Drug Safety Surveillance Initiatives

Relevance to PML

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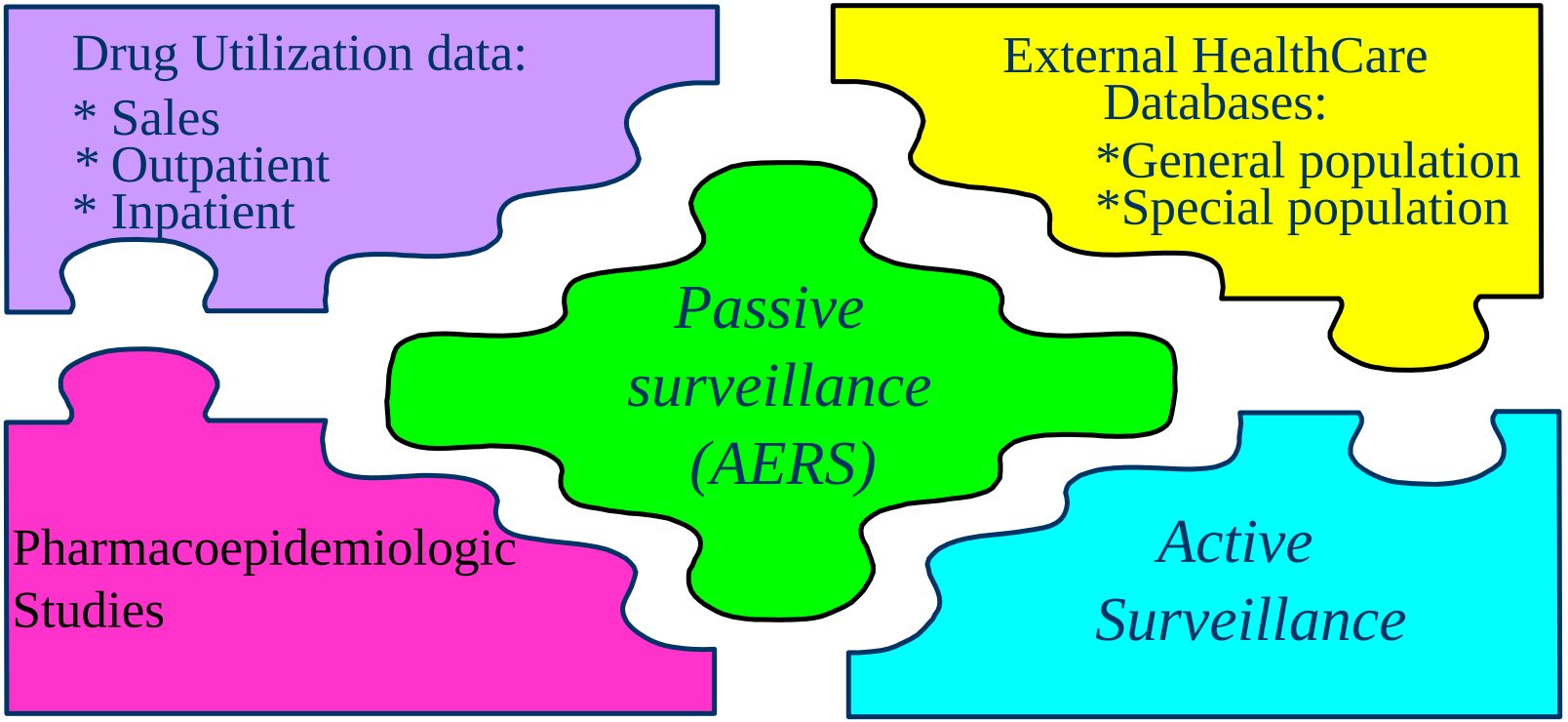
Goals of Drug Safety Surveillance

- To identify previously unknown drug-related adverse events
- To learn more about know drug-related adverse events
- To learn more about how drugs are used in ways that may not promote safe use
- The method you use depends on what you are tyring to learn

Components of a Comprehensive Post-marketing Surveillance Program at CDER



Passive Surveillance

- Individual case reports
  - Sent to regulator or to company
  - Company sends to regulator
- Based on clinical observations at the point of care
- Concise, accurate clinical details are critical
- Case reports, as a whole, often lack important clinical details

Qualities of a Good Case Report

- What makes a good case report?
  - Description of the event
  - Suspected product(s) and concomitant treatment details
  - Patient characteristics, medical history, treatment history
  - Documentation of the diagnosis
  - Clinical course and outcomes
  - Treatment and lab values at baseline, during therapy, and after therapy
  - Response to dechallenge and rechallenge
  - Any other relevant information
- For PML
  - Not sufficient to say simply that the patient “developed PML”

* *Source:* US FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. March 2005

Drug Utilization Studies

- Quantify drug use in a population
- Can get population-based estimates
- Can quantify prevalent users and incident users
- Can often stratify by age and gender
- Best for outpatient prescriptions
- Difficult to obtain data for over-the-counter medicines and medicines administered in a clinic or physician's office
  - An issue for many drugs implicated in PML

Pharmacoepidemioliogic Studies

- A broad term
  - Case-control studies
  - Cohort studies
  - Registries
- Case-control and cohort studies
  - Hypothesis driven
  - Not useful for extremely rare outcomes
- Registries
  - Can be treatment-based (eg, persons taking drug X)
  - Can be disease-based (ie, persons with cancer)
  - Good for rare exposures and rare diseases

Registries – An Example From Another Field

- Drug Liver Injury Network (DILIN)

Challenges in Studying DILI

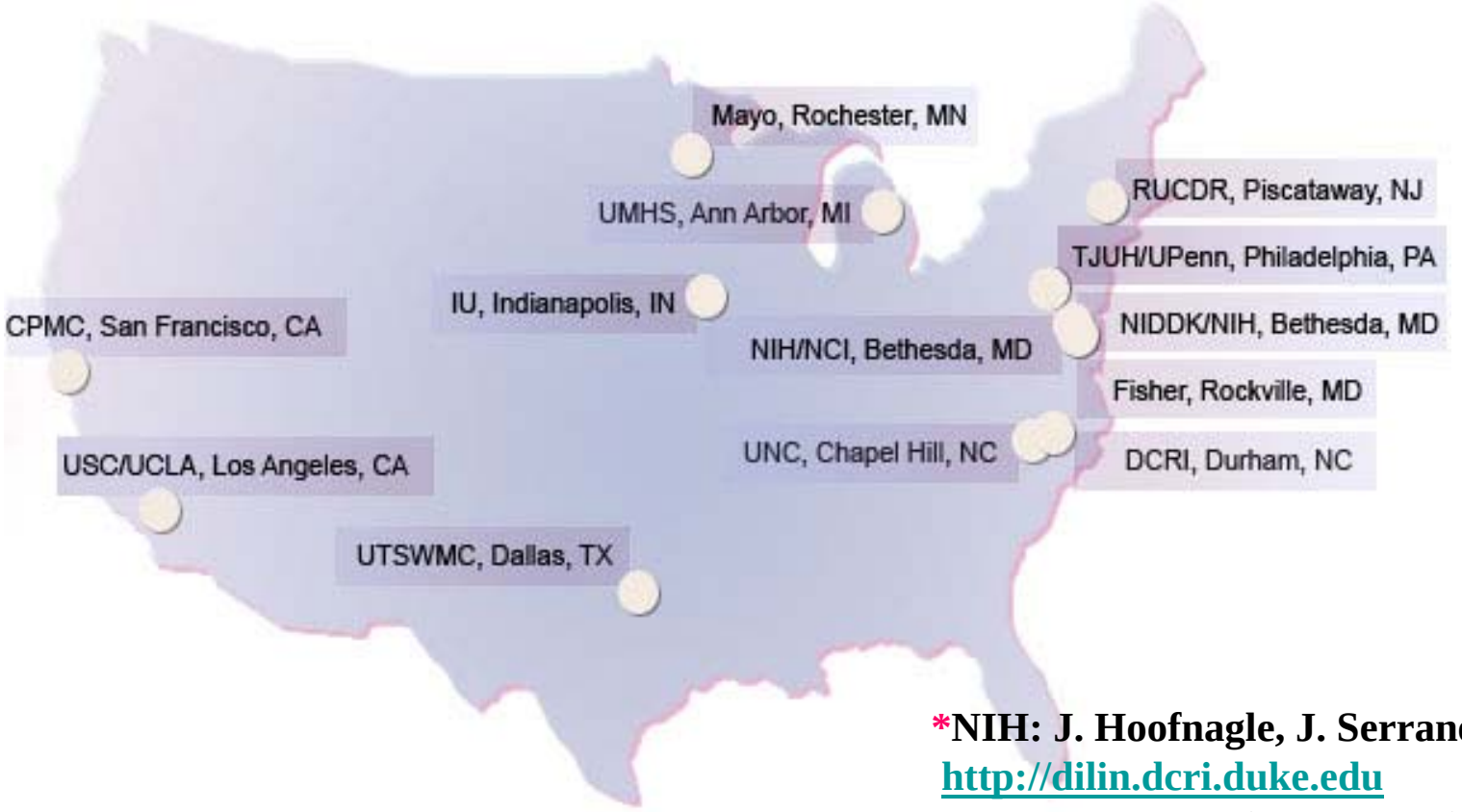
- DILI is a rare disease; 10 –15 per 100,000 pt-years
- < 1% of acute liver injury
- By drug, only 1 per 10^4 to 10^6 prescriptions
- Clinical diagnosis must exclude competing causes
- Variable latency, lab profile, & histology
- Polypharmacy is common
- Variable quantity and quality of prior reports
- No objective / confirmatory lab test

Approaches to Studying Post-approval DILI

- Reports to regulatory agencies
  - Underreporting ? Data quality/ confirmation
- Retrospective approaches
  - Medical records search ? Evaluation ? History ?Competing causes
- Population based studies
- Prospective multicenter registries
  - Interview, careful phenotyping
  - Expensive, labor intensive ? Referral bias

US DILI Network* (DILIN)

*NIDDK U-O1 Cooperative Agreement**



***NIH: J. Hoofnagle, J. Serrano**
http://dilin.dcri.duke.edu
FDA Reps: M. Avigan, J. Senior

DILIN Recruitment Methods

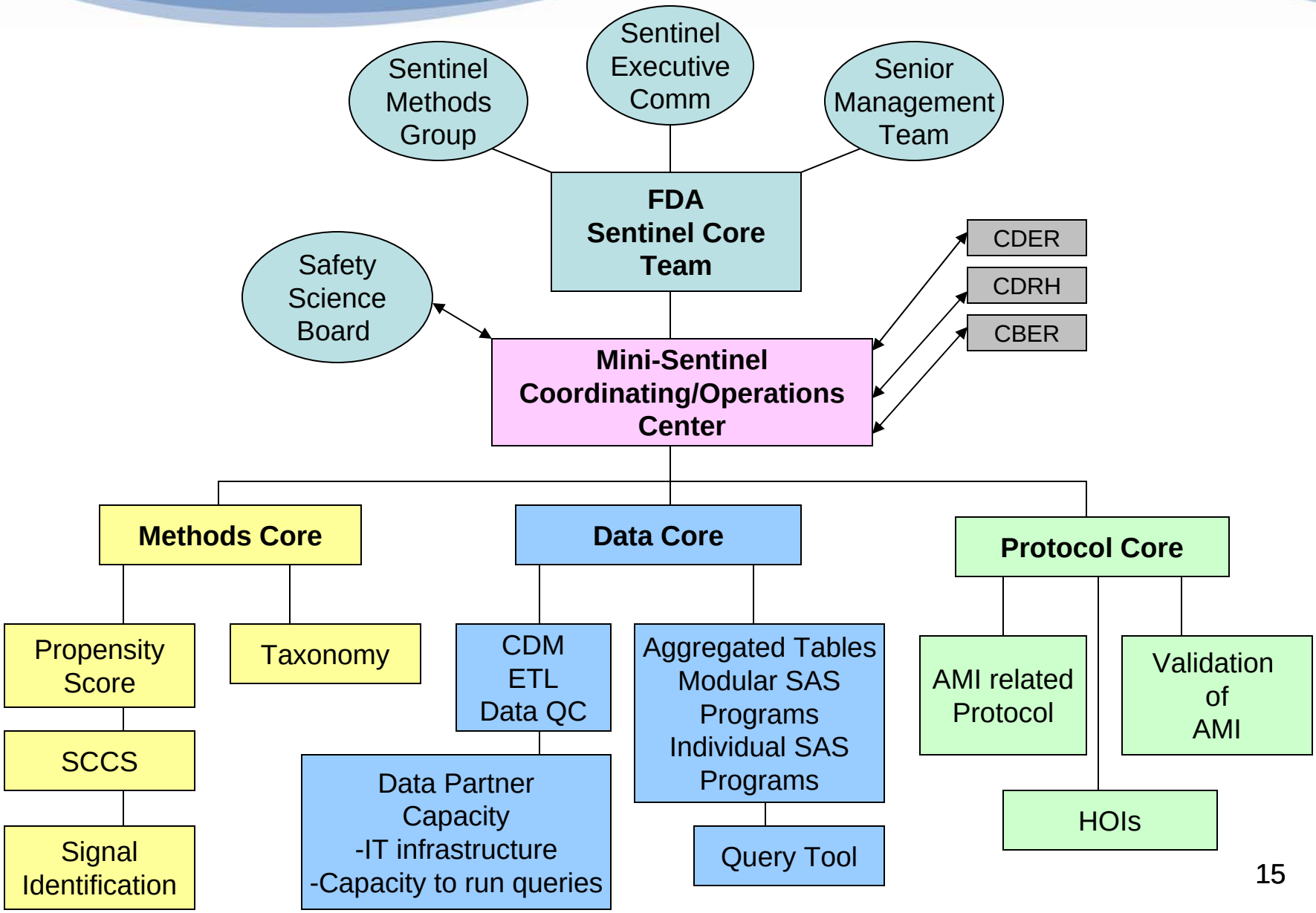
- Local site PIs
  - Conferences, e-mails, brochures
  - Outreach to MDs, subspecialists, dinner meetings
  - Annual newsletters
- Network-wide
  - Journal ads, website
  - DILI symposia at meetings
  - Publications
  - Other research networks
  - FDA, CDC

Active Surveillance

- Actively looking
- Can be:
  - Disease-based
  - Drug-based
  - Setting-based
- Can use large databases for surveillance

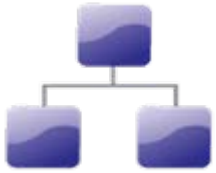
Sentinel Initiative

- FDA initiative
- Use large databases from multiple sources
- Cover a large number of lives
  - 25 million in 2010
  - 100 million in 2012
- Two components:
  - Mini Sentinel
  - Federal Partners Collaboration


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
Taxonomy
CDM ETL Data QC
Aggregated Tables Modular SAS Programs Individual SAS Programs
AMI related Protocol
Validation of AMI
SCCS
Signal Identification
Data Partner Capacity -IT infrastructure -Capacity to run queries
Query Tool
HOIs

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)

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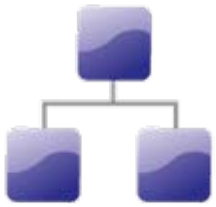
Common Data Model
Enhancement Year 2: Clinical Data

Labs



Vital Signs

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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

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

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

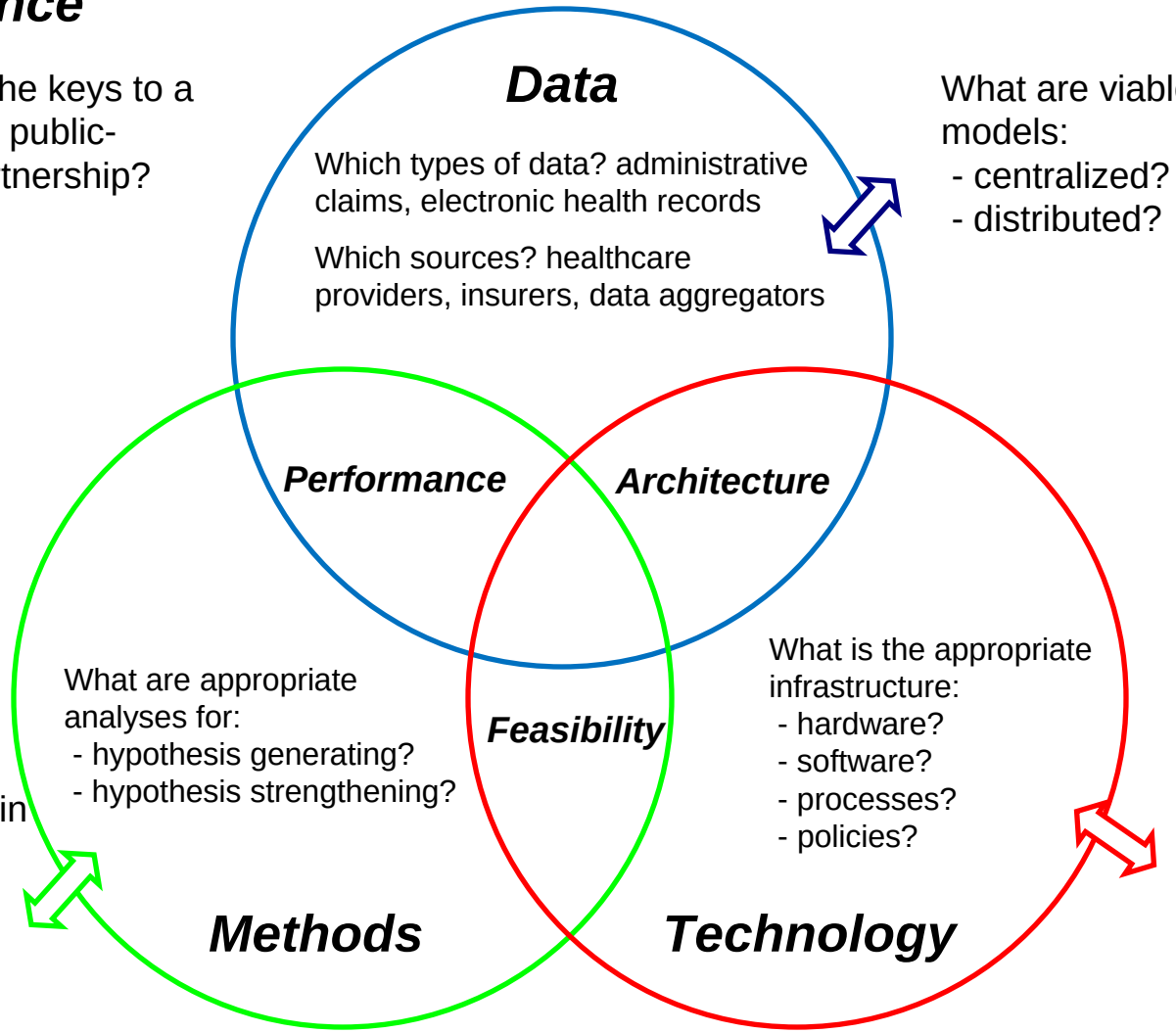
OMOP- Analysis problems under study

- **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

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?

Thank you

Questions?