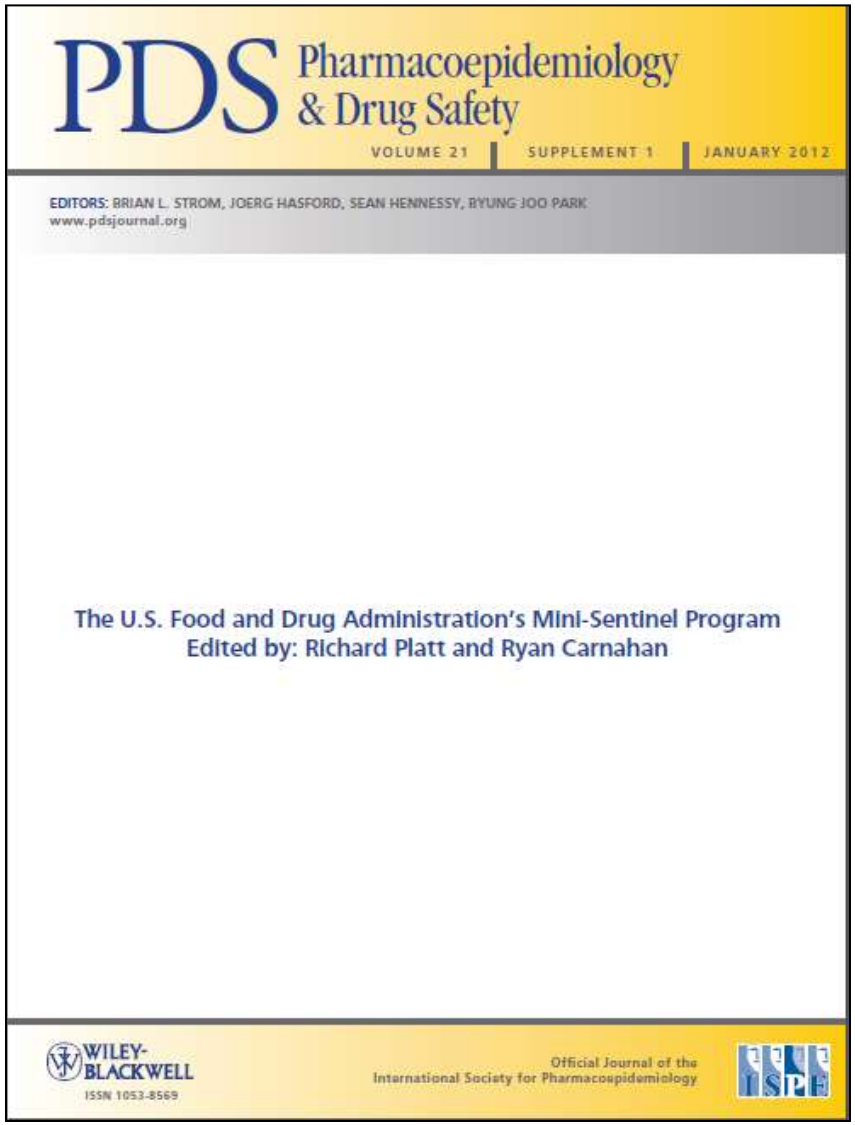
ONLINE FIRST

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 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

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Perspective

Dabigatran and Postmarketing Reports of Bleeding

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"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."

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Thank you