RUTGERS
BIOMEDICAL AND HEALTH SCIENCES

US Initiatives
OMOP and Sentinel

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Disclaimer

- I am a Mini-Sentinel investigator and an OHDSI collaborator.
- I do not speak on behalf of any of the organizations involved.
- Many of the slides were graciously provided by Richard Platt (Mini-Sentinel) and Patrick Ryan (OMOP/OHDSI).

Overview and Timeline

- **FDA Amendments Act (2007)**
  - Mandate to perform active surveillance of the safety of approved drugs through use of routinely collected electronic health information from the care of at least 100 million people.
- **FDA's Sentinel Initiative (2008-ongoing)**
  - Development and implementation of a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events linked to the use of its regulated products.
- **Mini-Sentinel (2009-ongoing)**
  - Pilot program charged with developing the framework, data resources, analytic capabilities, policies and procedures to satisfy the FDAA mandate.
- **Observational Medical Outcomes Partnership (2008-2013)**
  - Public-private partnership (PhRMA, FDA, FNIH) established to inform the appropriate use of observational healthcare databases for studying the effects of medical products.

THE OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP (OMOP)

OMOP Objectives

- Conduct methodological research to empirically evaluate the performance of various analytical methods on their ability to identify true associations and avoid false findings.

- Develop tools and capabilities for transforming, characterizing, and analyzing disparate data sources across the health care delivery spectrum.

- Establish a shared resource so that the broader research community can collaboratively advance the science.

OMOP Objectives

- Conduct methodological research to empirically evaluate the performance of various analytical methods on their ability to identify true associations and avoid false findings.

  → **OMOP Research Experiments**

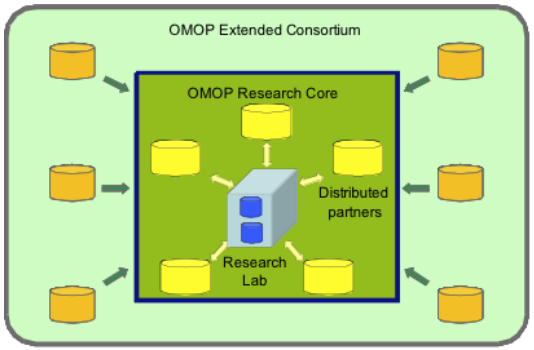
- Develop tools and capabilities for transforming, characterizing, and analyzing disparate data sources across the health care delivery spectrum.

  → **OMOP Common Data Model and Vocabulary, etc**

- Establish a shared resource so that the broader research community can collaboratively advance the science.

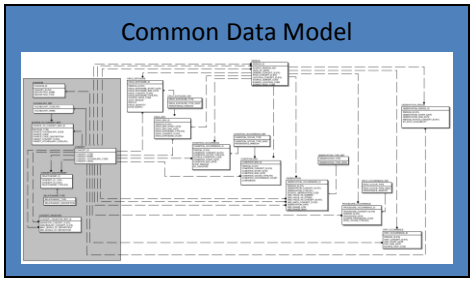
  → **OMOP Research Laboratory**

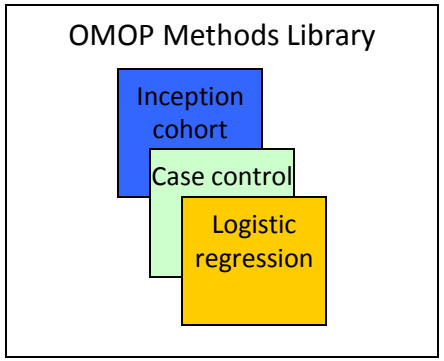
2010-2013 OMOP Research Experiments



- 10 data sources
- Claims and EHRs
- 200M+ lives

- Open-source
- Standards-based





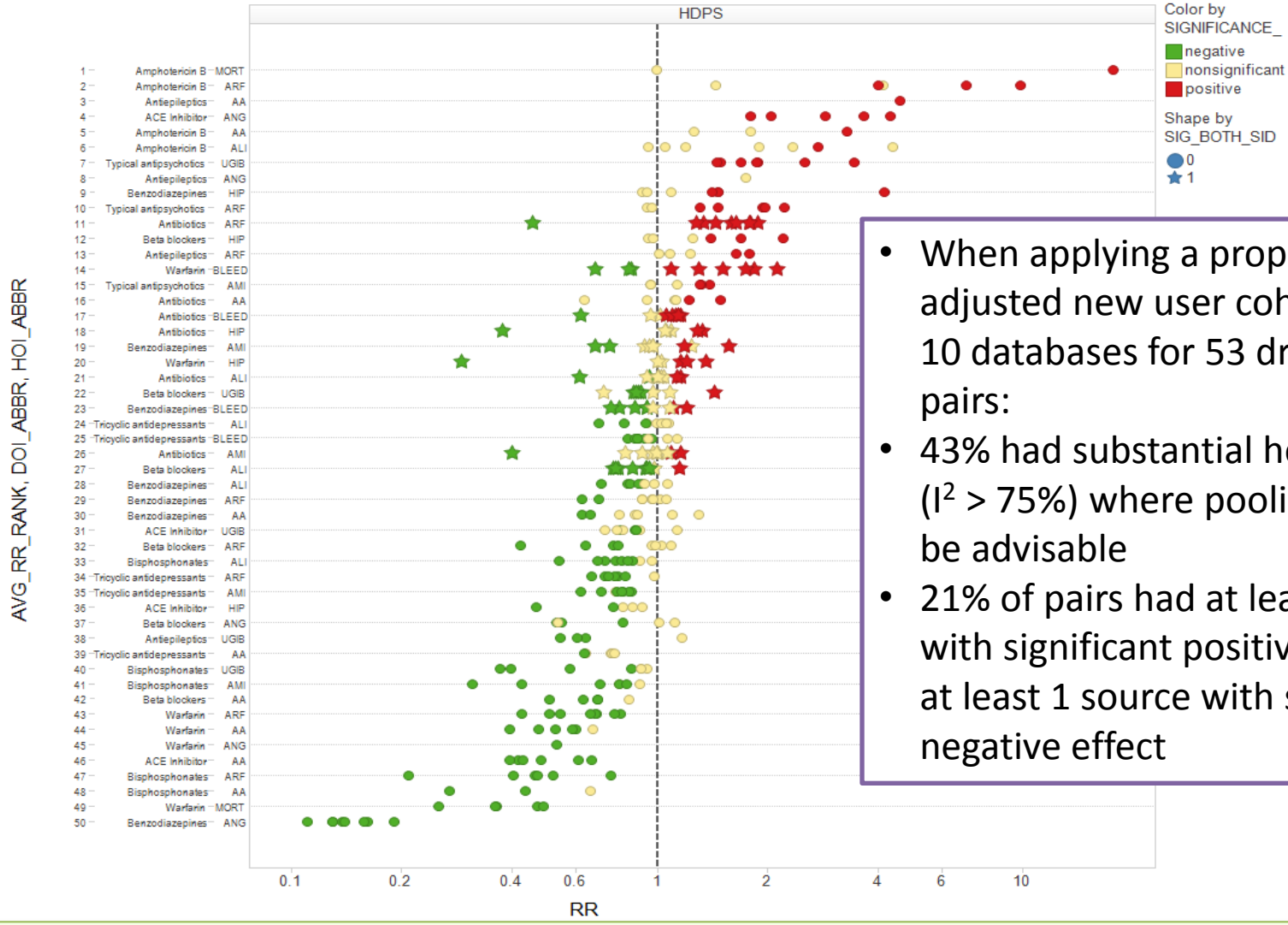
- 14 methods
- Epidemiology designs
- Statistical approaches adapted for longitudinal data

Drug

Outcome	ACE Inhibitors	Amphotericin B	Antibiotics: erythromycins, sulfonamides, tetracyclines	Antiepileptics: carbamazepine, phenytoin	Benzodiazepines	Beta blockers	Bisphosphonates: alendronate	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema										
Aplastic Anemia										
Acute Liver Injury										
Bleeding										
Hip Fracture										
Hospitalization										
Myocardial Infarction										
Mortality after MI										
Renal Failure										
GI Ulcer Hospitalization										

Legend	Total
True positive' benefit	2
True positive' risk	9
Negative control'	44

OMOP Finding 1: Database Heterogeneity
Holding analysis constant, different data may yield different estimates

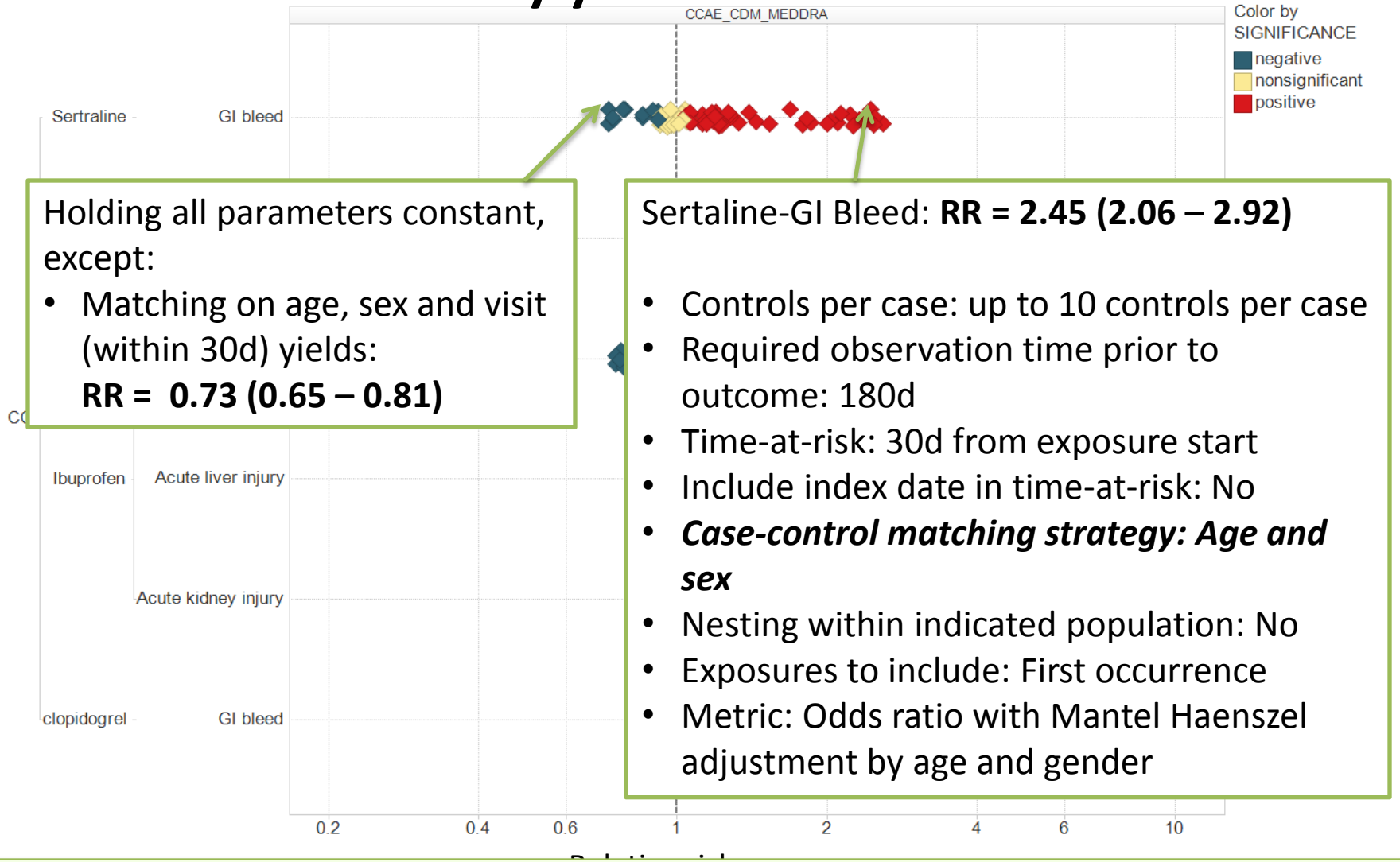


- When applying a propensity score adjusted new user cohort design to 10 databases for 53 drug-outcome pairs:
- 43% had substantial heterogeneity ($I^2 > 75\%$) where pooling would not be advisable
- 21% of pairs had at least 1 source with significant positive effect and at least 1 source with significant negative effect

Madigan D, Ryan PB, Schuemie MJ et al, American Journal of Epidemiology, 2013
"Evaluating the Impact of Database Heterogeneity on Observational Study Results"

OMOP Finding 2: Parameter Sensitivity
Holding data constant, different analytic design choices may yield different estimates

Test cases from OMOP 2011/2012 experiment



Holding all parameters constant, except:

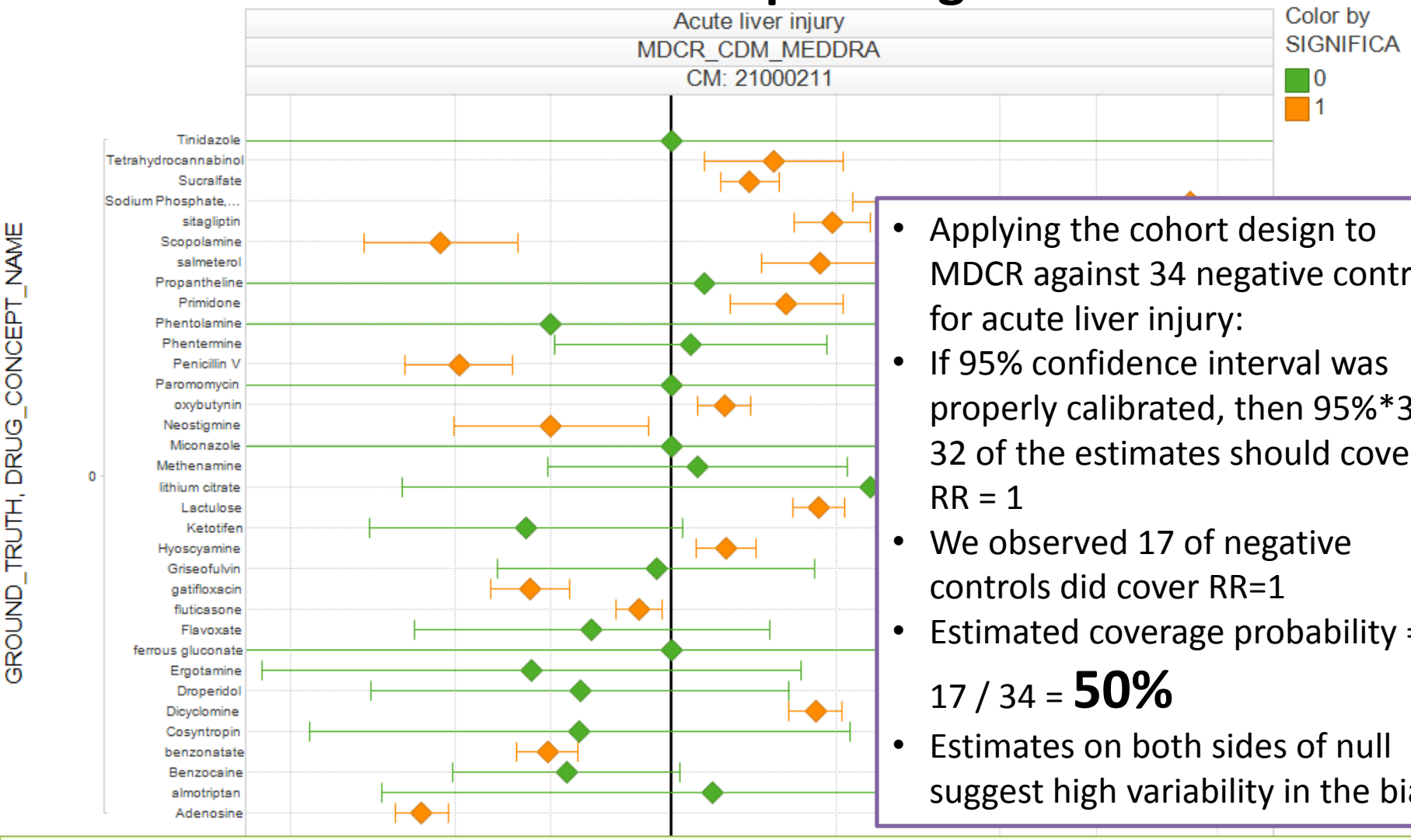
- Matching on age, sex and visit (within 30d) yields:
  RR = 0.73 (0.65 – 0.81)

Sertaline-GI Bleed: **RR = 2.45 (2.06 – 2.92)**

- Controls per case: up to 10 controls per case
- Required observation time prior to outcome: 180d
- Time-at-risk: 30d from exposure start
- Include index date in time-at-risk: No
- ***Case-control matching strategy: Age and sex***
- Nesting within indicated population: No
- Exposures to include: First occurrence
- Metric: Odds ratio with Mantel Haenszel adjustment by age and gender

Madigan D, Ryan PB, Scheumie MJ, Therapeutic Advances in Drug Safety, 2013: “Does design matter? Systematic evaluation of the impact of analytical choices on effect estimates in observational studies”

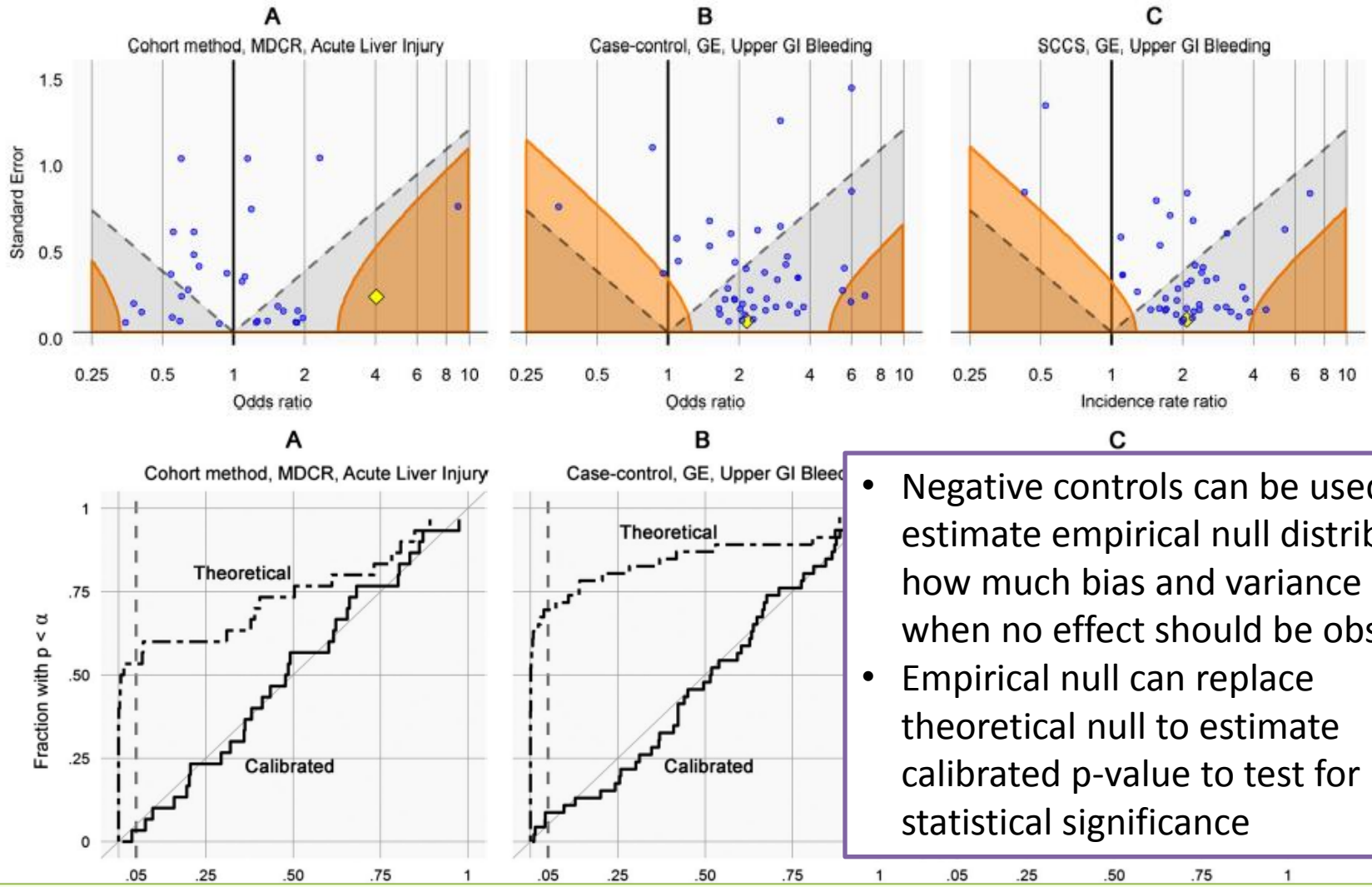
OMOP Finding 3: Empirical Performance
Most observational methods do not have nominal statistical operating characteristics



- Applying the cohort design to MDCR against 34 negative controls for acute liver injury:
- If 95% confidence interval was properly calibrated, then 95%*34 = 32 of the estimates should cover RR = 1
- We observed 17 of negative controls did cover RR=1
- Estimated coverage probability = 17 / 34 = **50%**
- Estimates on both sides of null suggest high variability in the bias

Ryan PB, Stang PE, Overhage JM et al, Drug Safety, 2013:
"A Comparison of the Empirical Performance of Methods for a Risk Identification System"

OMOP Finding 4: Empirical calibration can help restore interpretation of study findings



- Negative controls can be used to estimate empirical null distribution: how much bias and variance exists when no effect should be observed
- Empirical null can replace theoretical null to estimate calibrated p-value to test for statistical significance

Schuemie MJ, Ryan PB, DuMouchel W, et al, Statistics in Medicine, 2013:
"Interpreting observational studies: why empirical calibration is needed to correct p-values"

OMOP Journal Supplement

Drug Safety

Studying the Science of Observational Research: Empirical Findings from the Observational Medical Outcomes Partnership

Guest Editor
Stephen J. W. Evans
Professor of Pharmacoepidemiology, London School of Hygiene and Tropical Medicine, London, UK

Peer Reviewer
Olaf H. Klungel
Associate Professor, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands

This supplement was sponsored by the Foundation for the National Institutes of Health and the Reagan-Udall Foundation for the Food and Drug Administration.

Current Status

- **IMEDS:** The OMOP Research Lab has transitioned to the IMEDS (Innovation in Medical Evidence Development and Surveillance) program of the Reagan Udall Foundation for the FDA in 2013. IMEDS serves to advance the science and tools necessary to support post-market evidence generation on regulated products and to facilitate utilization of a robust secondary electronic healthcare data platform for generating better evidence on regulated products in the post-market settings.

http://imeds.reaganudall.org/

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About IMEDS | IMEDS Methods | IMEDS Evaluation | IMEDS Education | IMEDS Research Lab | Support for IMEDS | News & Events

Advancing Regulatory Science for Public Health

The IMEDS program is offered by the Reagan-Udall Foundation for the FDA through the FDA Amendments Act of 2007. IMEDS serves to advance the science and tools necessary to support post-market evidence generation on regulated products and to facilitate utilization of a robust secondary electronic healthcare data platform for generating better evidence on regulated products in the post-market settings.

Announcing the 2015 IMEDS-Methods Research Agenda

The 2015 IMEDS-Methods Research Agenda was formulated to build on the successes achieved during 2014, and to reflect the goals and priorities articulated by all stakeholder groups. The 2015 IMEDS-Methods Research Agenda can be found here.

For more information, please review the full announcement here.

Be a Part of the IMEDS Research Lab

Do you want to know about research that is being completed in the lab? Find out about the IMEDS Research Laboratory, how to gain access, and the available datasets and tools to complete your research. Review the IMEDS Research Lab information.

Symposium on Health Care Data Analytics - Sept 28-30, 2014

Join biostatisticians and other scientists Sept. 28-30, 2014, in Seattle, Washington for the the 1st Seattle Symposium on Health Care Data Analytics featuring research on pragmatic clinical trial design, inference and prediction using EHR data, and drug and vaccine safety surveillance. Susan Gruber will be addressing "Gaps and opportunities: Methodologic challenges in post-market safety surveillance." View conference agenda (PDF).

- Reagan-Udall Foundation for the FDA
- Food and Drug Administration Amendment Act (FDAAA)
- Mini-Sentinel
- Observational Medical Outcomes Partnership (OMOP)
- FDA Sentinel Initiative

Privacy Policy

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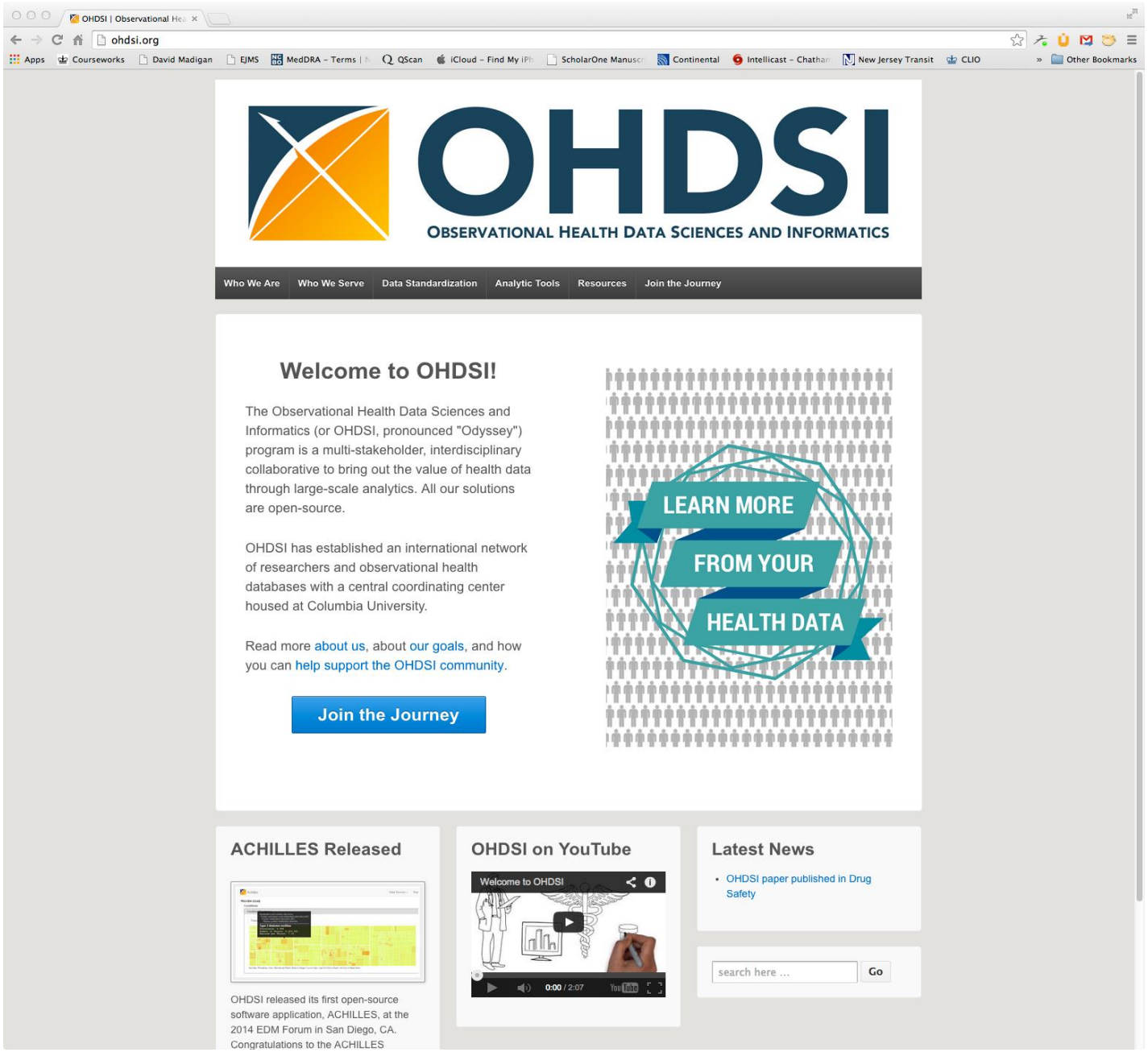
- **OHDSI:** The Observational Health Data Sciences and Informatics (OHDSI) program is a multi-stakeholder, interdisciplinary collaborative that includes all of the members of the OMOP investigator team. Whereas OMOP was restricted to methodological research, OHDSI develops and applies methods to observational data to answer real-world clinical questions.



http://ohdsi.org

Mini-Sentinel

Mini-Sentinel Partner Organizations

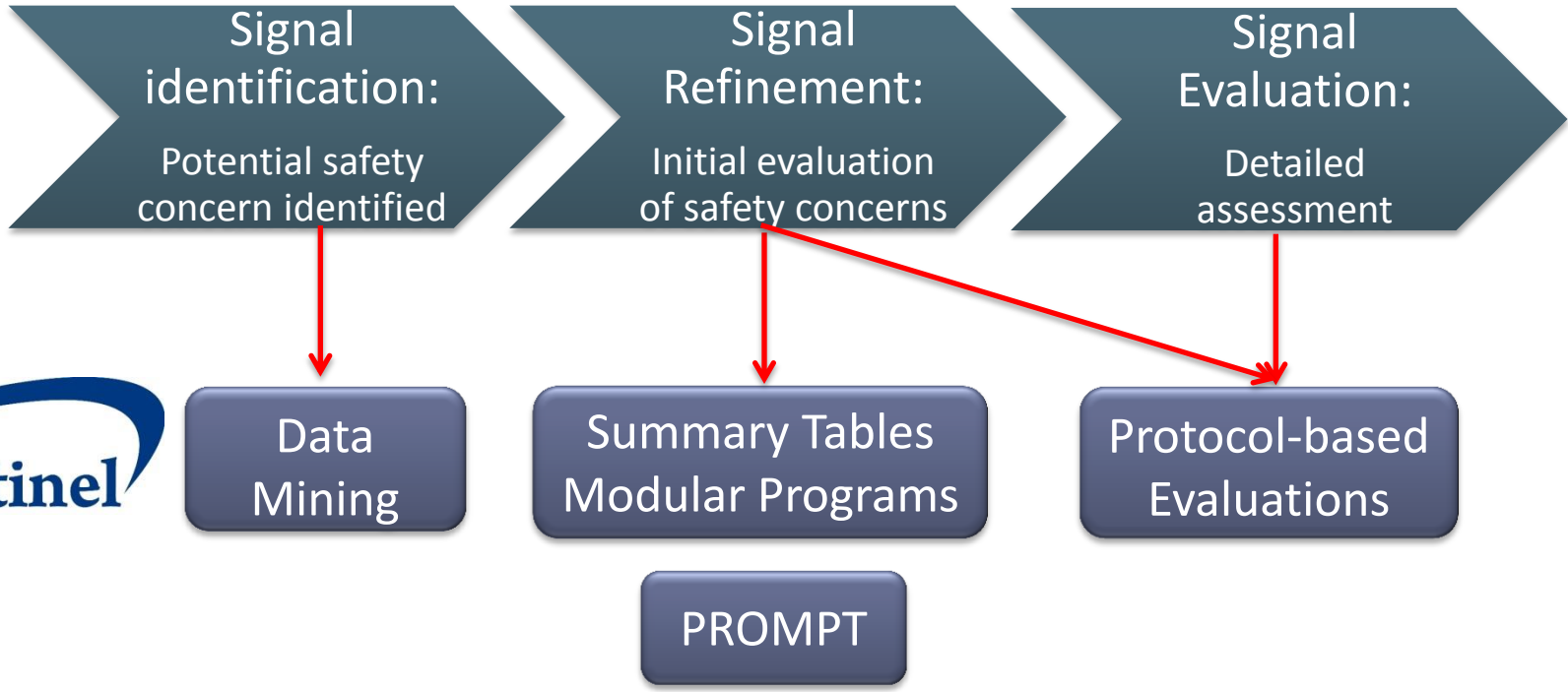
Lead – HPHC Institute

Data and scientific partners

Scientific partners

Post-Market Safety Surveillance

Post-Market Safety Surveillance

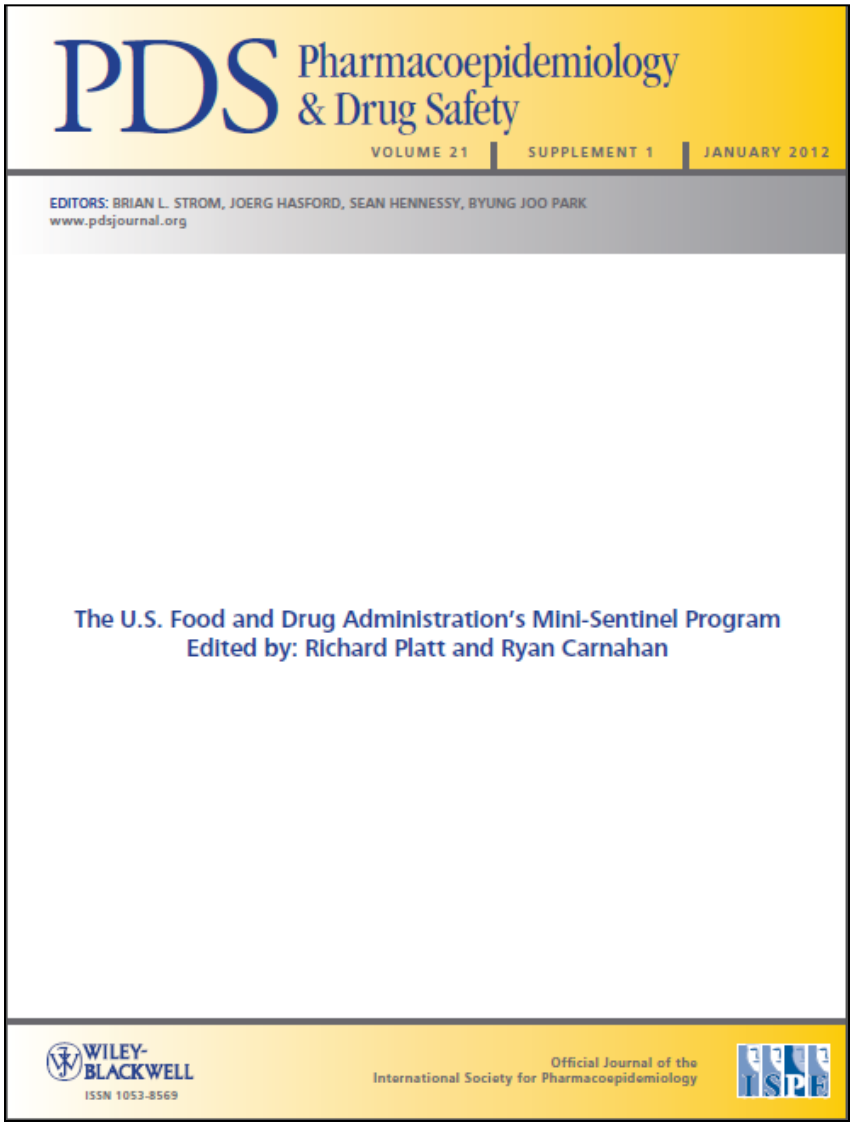


PROMT = Prospective Routine Observational Monitoring Program Tools

Impact / Dissemination

- 4 FDA drug safety communications
  - Tri-valent inactivated flu vaccine and febrile seizures (no increased risk)
  - RotaTeq, Rotarix and intussusception (label change for RotaTeq, no label change for Rotarix)
  - Dabigatran and bleeding (no increased risk)
  - Olmesartan and sprue-like enteropathy (label change)
- 26 Presentations by FDA
- 48 Methods reports / white papers
- 70 Peer-reviewed articles
- 137 Assessments of products, conditions, product-outcome pairs

Mini-Sentinel Journal Supplement



Three major domains

- Data
- Methods
- Active surveillance

Three major domains

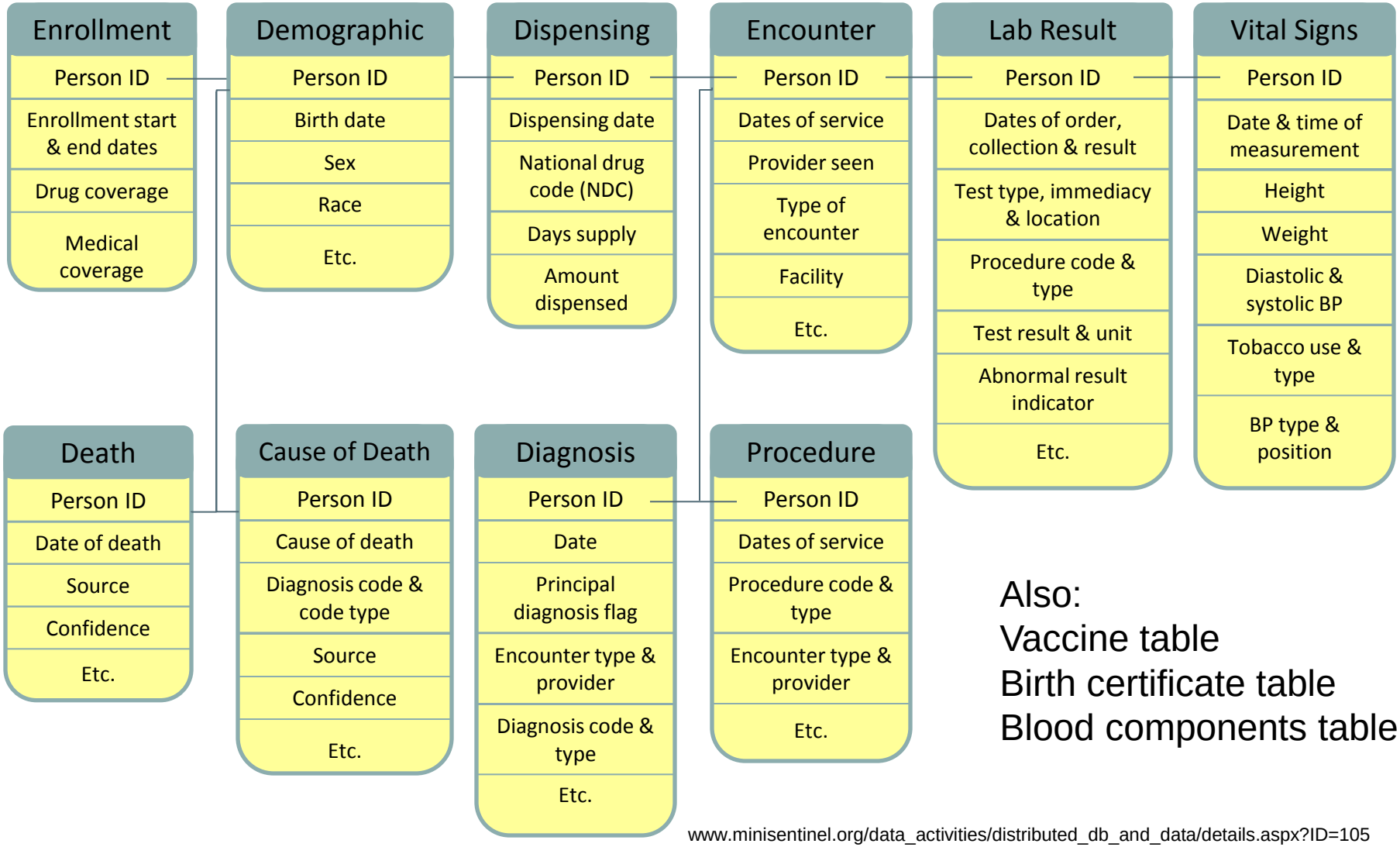
- **Data**
- Methods
- Active surveillance

Mini-Sentinel Distributed Database*

- Populations with well-defined person-time for which most medically-attended events are known
- 178 million members**
- 358 million person-years of observation time
- 48 million people currently accruing new data
- 4 billion dispensings
- 4.1 billion unique encounters
  - 42 million acute inpatient stays
- 30 million people with ≥1 laboratory test result

*As of July 2014
** Double counting exists for individuals who change health plans

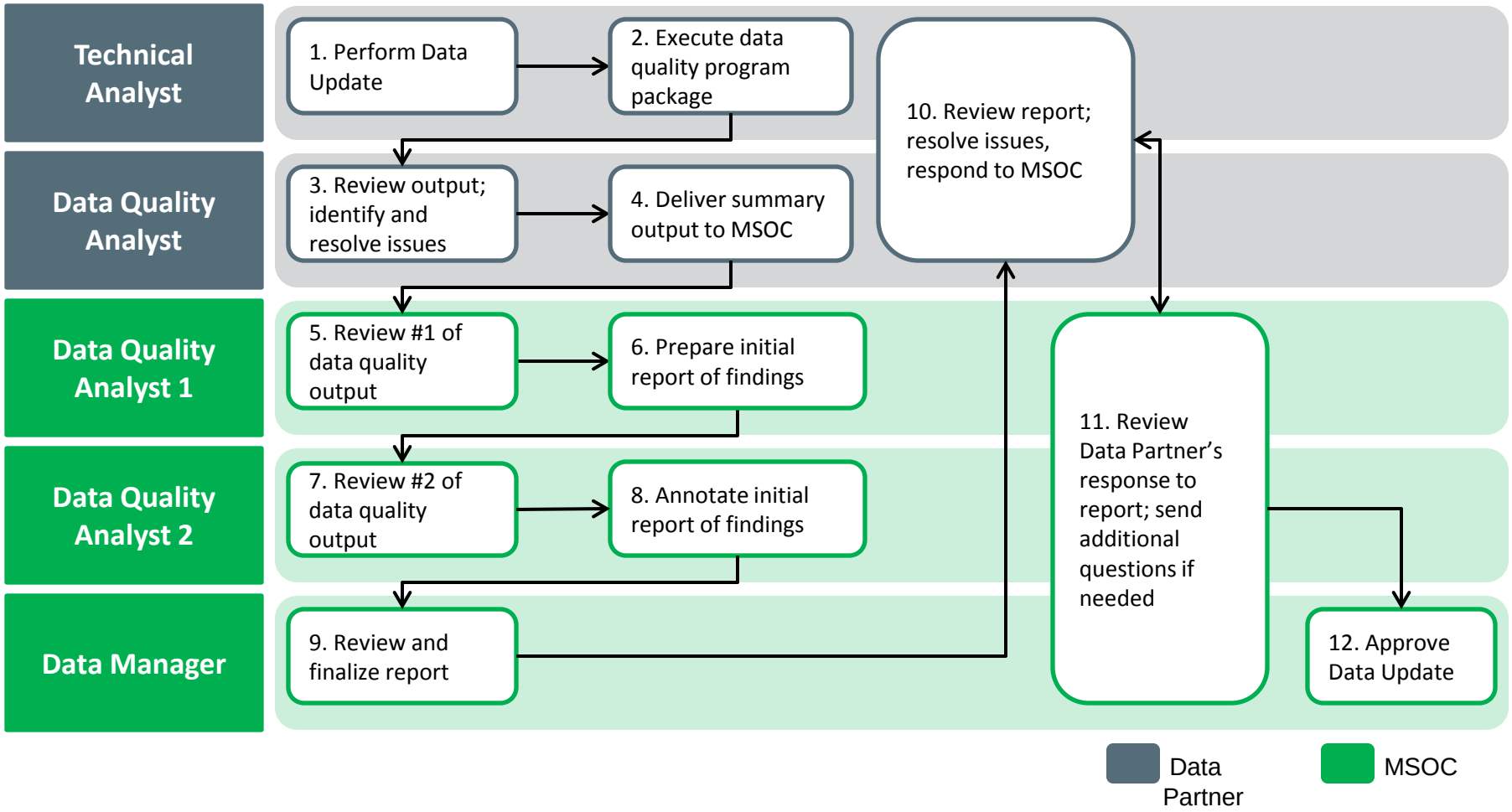
Mini-Sentinel's Common Data Model



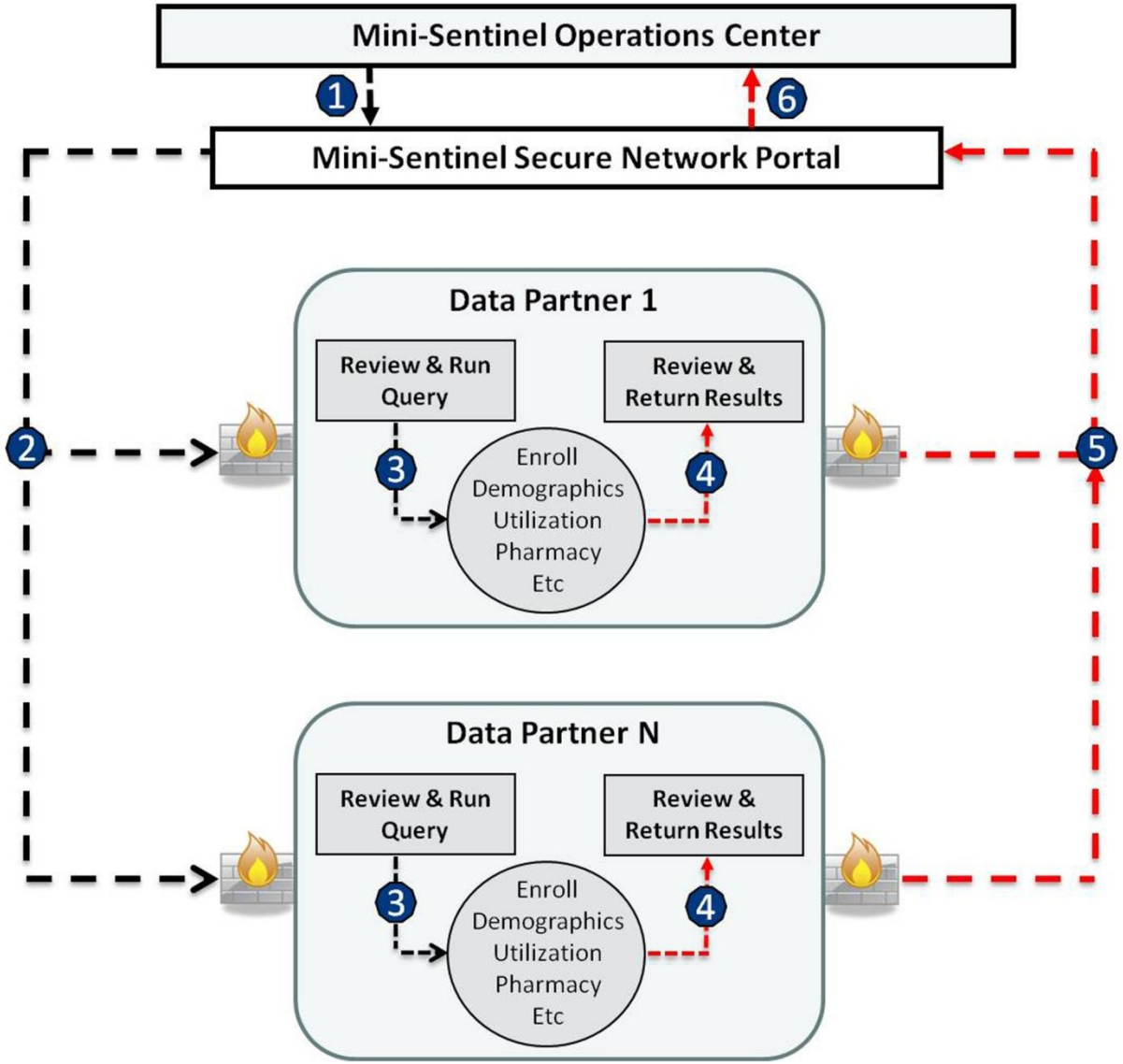
Also:
Vaccine table
Birth certificate table
Blood components table

www.minisentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=105

Data Quality Assurance review process



Mini-Sentinel Distributed Analysis



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

Three major domains

- Data
- **Methods**
- Active surveillance

Domains of methods development / examples

Data Fitness and Capacity	Evaluating Methods	Target Monitoring

• Integrity (validity, completeness)
• Environments
  – *Claims, EHR, registries*
  – *Outpatient, inpatient*
• Anonymous linkage
• Enriching the CDM
  – *Lab results*
• Data sharing
	• Validity, power/ robustness, time-to-signal detection
	• Empirical, simulation
	• Heterogeneity across databases
	• In collaboration with IMEDS
		• Preparedness Design
		  – *Systematic selection*
		  – *Self-controlled*
		  – *Cohort methods*
		• Analysis
		  – *Confounder adjustment*
		  – *Distributed methods*
		  – *Quantifying uncertainty*
		• Sequential Analysis

Signal Generation	**Signal Follow-up**	**Decision Making**
• Data mining (untargeted) • Sample size tools	• Data/code quality • Sensitivity analyses • Timing of signals • 2-phase designs	• Decision analysis framework

Health Outcome and Confounder Libraries

- Need standardized operational definitions for health outcomes and confounding conditions
- Summarize literature sources
- Document definitions used in protocol-based assessments

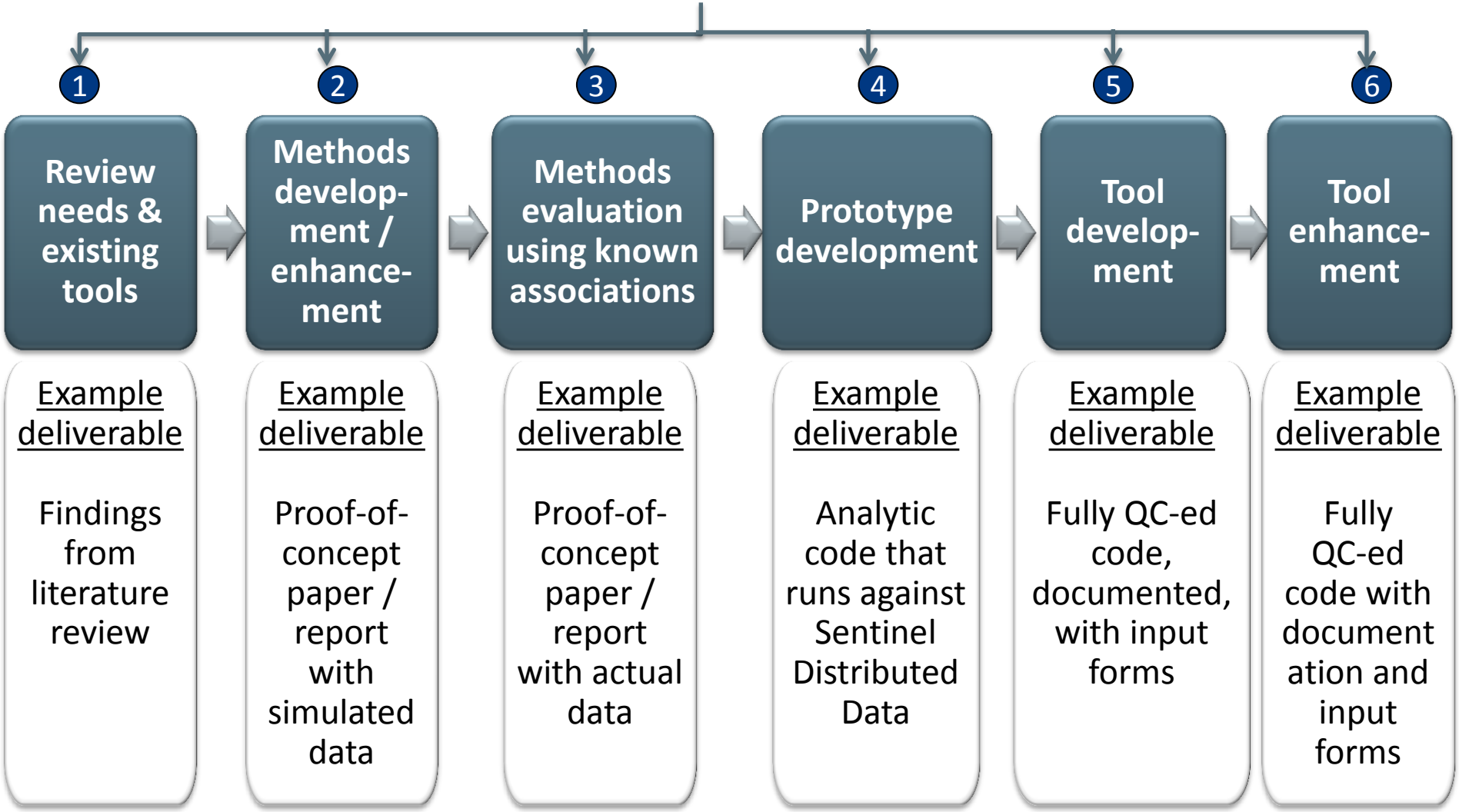
Taxonomy

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

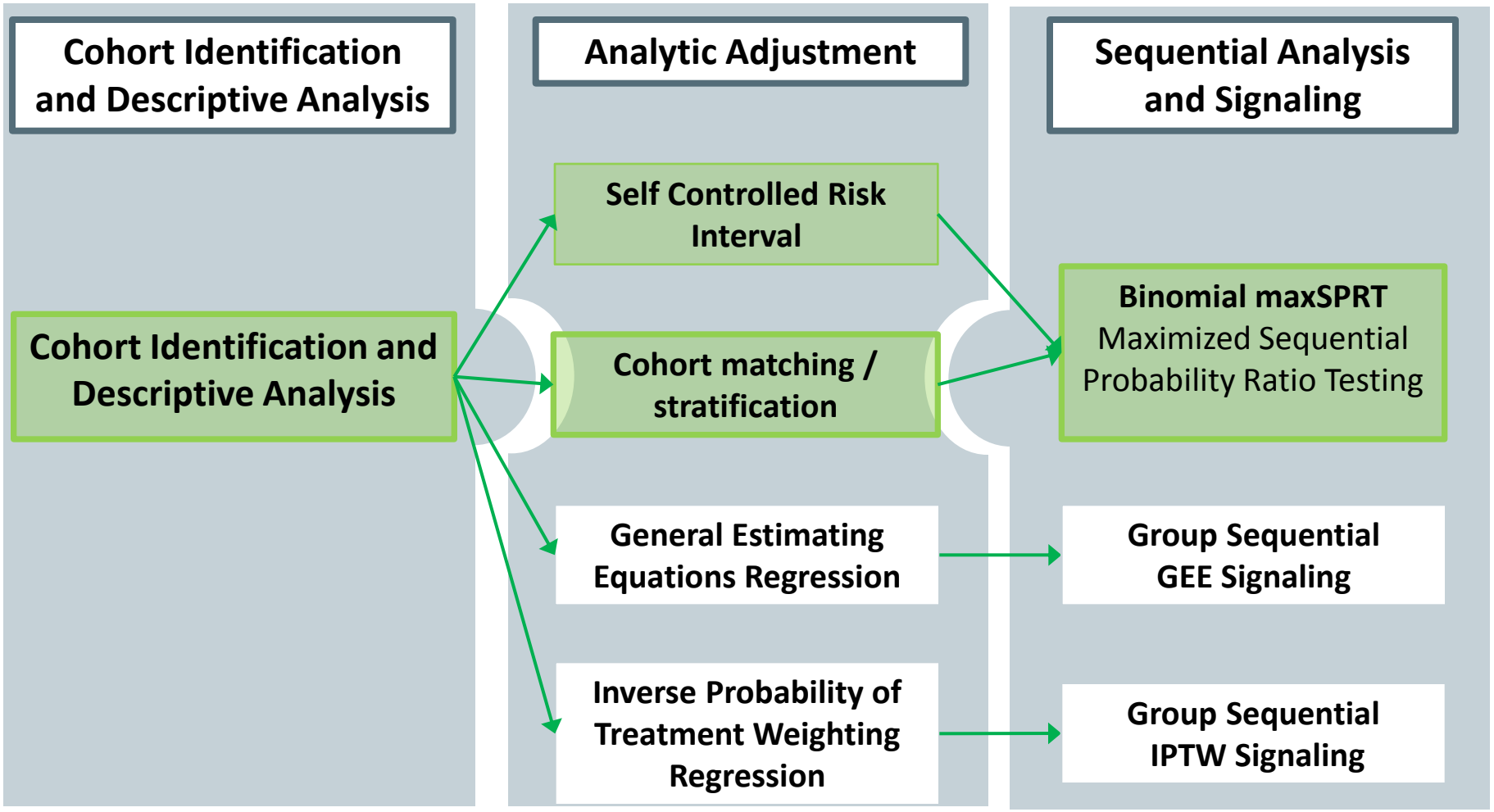
Monitoring scenario characteristics with implication for design choice[a]							Monitoring scenario characteristics with implication for analytic choice[a]		
	Characteristics of the (potential) exposure-HOI link								
			Strength of confounding						
Exposure persistence *(transient, sustained)*	**Onset 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

Tool development steps



Reusable Rapid Query Tools



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

- Used data for 3.9 million new users of anti-hypertensives in 18 organizations
- Propensity score matched stratified analysis
- No person-level data was shared
- **Five months and $250,000 required for programming and analysis – compared to 1-2 years and $2 million without analysis-ready distributed dataset**

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

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- Replication of the same study with the new rapid query tools: ACEI vs β-blocker: **HR = 3.1** (95% CI, 2.9-3.4)
- Toh *et al* findings: **HR = 3.0** (95% CI, 2.8-3.3)
- **Time and cost requirements: Weeks and 10s of thousands of $s**

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

Three major domains

- Data
- Methods
- **Active surveillance**

Query Fulfillment

- Year 5 Activities
  - 48 Summary Table Requests
  - 63 Modular Program Requests
    - Over 2000 “scenarios”
    - Over 90 reports to FDA

- To Date
  - ~350 Summary Table Requests
  - ~175 Modular Program Requests

Selected Protocol Based Assessments Planned or Under Way

- CDER
  - Mirabegron and several outcomes (prospective monitoring)
  - Rivaroxaban and several outcomes (prospective monitoring)
  - Dabigatran and several outcomes
  - Metabolic effects of 2nd generation antipsychotics in youth
  - Diabetes drugs and acute myocardial infarction
  - IV Iron and anaphylaxis
- CBER
  - IV Immune Globulin and thromboembolic events
  - Gardasil and venous thromboembolism
  - Influenza vaccines and pregnancy outcomes
  - Gardasil 9 and Pregnancy Outcomes
  - Prevnar 13 and Kawasaki disease
  - Blood components and Transfusion-Related Lung Injury (TRALI)

Current Status

- The program in the process of transitioning from its pilot stage to the full-fledged program
- The Sentinel Contract was awarded to Harvard Pilgrim Health Care Institute (PI: Richard Platt) in October 2014
- Within FDA's Center for Drug Evaluation and Research (CDER) the Sentinel Program is moving from the Office of Medical Policy to the Office of Surveillance and Epidemiology (OSE)

Plans for Sentinel: New Populations

- Part of Sentinel contract
  - BCBS Massachusetts
  - Hospital Corporation of America
  - PCORnet Clinical Data Research Networks

- Potential Future Populations
  - CMS data (Medicare, Medicaid)
  - Veterans Health Administration
  - Department of Defense

Plans for Sentinel: Methods Priorities

- Data linkage: National death index (NDI)
- Method evaluation: Comprehensive evaluation of Sentinel programs' operational and statistical performance
- Targeted prospective surveillance (enhancing PROMPT)
  - Historical comparison groups (vaccines, rare outcomes)
  - More flexible survival data estimation/signaling methods
  - Improving sequential design selection processes
  - Prospective temporal scans in self-controlled & cohort designs
- Signal follow-up from prospective surveillance
  - Practical guidance for follow-up of safety signal
  - Electronic claims profile retrieval tool to review HOIs
- Signal generation: extending tree scan data mining

Plans for Sentinel: External Engagements

- Clinical Trials Transformation Initiative
- PCORnet – Nat'l Patient Centered Research Network
- NIH Health Care System Collaboratory
- Reagan Udall Foundation – IMEDS
- ONC Standards & Interoperability Framework (Query Health)
- IOM Roundtable on Value & Science-Driven Health Care
- Academy Health EDM Forum


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 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
Spotlight
Brookings Seventh Annual Sentinel Initiative Public Workshop (February 5, 2015 from 9am–4pm - registration required)
Employment Opportunities
FDA Sentinel Contract Awarded to Harvard Pilgrim Health Care Institute
Latest Postings
Ongoing Projects
Decision Analysis for Surveillance and Health - Pandemic Influenza (PRISM)
Quantifying Uncertainty in Protocol Based

Summary

- "OMOP efforts have drawn important and cautionary attention to issues of design, data quality, and replicability of observational studies" (Psaty et al., *NEJM,* 2014)

- Methods work (including methods evaluation) is ongoing within Sentinel, IMEDS, and OHDSI. "We are not there yet, with the solution to problems of drug safety, but we are moving in the right direction" (Evans, *Drug Saf,* 2013)

- Mini-Sentinel is in the process of transitioning from its pilot stage to the full-fledged program. It is intended to complement the existing FDA post-marketing resources, not to replace existing activities and systems. Sentinel can be expected to continue to evolve and to play an integral role in the future of FDA's postmarketing activities.

Thank you!

Contact: tgerhard@rci.rutgers.edu