US FDA Sentinel Initiative

Leveraging Electronic Health Data in a National Strategy for Monitoring Medical Product Safety

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CDER/ FDA
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OLD DOC. WILEY'S
SURE CURE
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ADULTERATIONS
FAKE FOODS
QUACK REMEDIES
FAKER'S
DRUG TRUST
ANTI-WILEY
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EASY TO TAKE
WICKERSHAM
BITTERS
ENDORSED BY
ALL FOOD AND
MEDICINE

Sentinel Initiative - Goals

- Develop a national electronic safety monitoring system
  - Augment, not replace, existing safety monitoring systems
- Leverage multiple sources of electronic data by partnering with data holders
  - Common data model: healthcare systems, insurance companies, etc.
  - 100,000,000 patients by July 1, 2012
- Enhance active post-market monitoring of medical product safety
  - Rapidly, more effectively look at common outcomes (e.g. MI, fractures)
  - Increase population basis, sample size
  - Improved access to subgroups, special populations
- Use validated methods for signal refinement
  - Sequential monitoring
  - One time looks
  - Develop framework to include confounding adjustment
- Near real-time monitoring
  - Using sophisticated modular programs
  - “Library” of tools/resources

Sentinel Initiative - Goals

- Approaches for signal generation will be under development

Sentinel Initiative

Implementation Activities in FDA Center for Drug Evaluation and Research?

- Structure
  - Groups/Committees
  - Identifying and Selecting Candidate Evaluations
- Evaluations
  - New Molecular Entities
  - Drugs on Market > 2 years
  - Effects of FDA Regulatory Actions
  - Drug Utilization
  - Characterization of Populations

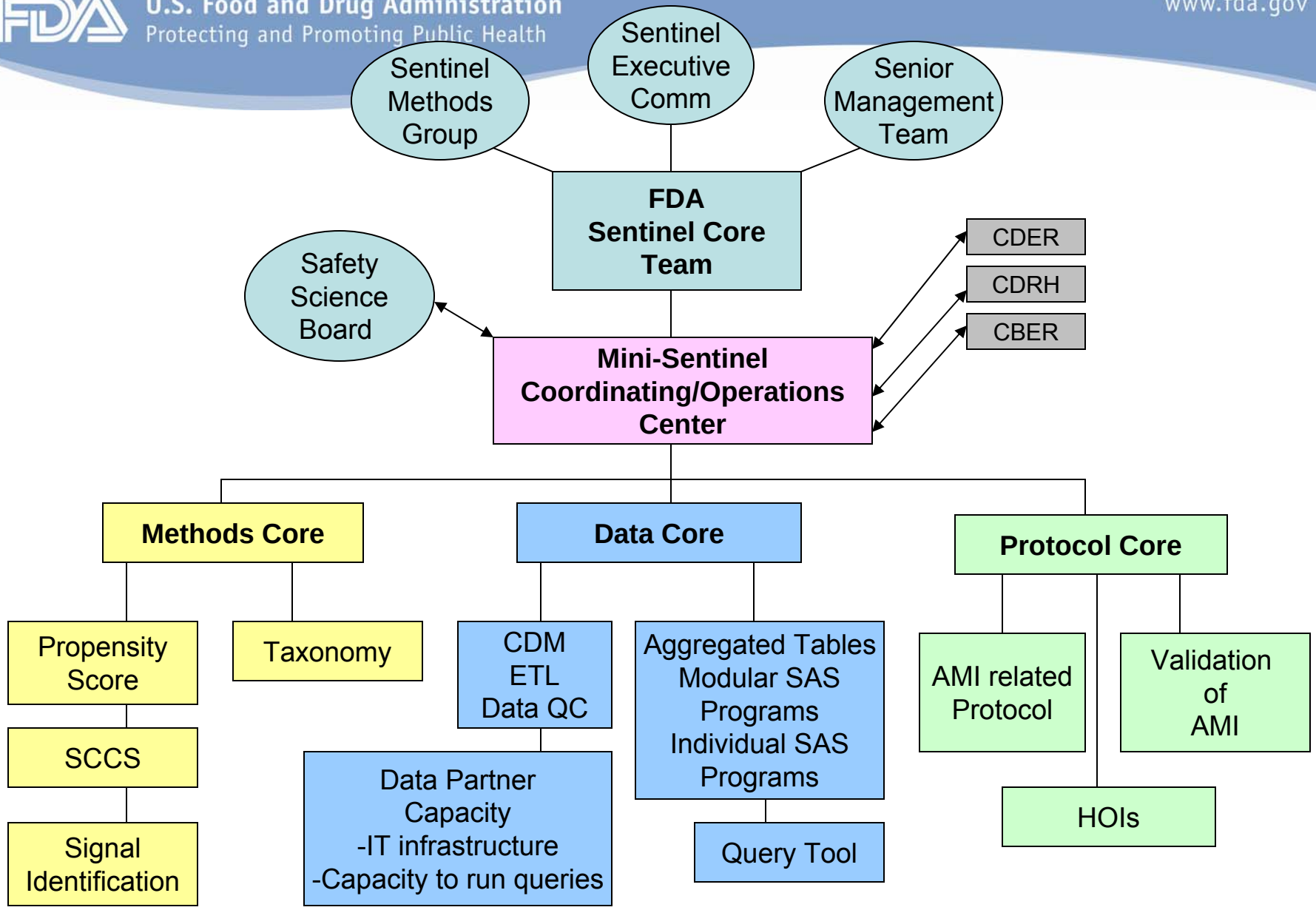
Sentinel Initiative – FDA Organization Agency/Center

Agency Sentinel Core Team – led by CDER Office of Medical Policy

- Leads agency development of tools/resources for medical product active surveillance
  - Janet Woodcock – Senior Executive Sponsor
  - Rachel Behrman – Executive Sponsor
  - Melissa Robb – Project Director
  - Judy Racoosin - Scientific Lead
  - Mitra Rocca - Medical Informatics Lead

CDER Sentinel Related Activities – led by CDER Office of Surveillance and Epidemiology

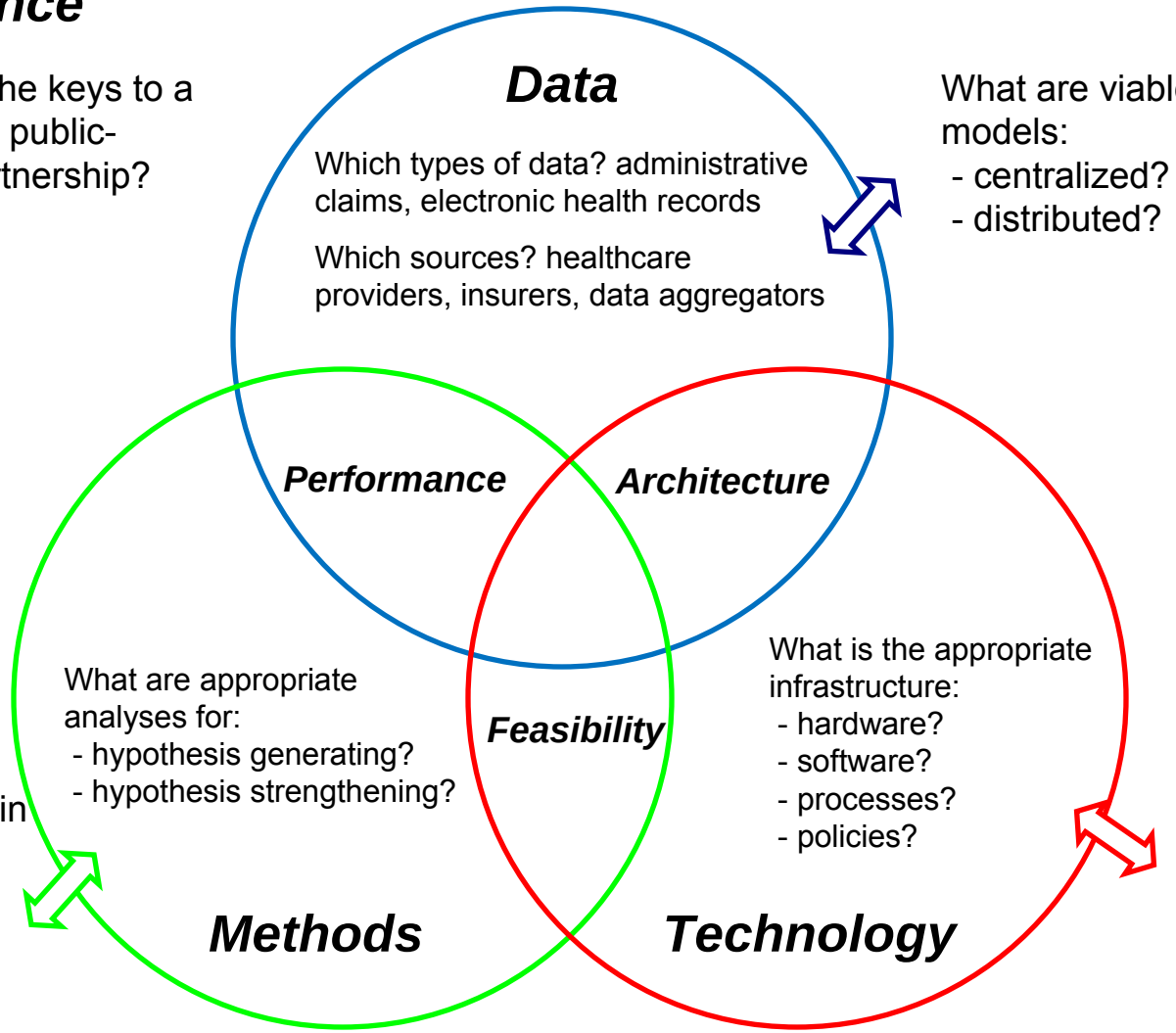
- Leads Center implementation of Sentinel tools/resources and their integration into existing CDER surveillance procedures
  - Gerald Dal Pan - Director, Office of Surveillance and Epidemiology
  - Marsha Reichman - CDER Lead for Implementation of Sentinel Activities


Sentinel Methods Group
Sentinel Executive Comm
Senior Management Team
FDA Sentinel Core Team
Safety Science Board
CDER
CDRH
CBER
Mini-Sentinel Coordinating/Operations Center
Methods Core
Data Core
Protocol Core
Propensity Score
SCCS
Signal Identification
Taxonomy
CDM ETL Data QC
Data Partner Capacity -IT infrastructure -Capacity to run queries
Aggregated Tables Modular SAS Programs Individual SAS Programs
Query Tool
AMI related Protocol
Validation of AMI
HOIs

Outstanding questions for active surveillance

Governance

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



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

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

How to maintain collaborations and engage research community?

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

What are best practices for protecting data?

Sentinel Initiative Components

- OMOP – Observational Medical Outcomes Partnership http://omop.fnih.org
- Federal Partners Collaboration
- Mini-Sentinel Pilot

Observational Medical Outcomes Partnership (OMOP)

Established to inform the appropriate use of observational healthcare databases for active surveillance by:

- **Conducting methodological research** to empirically evaluate the performance of alternative methods on their ability to identify true drug safety issues
- **Developing tools and capabilities** for transforming, characterizing, and analyzing disparate data sources
- **Establishing a shared resource** so that the broader research community can collaboratively advance the science

OMOP- Analysis problems under study

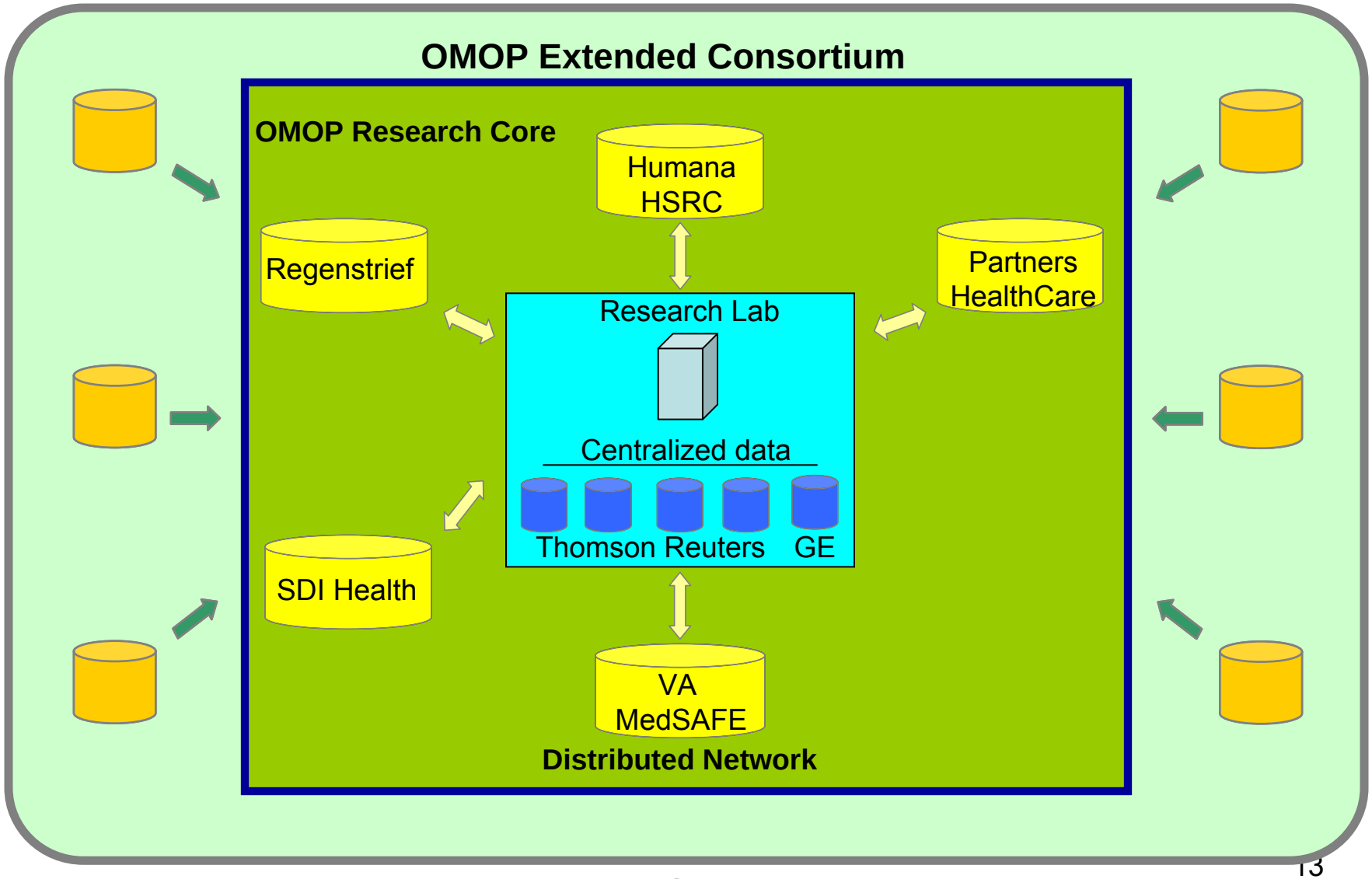
- **Monitoring of Health Outcomes of Interest (HOIs):**
  - Estimate the strength of the association between drug exposure and specific events (e.g. acute liver failure, bleeding, MI)
  - Modest in number so can customize analytic approach
  - Expert assessment of drug-HOI causal associations based on literature search
- **Identification of non-specified associations (NSA):**
  - More exploratory in nature
  - Same goal: estimate the strength of the association between drug exposure and conditions
  - Necessarily more generic analyses (e.g., adjust for age and sex)
  - Causality assessment relies on the product labels
- **Performance against simulated data**
  - Complement ‘real world’ experiments

A public-private partnership between industry, FDA and FNIH.

Partnership Stakeholders

Stakeholder Groups

- **FDA** – Executive Board [chair], Advisory Boards, PI
- **Industry** – Executive and Advisory Boards, two PIs
- **FNIH** – Partnership and Project Management, Research Core Staffing
- **Academic Centers & Healthcare Providers** – Executive and Advisory Boards, three PIs, Distributed Research Partners, Methods Collaborators
- **Database Owners** – Executive Board, Advisory Board, PI
- **Consumer and Patient Advocacy Organizations** – Executive and Advisory Board
- **US Veterans Administration** – Distributed research partner


OMOP Extended Consortium
OMOP Research Core
Humana HSRC
Regenstrief
Partners HealthCare
Research Lab
Centralized data
Thomson Reuters
GE
SDI Health
VA MedSAFE
Distributed Network

Accomplishments

OMOP Key Goal	What We Delivered
Establish OMOP Research Community	• Built the OMOP Research Lab to accommodate common data model and serve as central coordinating center • Established distributed network of Data Partners (6) • Launched Extended Consortium • OMOP Methods Collaborators (17) • Hosted OMOP Cup with 60+ participants • Created OMOP Website with 1000+ registered users • 2009 Symposium with 300+ attendees • Presented at over 15 conferences / meetings
Establish a consistent framework to use across disparate observational data sources	• Common Data Model (CDM) • Standardized terminology specifications • CDM reference tables that contain the standardized terminologies and mappings from source vocabularies • ETL specifications for all data partners • GE Centricity & Thomson ETL source code

Accomplishments (cont)

OMOP Key Goal	What We Delivered
Develop and test analysis methods within the OMOP Research Lab and other data environments	• Overview of methods (methods points-to-consider and inventory matrix) • 14 methods specifications & source code • 12 methods under evaluation • OMOP Cup Methods Competition • Observational Medical Dataset Simulator (OSIM I) - specification, source code, and datasets
Establish standard data characterization & facilitate comparisons across databases	• Observational Source Characteristics Analysis Report (OSCAR) Specification and Source Code • Natural History Analysis (NATHAN) Specification and Source Code • Generalized Review of OSCAR Unified Checking (GROUCH) for data quality and validation analysis

Accomplishments (cont)

OMOP Key Goal	What We Delivered
Implement Health Outcome of Interest definitions	• HOI definition process (literature review strategy & evidence table) • HOI process outputs for 10 HOIs • 35 definitions for 10 HOIs • Regularized Identification of Cohorts (RICO)- program to implement HOI definitions within CDM
Public-private partnership governance model with engagement on Executive Board and Advisory Boards	• 12 Executive Board members, chaired by FDA and managed by Foundation for NIH • 21 Advisory Board members • 6 research investigators and FNIH Program Management Office

Accomplishments (cont)

OMOP Key Goal	What We Delivered

Evaluate performance of methods and data in identifying drug safety issues	• 12 analysis methods released and executed across the OMOP data community
	  • Disproportionality Analysis
	  • Univariate Self-Controlled Case Series
	  • Observational Screening
	  • Multi-Set Case Control Estimation
	  • Bayesian Logistic Regression
	  • Case Control Surveillance
	  • IC Temporal Pattern Discovery
	  • Case-Crossover
	  • HSIU Population-Based Method
	  • Maximized Sequential Probability Ratio Test
	  • High-Dimensional Propensity Score
	  • Conditional Sequential Sampling Procedure
	• OMOP Research team conducting evaluation of data characteristics and methods performance metric scores
	• Implementing state-of-the-art visualization and summarization tools (e.g., Spotfire)

Accomplishments (cont)

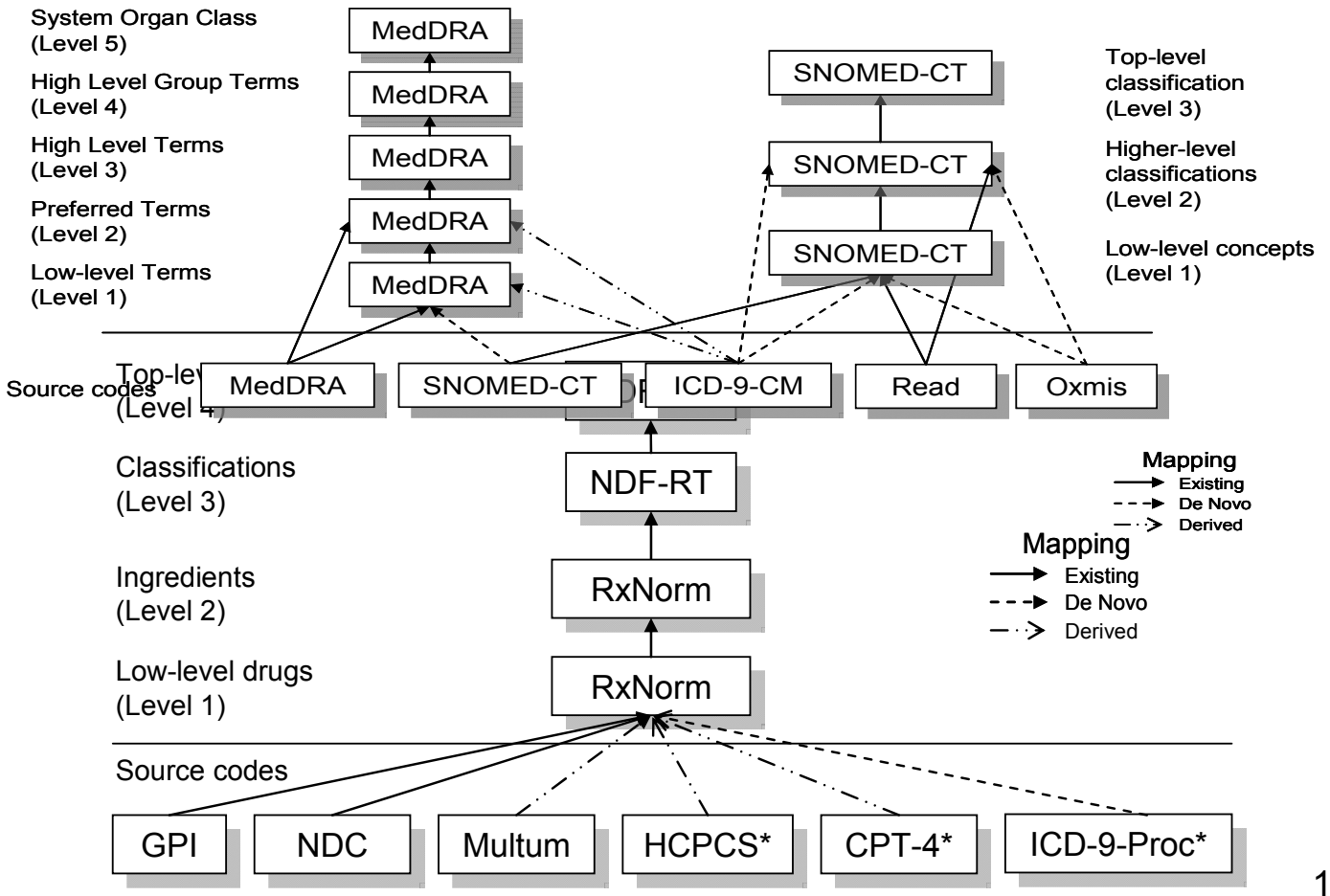
Research Laboratory Details

- Accommodates research databases, methods development and testing, and collaboration and coordination activities
- 2 high-end compute servers and 1 Oracle server with a total of 37 Terabytes of observational or interim data
- Execution of the experimental test of 12 computationally intensive methods with dozens of parameter sets across 5 central databases
- Secure communications and controlled information exchange infrastructure with distributed partners
- Foundation for a secure cloud-based Research Lab for additional computational capacity with a total of up to 250 processing units and significant storage capacity
- Strong access management and protection of sensitive data
- Implementation of an experimental graphics processing unit (GPU) processing platform

Standardized Terminologies To Accommodate Disparate Observational Data Sources

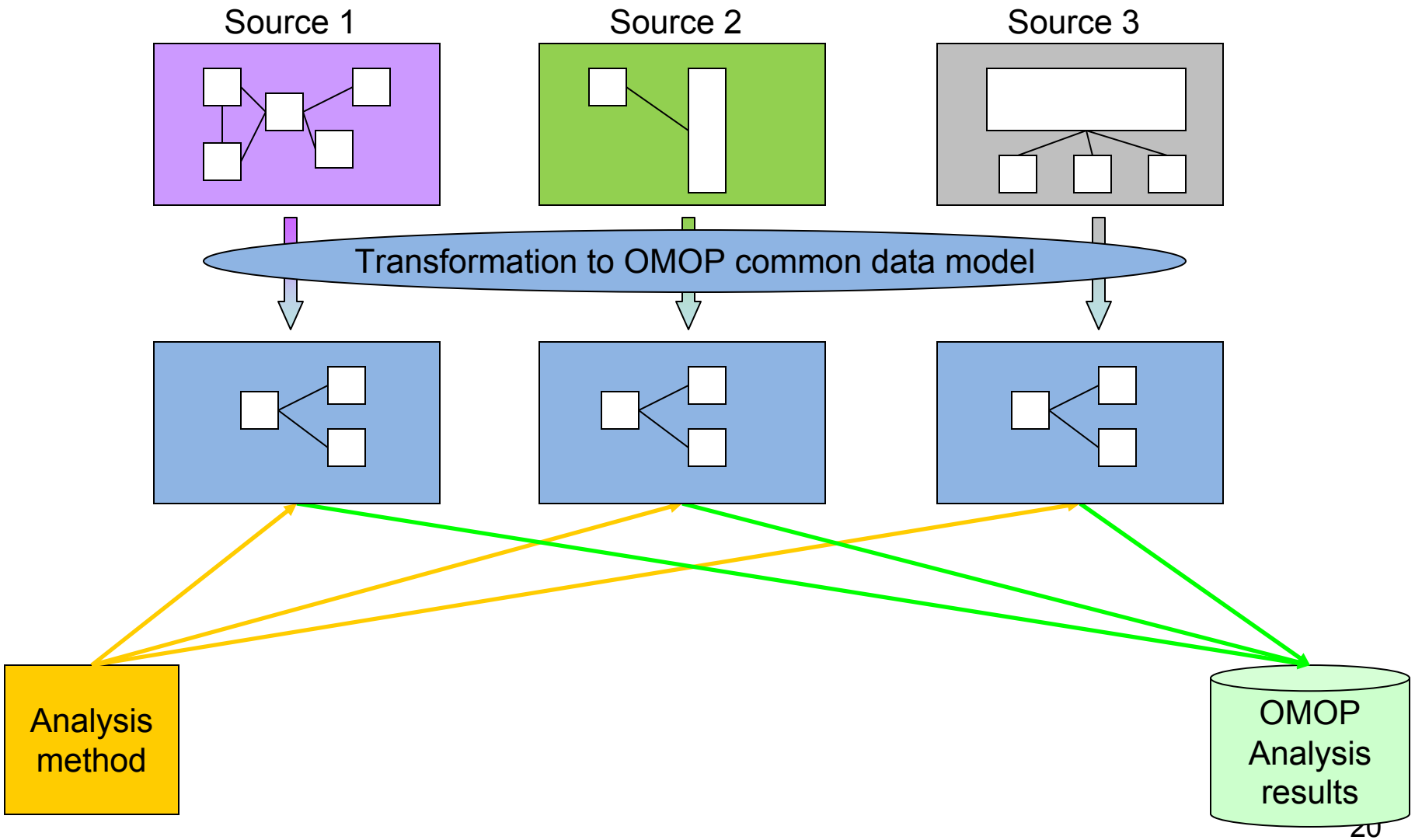
Standardizing conditions:

Standardizing drugs:



http://omop.fnih.org/Vocabularies

OMOP Analysis Process

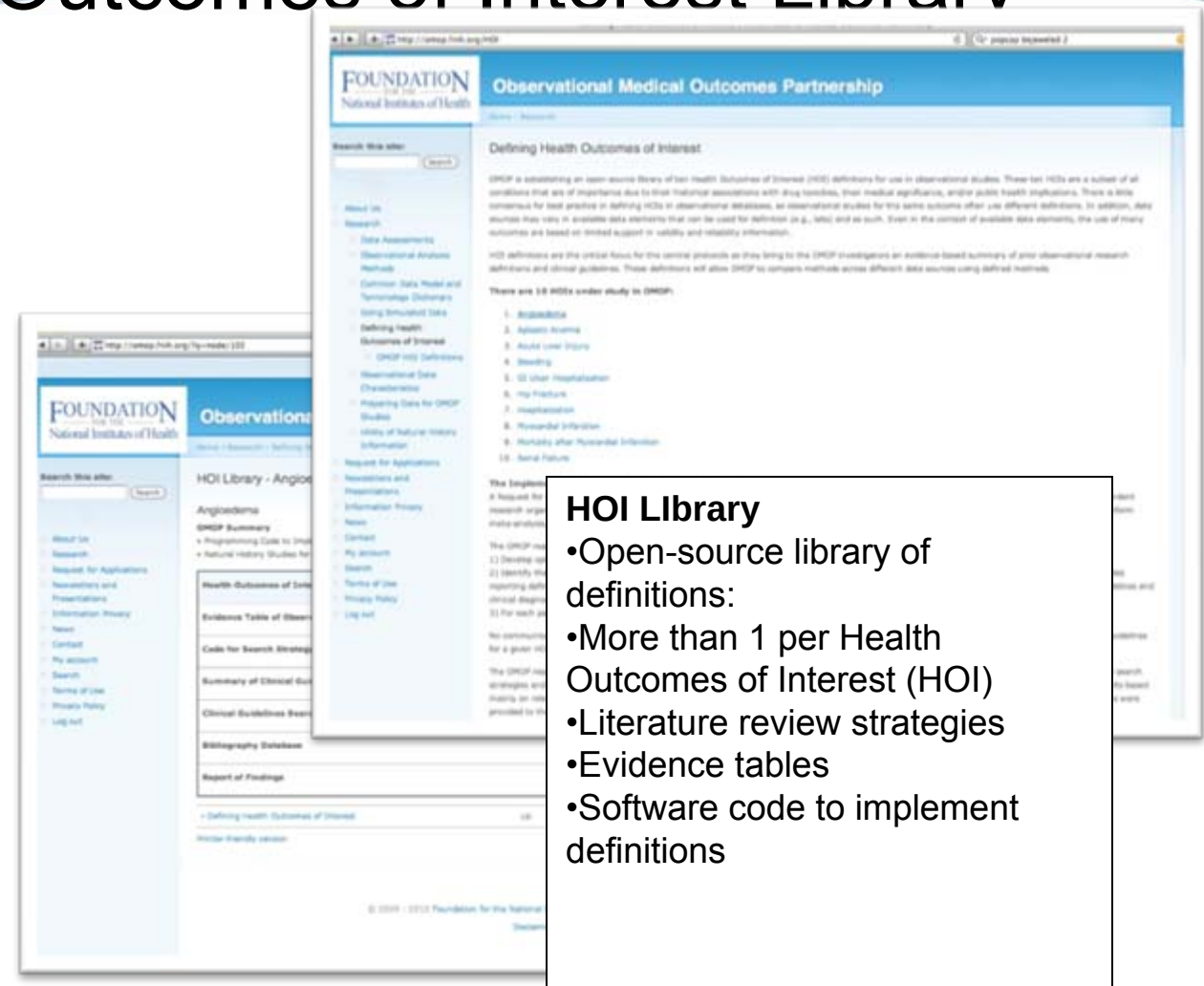


Health Outcomes of Interest Library

Current Health Outcomes of Interest Under Study

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

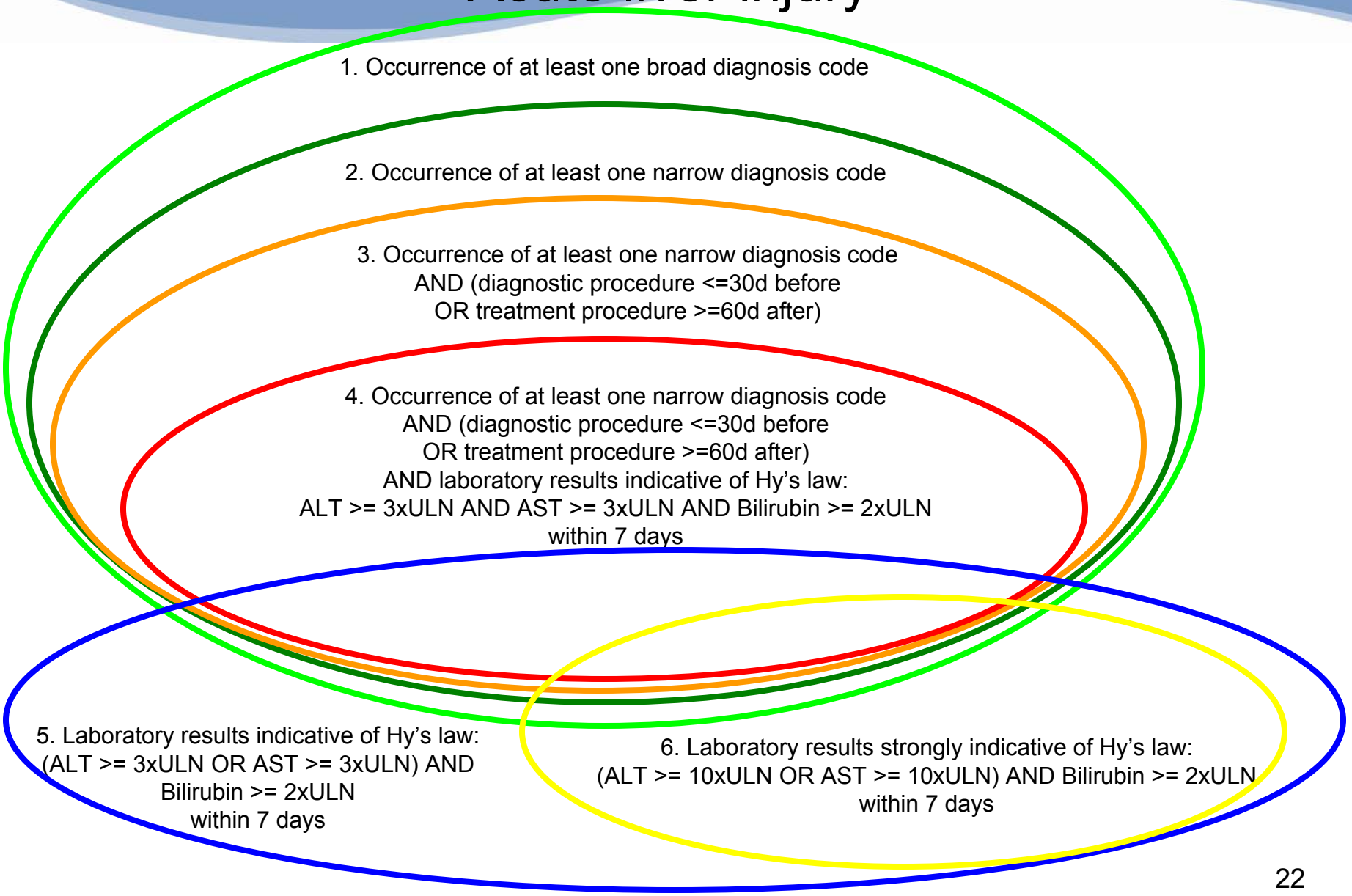
http://omop.fnih.org/HOIDefinitions



HOI LIbrary

- Open-source library of definitions:
- More than 1 per Health Outcomes of Interest (HOI)
- Literature review strategies
- Evidence tables
- Software code to implement definitions

Acute liver injury



Federal Partners Collaboration

- Intra-agency agreement participants include FDA, CMS, VA, DoD
- Address medical product safety surveillance using a distributed data model where each partner has a unique database structure
- FDA proposes medical product – AE pairs to evaluate
  - Develop a shared protocol
- Small distributed system
  - Each partner has unique data infrastructure
  - No common data model being utilized
  - Decentralized analytic approach

Federal Partners Collaboration

- Dronedarone / Heart Failure
  - Amiodarone (comparator)
  - Analysis and report nearing completion
- Dronedarone / Liver failure-severe liver injury
  - Developing protocol
- Uptake of Dabigatran
- Antiviral drugs / neuropsychiatric AE

Federal Partners Collaboration

- Challenges
  - Develop approaches to make the most of claims data to enhance outcome validation given limited access to source data
  - Interpretation of evaluation findings given diverse FPC populations and differences in clinical guideline and practice
  - Limits to analysis approaches with rare outcomes

Mini-Sentinel Yr 1 Activities

- Established Operations/Coordinating Center
- Designed common data model (MSCDM)
- Implemented MSCDM (Humana, Healthcore, HMORN, Kaiser)
- Data Quality Activities / Data Partner IT infrastructure

Mini-Sentinel Pilot Year 1 Activities

- Generated 4 modular SAS programs
- Taxonomy Working Group; Specific method groups
- Anti-diabetics / AMI protocol developed
- Researched validation efforts for 20 Health Outcomes of Interest (HOIs)
- Validation of AMI using medical records

Mini-Sentinel
Modular SAS Programs

Year 1: Currently Available for Use:

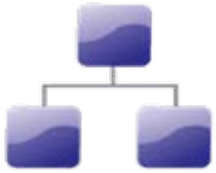
1. Drug Use and Exposure
2. Drug Use among Members with a Specific Diagnosis
3. Frequency of Select Incident Events/Outcomes among Members Exposed to Drugs with or without a Given Pre-Existing Condition
4. Concomitant Drug Use among Members with or without a Given Pre-Existing Condition

Year 2: Likely to be Developed this Year:

1. Background Rates
2. Drug and/or Procedure Use after a Diagnosis
3. Diagnoses/Drugs/Procedures before or after an Event / Patient Characterization

Common Data Model Version 1.1
Domain: Administrative and Claims Data

Enrollment



Demographics

Outpatient Pharmacy Dispensing

Utilization (Encounters, Diagnosis, Procedures

Mortality (Death, Cause of Death)

29

CDM Tables & Data Elements

Enrollment
PatID
Enc_Start
Enc_End
Med_Cov
Drug_Cov

Demographic
PatID
Birth_Date
Sex
Hispanic
Race

Dispensing
PatID
RxDate
NDC
RxSup
RxAmt

Encounter
PatID
EncounterID
Adate
Ddate
Provider
Facility_Location
EncType
Facility_Code
Discharge_Disposition
Discharge_Status
DRG
DRG_Type
Admitting_Source

Diagnosis
PatID
EncounterID
Adate
Provider
EncType
Dx
Dx_Codetype
OrigDX
PDX

Procedure
PatID
EncounterID
Adate
Provider
EncType
PX
PX_Codetype
OrigPX

Death
PatID
DeathDt
DtImpute
Source
Confidence

Cause of Death
patID
COD
CodeType
CauseType
Source
Confidence

Mini-Sentinel Year 2 Activities

Base/Core Contract includes:

- Continuation of Year 1 activities
- Expansion of CDM to include additional data types
- Quarterly updating of data in CDM
- Generation of additional modular SAS programs
- Executing analyses using modular programs and summary tables

Task Orders include:

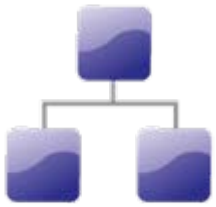
- CDER task order
- CBER task order (Vaccine Safety/Prism)
- Foundational Elements (HOI validation/adjudication, statistical methods development, linking datasets)

Mini-Sentinel Year 2 Activities
CDER Task Order

- New molecular entities (NMEs) on the market <2yrs
  - Sequential analysis
- Drugs on the market >2yrs
  - Examinations at a particular point in time
- Evaluation of Effects of FDA's Regulatory Actions
  - Compare MS results with results from national drug utilization databases
  - Possibility of looking at outcomes
- Drug Utilization
  - Drug usage analyses – patterns of use, persistence, concomitant drug usage, etc.
  - Potential capacity to retrieve medical records through MS

Common Data Model
Enhancement Year 2: Clinical Data

Labs



Vital Signs

Clinical Data: Selected Lab Tests and Vital Signs

LabTests
Alkaline Phosphatase (ALP)
Alanine Aminotransferase (SGPT)
Total Bilirubin
Glucose
Glycosylated hemoglobin (HbA1c)
Creatinine
Hemoglobin
International Normalized Ratio (INR)
Fibrin d-dimer
Lipase
Absolute Neutrophil count (ANC)

Lab DD
MRN
Test_Type
LOINC
Stat
Pt_Loc
Result_Loc
LOCAL_CD
PX
Codetype
Order_ID
Order_dt
Lab_dt
Lab_tm
Result_dt
Result_tm
Result_C
Result_unit
Normal_low_C
Modifier_low
Normal_high_C
Modifier_high
Order_dept
Facility_code

Vital Signs
Weight
Height
Systolic Blood Pressure
Diastolic Blood Pressure
Smoking Status

Mini-Sentinel Year 2 Activities

Drugs on Market > 2yrs

Safety Evaluations

- ACEI/ARBs/Aliskiren/β-blockers and Angioedema
  - Protocol development/refinement underway
- Additional evaluation(s)

Modular SAS Programs

- Stalevo/Entacapones and Myocardial Infarction
  - Also studies in CMS and VA

Mini-Sentinel Year 2 Activities

Characterize Populations

Population 65 years and older

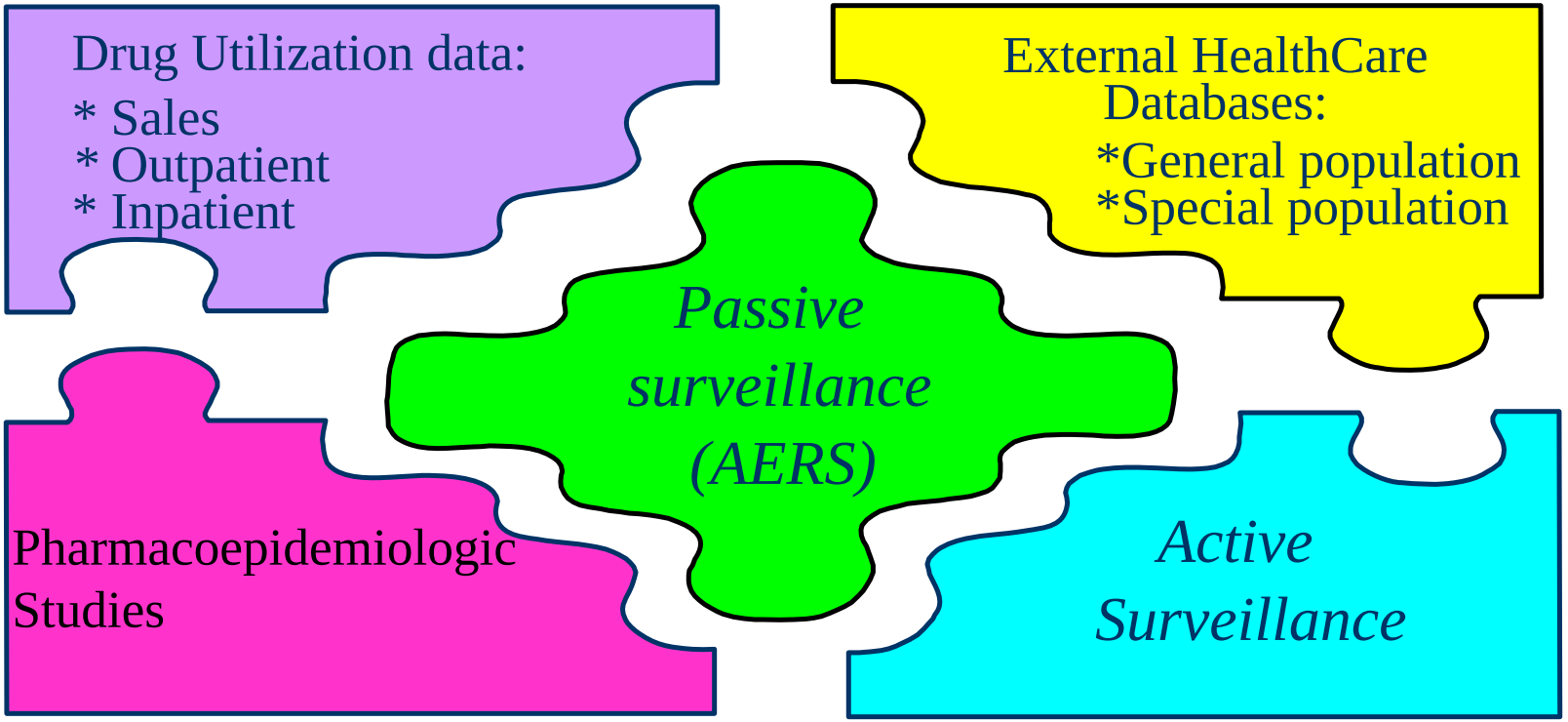
- Mini-Sentinel and CMS
- Start:
  - 100 most frequent diagnoses
  - 100 most frequent drugs being dispensed
- Consider adding:
  - Number of diagnoses per person
  - Number of unique drugs being dispensed per person

Mini-Sentinel Year 2 Activities

Open Challenges:

- Balancing priorities from post-market tracking of safety issues with capabilities/capacity of Mini-Sentinel data (e.g. population structures, formularies, available data fields, etc)
- Implementing results from methods development; taking methods from exploratory towards “off the shelf” tools
- Rapidly identify results which merit more detailed studies or contribute to regulatory actions (e.g. when to stop sequential analyses, what boundary criteria determine further action is needed or not needed)
- How to combine active and passive surveillance data with detailed epidemiologic studies to reach regulatory decisions rapidly

Components of a Comprehensive Post-marketing Surveillance Program at CDER



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- Observational Medical Outcomes Partnership