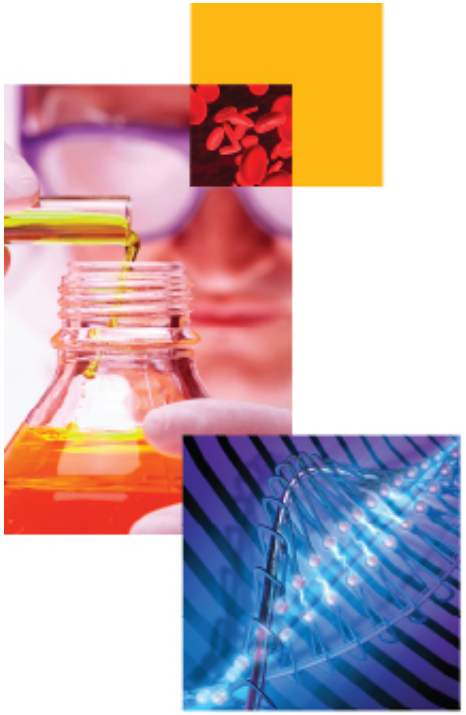

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FOUNDATION FOR THE National Institutes of Health

OMOP: Overview of Methods Development and Evaluation

Patrick Ryan, David Madigan
on behalf of OMOP Research Team
12 January 2010

Observational Medical Outcomes Partnership

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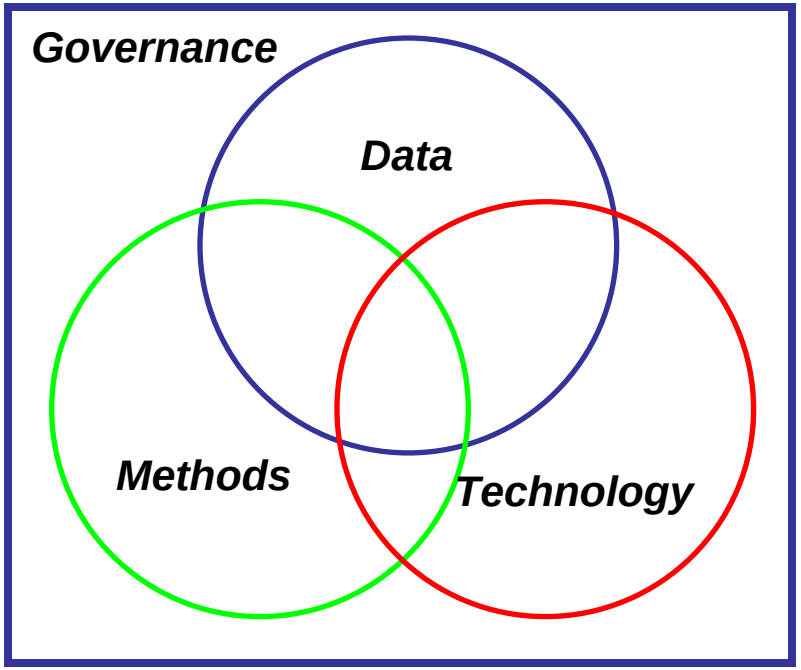
A public-private partnership to serve the public health by testing whether multi-source observational data can improve our ability to assess drug safety and benefits.



- 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

Outstanding questions for active surveillance

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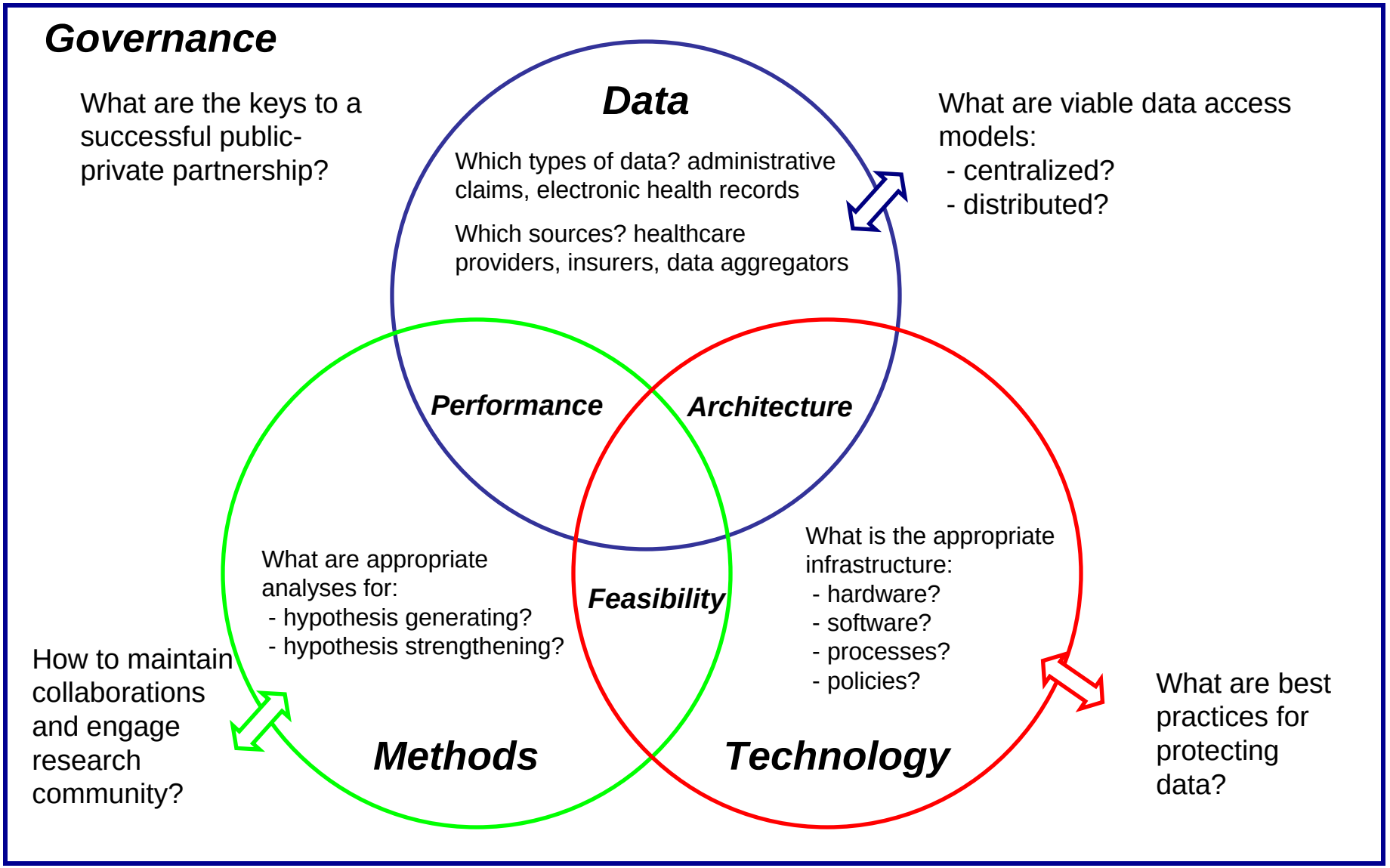

OMOP Phases

- **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

Diversity across OMOP data community

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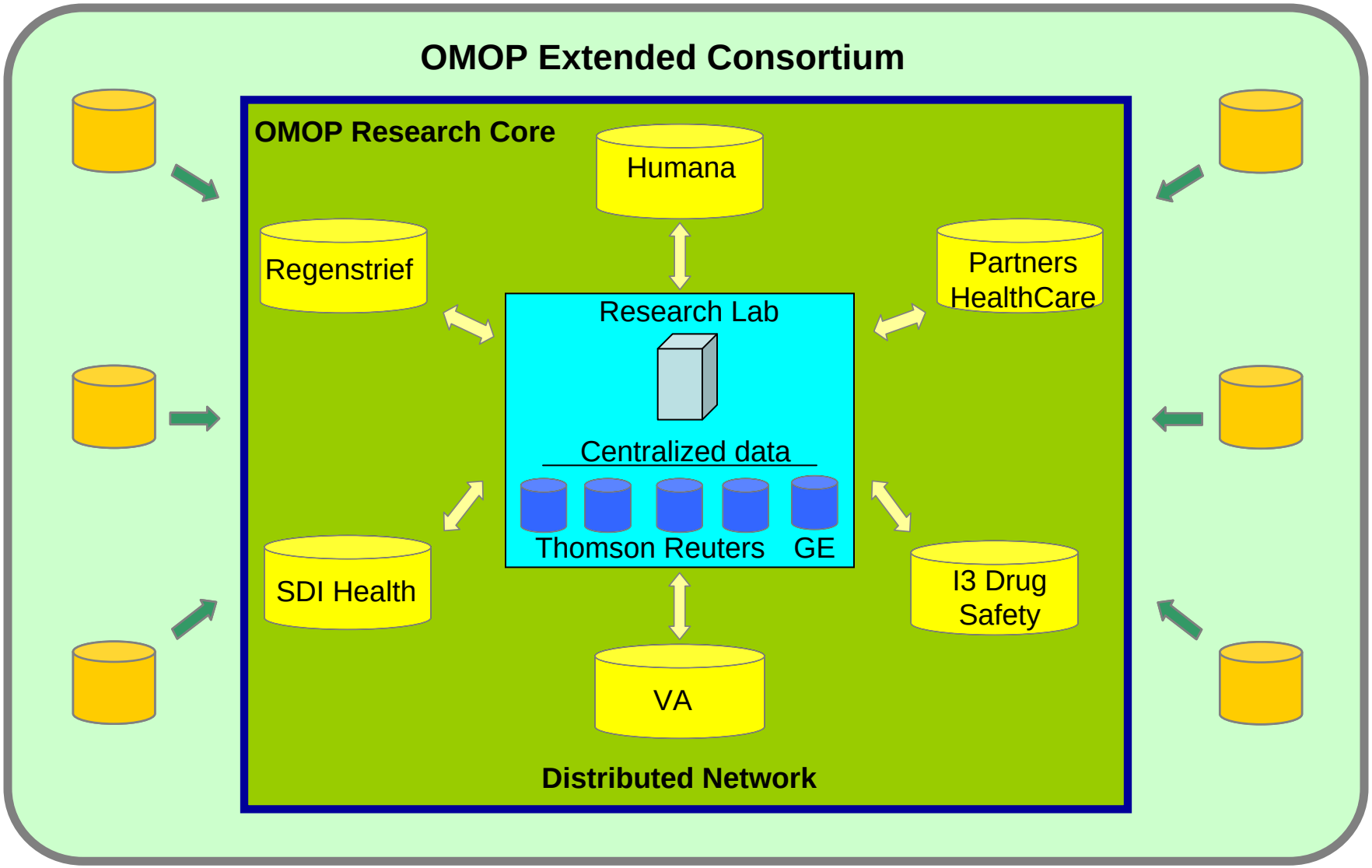
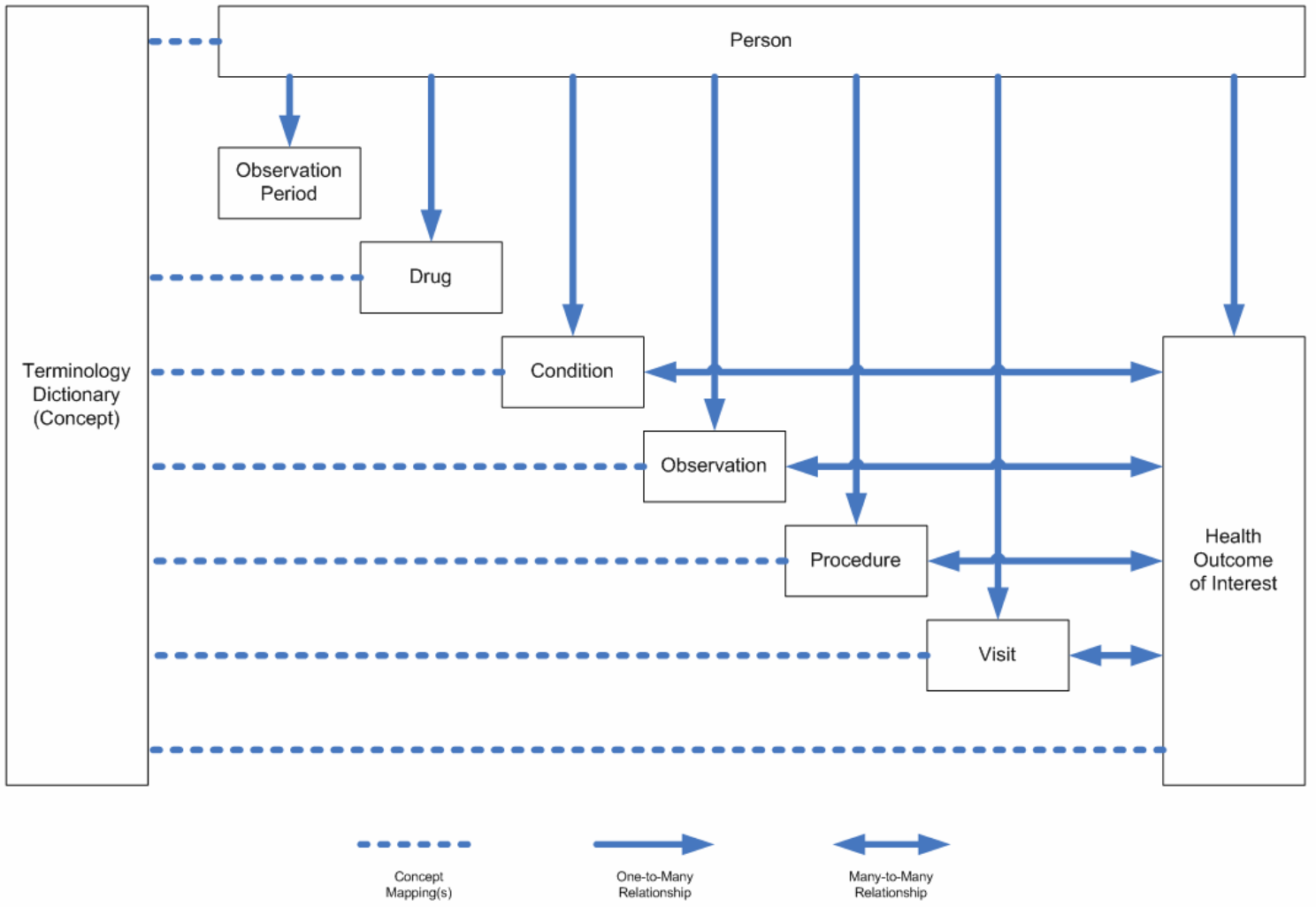


Conceptual Schematic of OMOP Common Data Model



Standardizing terminologies to accommodate disparate observational data sources

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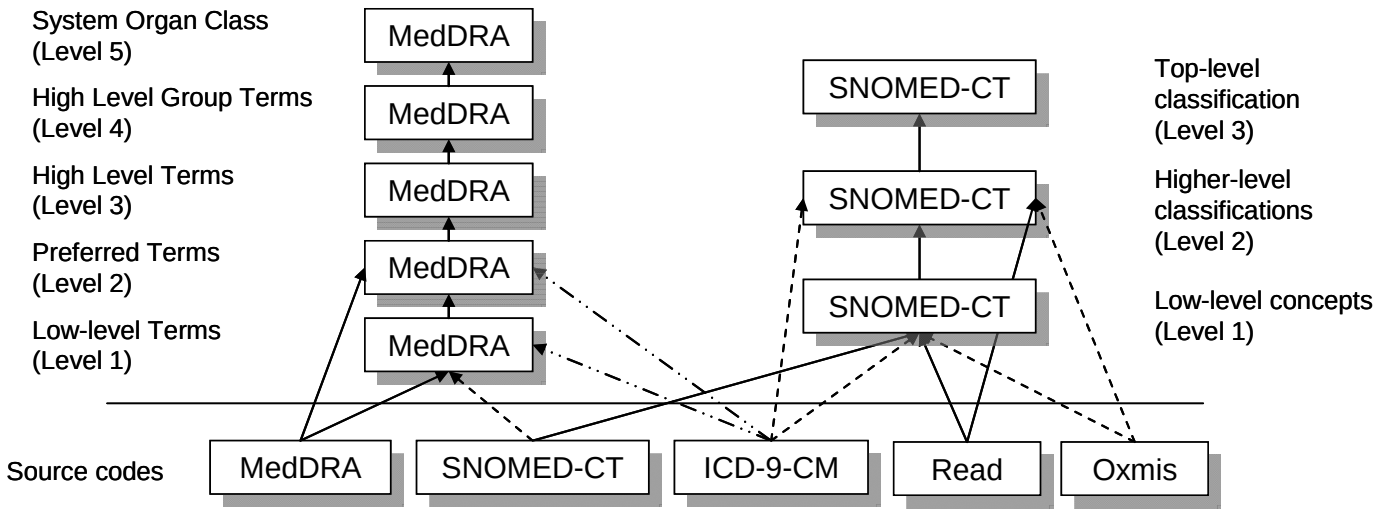
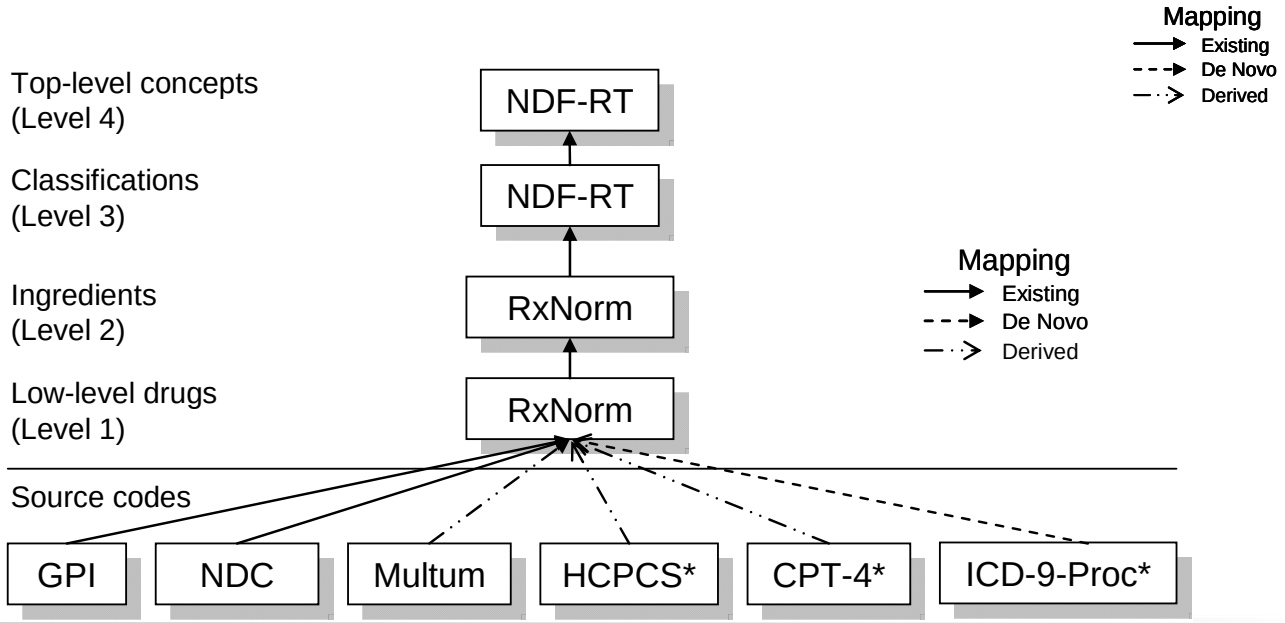
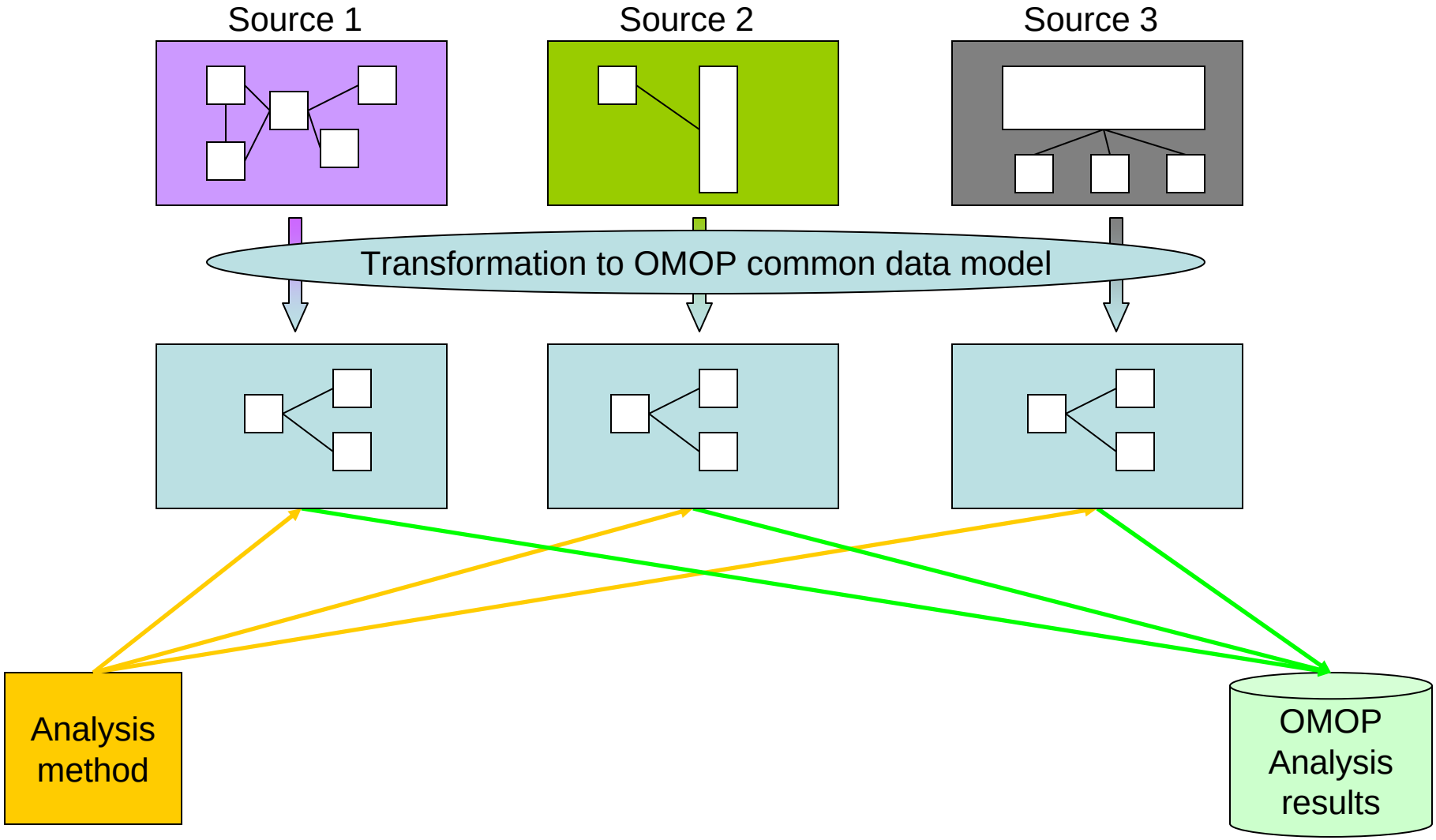
Standardizing conditions:



Standardizing drugs:



Role of common data model in OMOP Analysis process



Opportunities for observational data in active surveillance

- Natural history summary of populations of interest
  - Exposed population (e.g. patients taking antibiotics)
  - Cases (e.g. patients with acute liver injury)
  - Exposed cases (e.g. patients taking antibiotics with acute liver injury)
- Case detection
- Drug-outcome associations

Observational Source Characteristics Analysis Report (OSCAR)

- Provides a systematic approach for summarizing observational healthcare data stored in the OMOP common data model
- Uses
  - Validation of transformation from raw data to OMOP common data model
  - Comparisons between data sources
  - Comparison of overall database to specific subpopulations of interest (such as people exposed to a particular drug or people with a specific condition)
  - Providing context for interpreting and analyzing findings of drug safety studies
- OSCAR can provide transparency into contributing data sources across an active surveillance network

http://omop.fnih.org/OSCAR

Characterizing Drug-Outcome Associations

Screening

Fishing expedition

Identification of non-specified conditions

Prioritization

Hypothesis strengthening

Monitoring of Health Outcomes of Interest

Data dredging

Rapid cycle analysis

Signal substantiation

Signal detection

Exploratory analysis

Data mining

Active surveillance

Risk estimation

Signal amplification

Drug safety monitoring

Hypothesis generating

Confirmation

Evaluation

Full epi study

Signal validation

Hypothesis testing

Causal assessment

Fundamental task: *Estimate* the strength of the drug-outcome relationship

Utility and scope of methods within context of active surveillance

- Initial goal: screen to identify and prioritize drug-condition pairs which may require further evaluation

Non-specified vs Health Outcome of Interest

- Ultimate objective: elicit a valid estimate of a temporal relationship between a drug and an outcome

- No conceptual reason why any method cannot be applicable throughout the continuum of association estimation

- Practical tradeoffs: Methodological sophistication vs. scalable execution across large databases
  1. Method designed for specific exposure and outcome
  2. Method generalized for any drug and any outcome
  3. Method scalable to be applied concurrently to multiple drugs and multiple outcomes

OMOP's methods landscape

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Disproportionality analysis

- Proportional reporting ratio
- Multi-item Gamma Poisson Shrinker
- Bayesian confidence propagation neural network
- Temporal pattern discovery

Other novel approaches? OMOP Cup

Exposure-based approaches

- Cohort Screening
- Incident user designs
- High dimensional propensity scoring
- Local control

Case-based approaches

- Case-control surveillance
- Case-crossover
- Self-controlled case series

Sequential methods

- Maximized sequential probability ratio test
- Conditional sequential sampling procedure

- Bayesian logistic regression
- Statistical relational learning

OMOP Methods Library at: http://omop.fnih.org/MethodsLibrary

Methodological considerations common across multiple approaches

- Exposure definition
  - Incident vs. prevalent exposure
  - Source of data capture
- Outcome definition
  - Incident vs. prevalent events
  - Diagnosis codes vs. rules across data elements
- Defining temporal relationship
  - Time from exposure start
  - Time after exposure end
- Comparator selection
- Inclusion/exclusion criteria
  - Baseline history
  - Follow-up time
- Covariate selection and adjustment
  - Matching
  - Stratification
  - Clustering
  - Multivariate modeling
- Output metric/statistic
  - Test threshold vs. effect estimate
  - Relative vs. attributable risk
  - Measure of uncertainty

Multi-set case control estimation

- Traditional case-control surveillance provides an efficient design for identifying exposure relationship to rare conditions

- Challenge: traditional ‘case-control evaluation’ strategy processes only one drug-event pair

- Solution: multi-set case control estimation provides a novel solution for simultaneously estimating relationships between multiple conditions and multiple drugs
  - First occurrence of distinct conditions selected as ‘case sets’
  - Controls matched to each case by age, gender, time
  - OR estimates for each drug once cases and controls selected

By adapting the case-control design, we can apply one analysis to a database to yield multiple estimates for ANY drug and ANY condition

Bayesian logistic regression

Goal: Predict likelihood of adverse event from prior exposure to any medicine

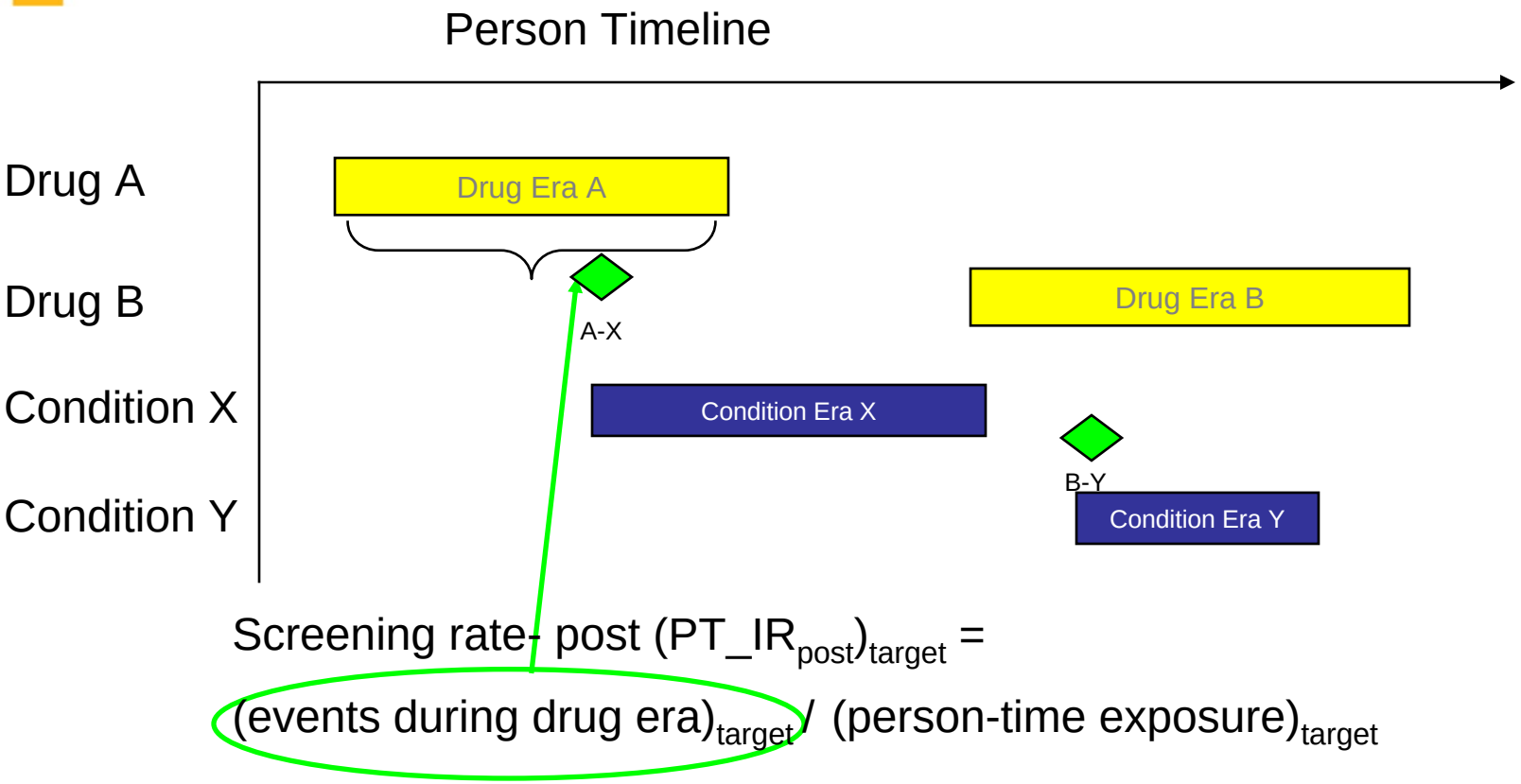
Challenge: too many covariates to adjust (demographics, all drugs, all conditions)

Solution: Bayesian logistic regression can handle thousands of covariates and provide robust estimates of coefficients

$$\log\left(\frac{PR(AE)}{PR(noAE)}\right) = \beta_0 + \beta_1 * AGE + \beta_1 * GENDER + \sum_i \beta_i * DRUG_i$$

For each outcome, estimate effect of ANY drug, while accounting for ALL other drugs

Observational screening



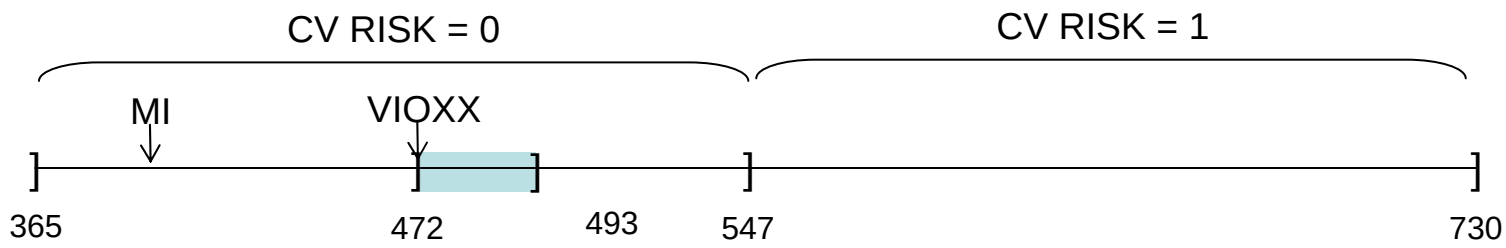
Screening rate- post $(PT\_IR_{post})_{target}$ =

$(\text{events during drug era})_{target}$ / $(\text{person-time exposure})_{target}$

Screening rate ratios: 3 alternative comparisons

- Self-controlled cohort: Screening rate-post / Screening rate-pre
- Relative assessment: Screening rate- target / Screening rate- comparator
- Absolute assessment: Screening rate- post / screening rate - overall

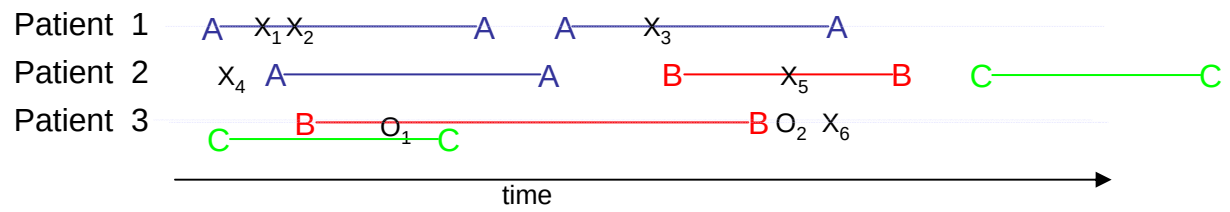
Self-controlled case series



- assume conditions arise according to a non-homogeneous Poisson process
- compare the condition rate on-drug versus off-drug within person
- controls for all fixed covariates automatically
- multivariate version estimates many drug effects simultaneously

Disproportionality analysis

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



Counting options:

	X	¬X
A	1	1
¬A	1	0

"Distinct patients"

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

	X	¬X
A	3	0
¬A	1	2

On-drug events, "SRS"

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

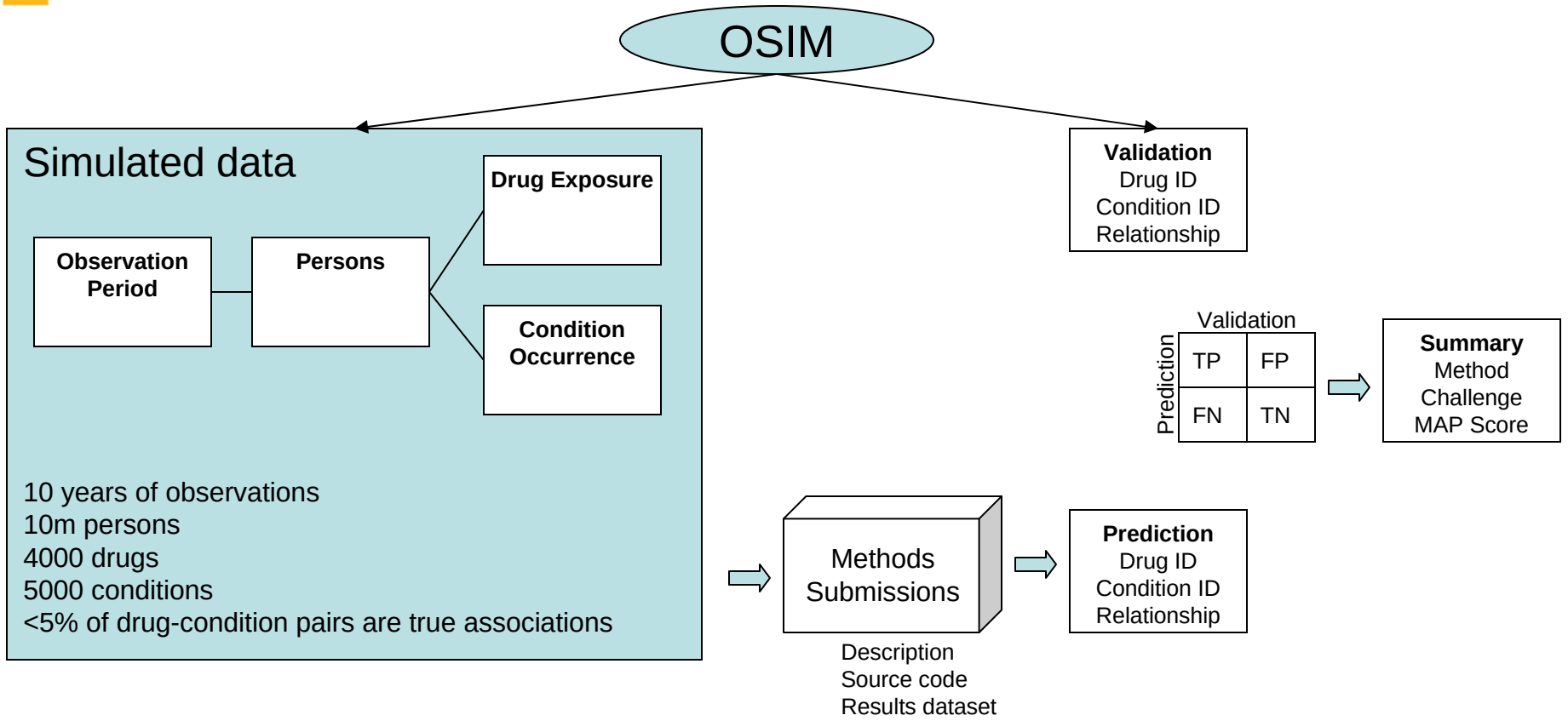
	X	¬X
A	3	1
¬A	3	4

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

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

- Event options: first occurrence, all occurrences
- Metrics: MGPS, PRR, ROR, IC, …
- Optional stratification by age, gender, year of event

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

Methods testing strategy: Monitoring of Health Outcomes of Interest

- Each Health Outcome of Interest has one or more operational definitions that are applied to each database to determine cases for analysis
- Each method will be implemented in the OMOP Research Lab against the central databases
- Feasible methods will be tested across the OMOP data community
- Methods performance tested in two dimensions
  - Identifying drug-condition associations within an entire observational dataset
  - Identifying drug-condition associations as data accumulates over time
- Evaluation focuses on degree to which method maximizes ‘true positives’ while minimizing ‘false positives’
- Monitoring of Health Outcomes of Interest studies for each method will a pre-defined set of relationships (true association and negative control) between 10 HOIs and 10 drugs

Drug-Health Outcomes of Interest pairs under study

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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, 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

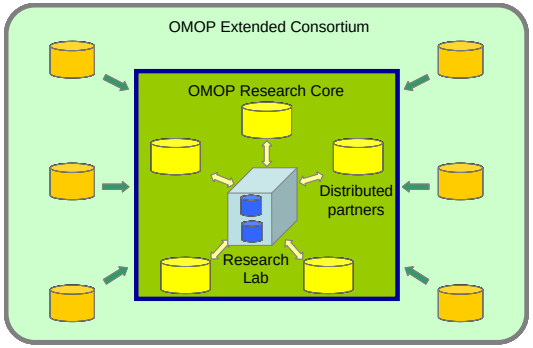
Methods testing strategy: Identification of non-specified conditions

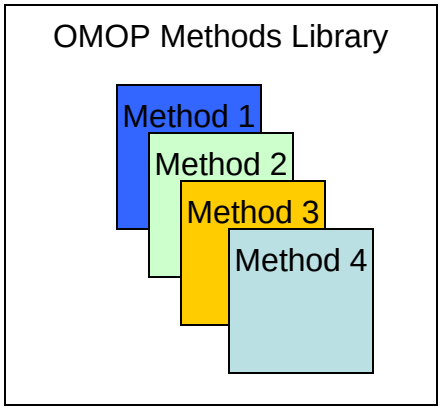
- Each method will be implemented in the OMOP Research Lab against the central databases, and tested against simulated data and across the OMOP data community
- Methods performance tested within an entire observational dataset and as data accumulates over time
- Studies across OMOP data community will explore all outcomes for 10 drugs and compare to 'labeled events'
  - 'Labeled event' extracted from structured product labels through natural language processing program developed by Regenstrief
  - 'Labeled events' characterized by where they are listed on label
    - Warning
    - Precautions
    - Adverse Reactions
    - Postmarketing Experience
  - For purposes of methodological research, 'labeled events' will be classified as 'true' associations and conditions unrelated to 'labeled events' in the the reference condition ontology will be classified as 'negative controls'. Any association identified by the method that is not a 'true' association is to be considered a 'false positive' and will not be further reviewed.

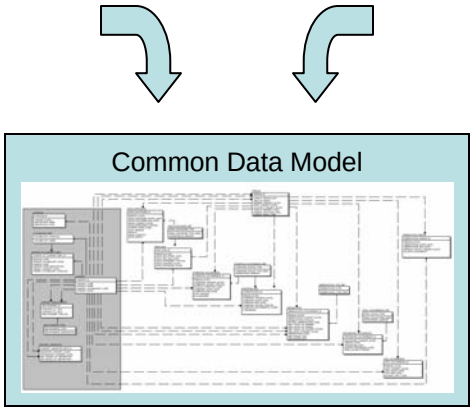
Evaluating the performance of methods: Mean Average Precision

		Original Values			Sorted Values		
Drug	**Condition**	z_i	y_i		$z_{(i)}$	$y_{(i)}$	$P^{(K)}$
D1	C1	5	1		9	1	1/1=1
	C2	0	1		8	1	2/2=1
	C3	9	1		7	0	
D2	C1	8	1		5	1	3/4=0.75
	C2	4	1		4	1	4/5=0.8
	C3	3	0		3	0	
D3	C1	1	0		2	0	
	C2	2	0		1	0	
	C3	7	0		0	1	5/9=0.55
						Total Score	(1+1+0.75+0.8+0.55)/5 =0.82

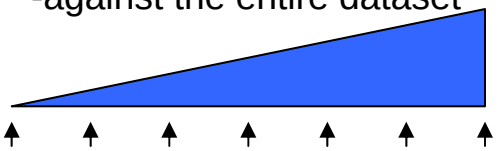
Methods experiment workflow







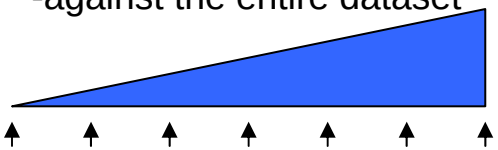
Testing in each source:
-accumulating over time
-against the entire dataset



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

Open discussion

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