

# The Role of Statistics and Opportunities for Statisticians in Active Drug Safety Surveillance



46th Annual Meeting  
Washington, DC - 2010

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GlaxoSmithKline  
Observational Medical Outcomes  
Partnership (OMOP)



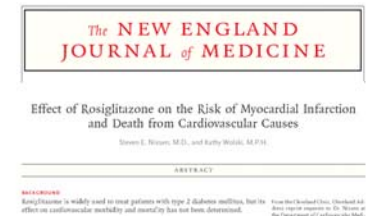
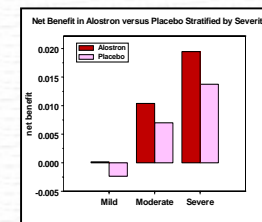
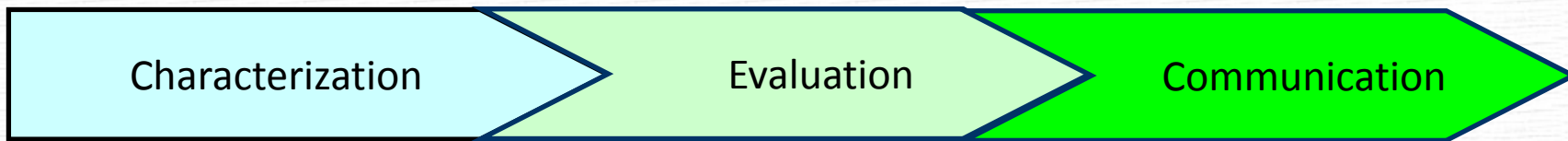
# Disclaimer

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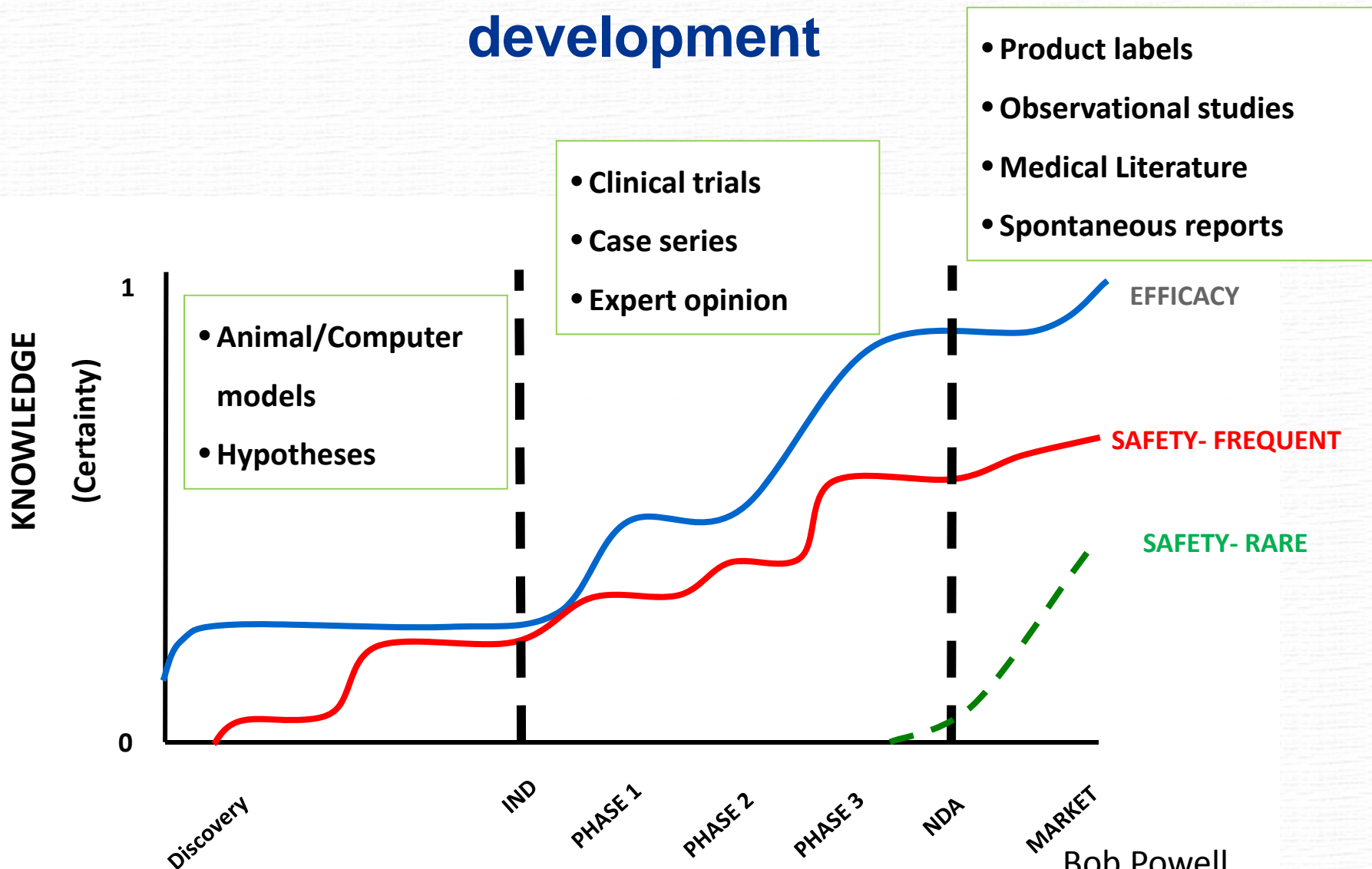
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# Steps within the process of understanding of medicines



# Diversity in data and analyses throughout development



Bob Powell,  
ISPOR 2008



# Post-approval opportunities for statisticians

- Identify and evaluate emerging safety concerns of medical products using observational healthcare databases (***active surveillance***)
- Explore patient subgroups that have differentiated response (***personalized medicine***)
- Study long-term outcomes of alternative treatments in real-world populations (***comparative effectiveness***)
- Integrate disparate data sources to provide composite evaluation that weighs the evidence of the all potential effects of a medicine (***benefit-risk analysis***)



# Outstanding questions for active surveillance

## Governance

What are the keys to a successful public-private partnership?

### Data

Which types of data? administrative claims, electronic health records  
Which sources? healthcare providers, insurers, data aggregators

What are viable data access models:  
- centralized?  
- distributed?

### Performance

### Architecture

### Feasibility

What are appropriate analyses for:  
- hypothesis generating?  
- hypothesis strengthening?

What is the appropriate infrastructure:  
- hardware?  
- software?  
- processes?  
- policies?

How to maintain collaborations and engage research community?

### Methods

### Technology

What are best practices for protecting data?

# Observational Medical Outcomes Partnership

*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.*

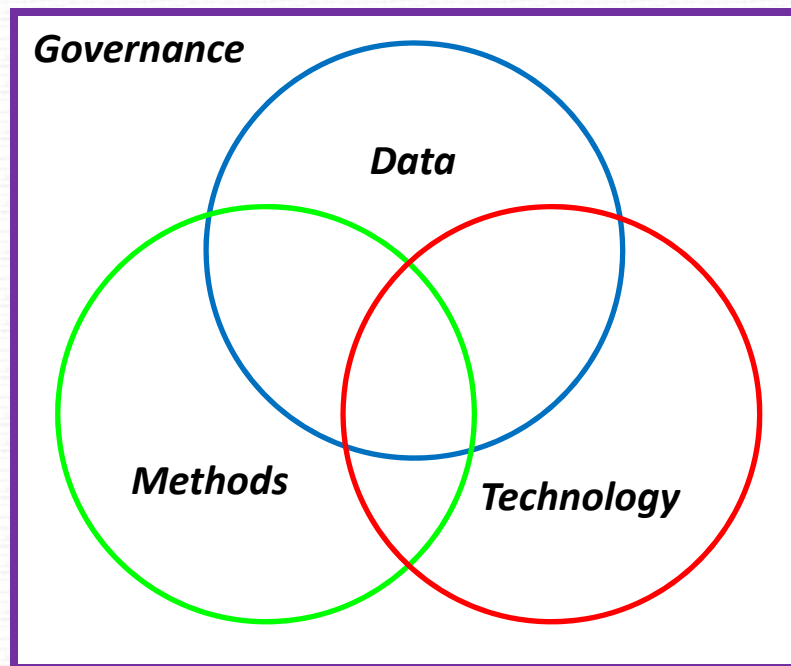
- Assess the appropriate technology and data infrastructure required for systematic monitoring of observational data
- Develop and test the feasibility and performance of the analysis methods
- Evaluate required governance structures

OMOP: <http://omop.fnih.org>



# Breadth and diversity of OMOP research community

*OMOP's research community requires active participation from all key stakeholders, including government, academia, industry, health care organizations, and patient groups.*



*Over 100 collaborating partners*

## **Governance**

- 10 Executive Board members, chaired by FDA and managed by Foundation for NIH
- 21 Advisory Board members
- Led by 6 research investigators and PMO

## **Methods**

- 17 methods collaborators

## **Data**

- 6 distributed research partners
- 5 central databases included in the OMOP Research Lab

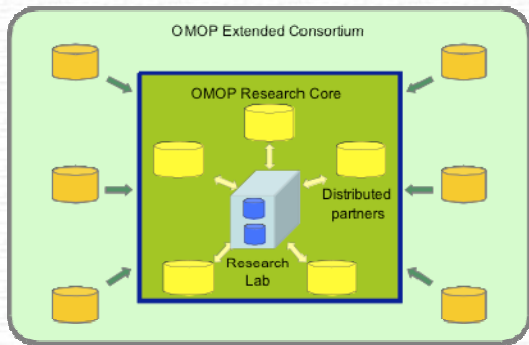
## **Technology**

- 2 data access models, 7 different systems architectures

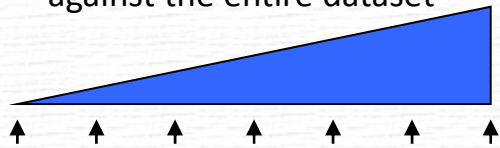




# OMOP research experiment workflow



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



## Health Outcomes of Interest

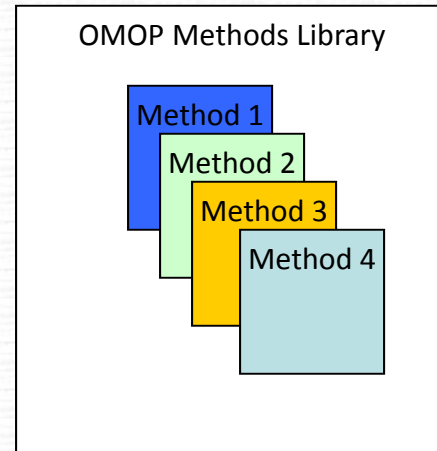
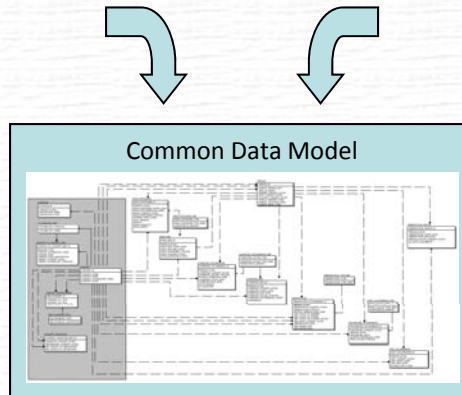
- Angioedema
- Aplastic Anemia
- Acute Liver Injury
- Bleeding
- GI Ulcer Hospitalization
- Hip Fracture
- Hospitalization
- Myocardial Infarction
- Mortality after MI
- Renal Failure

## Drugs

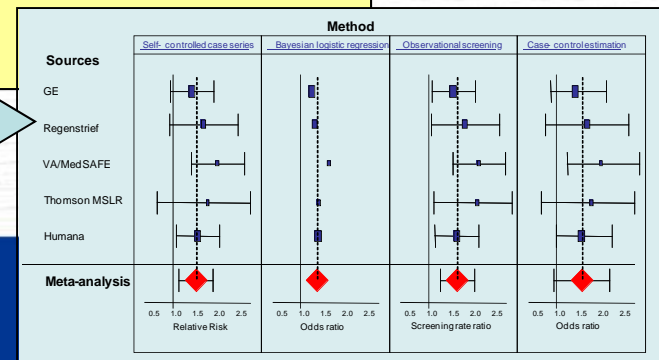
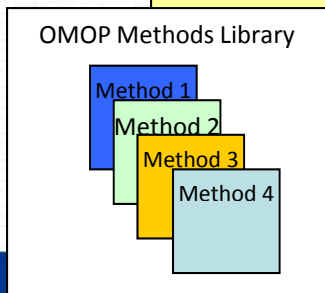
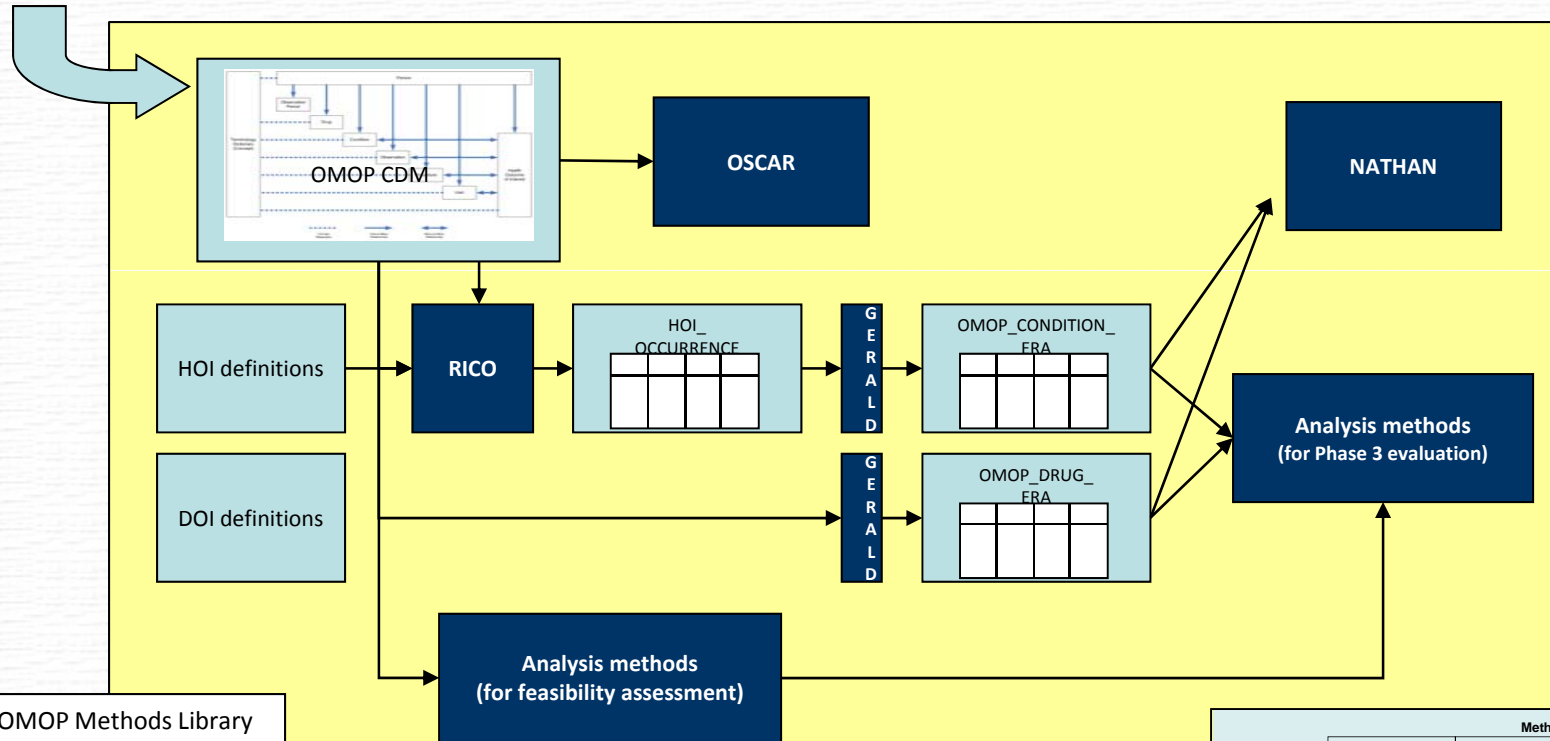
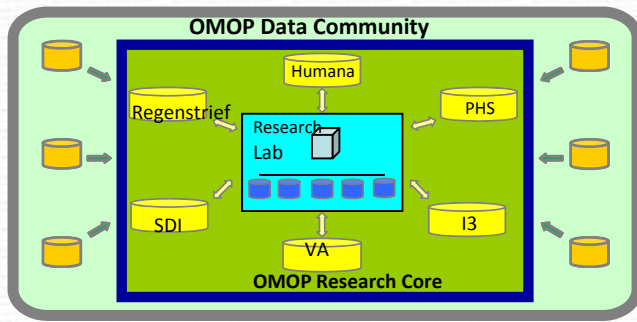
- ACE Inhibitors
- Amphotericin B
- Antibiotics
- Antiepileptics
- Benzodiazepines
- Beta blockers
- Bisphosphonates
- Tricyclic antidepressants
- Typical antipsychotics
- Warfarin

## Non-specified conditions

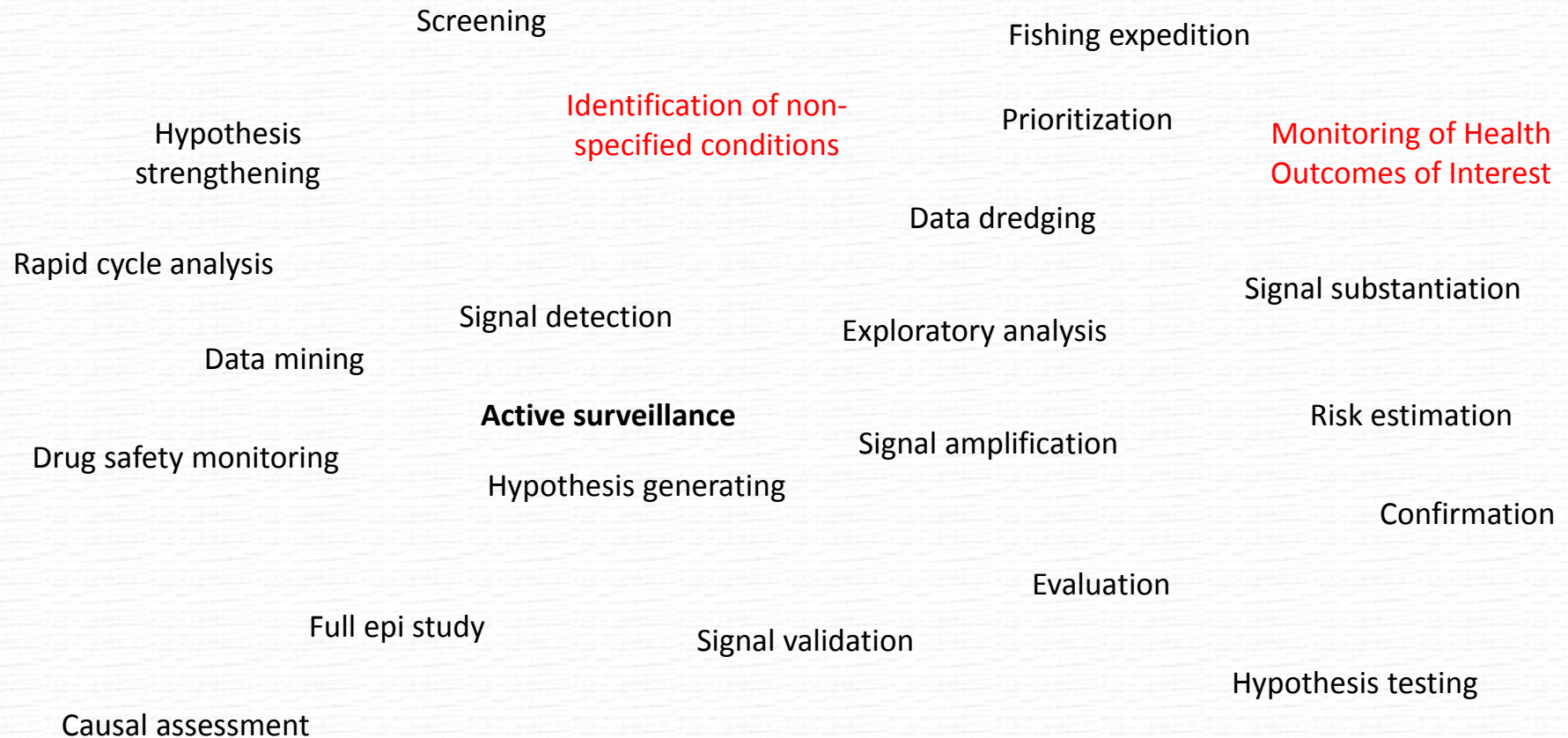
- All outcomes in condition terminology
- 'Labeled events' as reference
- Warning
- Precautions
- Adverse Reactions
- Postmarketing Experience



# OMOP Progression



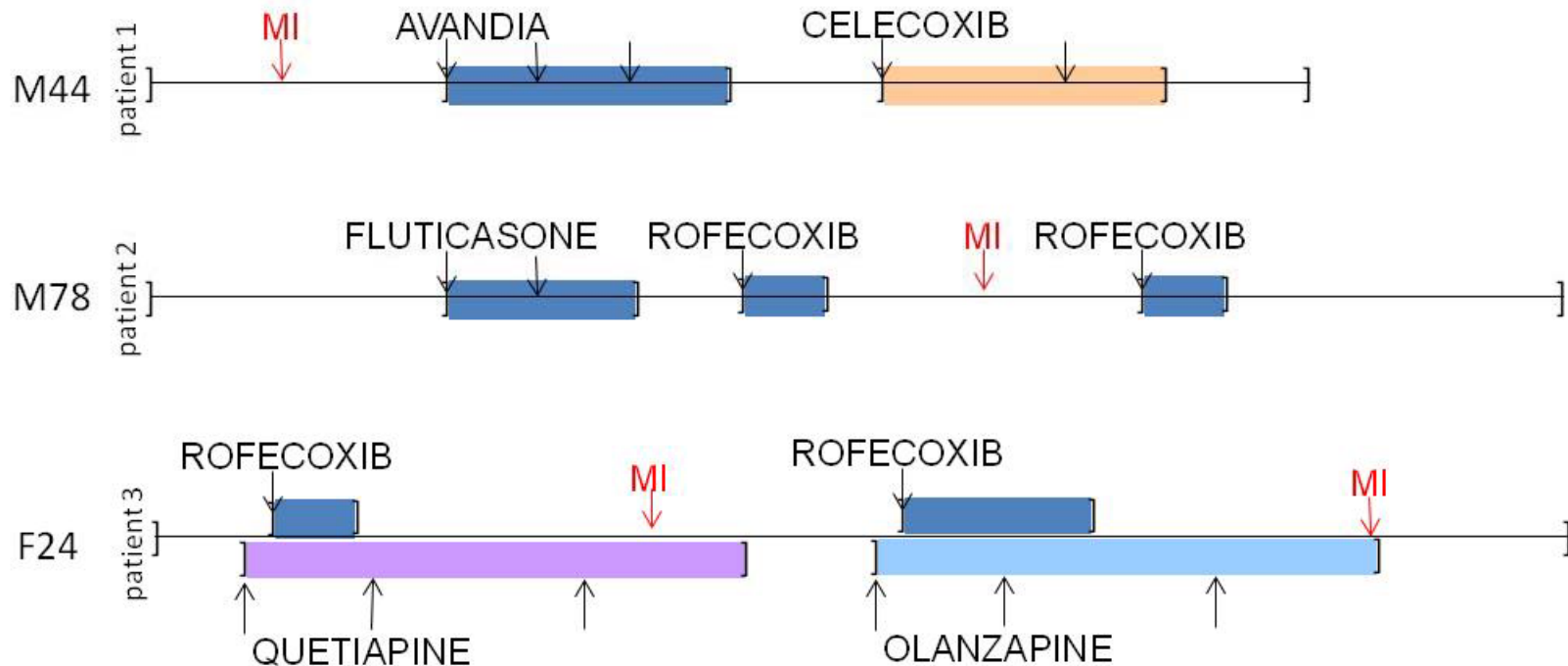
# Characterizing Drug-Outcome Associations



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



# What do the data look like?



***Database contain millions of persons with years of (incomplete) longitudinal data***  
***Computational considerations require efficient use of data in analyses***



# OMOP's Methods Landscape

## Disproportionality Analysis

	<i>AE j = Yes</i>	<i>AE j = No</i>
<b>Drug <i>i</i> = Yes</b>	<i>a=20</i>	<i>b=100</i>
<b>Drug <i>i</i> = No</b>	<i>c=100</i>	<i>d=1080</i>

- Distinct Patients
  - SRS
  - Modified SRS
- X
- MGPS
  - BCPNN
  - PRR
  - Chi
  - etc.
- X
- Stratified

## Sequential Methods

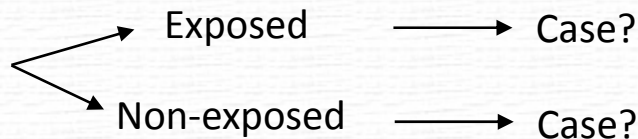
	<i>AE j = Yes</i>	<i>AE j = No</i>
<b>Drug <i>i</i> = Yes</b>	<i>a=20</i>	
<b>Drug <i>i</i> = No</b>		

← *Compare to baseline Poisson*

- Temporal Pattern Discovery (WHO)

- Maximized Sequential Probability Ratio Teat (MaxSPRT)
- Conditional Sequential Sampling Procedure (CSSP)

## Exposure Based Methods



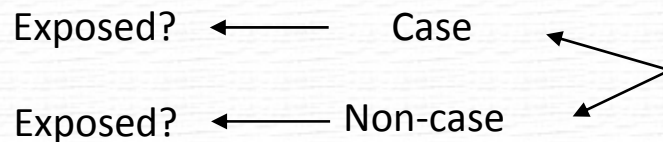
- Observational screening
- HSIU
- Incident User Designs
- High-Dimensional Propensity Scoring
- Local control

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



# OMOP's Methods Landscape

## *Case Based Methods*



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

## *Other Methods*

- Hi-Dimensional logistic regression
- Statistical relational learning

## *Future Methods*

- Multivariate self-controlled case series
- Case-time control
- Lasso propensity scoring
- Online algorithms
- OMOP Cup (60+ submissions)

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# 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. HOI
- 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
  - Multivariate modeling
- Output metric/statistic
  - Estimation vs. testing
  - Relative vs. attributable risk
  - Measure of uncertainty

*Each method has user input parameters that encode these choices*



# OMOP Methods Library

OMOP Methods Library - Download Methods

OMOP is building a library of methods, developed for the OMOP Common Data Model, to address the problems of Monitoring of Health Outcomes of Interest and Identification of Non-Specific Health Outcomes. These methods will be tested across the OMOP Data Community. These methods are available under the OMOP License.

If you would like to contribute to the methods, please contact OMOP by adding a new document to the library.

**Downloads Available**

**Guidelines**

- **OMOP Methods development guidelines**

**Disproportionality Analysis Method - OMOP Research Team**

- **Disproportionality Analysis Method specification** 7Dec 2009
- **Disproportionality Analysis Method Source Code and Examples** 2Feb 2010
- **Disproportionality Analysis Feasibility Test #1** 17Jan 2010
- **Disproportionality Analysis Feasibility Test #2** 17Jan 2010

**Multi-Set Case-Control Estimation - OMOP Research Team**

- **Multi-set case-control Method specification** 7Dec 2009
- **Multi-set case-control Method Source Code and Examples** 2Feb 2010
- **Multi-set case-control Feasibility Test #1** 17Jan 2010
- **Multi-set case-control Feasibility Test #2** 17Jan 2010

**Bayesian Logistic Regression - OMOP Research Team**

- **Bayesian logistic regression specification** 2Feb 2010

- Standardized procedures are being developed to analyze *any* drug and *any* condition
- All programs being made publicly available to promote transparency and consistency in research
- Methods will be evaluated in OMOP research against specific test case drugs and Health Outcomes of Interest



# Summary

- Increased focus on post-approval analyses presents significant opportunities for statisticians
- Post-approval analyses can meaningfully inform health care policy, but appropriate use of data and methods needs to be established
- Further research and application require statisticians to play a more active role in the design, conduct, and evaluation of analyses



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