Meta Analysis for Active Surveillance – Applied Points to Consider

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Statistical and Epidemiological Issues in Active Medical Product Surveillance
The Brookings Institution • Washington, DC
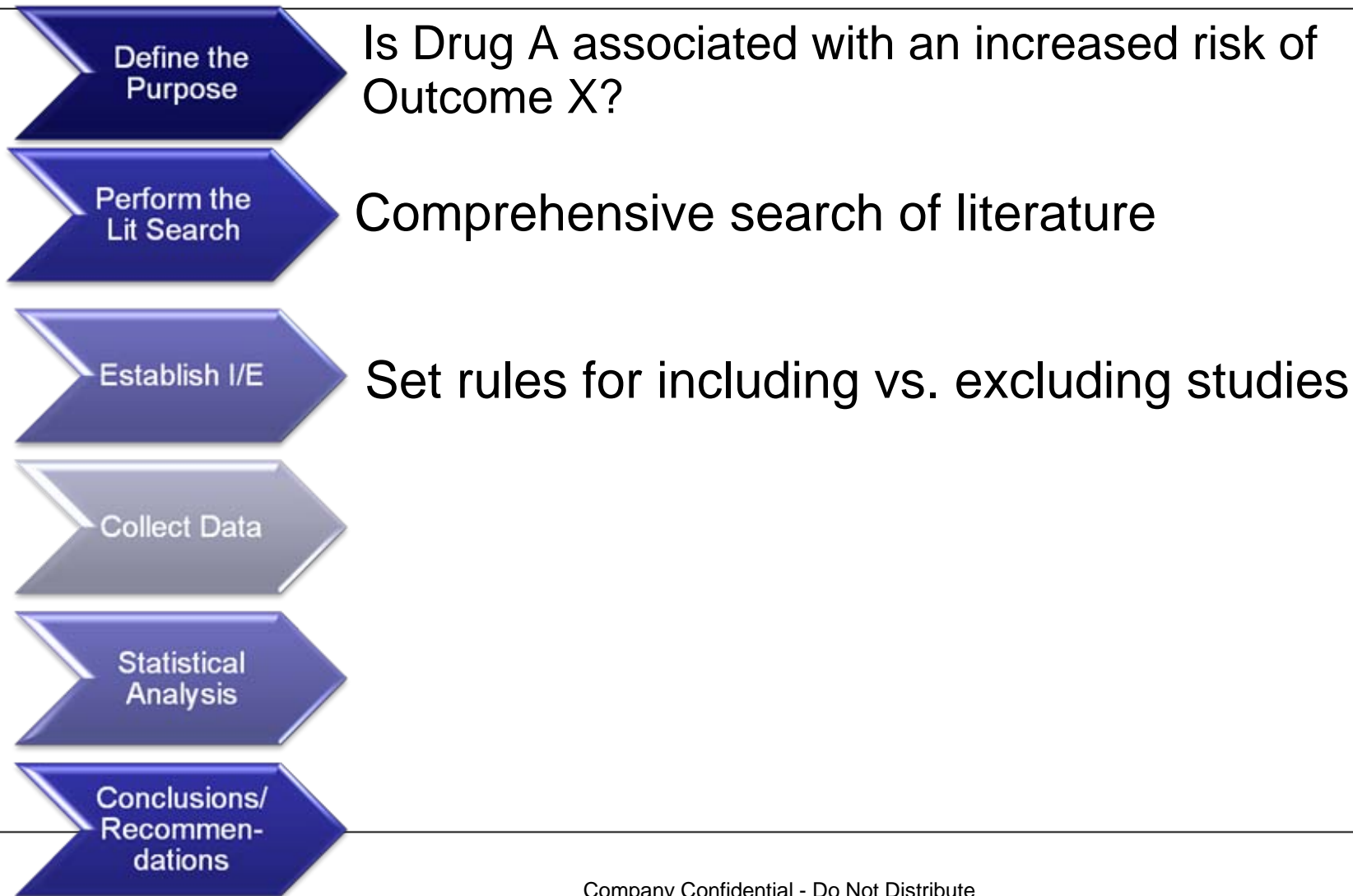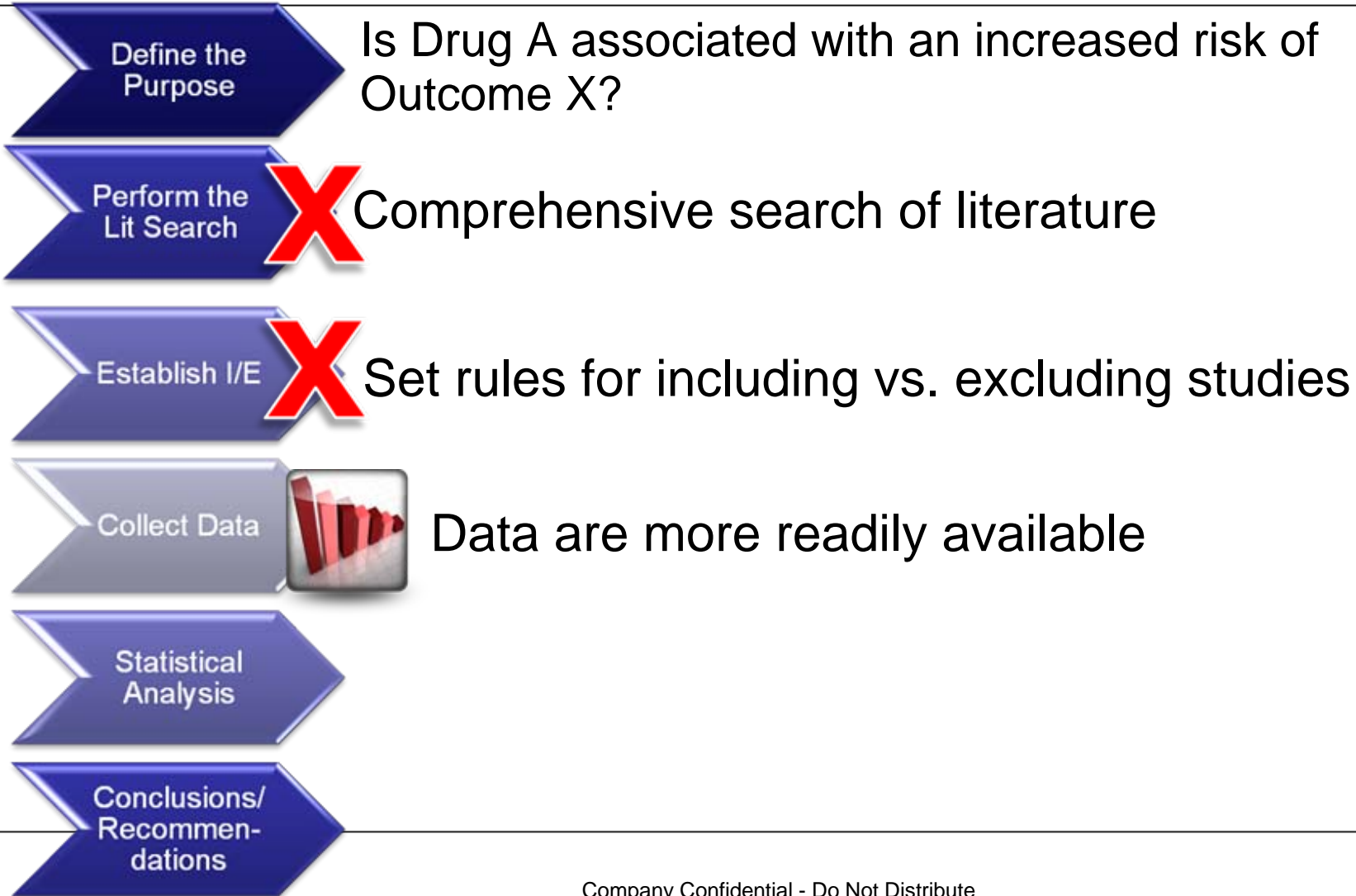*February 16, 2011*

Lilly

Answers That Matter.

Presentation Outline

- Steps for Conducting Meta-Analysis
  - General Approach vs. Distributed Network Model
- Issues to Consider
- Case Examples
- Opportunities

General Steps Involved in Conducting a Meta-Analysis – (Traditional Approach) (Strom B. Pharmacoepidemiology 4th ed, 2005)

Define the Purpose
Is Drug A associated with an increased risk of Outcome X?

Perform the Lit Search
Comprehensive search of literature

Establish I/E
Set rules for including vs. excluding studies

Collect Data

Statistical Analysis

Conclusions/ Recommen- dations

General Steps Involved in Conducting a Meta-Analysis – (Distributed Network with CDM & Common Methods) (Strom B. Pharmacoepidemiology 4th ed, 2005)

Define the Purpose — Is Drug A associated with an increased risk of Outcome X?

Perform the Lit Search ✗ — Comprehensive search of literature

Establish I/E ✗ — Set rules for including vs. excluding studies

Collect Data — Data are more readily available

Statistical Analysis

Conclusions/ Recommen- dations

Heterogeneity - Comparison

Traditional Meta-Analysis

Distributed Network w/ CDM

- Data Sources
- Study Designs
- Exposure Definition
- Outcome Definition
- Data Collection (i.e., retrospective vs. prospective)
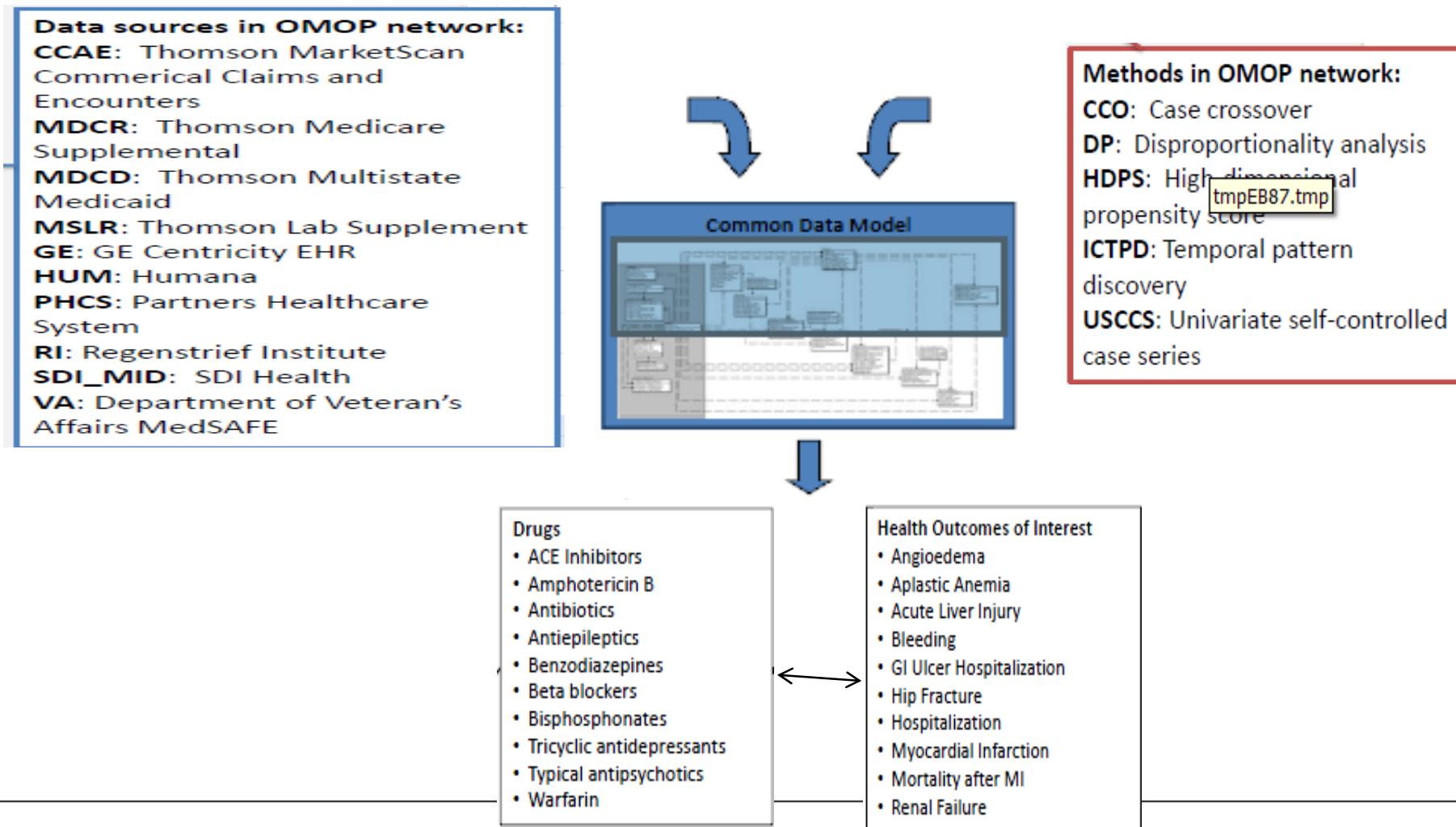- Statistical Analysis (i.e., unadjusted vs. adjusted)

Other Considerations

- Validity
  - Sensitivity and Specificity
  - False Positive and False Negative Rates
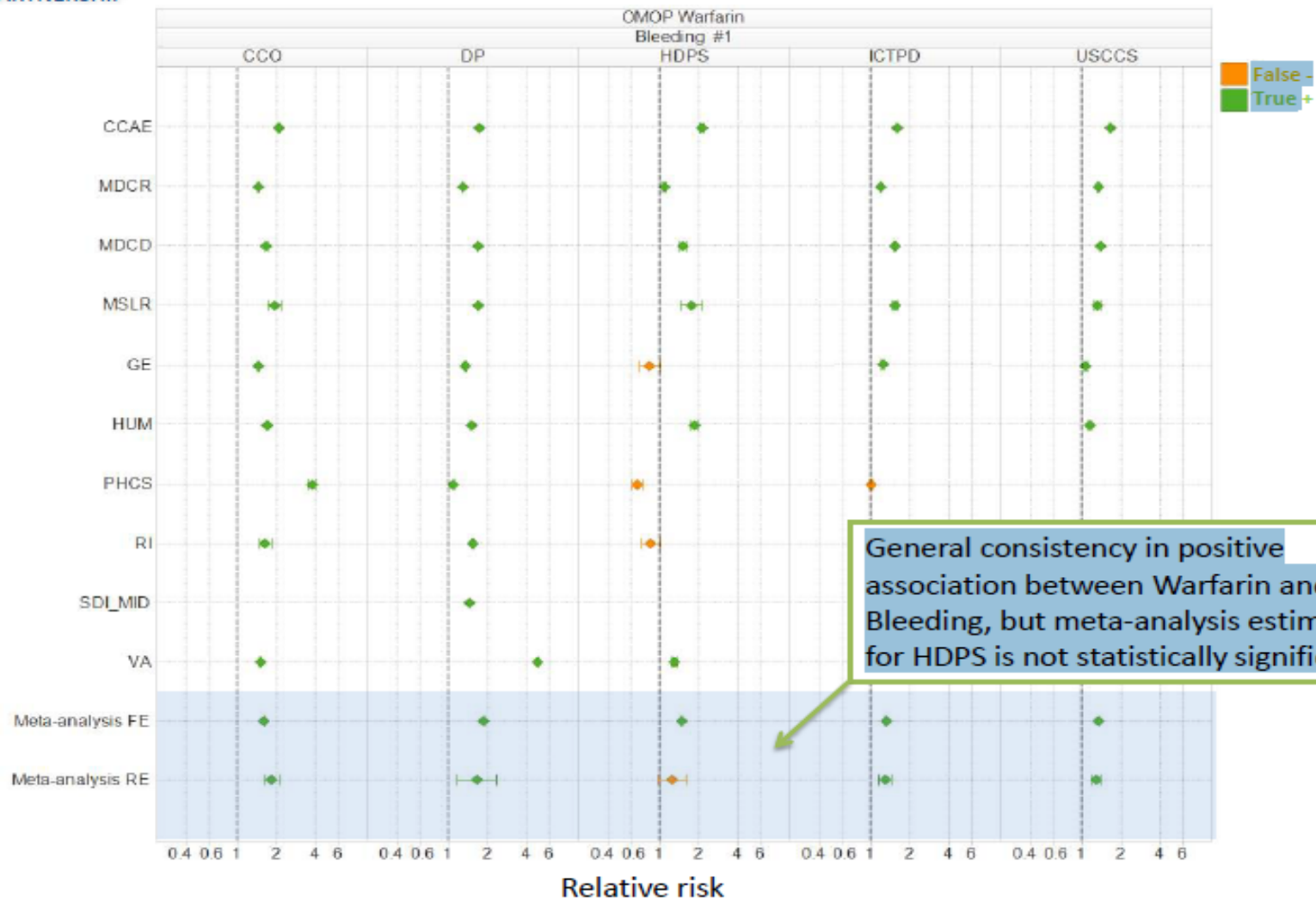- Reliability
  - Consistency of Results

CASE EXAMPLES
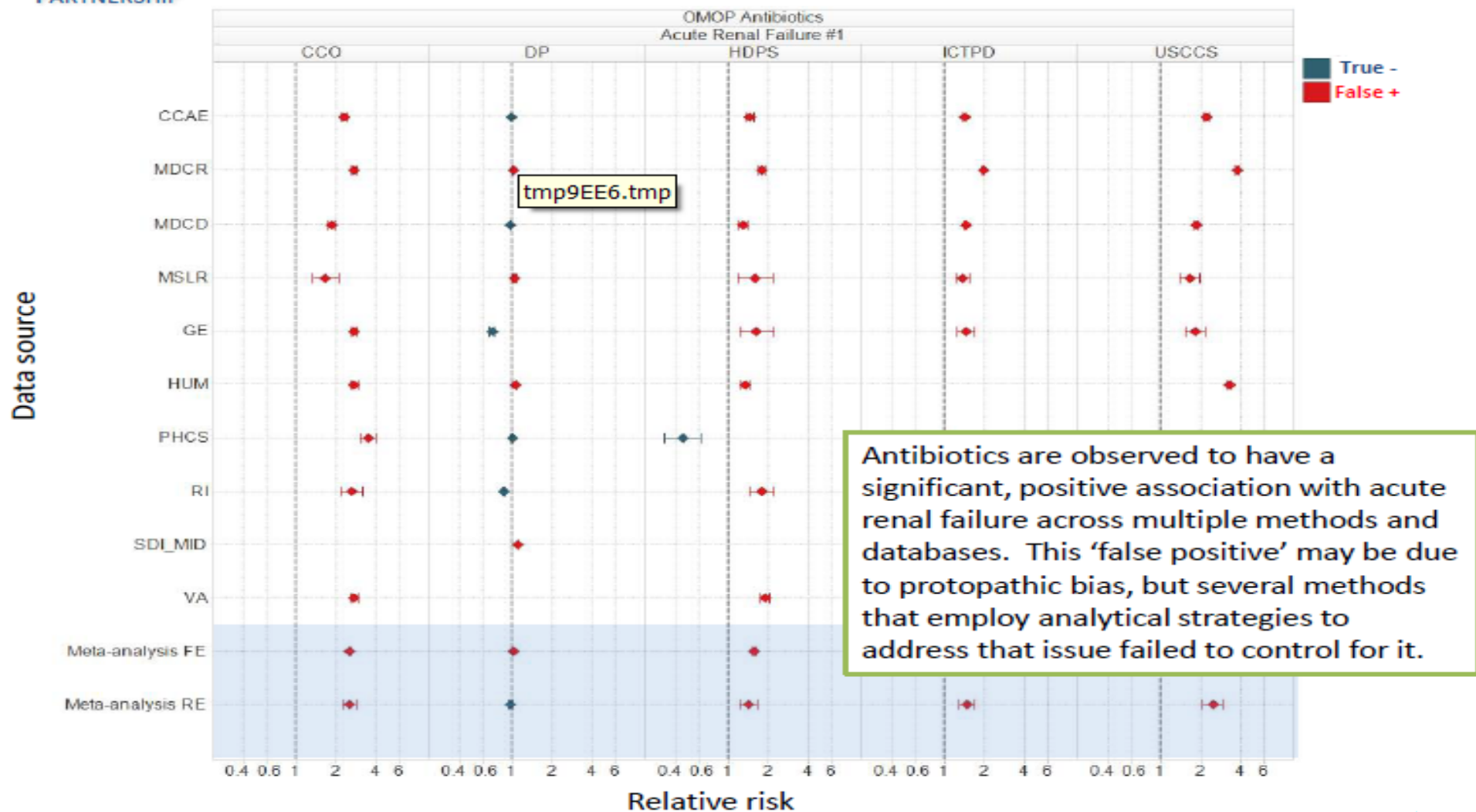
OMOP Research Experiment Workflow

Data sources in OMOP network:
CCAE: Thomson MarketScan Commerical Claims and Encounters
MDCR: Thomson Medicare Supplemental
MDCD: Thomson Multistate Medicaid
MSLR: Thomson Lab Supplement
GE: GE Centricity EHR
HUM: Humana
PHCS: Partners Healthcare System
RI: Regenstrief Institute
SDI_MID: SDI Health
VA: Department of Veteran's Affairs MedSAFE

Common Data Model

tmpEB87.tmp

Methods in OMOP network:
CCO: Case crossover
DP: Disproportionality analysis
HDPS: High-dimensional propensity score
ICTPD: Temporal pattern discovery
USCCS: Univariate self-controlled case series

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

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

Evaluating the association between Warfarin and Bleeding

Consistent 'false positive' observed for 'negative control' of Antibiotics and Acute Renal Failure

Antibiotics are observed to have a significant, positive association with acute renal failure across multiple methods and databases. This 'false positive' may be due to protopathic bias, but several methods that employ analytical strategies to address that issue failed to control for it.

Opportunities

- Active surveillance initiatives allow near real-time analyses in large populations.

- Supplements current post-marketing surveillance system (especially for rare events)

- Ongoing research needed
  - Small p-values and large effect sizes (statistical perspective)
  - Multiplicity – potential for false positives
  - Routine automation

- Clinical judgment is essential