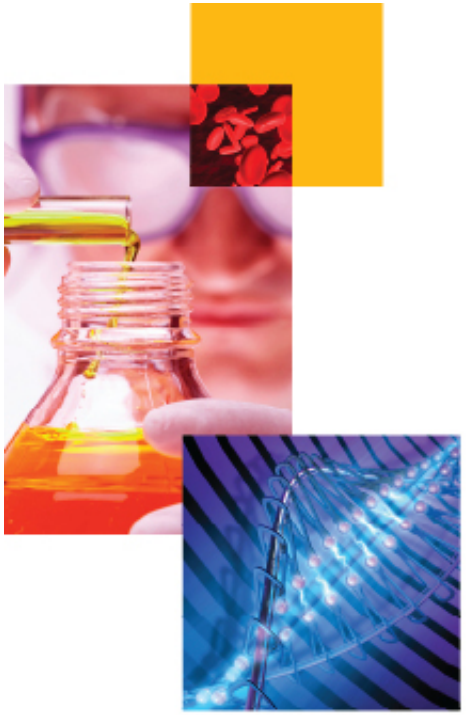


OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

FOUNDATION FOR THE National Institutes of Health

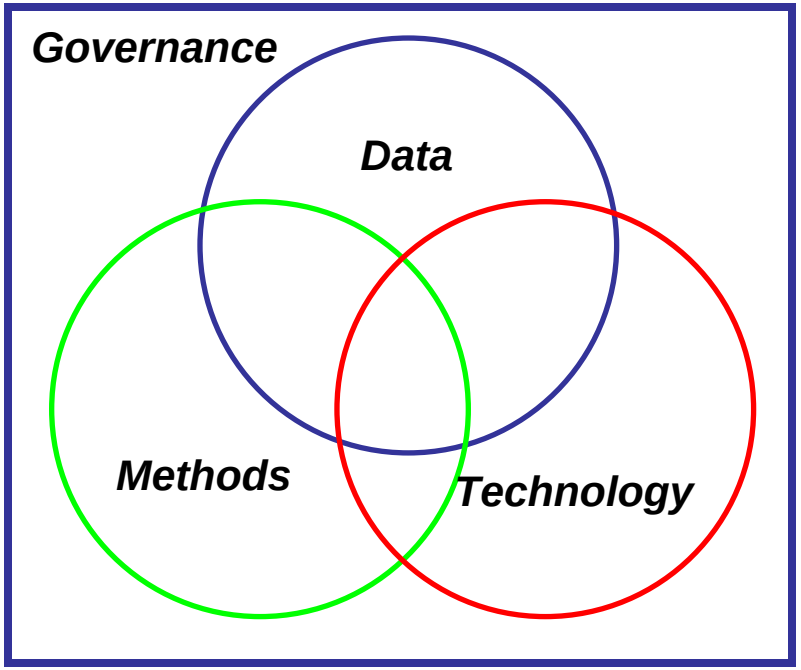
Improving drug safety through data mining of observational healthcare databases: An overview of the Observational Medical Outcomes Partnership

Patrick Ryan
OMOP Research Investigator
26 October 2009

Observational Medical Outcomes Partnership

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP
FOUNDATION FOR THE National Institutes of Health

A public-private partnership to serve the public health by testing whether multi-source observational data can improve our ability to assess drug safety and benefits.

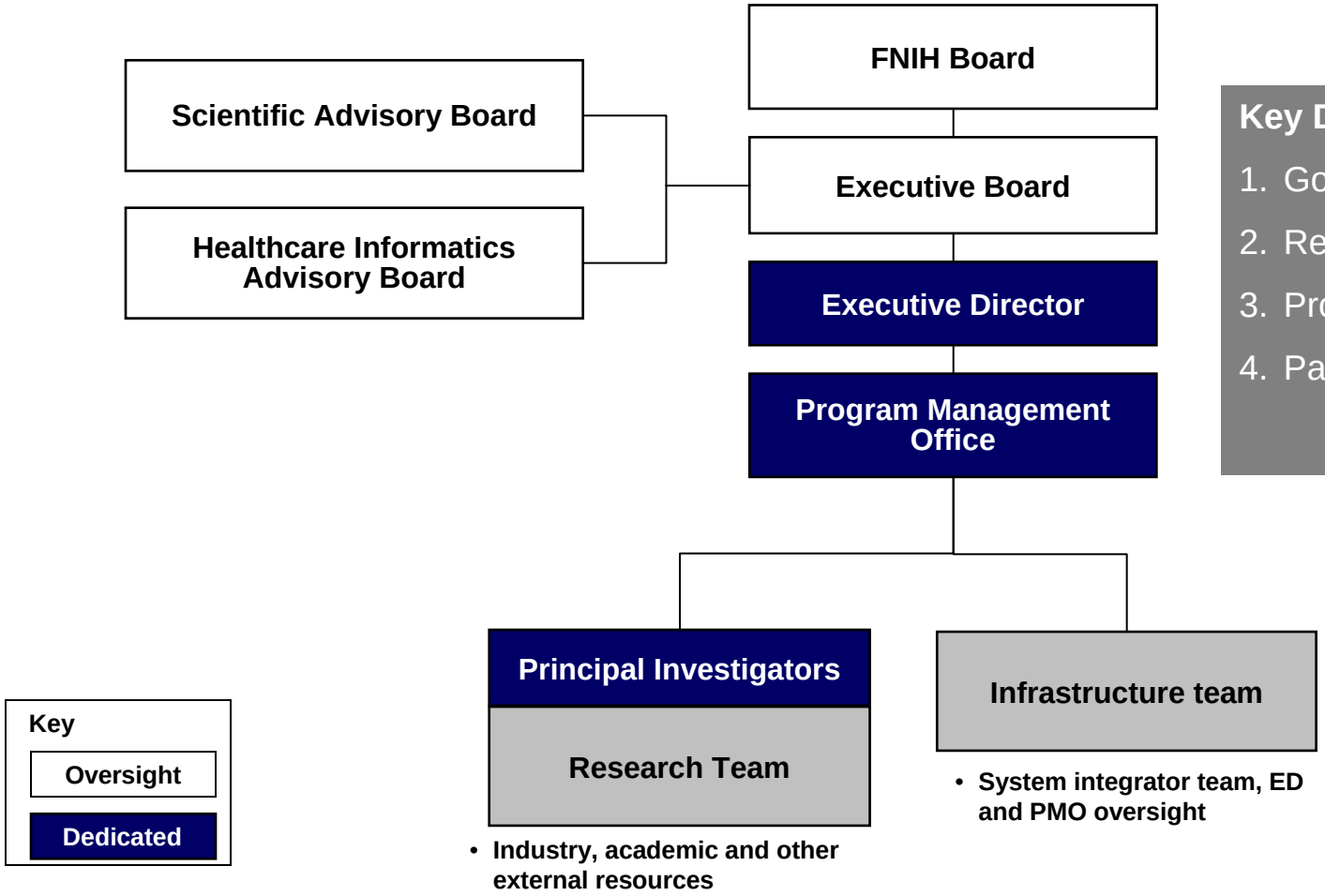


- Assess the appropriate technology and data infrastructure required for systematic monitoring of observational data
- Develop and test the feasibility and performance of the analysis methods
- Evaluate required governance structures

Partnership Structure

Governance Provided by an Executive Board

Scientific and Informatics advisory boards inform decisions



Key Design Elements:

1. Governance and Oversight
2. Research Leadership
3. Program Management
4. Partners & Collaborators

Executive Board

A multi-stakeholder group, the OMOP Executive Board oversees the operation of the Partnership.

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

FOUNDATION FOR THE National Institutes of Health

Janet Woodcock, MD
Director, Center for Drug Evaluation and Research, Food and Drug Administration
Chair, Observational Medical Outcomes Partnership Executive Board

Rebecca Burkholder
Vice President of Health Policy, The National Consumers League

Sherine Gabriel, MD, MSc
Professor of Medicine and Epidemiology, The Mayo Clinic

Cynthia Gilman, JD
Special Assistant to the President for Advancement of Cancer Research and Collaborative Partnerships, Henry Jackson Foundation

Jesse L. Goodman, MD, MPH
Director, Center for Biologics Evaluation and Research, Food and Drug Administration

Ronald L. Krall, MD
Former Senior Vice President and Chief Medical Officer, GlaxoSmithKline

Richard Platt, MD, MSc
Professor and Chair of the Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care

Stephen Spielberg, MD, PhD
Marion Merrell Dow Chair in Pediatric Pharmocogenomics, Children's Mercy Hospital and Dean Emeritus, Dartmouth Medical School

Brian Strom, MD, MPH
George S. Pepper Professor of Public Health and Preventive Medicine; Professor of Biostatistics and Epidemiology, Medicine, and Pharmacology; Chair, Department of Biostatistics and Epidemiology; Director, Center for Clinical Epidemiology and Biostatistics; Vice Dean for Institutional Affairs, University of Pennsylvania School of Medicine
Senior Advisor to the Provost for Global Health Initiatives, University of Pennsylvania

David Wheadon, MD
Senior Vice President, Pharmaceutical Research and Manufacturers of America (PhRMA)

Research Investigators

The Principal Investigators (PIs) are the lead scientists for the OMOP project and guide and participate in the research across all four project phases

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

FOUNDATION FOR THE National Institutes of Health

Abraham G. Hartzema PharmD, MSPH, PhD, FISPE: Professor and Eminent Scholar, Perry A. Foote Chair in Health Outcomes and Pharmacoeconomics
Professor, Department of Epidemiology and Biostatistics, College of Public Health and Health Professions - University of Florida

Marc Overhage, MD, PhD: Director, Medical Informatics and Research Scientist, Regenstrief Institute, Inc.; Regenstrief Professor of Medical Informatics, Indiana University School of Medicine,CEO; President of the Indiana Health Information Exchange

Judith A. Racoosin, MD, MPH
Sentinel Initiative Scientific Lead, FDA

Paul Stang, PhD, FISPE: Senior Director, Epidemiology, Johnson & Johnson Pharmaceutical Research and Development

Patrick Ryan: Manager Drug Development Sciences, GlaxoSmithKline R&D

OMOP Co-Investigator

Foundation for the NIH Program Staff

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

FOUNDATION FOR THE National Institutes of Health

Thomas Scarnecchia, MS
Executive Director, OMOP

Emily Welebob, RN, MS
Senior Program Manager, Research

Christian Reich, MD, PhD
Senior Program Manager, Technology

Advisory Boards

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

FOUNDATION FOR THE National Institutes of Health

A Scientific Advisory Board (SAB) will provide independent review of and expert input into the scientific aspects of OMOP's activities.

- Elizabeth Andrews, RTI Health Solutions
- Andrew Bate, Pfizer
- Jesse Berlin, Johnson & Johnson
- Robert Davis, Kaiser Permanente
- Steve Findlay, Consumer Union
- Sean Hennessy, University of Pennsylvania
- Mike Katz, FDA patient representative
- Allen Mitchell, Boston University
- David Page, University of Wisconsin
- Ken Rothman, RTI Health Solutions
- Judy Staffa, FDA
- Alec Walker, WHISCON

A Health Informatics Advisory Board (HIAB) will provide independent review and expert input into the OMOP's technology governance and project requirements related to privacy and security, terminology and coding, data and data models.

- Col. Kevin Abbott
- Jeff Brown, Harvard Medical School
- Stan Huff, Intermountain Healthcare
- Diane MacKinnon, IBM (retired)
- Ken Mandl, Harvard University
- Clem McDonald, National Library of Medicine
- David Memel, previously at Aetna
- Joy Pritts, Georgetown University
- Rob Thwaites, United BioSource Corporation

Partnership Stakeholders

Sustained Commitment Over 2 Years

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

FOUNDATION FOR THE National Institutes of Health

Funding Organizations

- Abbott
- Amgen Inc.
- AstraZeneca
- Bayer
- Bristol-Myers Squibb
- Eli Lilly & Company
- GlaxoSmithKline
- Johnson & Johnson
- Merck & Co., Inc.
- Novartis Pharmaceuticals Corporation
- Ovation Pharmaceuticals
- Pfizer, Inc
- Pharmaceutical Research Manufacturers of America (PhRMA)
- Roche Pharmaceuticals
- sanofi-aventis
- Schering-Plough Corporation

Stakeholder Groups

- Principal Investigators seconded from academia, FDA, and industry
- Executive Board and two advisory boards drawn from academia, healthcare providers, consumer and patient advocacy organizations, government, and industry
- Distributed Research Core include academic and healthcare research centers as funded research partners
- Extended Research Consortium will include academic, healthcare, technology, industry, and government participants

Research Collaborators

as of 10/9/09

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

FOUNDATION FOR THE National Institutes of Health

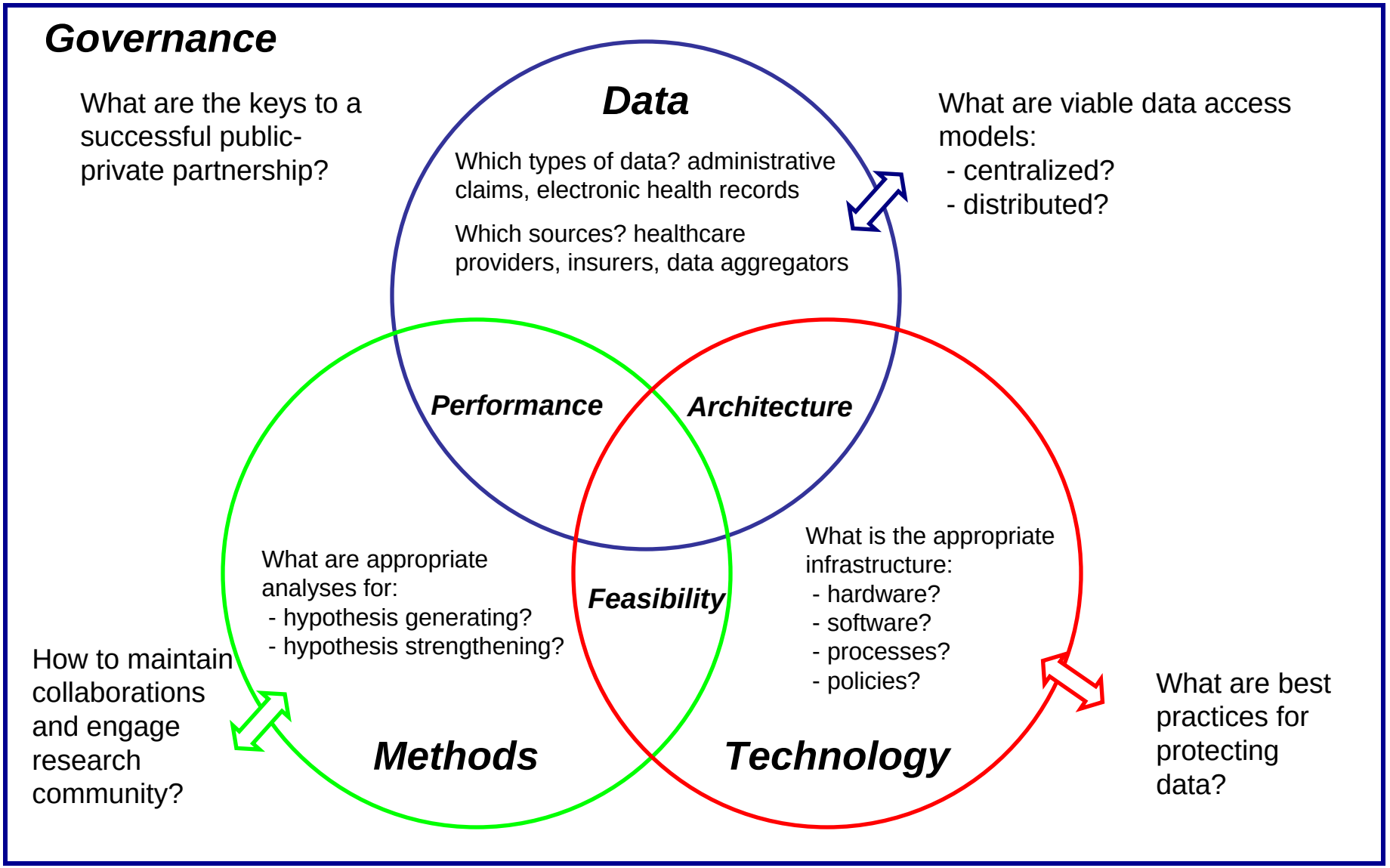
Organization	Team Leader	Activity
Columbia University	David Madigan	Methods Lead
Computer Sciences Corporation	Dan Foltz	Research Lab
Eli Lilly and Company	Karin L. Benoit	Methods Partner
GE Healthcare	Michael Lieberman, MD	Research Lab
Harvard University	Lingling Li, Ph.D.	Methods Partner
i3 Drug Safety	Arnold Chan, M.D., Sc.D.	Distributed Research Partner
Indiana University - Regenstrief Institute	Siu L. Hui, Ph.D,	Methods Partner
Indiana University - Regenstrief Institute	J. Marc Overhage, MD, PhD	Distributed Research Partner
Merck Research Laboratories	Dr. A. Lawrence Gould	Methods Partner
Partners HealthCare System	Shawn Murphy, MD, PhD	Distributed Research Partner
ProSanos Corporation	Stephanie Reisinger	Simulated Data, Methods
Risk Benefit Statistics LLC	Robert L. (Bob) Obenchain, PhD, FASA	Methods Partner
RTI International	Suzanne L. West, MPH, PhD	HOI Library
SDI Health	Gregory Hess, MD, MBA, MSc	Distributed Research Partner
Thomson Reuters	Stella Chang, MPH	Research Lab
United BioSource Corporation	Matthew W. Reynolds, PhD	HOI Library
University of Miami-Humana Health Services Research Center	Vinit Nair, BS Pharm., MS, RPh	Distributed Research Partner
University of Wisconsin-Madison	David Page, PhD	Methods Partner

OMOP Research Plan

Overview

Outstanding questions for active surveillance

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP | FOUNDATION FOR THE National Institutes of Health

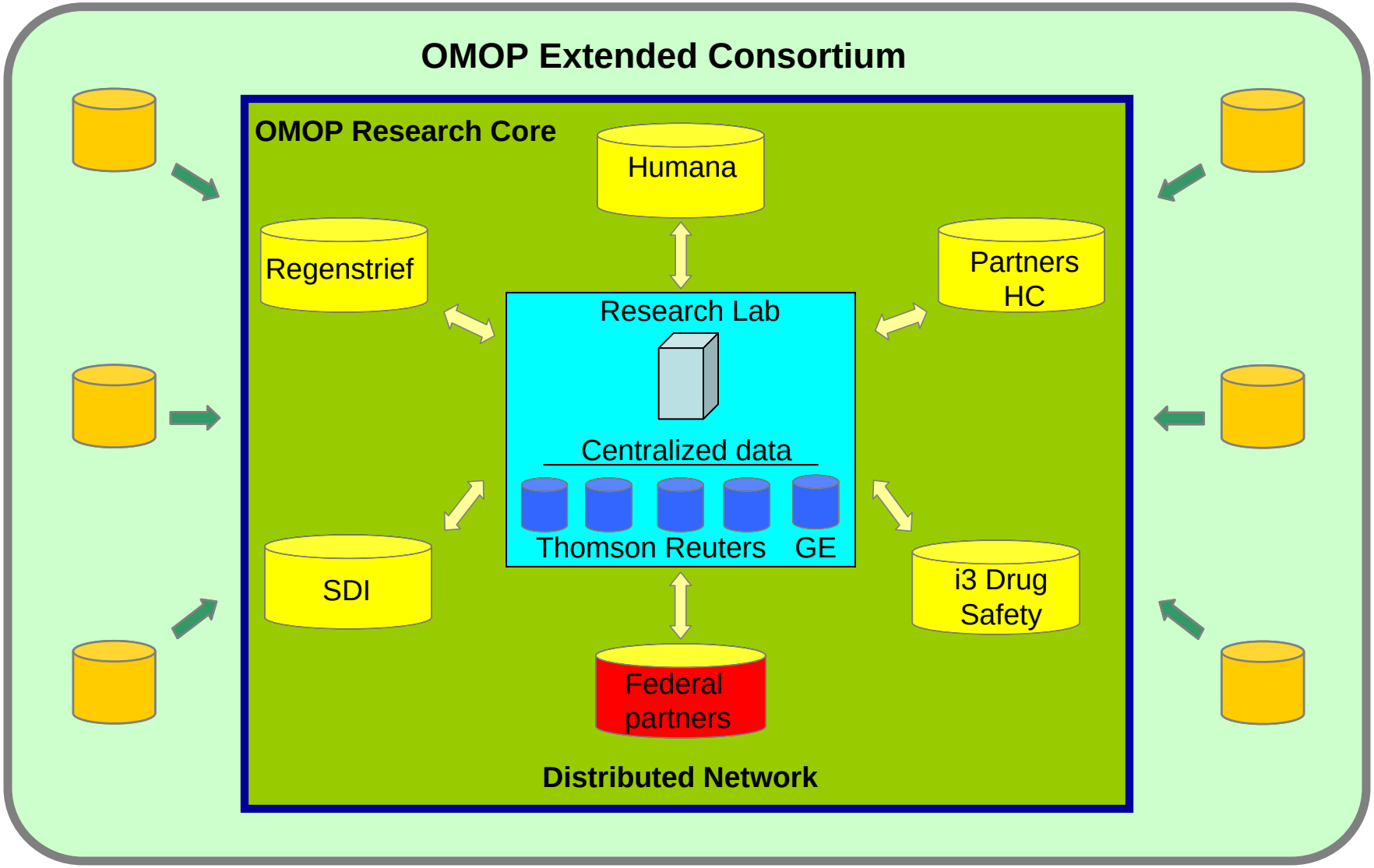


OMOP Phases

- **Phase 1:** FEASIBILITY OF DATA INFRASTRUCTURE (Feb – July 2009)
  - Establish a consistent framework to use across disparate observational data sources
  - Establish OMOP Research Community
- **Phase 2:** FEASIBILITY OF ANALYSES (Aug – Dec 2009)
  - Develop and test analysis methods within the OMOP Research Lab and other data environments
  - Establish standard data characterization procedures
  - Implement health outcomes of interest definitions
  - OMOP to facilitate comparisons across databases
- **Phase 3:** PERFORMANCE MEASUREMENTS (Jan – July 2010)
  - Evaluate performance of methods and data in identifying drug safety issues
  - OMOP to facilitate comparisons across databases
- **Phase 4:** UTILITY OF ANALYSES & PROCESS (July – Dec 2010)
  - Assess the effectiveness and usefulness of how the results and comparisons contribute to decision-making

Overview of Partnership Design

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP
FOUNDATION FOR THE National Institutes of Health

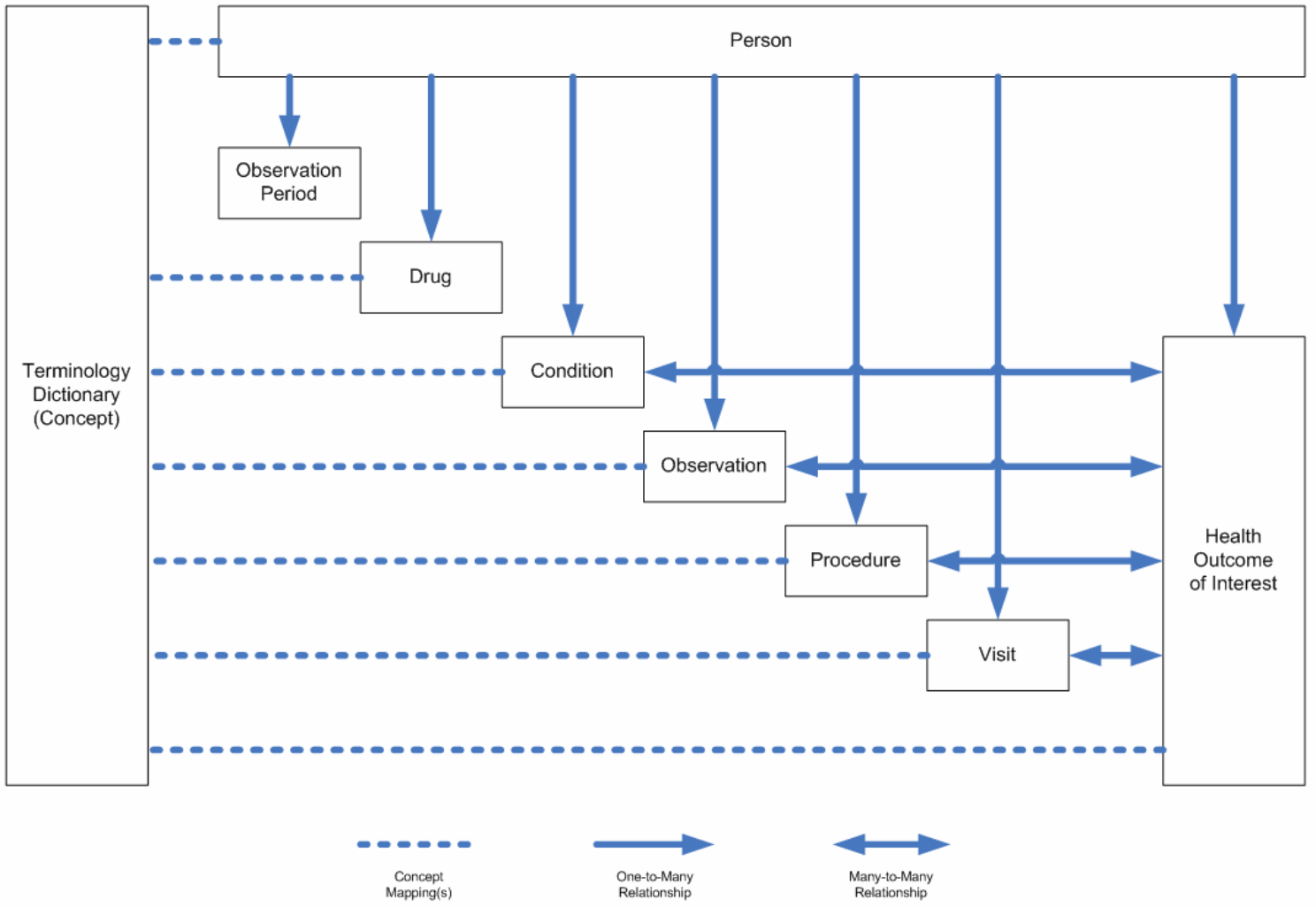


Common Data Model

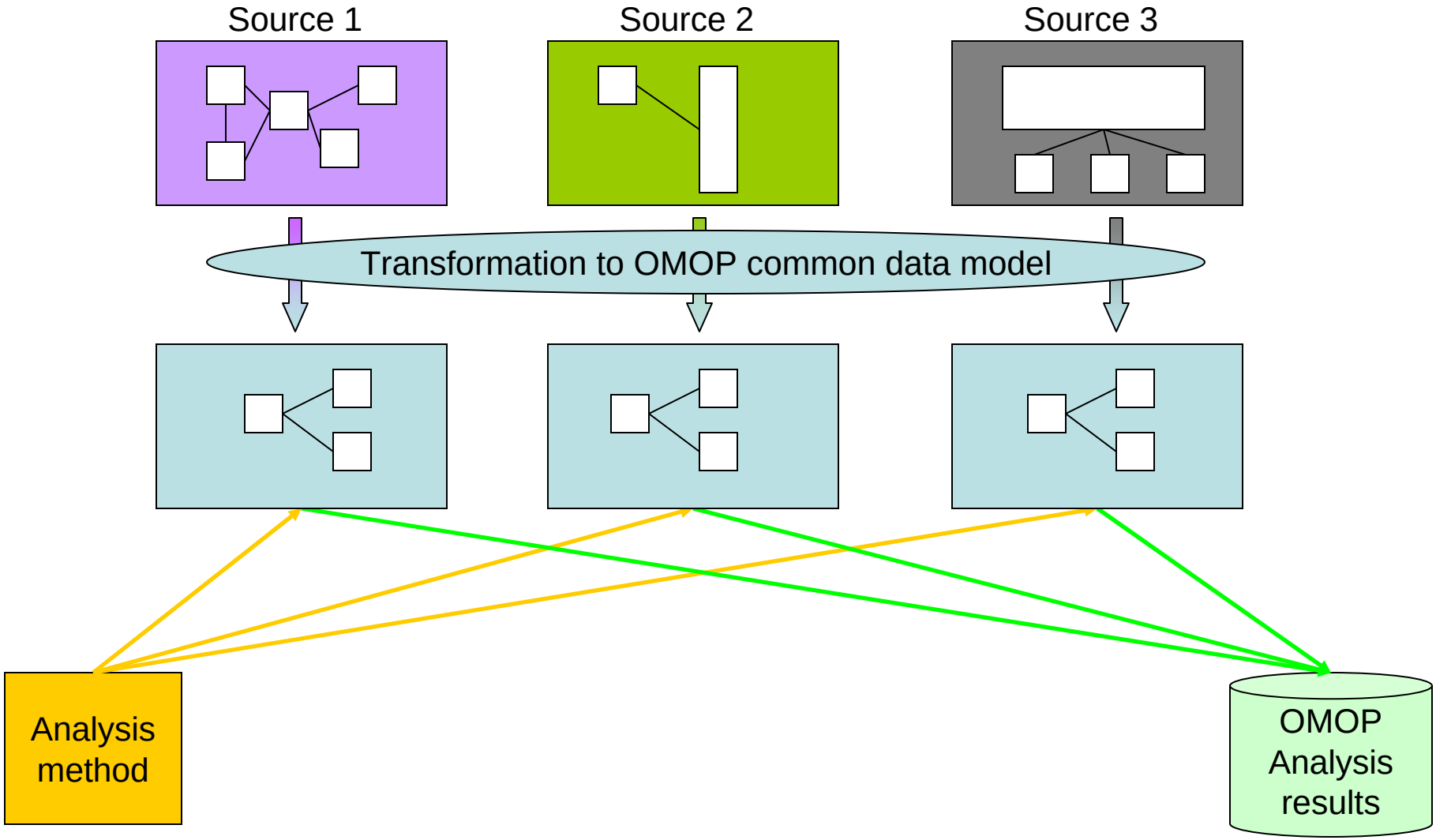
- The common data model includes:
  - A single data schema that can be applied to disparate data types
  - Standardized terminologies
  - Consistent transformation for key data elements
- A common data model can:
  - Enable consistent and systematic application of analysis methods to produce comparable results across sources
  - Create a community to facilitate the sharing of tools and practices
  - Impose data quality standards
  - Create implementation efficiencies

Common Data Model	
What We Are Doing	**What We Are Not Doing**
• Creating one model that could accommodate any relevant type of observational data • Facilitating comparison of analysis results across sources • Providing a conceptual model to allow researchers to develop analysis methods that are be portable across data sources	• Combining multiple datasets into one centralized database • Trying to force claims data into a EHR model or vice versa • Developing a graphical user interface to automatically create structured queries

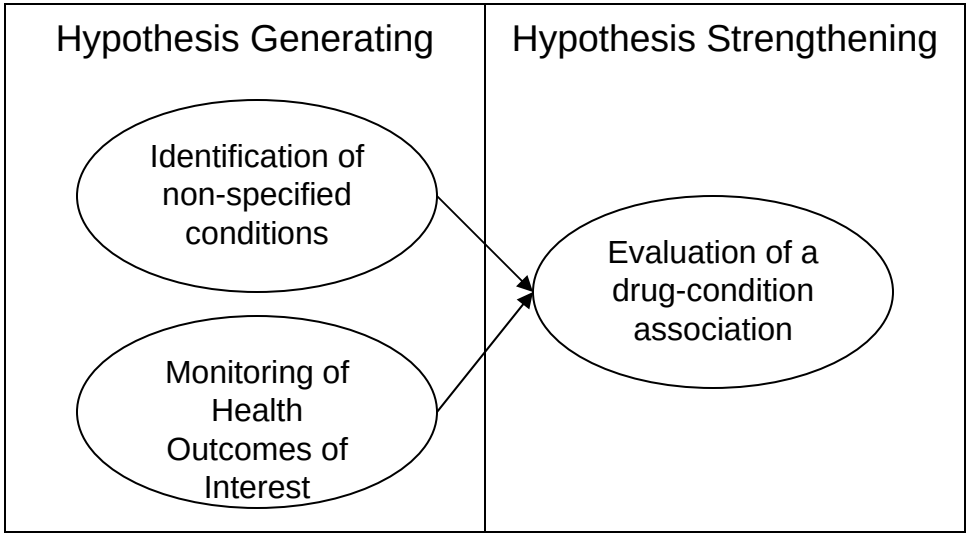
Conceptual Schematic of OMOP Common Data Model



Role of common data model in OMOP Analysis process



OMOP analysis problems



Identification of non-specified associations: This exploratory analysis aims to generate hypotheses from observational data by identifying associations between drugs and conditions for which the relationships were previously unknown. This type of analysis is likely to be considered an initial step of a triaged review process, where many drug-outcome pairs are simultaneously explored to prioritize the drugs and outcomes that warrant further attention.

Monitoring of Health Outcomes of Interest: The goal of this surveillance analysis is to monitor the relationship between a series of drugs and specific outcomes of interest. These analyses require an effective definition of the events of interest in the context of the available data.

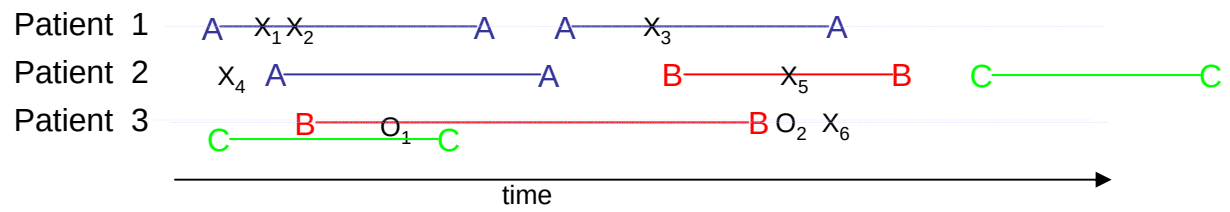
Enabling Methods Research and Development

- Develop new methods
- Implement and standardize existing approaches
- Adapt and apply techniques from other domains
- Evaluate the performance across disparate data sources

Analysis Method
Epidemiology designs
Cohort Case-control Case-crossover Self-controlled case series
Sequential methods
Maximized sequential probability ratio test Conditional Sequential Sampling Procedure
Disproportionality Analysis
Proportional reporting ratio Multi-item Gamma Poisson Shrinker Bayesian screening Bayesian confidence propagation neural network Adjusted residual score
Other methods
Local Control Tree-based scan statistic Statistical relational learning Bayesian Logistic Regression Information-theoretic similarity measure Temporal pattern discovery
Other analytical considerations
Propensity score adjustment False discovery rate Matching and stratification

One approach: Applying disproportionality analysis

Consider 3 patients; 3 drugs (A,B & C); 2 conditions (x and o)



First consider prevalent, on-drug events. Three different counting approaches:

	X	¬X
A	1	1
¬A	1	0

"not A" means "never take A" hence patients 1 & 2 counted once only as A patients

"Distinct patients"

	X	¬X
A	3	0
¬A	1	2

Reports:
1: A+X_1
2: A+X_2
3: A+X_3
4: B+X_5
5,6: BC+O_1

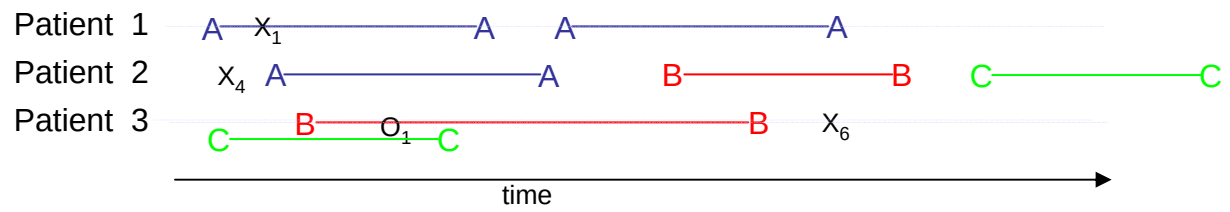
On-drug events, "SRS"

	X	¬X
A	3	1
¬A	3	4

Reports:
1: A+X_1
2: A+X_2
3: A+X_3
4: *+X_4
5: A+*
6: B+X_5
7: C+*
8,9: BC+O_1
10: *+O_2
11: *+X_6

On drug events + "non-drug" events + "non-event" drug eras
"Modified SRS"

Consider 3 patients; 3 drugs (A,B & C); 2 conditions (x and o)



Next consider incident, on-drug events. Same three different counting approaches:

	X	¬X
A	1	1
¬A	1	0

If patient 2 had an X event on A it would not change the numbers

"Distinct patients"

	X	¬X
A	1	0
¬A	0	2

Reports:
1: A+X_1
2,3: BC+O_1

On-drug events, "SRS"

	X	¬X
A	1	2
¬A	2	4

Reports:
1: A+X_1
2: A+*
3: *+X_4
4: A+*
5: B+*
6: C+*
7,8: BC+O_1
9: *+X_6

On drug events + "non-drug" events + "non-event" drug eras
"Modified SRS"

One more alternative application!

•Curtis et al "file" an SRS report for every patient for every month in which the patient consumed a drug and/or experienced an event

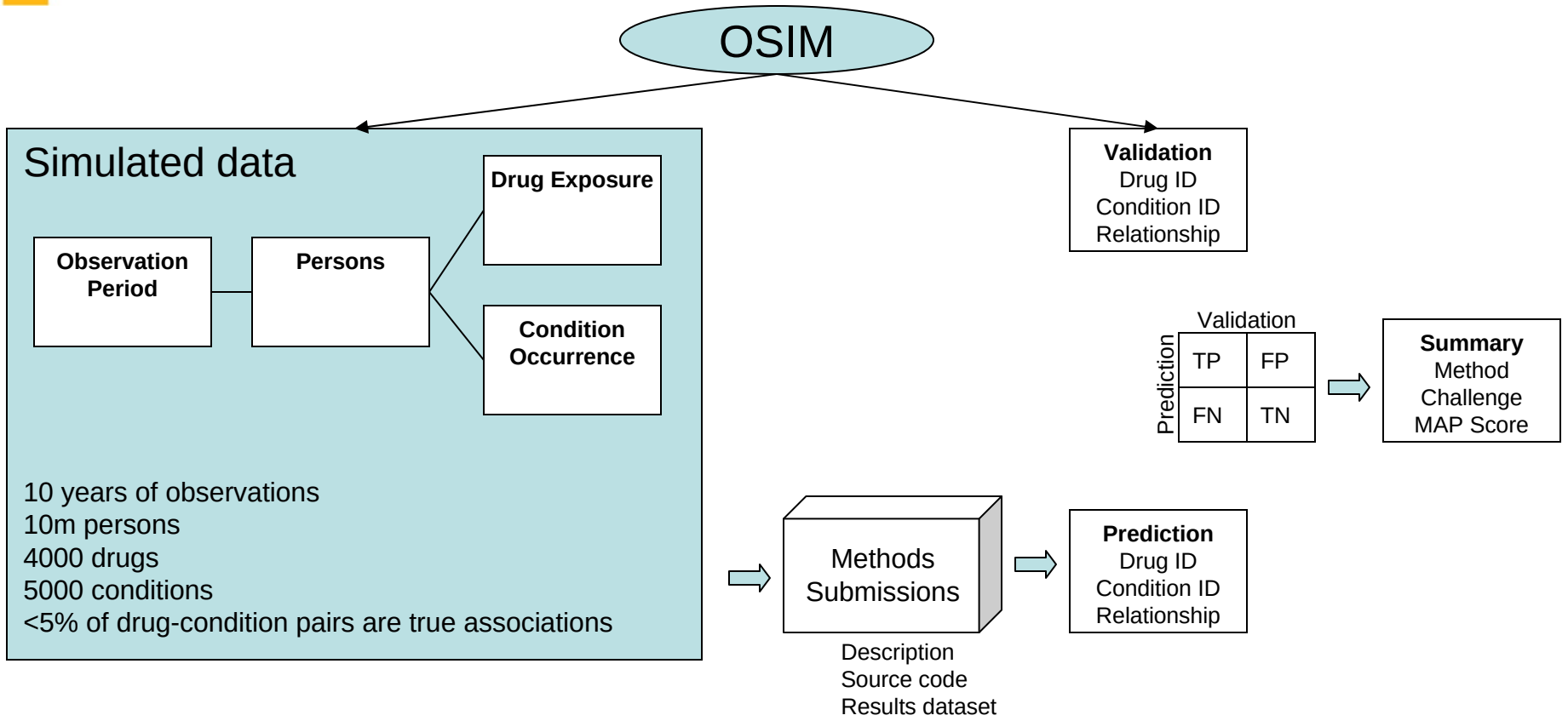
•Accounts for drug duration to some extent

•If in a given month, patient 1 took A and B and experienced x, patient 2 took B and C and had no conditions, and patient 3 experienced o then have:

	X	¬X
A	1	0
¬A	1	3

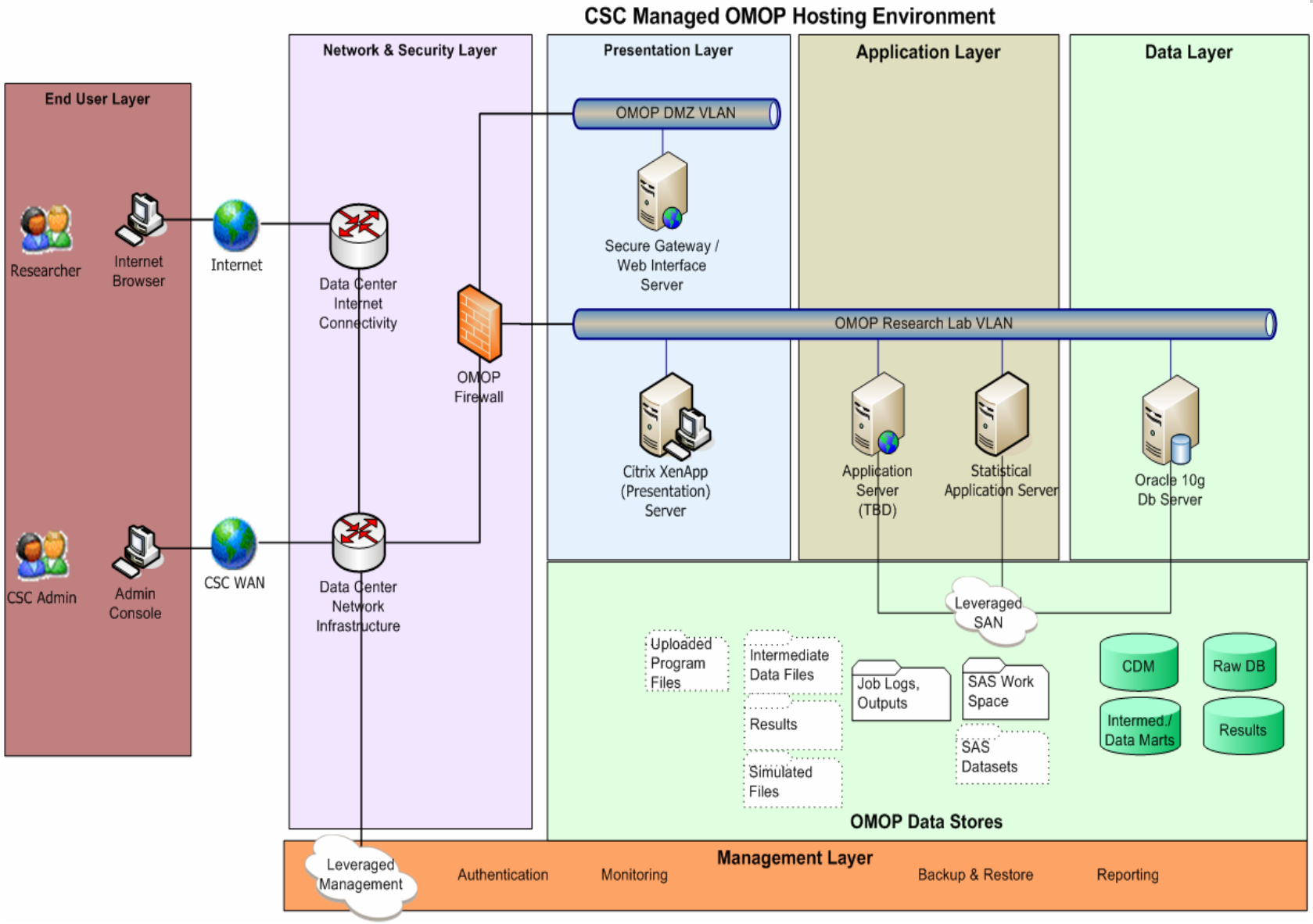
1. A x
1. B x
2. B N
2. B N
3. N o

OMOP Cup: Methods Competition



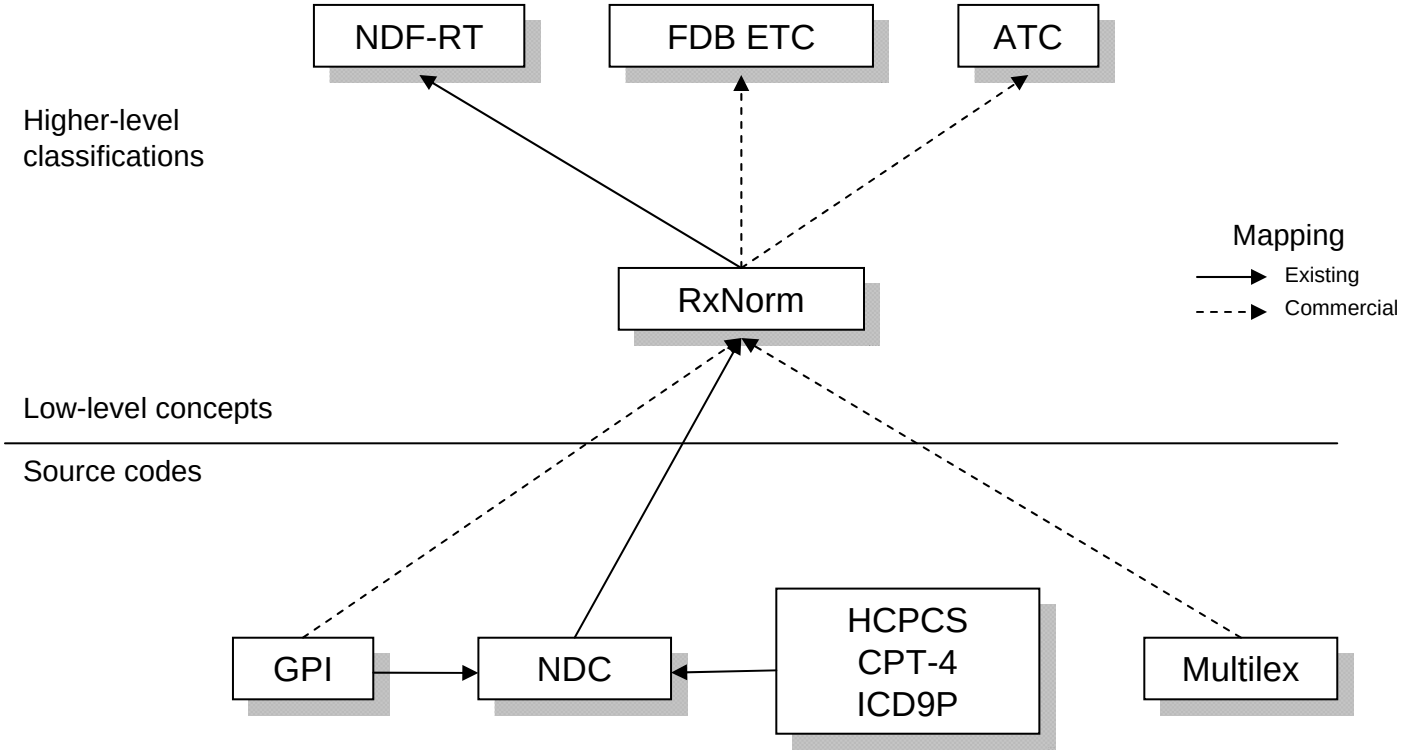
- Two competitions: http://omopcup.orwik.com
  - Challenge 1: Identifying drug-condition associations within an entire observational dataset
  - Challenge 2: Identifying drug-condition associations as data accumulates over time
- Evaluation criteria: Weighted Mean Average Precision
- Winning entries will be given cash prize and methods will be further tested against OMOP data community

Research Laboratory

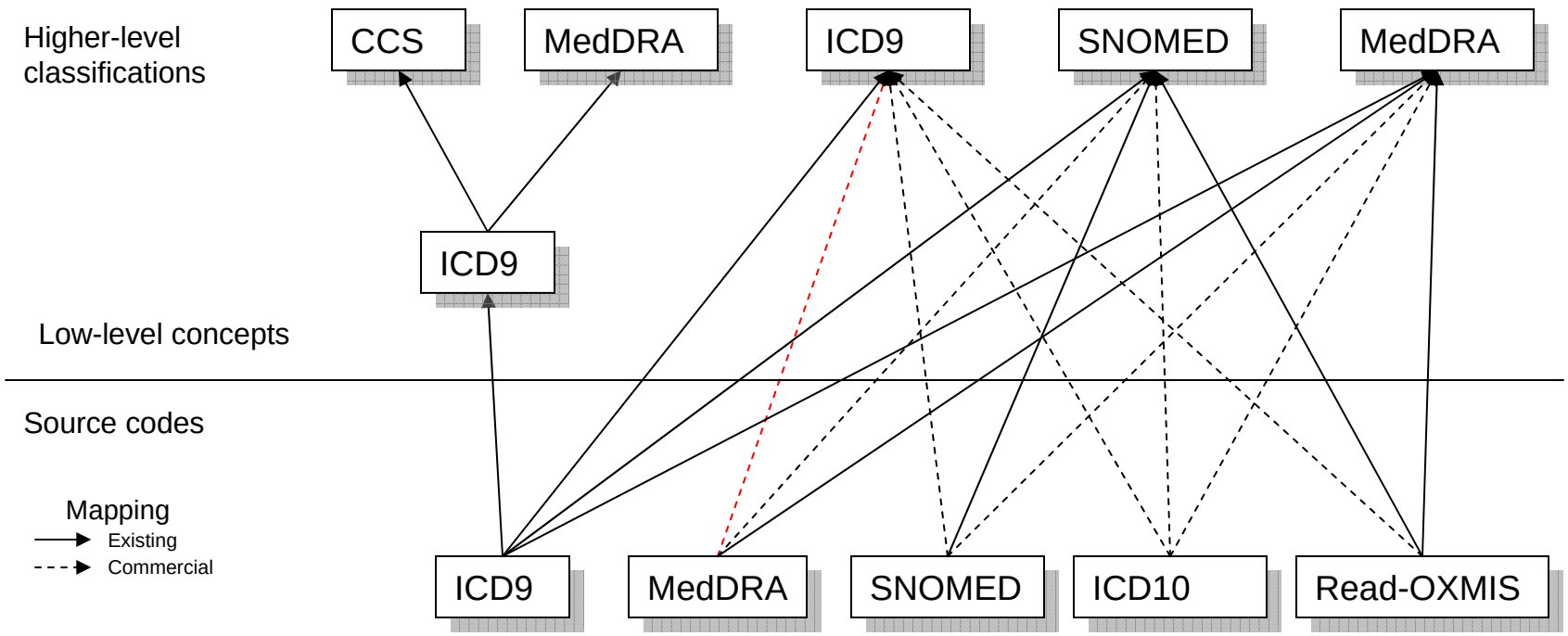


Using standardized terminologies for representing drugs

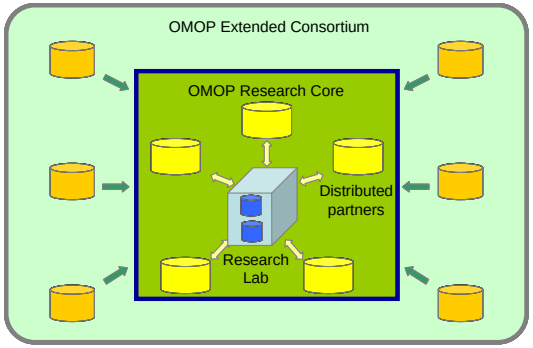
Mechanism of Action
Physiological Effect
Chemical Structure
Indication
Contraindication

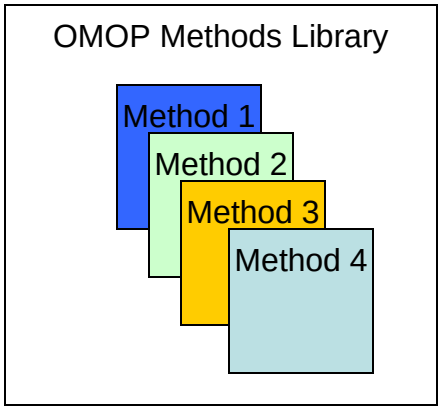


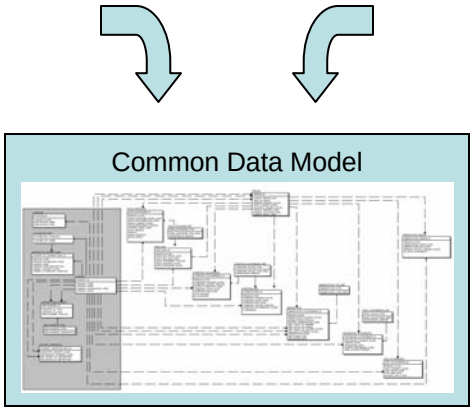
Using standardized terminologies for representing conditions



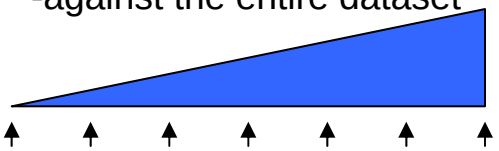
Methods experiment workflow







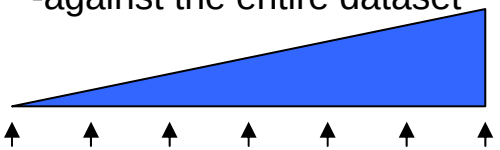
Testing in each source:
-accumulating over time
-against the entire dataset



Health Outcomes of Interest
1. Angioedema
2. Aplastic Anemia
3. Acute Liver Injury
4. Bleeding
5. GI Ulcer Hospitalization
6. Hip Fracture
7. Hospitalization
8. Myocardial Infarction
9. Mortality after MI
10. Renal Failure

Drugs
1. ACE Inhibitors
2. Amphotericin B
3. Antibiotics
4. Antiepileptics
5. Benzodiazapines
6. Beta blockers
7. Bisphosphonates
8. Tricyclic antidepressants
9. Typical antipsychotics
10. Warfarin

Testing in each source:
-accumulating over time
-against the entire dataset



Non-specified conditions

-All outcomes in condition terminology

-'Labeled events' as reference
-Warning
-Precautions
-Adverse Reactions
-Postmarketing Experience

Contact information

Patrick Ryan
Patrick.b.ryan@gsk.com

OMOP website: http://omop.fnih.org
OMOP Cup website: http://omopcup.orwik.com

OMOP Deliverables

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Phase 1
Feasibility of Data Infrastructure

February 2009-July 2009

Research Questions:
- Can we establish a consistent framework to use across disparate observational data sources?
- Does normalizing conditions in observational data improve identification of non-specified conditions?

Reports and Tools:
- Common data model, and data transformation applications
- Common drug and condition vocabularies, and mapping tools
- Report: Comparison of condition vocabularies for observational screening
- Health Outcomes of Interest library
- Simulated dataset
- Systems integration design and lessons learned

Phase 2
Feasibility of Analyses

August 2009-December 2009

Research Questions:
- Which identification methods are feasible within the current systems infrastructure?
- Can we establish standard data quality and characterization procedures to assess the viability of data sources for observational analyses?

Reports and Tools:
- Research Core Data quality summary
- Data quality assessment procedure
- Feasibility of Identification methods
- Library of method implementations
- Reference set of drug labeled events for screening studies
- Health Outcomes of Interest natural history

Phase 3
Performance Measurements

January 2010-June 2010

Research Questions:
- What is the performance of each identification method in simulated data? For non-specified conditions?
- What is the performance of each observational data source in identifying associations between drugs and non-specified conditions? In monitoring Health Outcomes of Interest (HOI)? In evaluating associations between drugs and HOI?

Reports and Tools:
- Library of applications to conduct methodological research against common data model
- Performance of identification methods in a simulated dataset and on non-specified conditions
- Performance and consistency of identification methods on non-specified conditions
- Concordance of identification methods and observational evaluation of HOI

Phase 4
Utility of Analyses and Process

July 2010-December 2010

Research Questions:
- How does natural history information from observational data contribute to a decision regarding the results of observational analysis?
- How do decision-makers interpret observational database analyses?
- How does the performance of identifying associations in observational data differ from other surveillance approaches?

Reports and Tools:
- Utility of Natural History information
- Utility of observational screening and observational evaluation of Health Outcomes of Interest over time
- Efficiency of Identification: Comparison of observational data and other surveillance systems
- Systems integration design and lessons learned
- Partnership governance design and lessons learned

Drug-HOI Pairs

Drug/class	Health Outcome of Interest
ACE inhibitors	Angioedema
ACE inhibitors	Hospitalization (including readmission and mortality)
Amphotericin B	Renal failure
Antibiotics: erythromycins, sulfonamides, and tetracyclines	Acute liver injury (symptomatic hepatitis)
Antiepileptics: carbamazepine, valproic acid, and phenytoin	Aplastic anemia
Benzodiazepines	Hip fracture
Beta blockers	Mortality after MI
Bisphosphonates: alendronate	GI ulcer hospitalizations
Tricyclic antidepressants	Myocardial infarction
Typical antipsychotics	Myocardial infarction
Warfarin	Bleeding