AMCP Webinar Series

Biosimilars Surveillance: Applying the Science of Proven Data Consortium Models

Academy of Managed Care Pharmacy®

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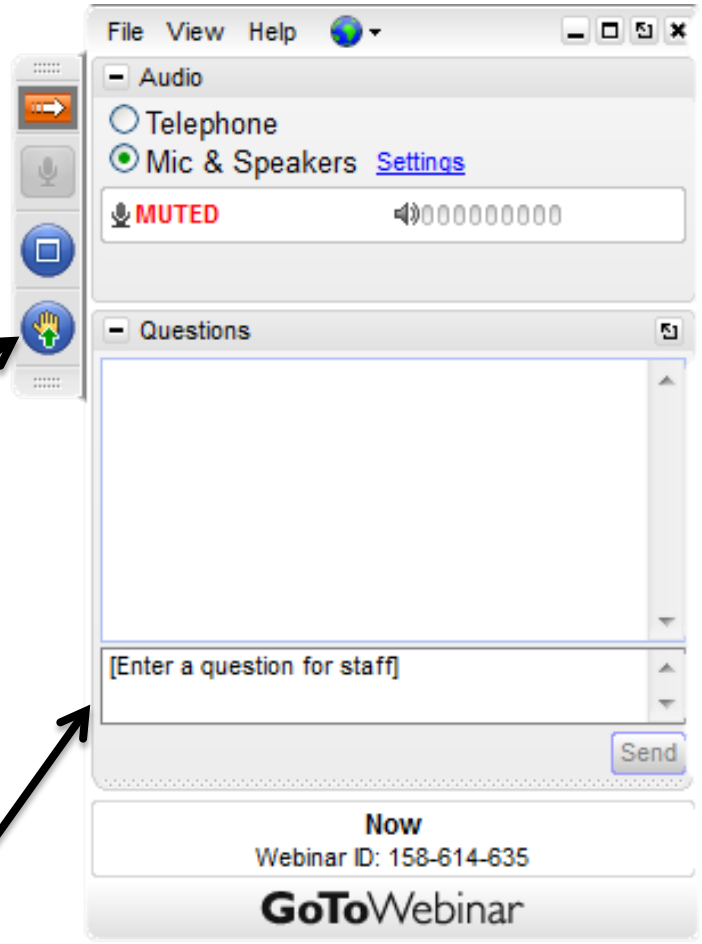
10 March 2014

How to Ask A Question



Raise your hand to ask verbally

Or, type your question in the 'Questions' area

AMCP Biosimilars Collective Intelligence Project

- **Our Mission:** Furthering Biosimilar adoption by assuring physicians and the public that managed care and industry are working together to monitor biosimilars

- **Our Strength:** our large managed care databases, and our primary focus on biosimilars and their active and early surveillance.

- **Why AMCP Biosimilars Collective Intelligence?**
  - Huge specialty pipeline requires some cost-relief
  - $250B in Biosimilar potential sales (over 10 year) creates opportunities for patients to save $ on copays and biosimilar manufacturers to provide a very important cost-savings

AMCP Biosimilars Collective Intelligence Project

Are Managed Care Organizations Supporting This Initiative?

- Our members have devoted significant resources to developing an infrastructure that makes active surveillance possible.
- At our Task Force meeting on November 12 several large managed care organizations and PBMs indicated their full support for this project and thanked AMCP for the leadership it is providing on this important specialty drug issue

Why is AMCP The Ideal Organization To Lead This Surveillance Effort?

- AMCP members are aligned on using sound medication management principles and strategies to improve health care.
- Our members comprise the broad spectrum of specialty drug interests including managed care pharmacists, pharmacoeconomists, researchers, industry, PBMs, specialty pharmacies
- It is important for managed care pharmacy to marshal its resources for the important public health benefit inherent in monitoring biosimilar safety and effectiveness

AMCP Biosimilars Collective Intelligence Approach

How Will the AMCP Biosimilars Collective Intelligence Work?

- An off-the-shelf approach using proven network tools and technology to provide Active, Early and Focused surveillance
  - Similar Operational Distributed Research Networks (DRNs): HMO Research Network, Mini-Sentinel
- Tested machine learning technologies that are able to distinguish Real vs Background noise

AMCP Surveillance: Prospective, Active, Sequential

- Start reviewing data as early as possible. Over time, more observational information is added to the surveillance database.
- Data are extracted, manipulated, summarized, and analyzed *continuously* as more information *accumulates* to search for safety and effectiveness signals.
- Data are being subjected to repeated statistical testing, looking for “signals.”

AMCP Biosimilars Collective Intelligence Approach

Will AMCP Consortium Look at Innovators *And* Biosimilars?

- Yes
- Biosimilar and Innovator drug data are compared for differences in signals

How Do We Account for Improvements in Pharmacovigilance Since An Innovator Was Launched?

- We will look at historical data but we will *also* begin accumulating data on both the Innovator and Biosimilar as soon as the biosimilar is launched

What Is the Role of the Manufacturer?

- Successful consortiums provide Timely Access, Collaboration, Transparency
- Managed care and industry are aligned on assuring the public and physicians that biosimilars are being actively monitored
- The AMCP biosimilars consortium will be overseen by an Advisory Council consisting of key stakeholders, including industry

AMCP Biosimilars Collective Intelligence Approach

When Will the AMCP Biosimilars Collective Intelligence Be Needed?

- While FDA has not approved final regulations – we are gearing up so that we are not in a reactive mode, that Managed Care Pharmacy is proactive

What Are the Risks of Not Being Proactive?

- Adverse events are attributed to a biosimilar that are background noise
- Members and physicians lose confidence
- Biosimilars industry can lose significant market share due to an adverse event that is not investigated using rigorous statistical methods

Why Don't We Let FDA Do the Monitoring?

- FDA will likely be doing some post-approval monitoring and has passive reporting systems in place
- Typically FDA's active surveillance is not proactive—not started as soon as the biosimilar is available

Speaker

- Jeff Brown, PhD
  - Assistant Professor, Department of Population Medicine (DPM) at Harvard Medical School and the Harvard Pilgrim Health Care Institute.

Biosimilar Collective Intelligence System: Utilizing Data Consortiums to Monitor the 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

Jeffrey Brown, PhD

March 10, 2014

Department of Population Medicine
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

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
- Meningococcal Vaccine Safety Study
- EU-ADR
- 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

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

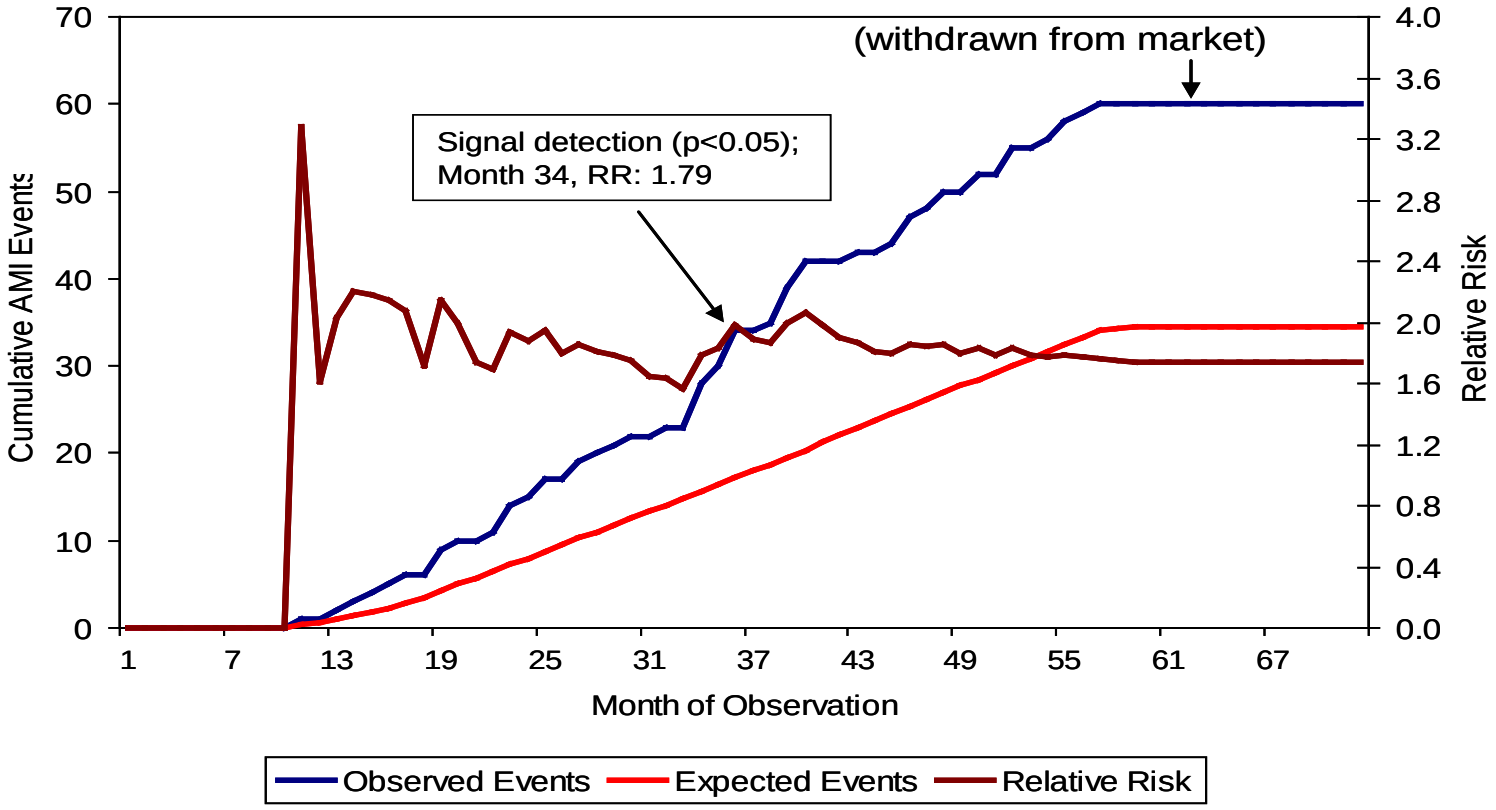
PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1275–1284
Published online 22 October 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1509

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]

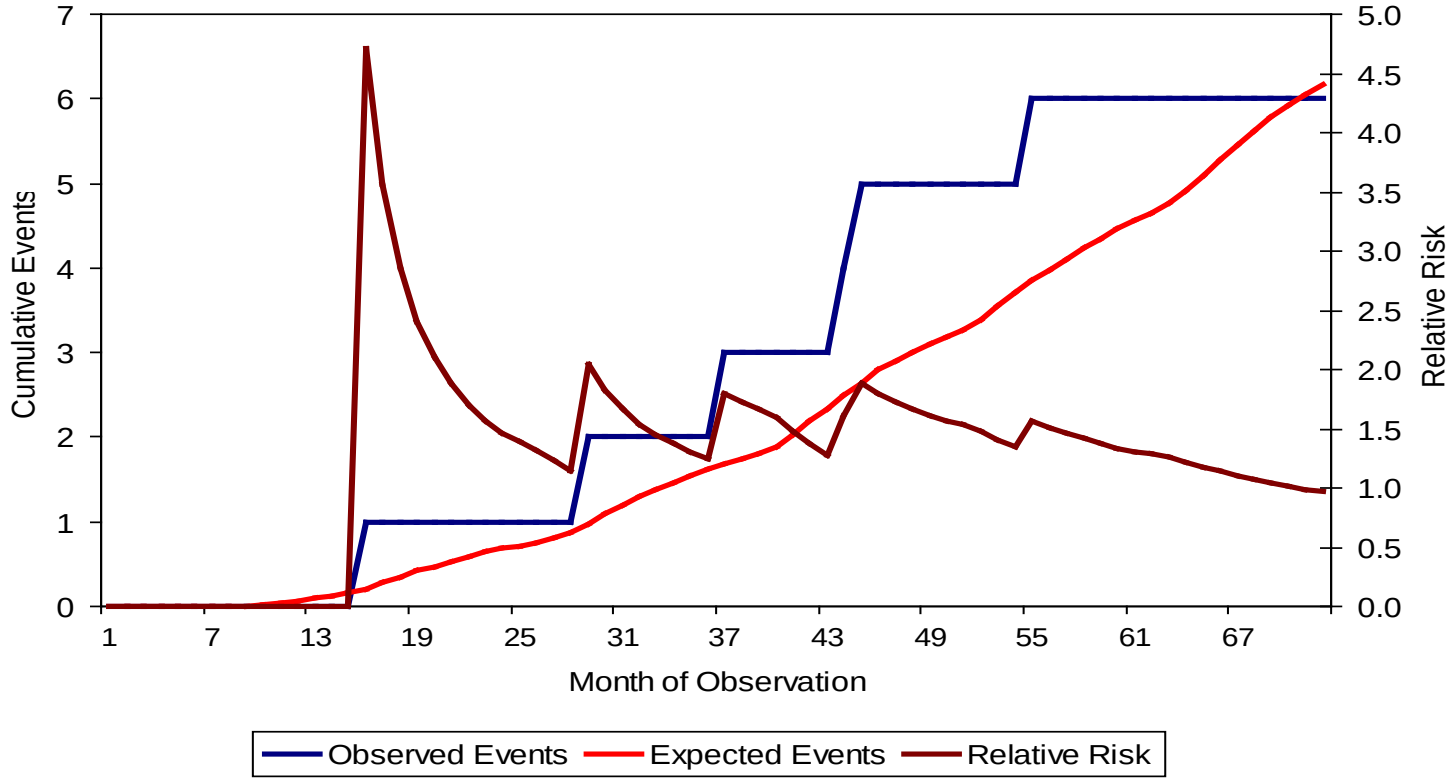
Observed and expected events for rofecoxib versus naproxen users: 2000-2005



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
- Distributed data model → no transfer of PHI
- Requires strong coordinating center

Mini-Sentinel

2009

- 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

Mini-Sentinel Partner Organizations

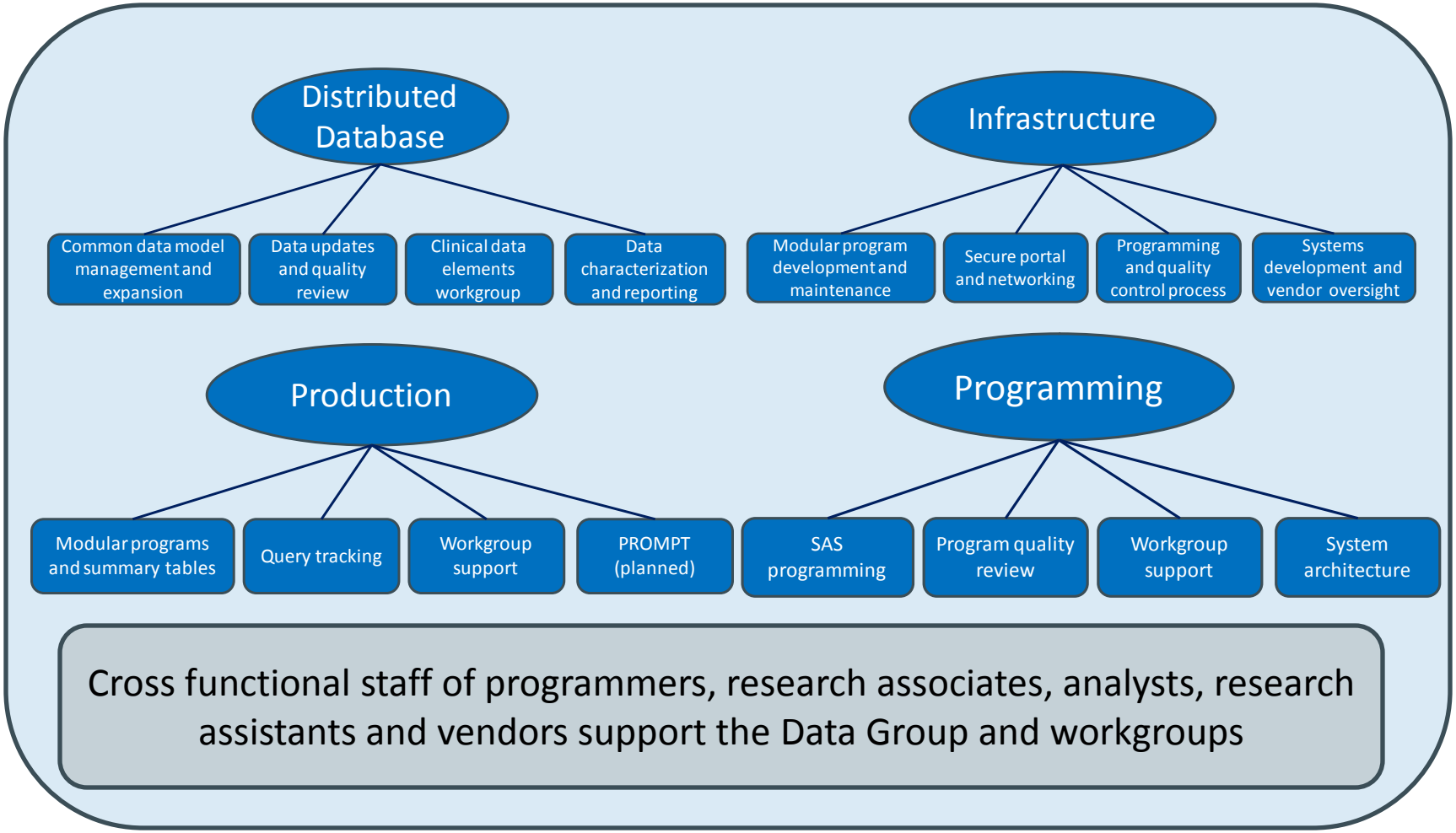
Lead – HPHC Institute

Data and scientific partners

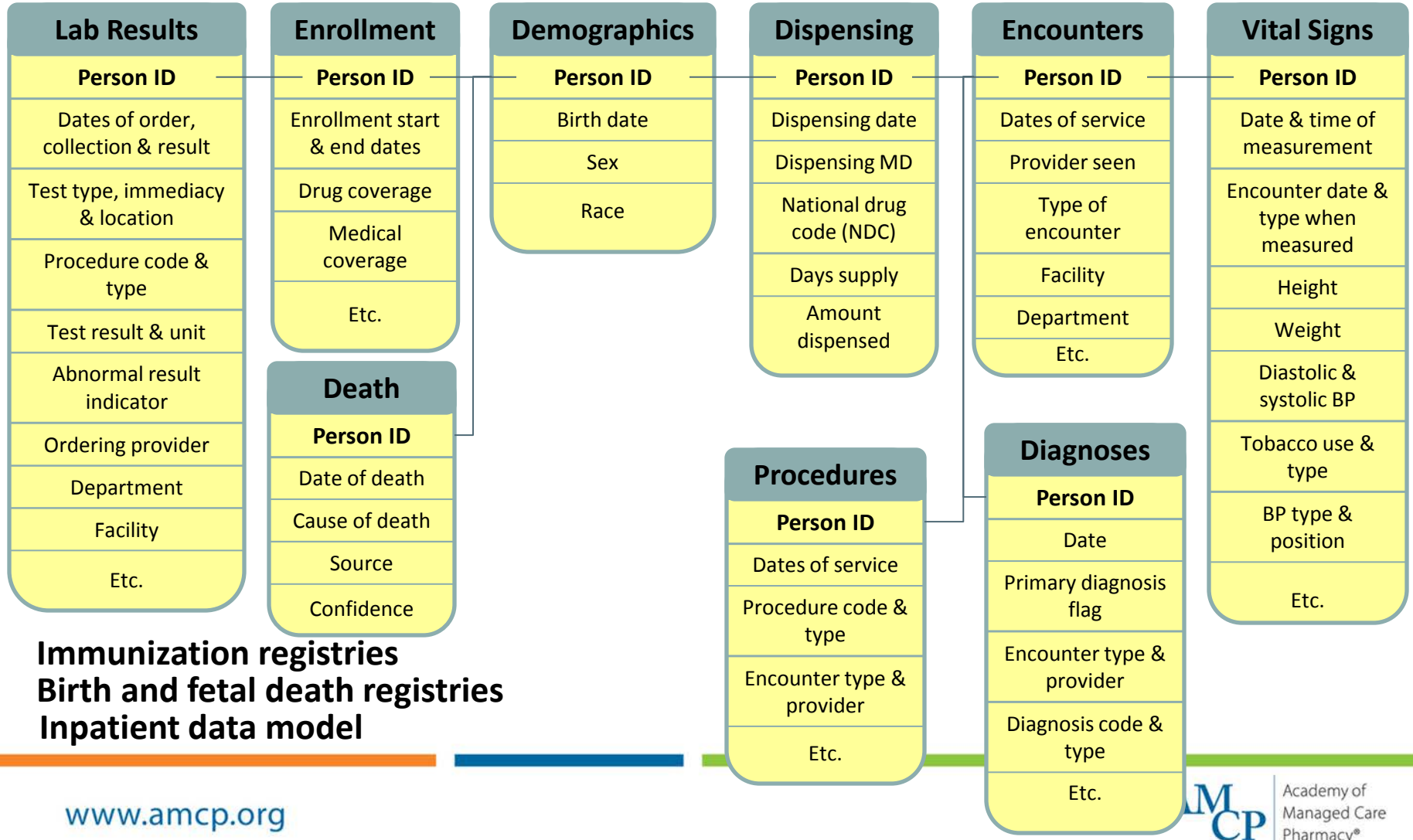
Scientific partners

The Mini-Sentinel Coordinating Center Data Group

Structure of the data group

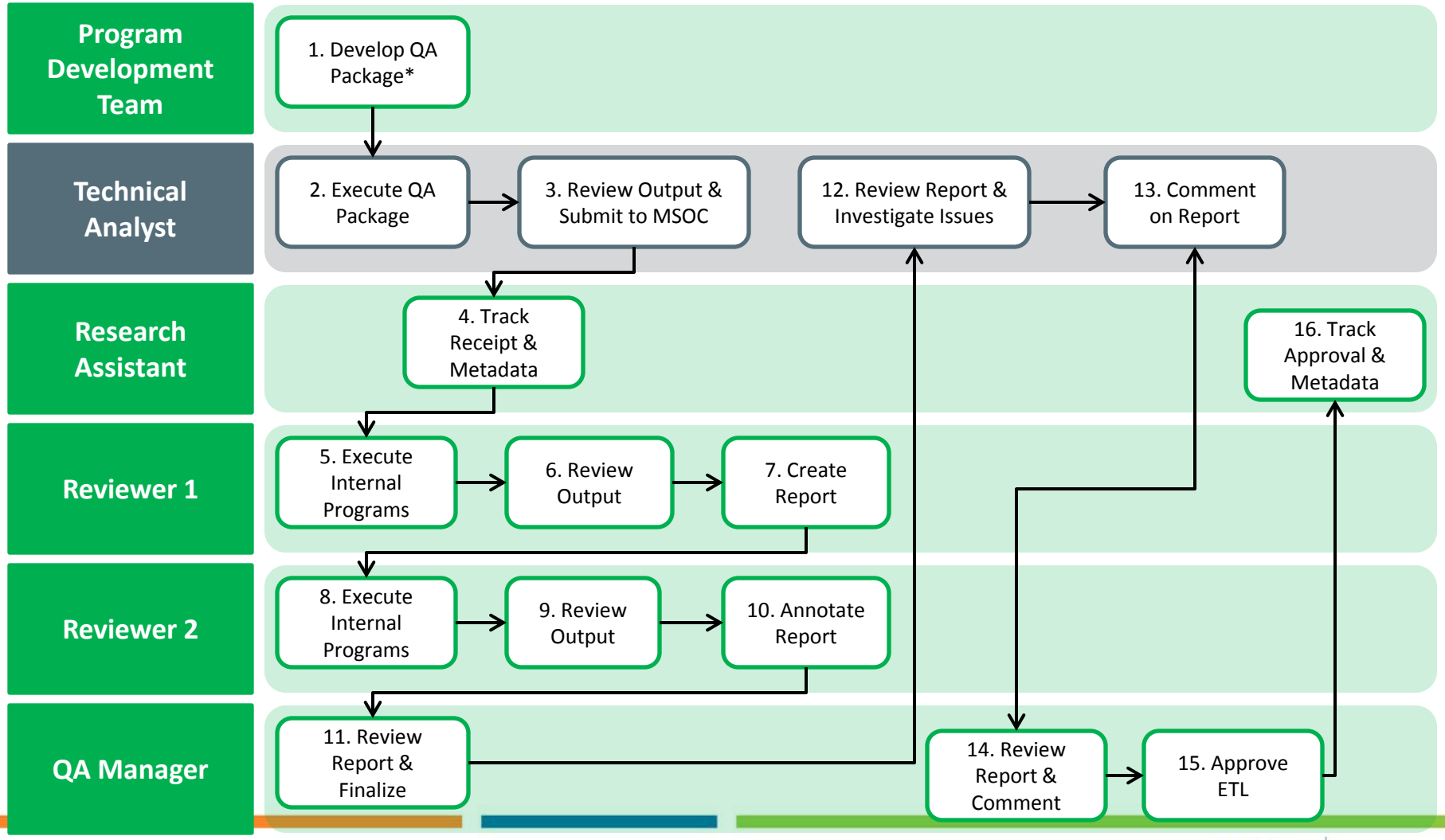


Mini-Sentinel Common Data Model



Immunization registries
Birth and fetal death registries
Inpatient data model

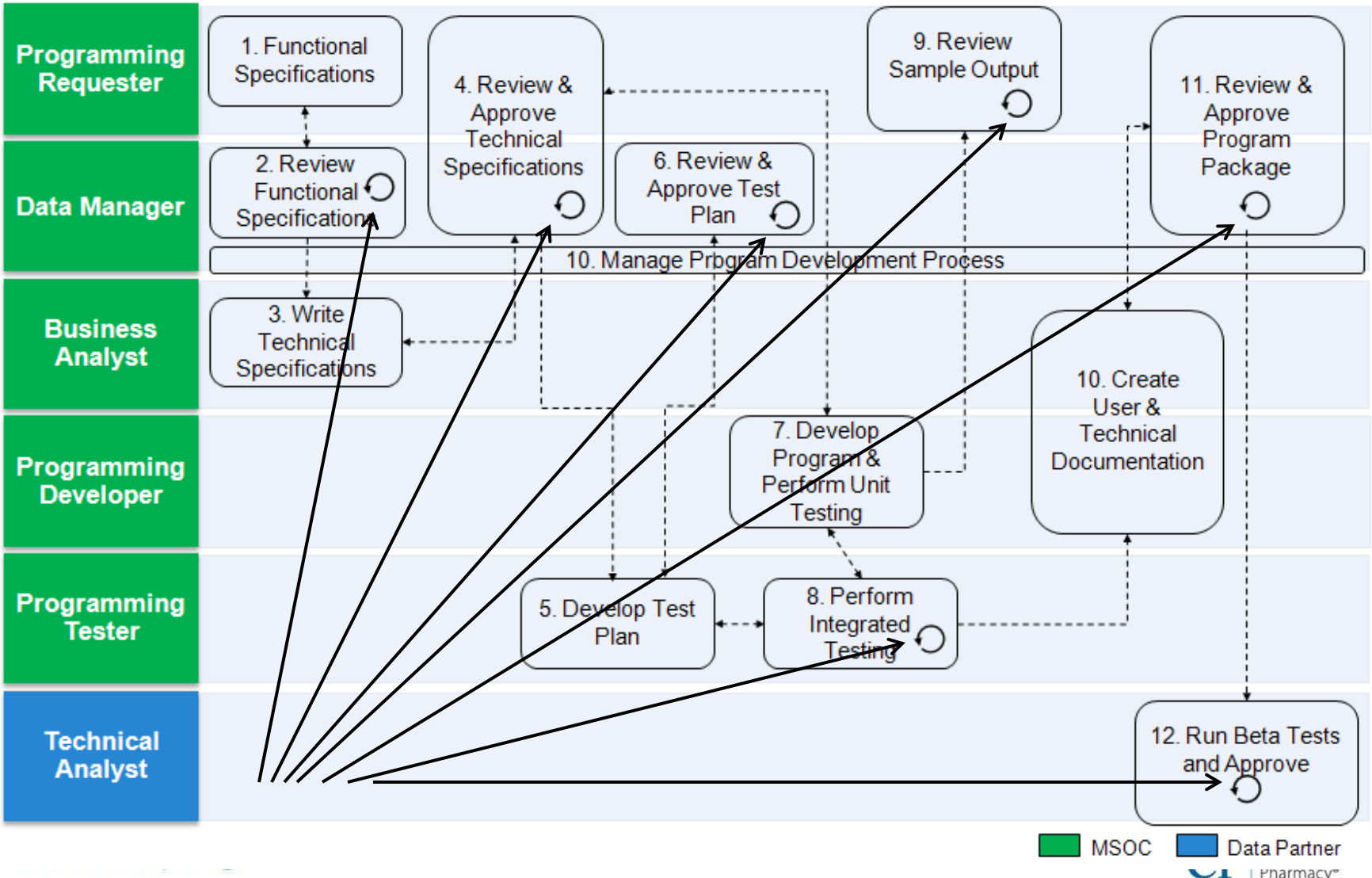
Data QA and characterization



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

Data Partner MSOC

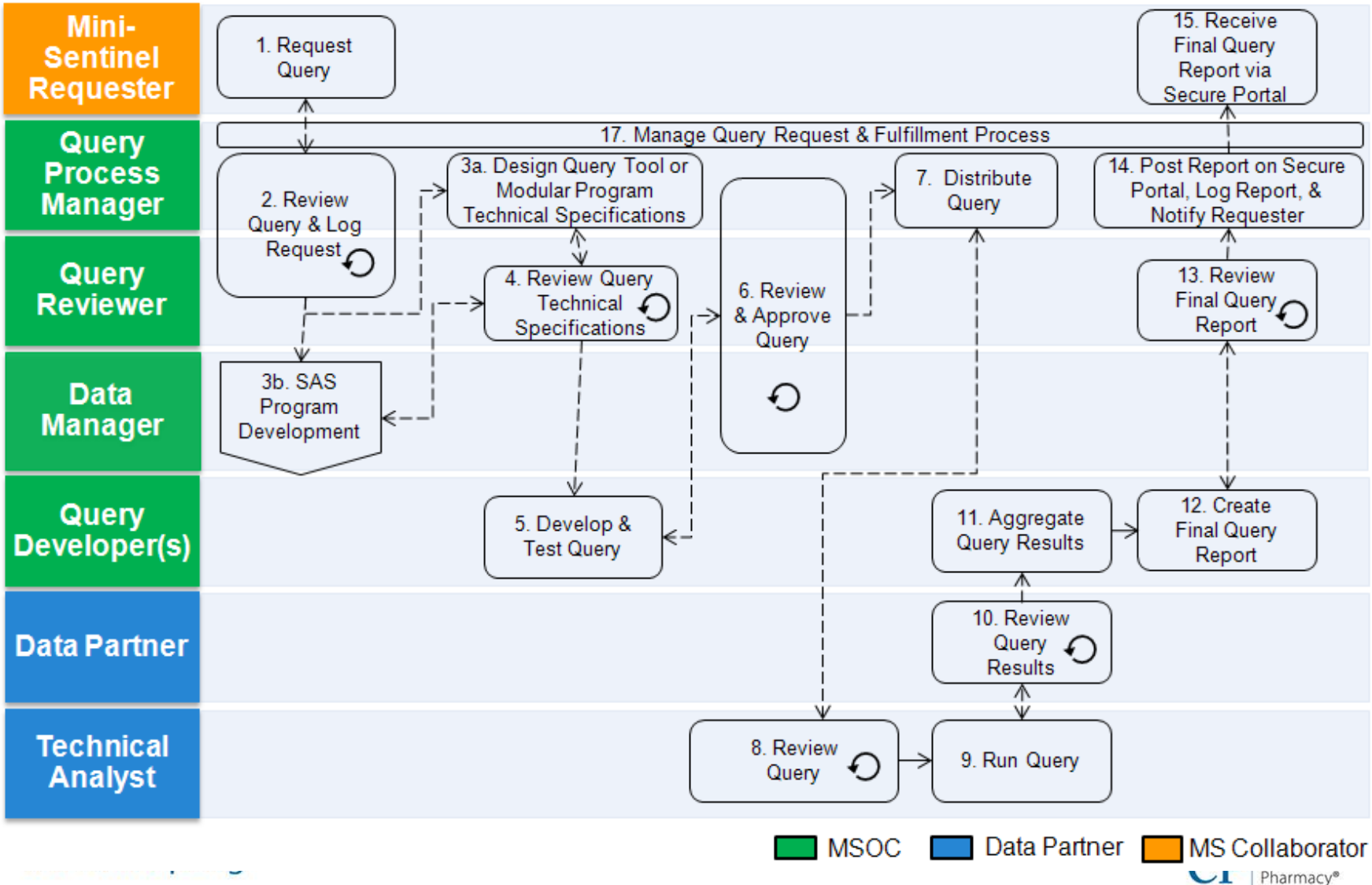
New program development



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



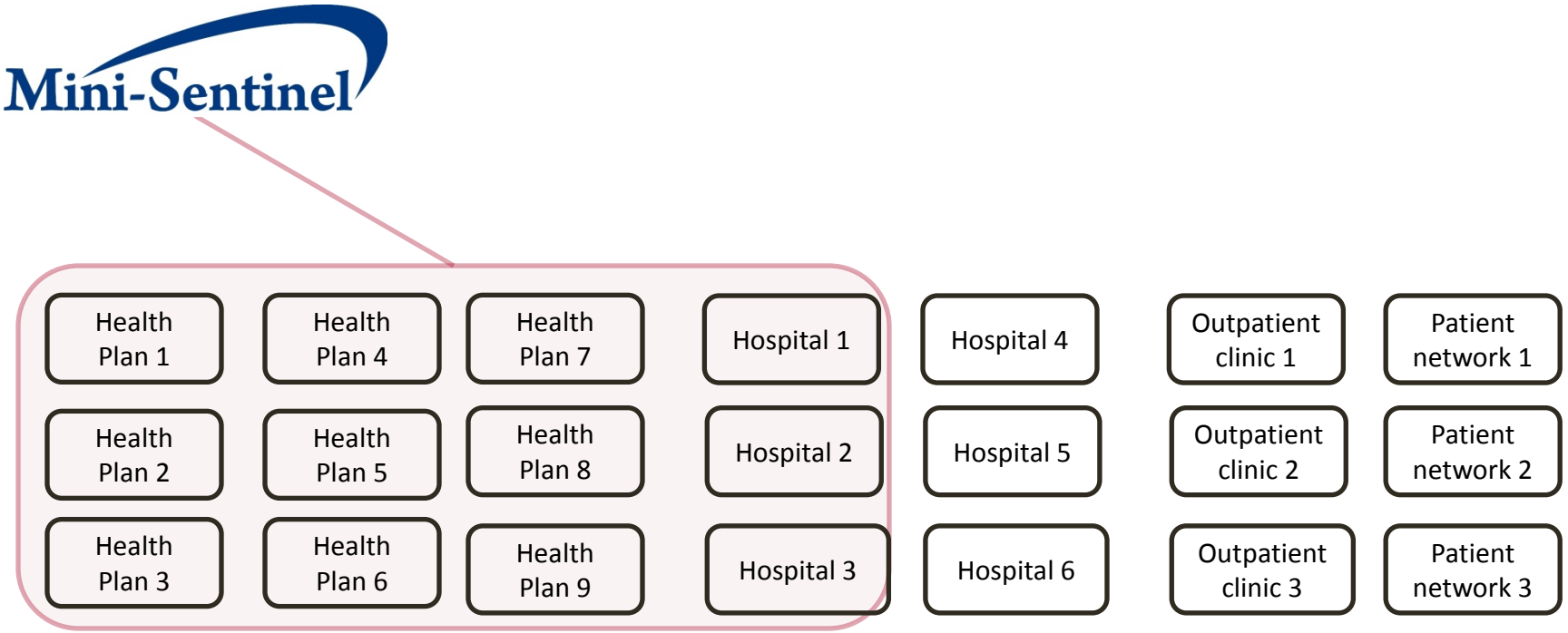
Mini-Sentinel infrastructure systems

- Operations are all based on SOPs
- Tools are treated like software
- FISMA compliant secure portal
- Activity tracker
- Secure distributed query tool

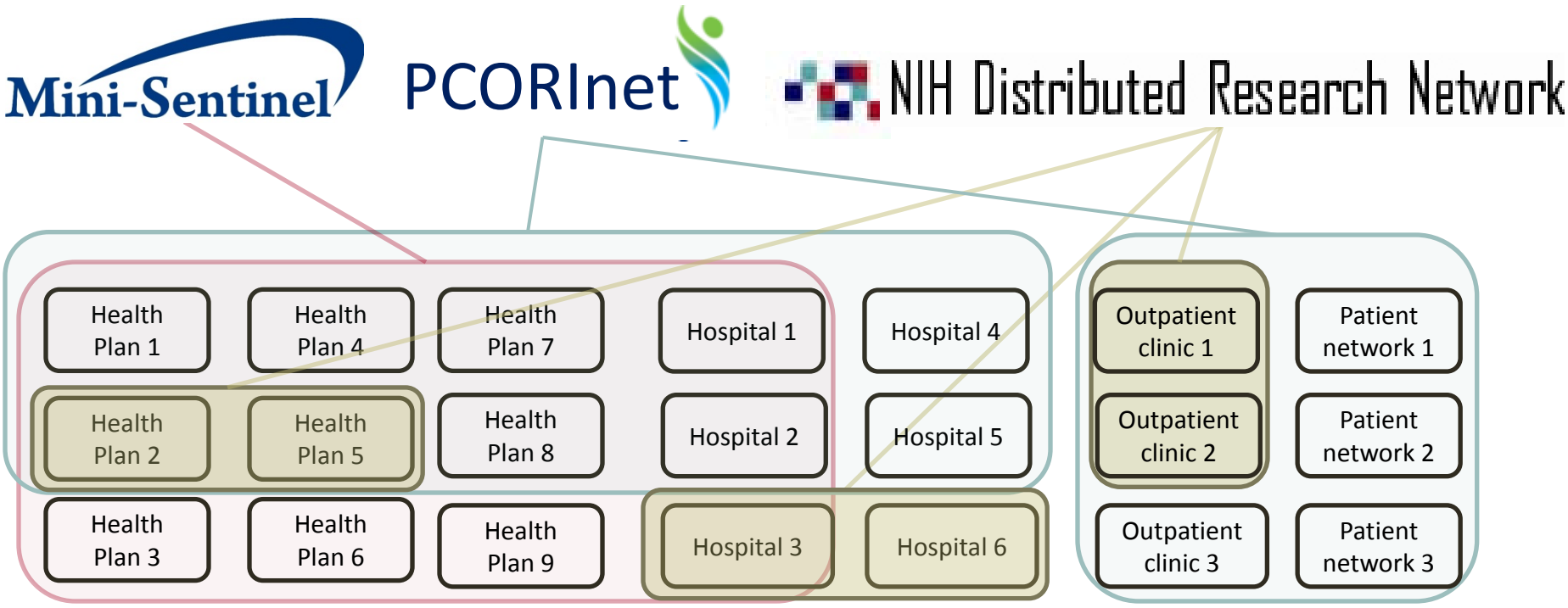
Mini-Sentinel querying tools

- 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



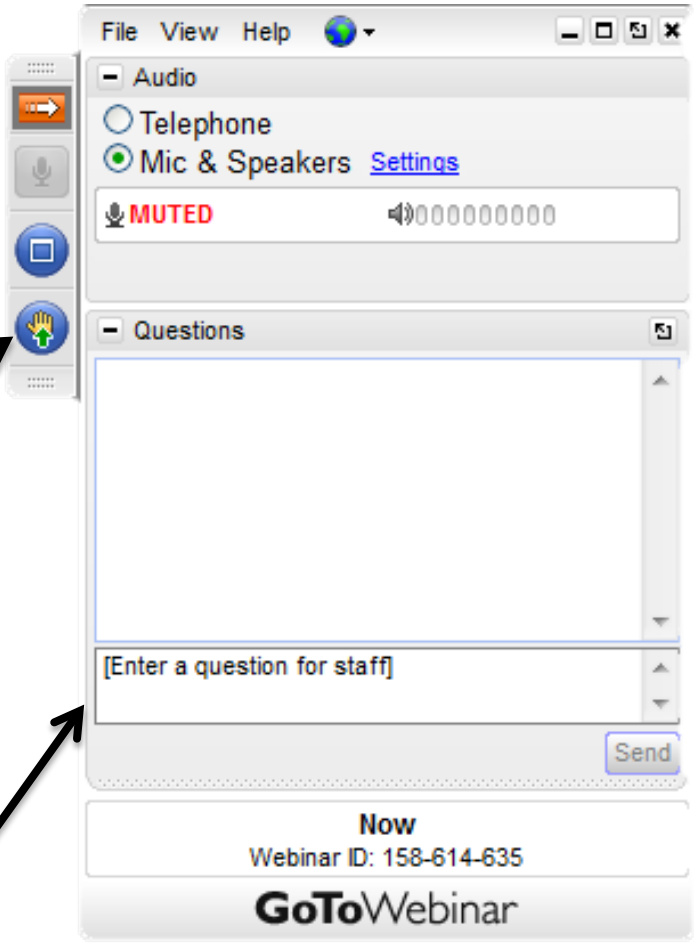
- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, data curation, analytics, lessons, security, software development

Thank you

Questions

Email comments to AMCP:
tsega@amcp.org

How to Ask A Question



Raise your hand to ask verbally

Or, type your question in the 'Questions' area

Appendix

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

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

Label change

Symptoms of sp diarrhea with substantial weight loss. The enteropathy may sartan, and sometimes requires hospitalization (artan 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[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 [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.

ORIGINAL INVESTIGATION

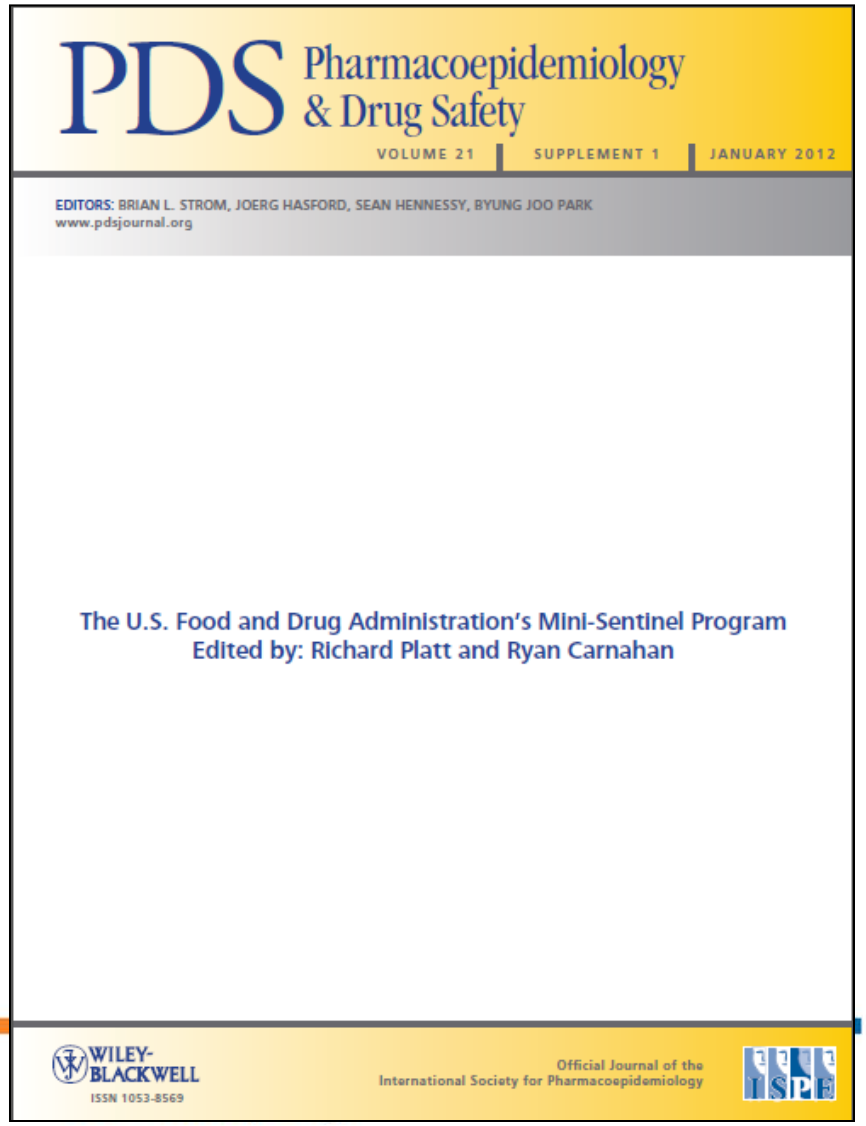
ONLINE FIRST

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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