Cohort Screening Methods for Identifying Unspecified Outcomes and Outcomes of Interest in Observational Databases

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Today's Agenda

- **Background / Context**
  - Systematic Analysis of Observational Data
- **Observational Screening Method**
  - Overview
  - Calculating a Screening Rate
  - Options and Parameters
  - Signal Detection: Comparing Screening Rates
- **Preliminary Research**
  - Outcomes of Interest Definitions
  - Parameter Combinations
  - Results

Disclosure

- **In 2005, GlaxoSmithKline (GSK) initiated a large-scale R&D project (SafetyWorks) to research and develop methodologies to enable the systematic use of observational data**
- **GSK and ProSanos® worked in partnership to implement the methodologies in web based software for access by GSK Safety Scientists, which was implemented in 2008**
- **Observational Screening is one of the methodologies implemented as part of this research**
- ***ProSanos markets a commercial version of this software***

Characteristics of Observational Data

- **Data for all conditions (not just AE's)**
  - Unspecified Outcomes – all by all analysis
  - Outcomes of Interest – specified drug / outcome pairs
- **Data is longitudinal**
  - One patient can have multiple exposures
  - Exposure length is available
  - Temporal patterns can be analyzed
- **No standardization of data format / organization**

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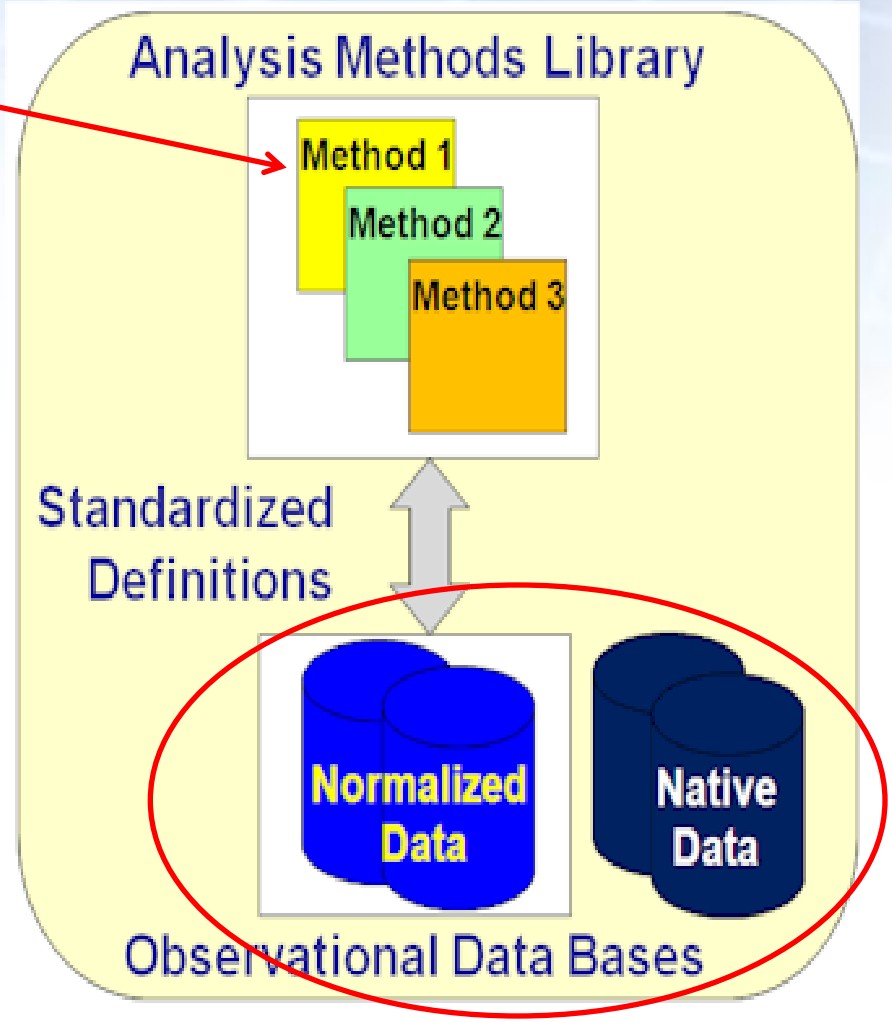
Systematic Observational Analysis

Observational Screening is part of the OMOP Analysis Methods Library

Application of analytic methods to disparate observational databases without requiring custom programming or intervention for each data source



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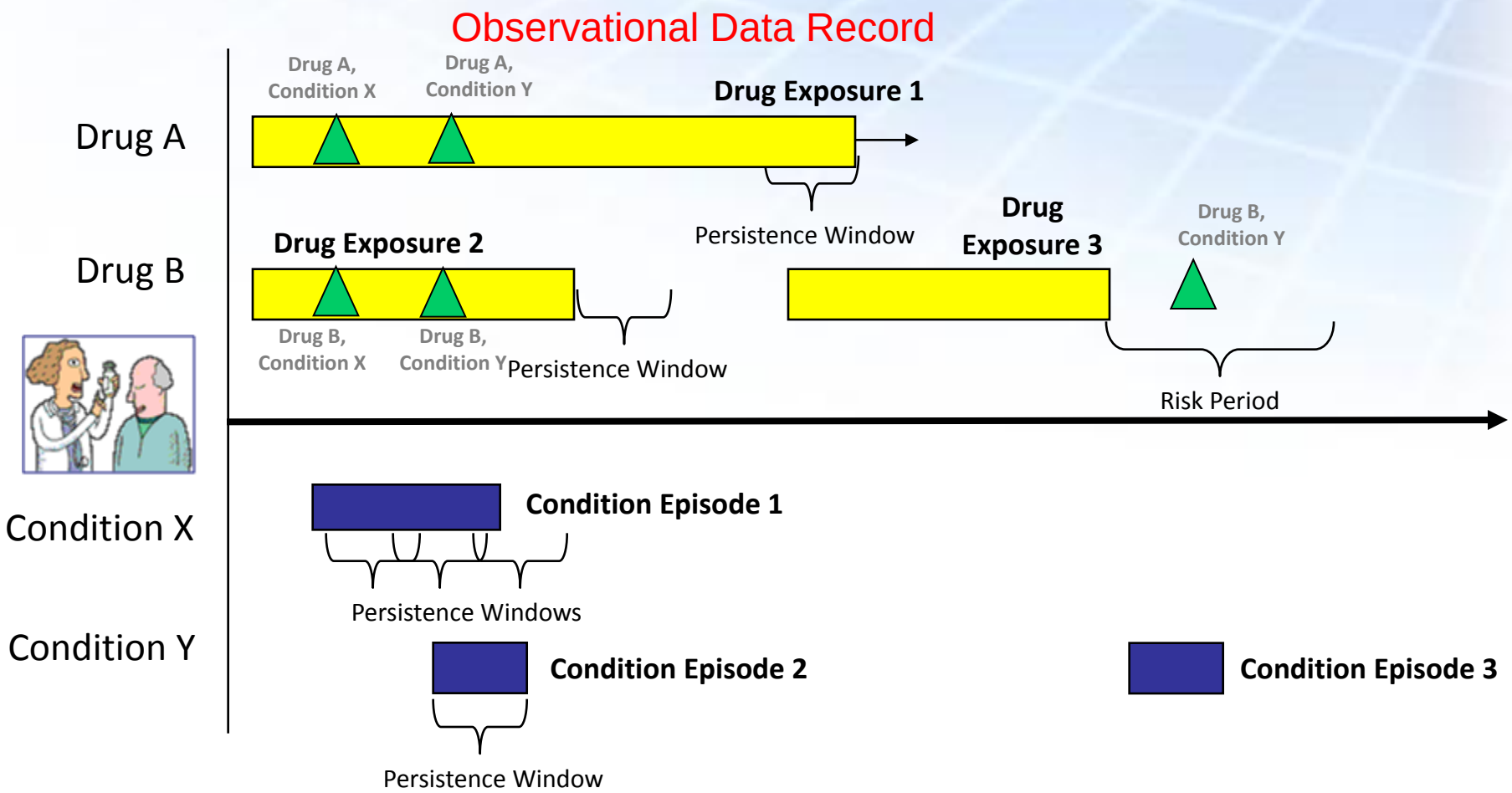
Common Data Model Illustration



Prescription

Diagnosis

Drug-Condition Pair

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Analytic Considerations

- **Case Reports**
  - Disproportionate reporting
  - Denominator not available
  - Exposure not considered: event after 1 day of exposure treated the same as after 100 days of exposure
  - Represents a point in time (when suspected AE occurs)
- **Observational Data**
  - Includes exposure and denominator information
  - Metrics such as rates and proportions can also be produced using exposure and denominator information
  - Longitudinal view of patient status over time

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Observational Screening

Method for analysis of observational databases to identify drug / outcome pairs occurring more frequently than expected

Screening Rate: Approximate rate of occurrence of a given condition per 1,000 years of exposure

Number of Events / Total Time at Risk

Similar concept as an Incidence Rate though not exactly the same

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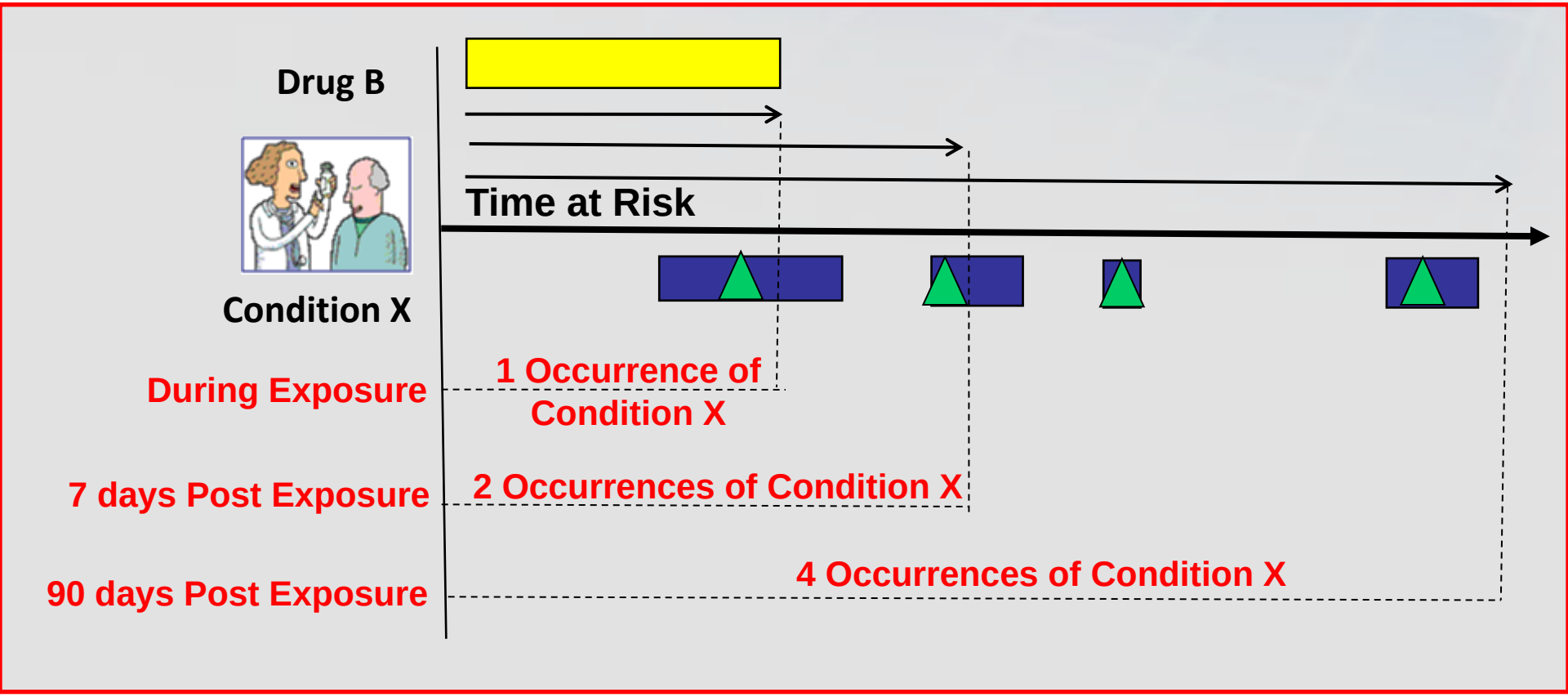
Calculating a Screening Rate

Number of Events / Total Time at Risk



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Observational Screening Parameters

- ***All Adverse Events are not created equal***
  - mechanism of action, relationship to exposure, time to onset, acute vs chronic, etc.
- **Alternative parameter combinations may provide performance characteristics suited for detecting different types of outcomes**
  - Vary “time at risk”
  - Specify which exposure(s) to study
  - Specify which outcomes too count
  - Include Day of Initiation (index date)?
  - Alternative study designs

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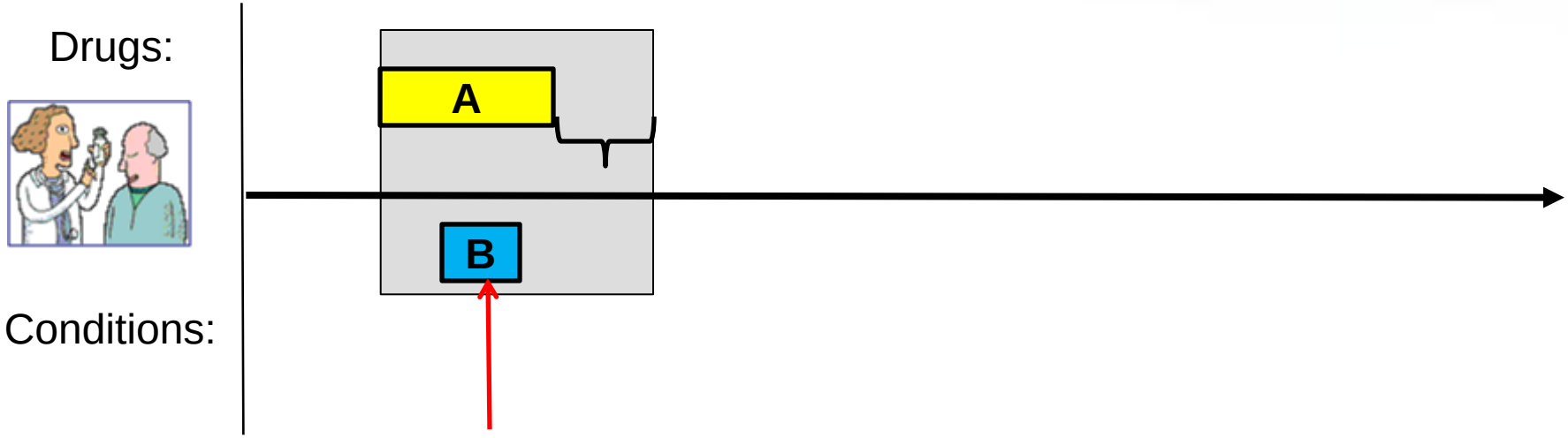
Counting Outcomes

- **Outcomes are conditions that occur within the Time at Risk period for a specific exposure**
- ***Observational Screening does not censor time at risk when an outcome is counted***



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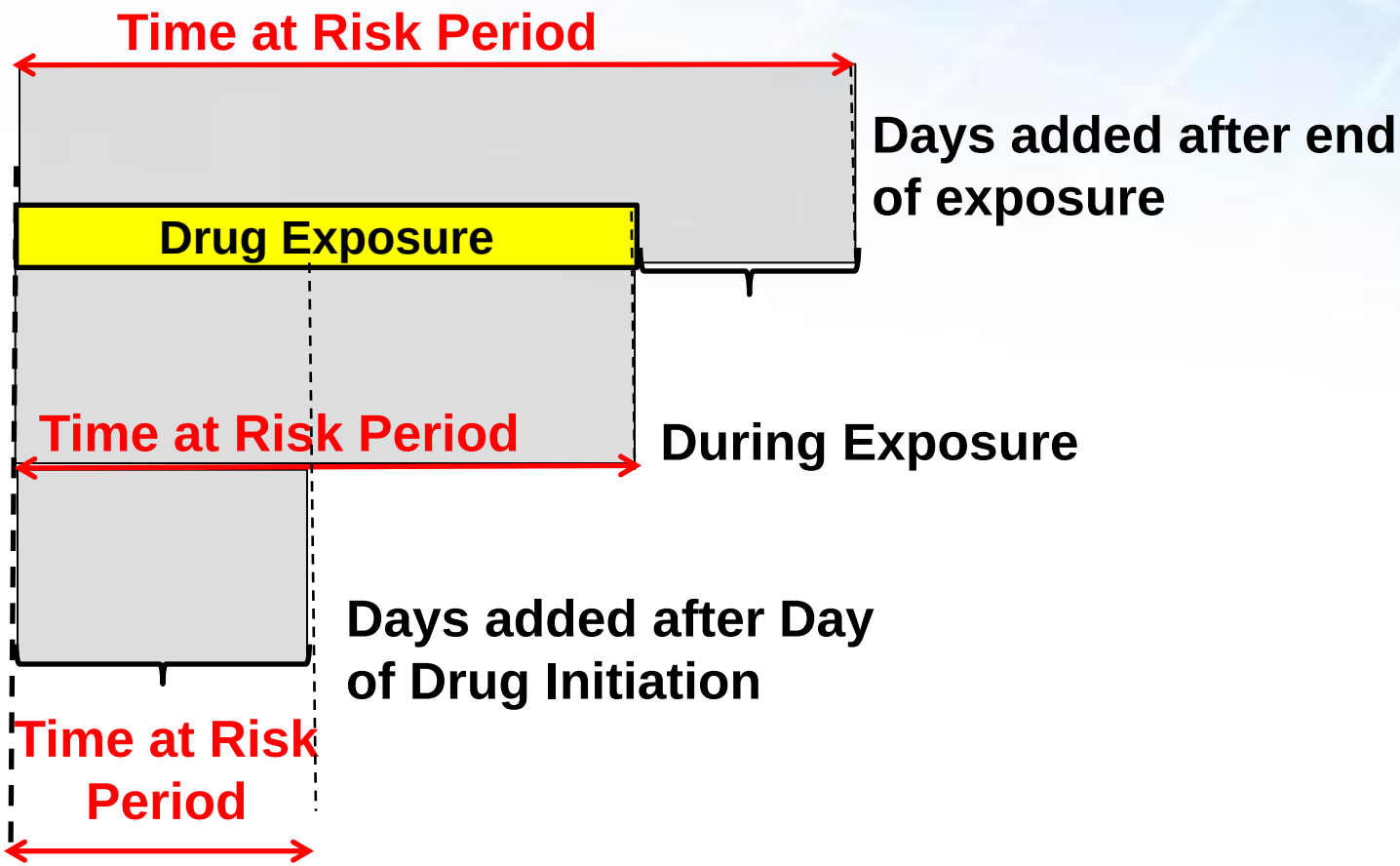
Options for Varying Time at Risk

End Date of Risk Period – Start Date of Risk Period



"Surveillance Window" Input Parameter:
surveillance_window_post_in_days_list_0_to_99999

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Options that Impact Outcome Identification

- **First versus all exposures?**
  - *drug_first-exposure_only_0_or_1*
- **First versus all versus incident outcomes?**
  - *outcome_first_occurrence_only_0_to_1*

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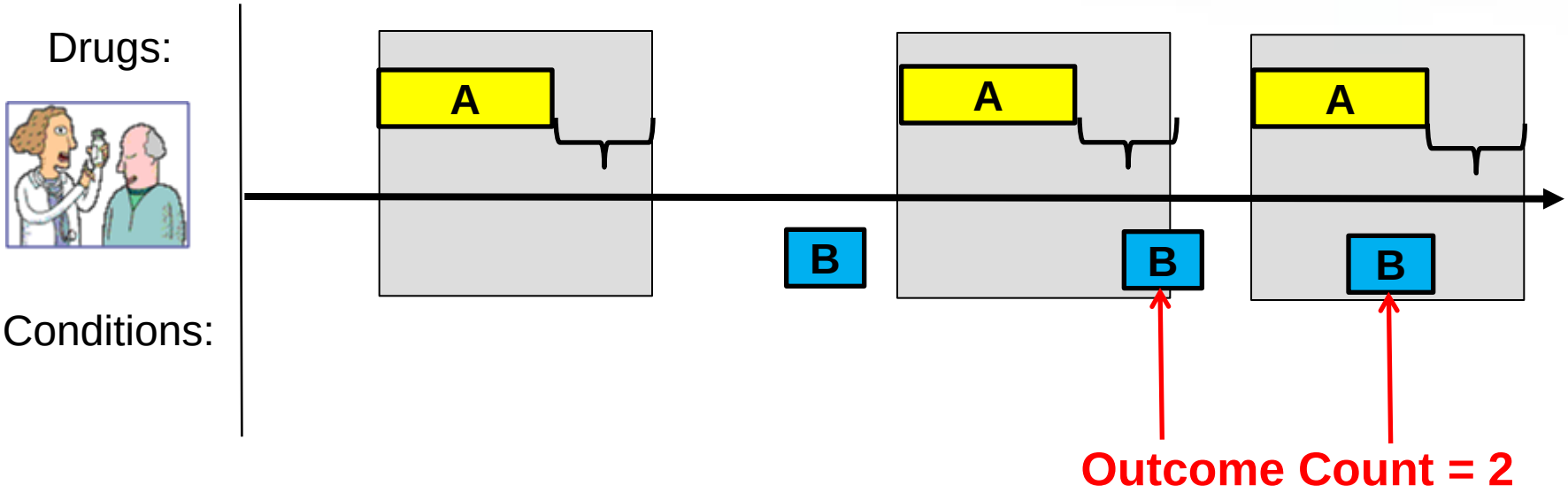
Screening Rate: Example 1

Number of Events / Total Time at Risk

Input Parameters:

- 30 Day Surveillance Window after exposure ends
- All Drug Exposures
- All Outcome Occurrences



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Screening Rate: Example 2

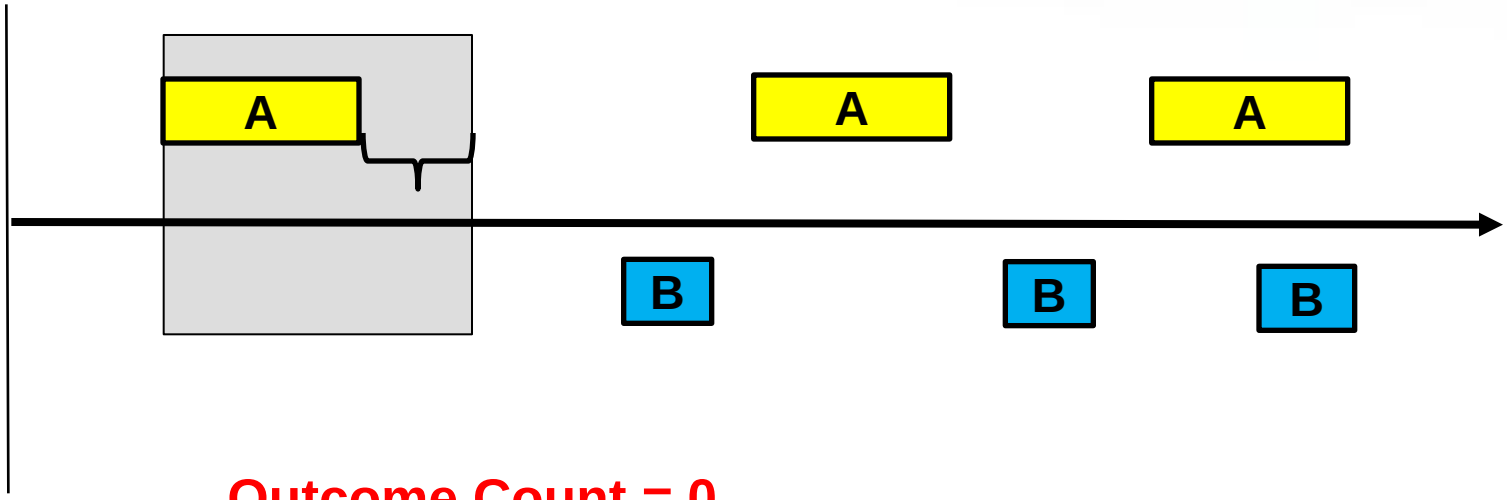
Number of Events / Total Time at Risk

Input Parameters:

- 30 Day Surveillance Window after exposure
- First Drug Exposure
- All Outcome Occurrences

Drugs:

Conditions:



Outcome Count = 0

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Screening Rate: Example 3

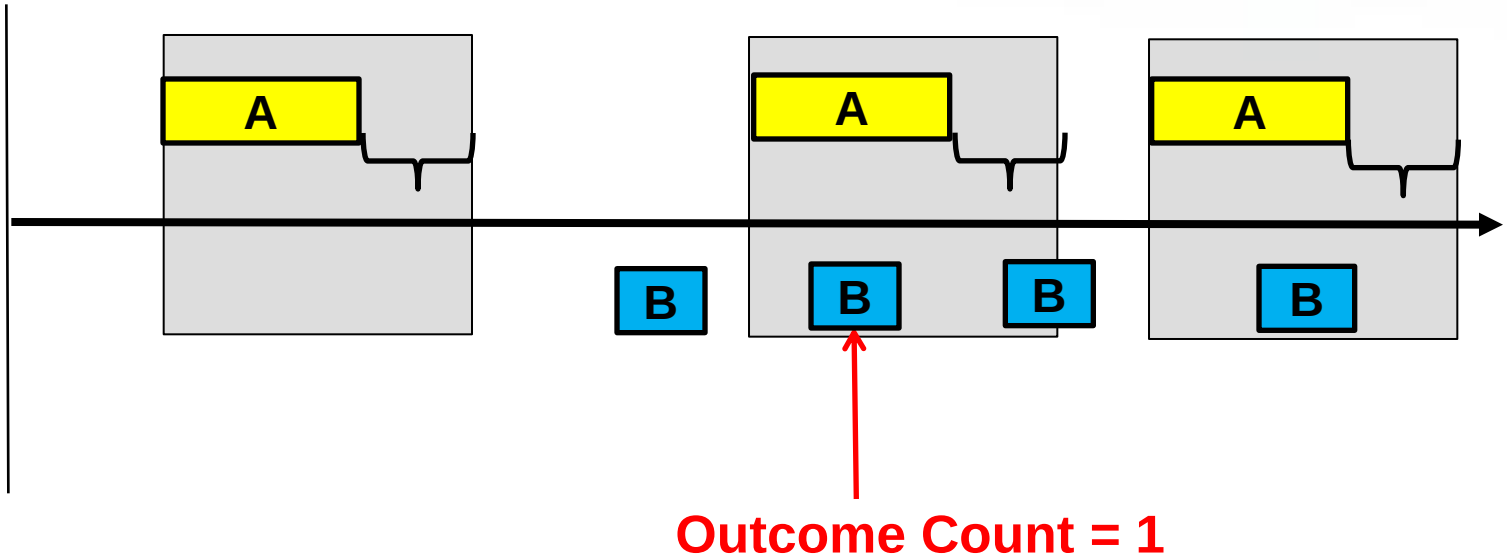
Number of Events / Total Time at Risk

Input Parameters:

- 30 Day Surveillance Window after exposure
- All Drug Exposures
- First Outcome Occurrence

Drugs:

Conditions:



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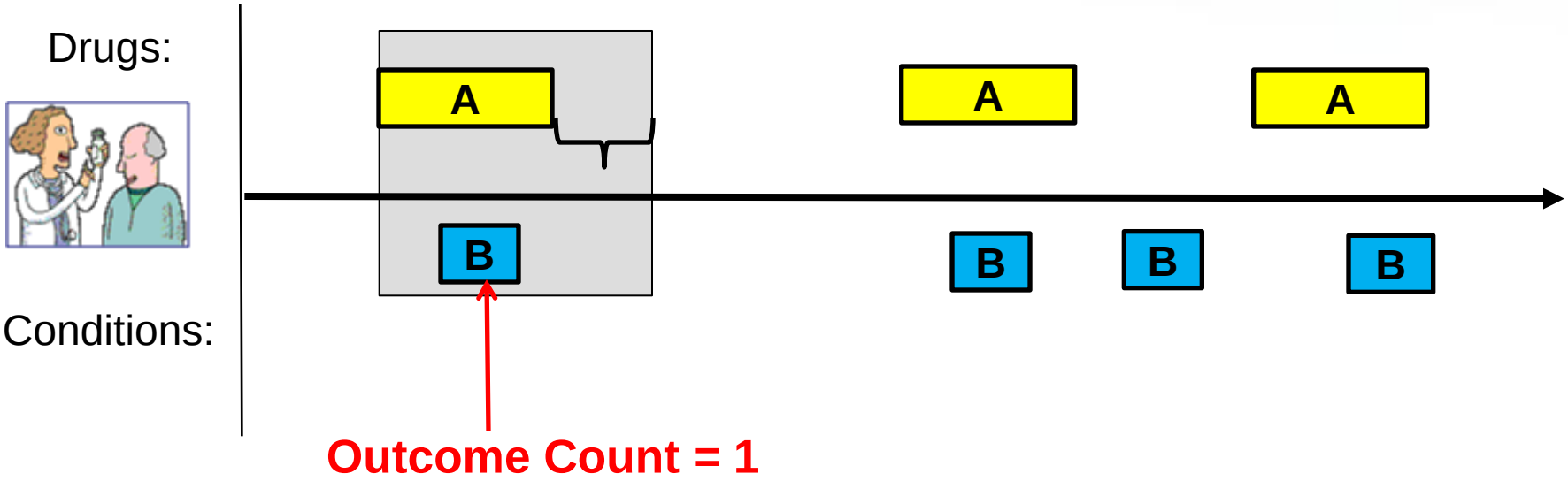
Screening Rate: Example 4

Number of Events / Total Time at Risk

Input Parameters:

- 30 Day Surveillance Window
- First Drug Exposure
- First Outcome Occurrence



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Screening Rate: Example 5

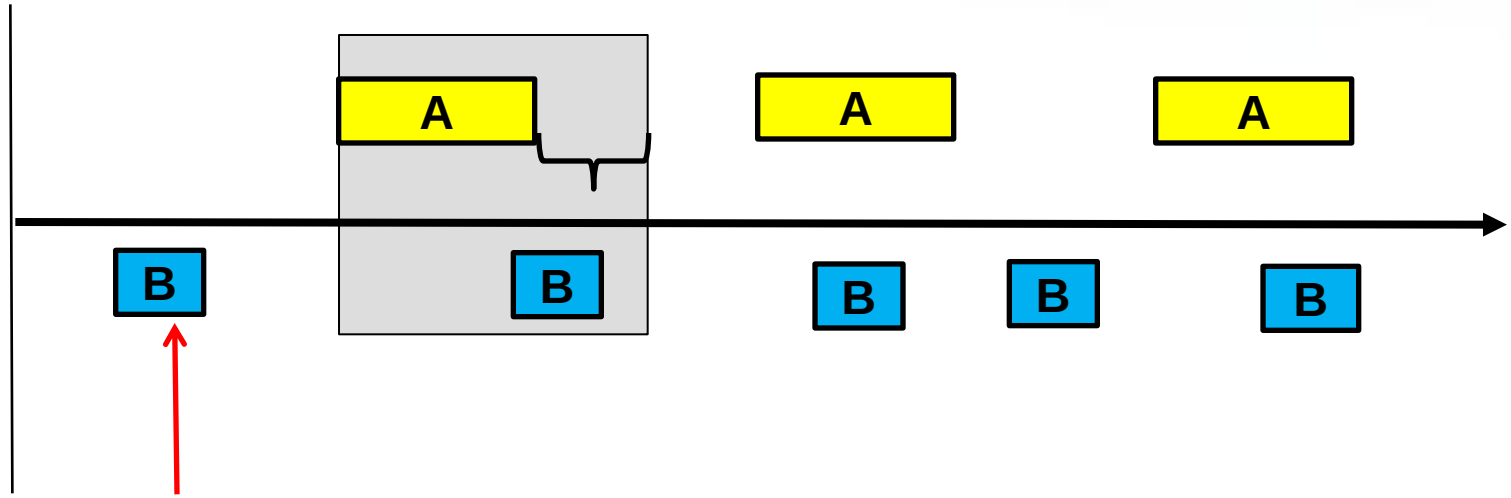
Number of Events / Total Time at Risk

Input Parameters:

- 30 Day Surveillance Window
- First Drug Exposure
- Incident Outcome Occurrence

Drugs:

Conditions:



Outcome Count = 0

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Signal Detection Using Screening Rates

- **Screening Rate Ratio (SRR):** Ratio of Screening Rates for two comparable populations to identify differences in event rates that may be indicative of increased risk on one of the populations

SRR = Screening Rate 1 / Screening Rate 2

UB and LB Confidence intervals: *assume ratio of two rates following Poission Distribution Graham, PL, Mergenson K, Morton AP, Confidence limit for the ratio of two rates based on likelihood scores: non iterative method: Statist. Med 2008 22-2071-2083:*

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Observational Screening Designs

1. **Self Controlled**
   - Target and Comparator cohorts are the same population
   - SRR compares Screening Rates calculated prior to exposure to those calculated after exposure
2. **Background Comparator**
   - SRR compares target population Screening Rates to background database Screening Rates
3. ***Cohort Comparison***
   - *SRR compares Screening Rates calculated for two different cohorts (not included in this research)*

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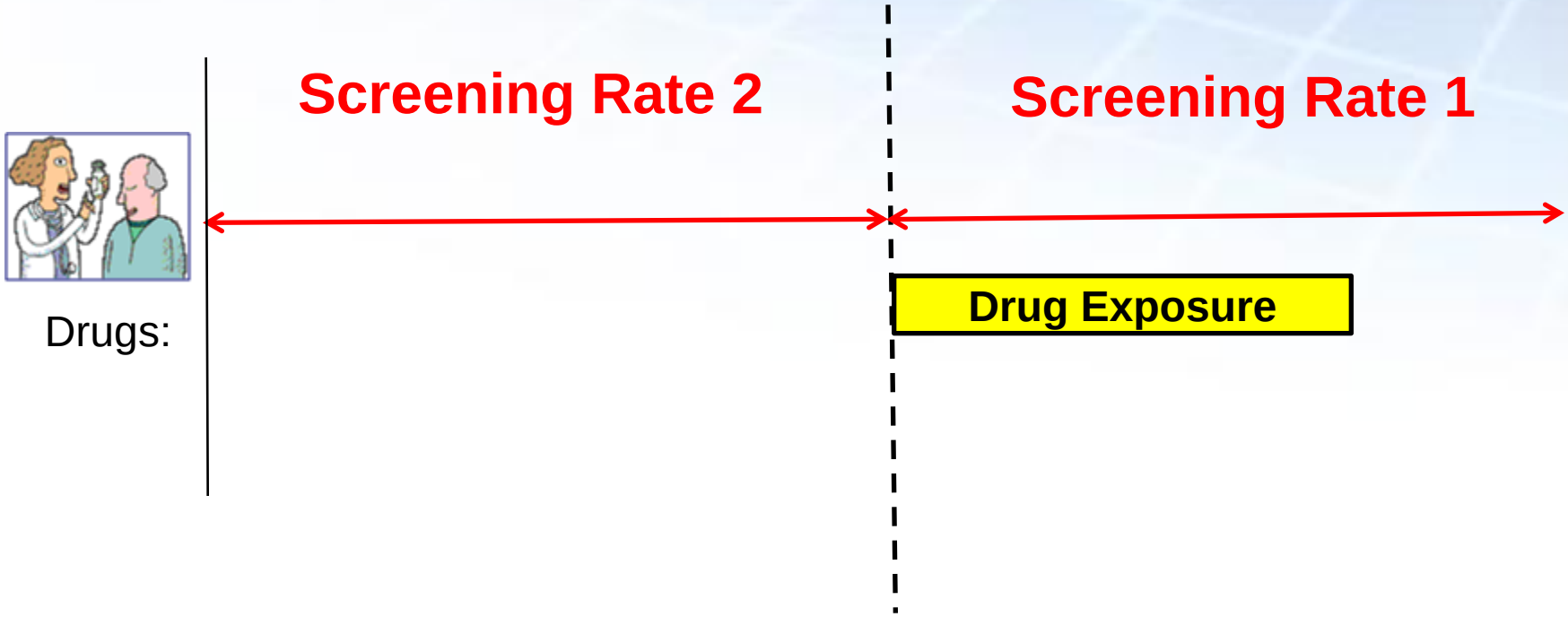
Self Controlled Design



SRR = Screening Rate 1 / Screening Rate 2

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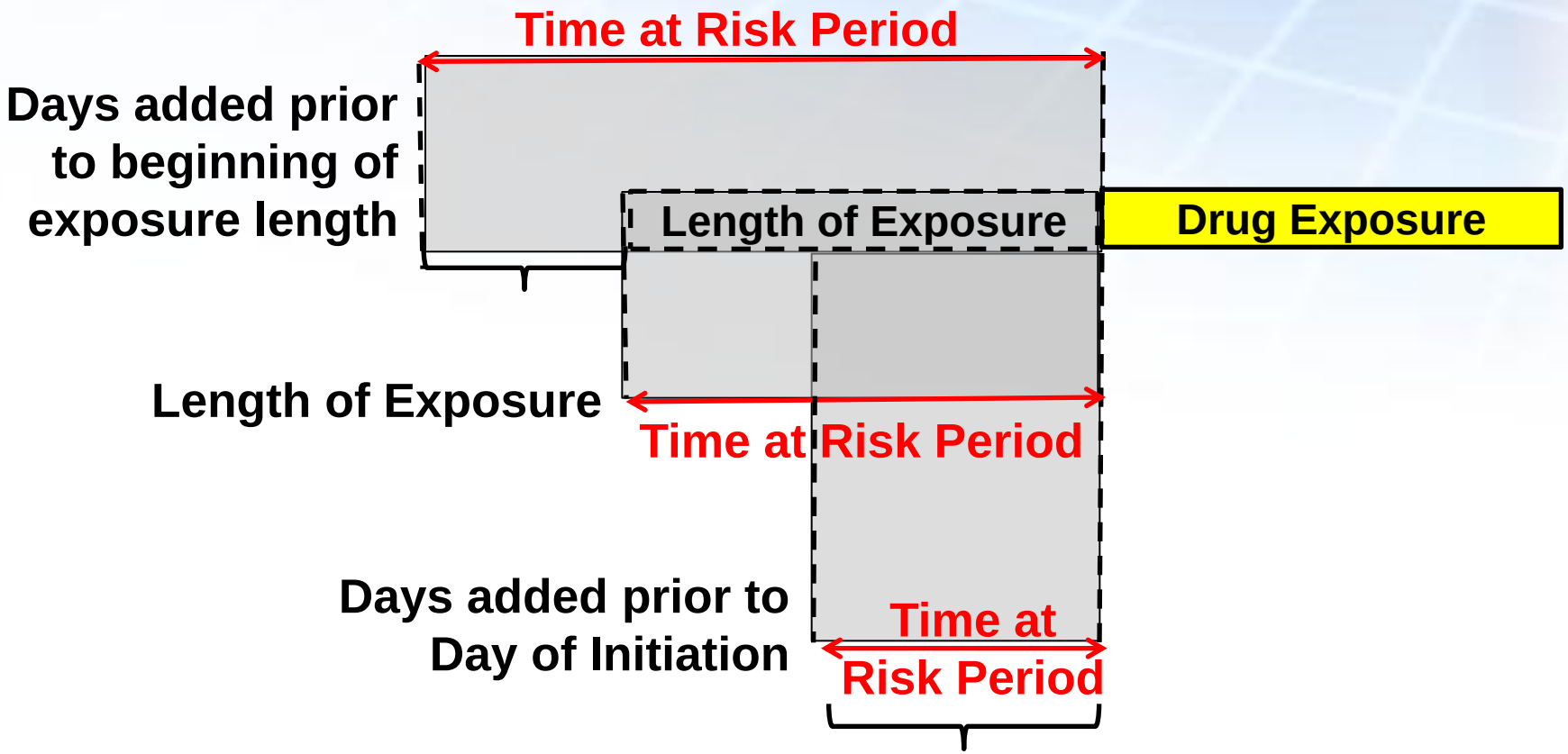
Time at Risk for Self Controlled Design



"Surveillance Window" Input Parameter:
surveillance_window_pre_in_days_list_0_to_99999

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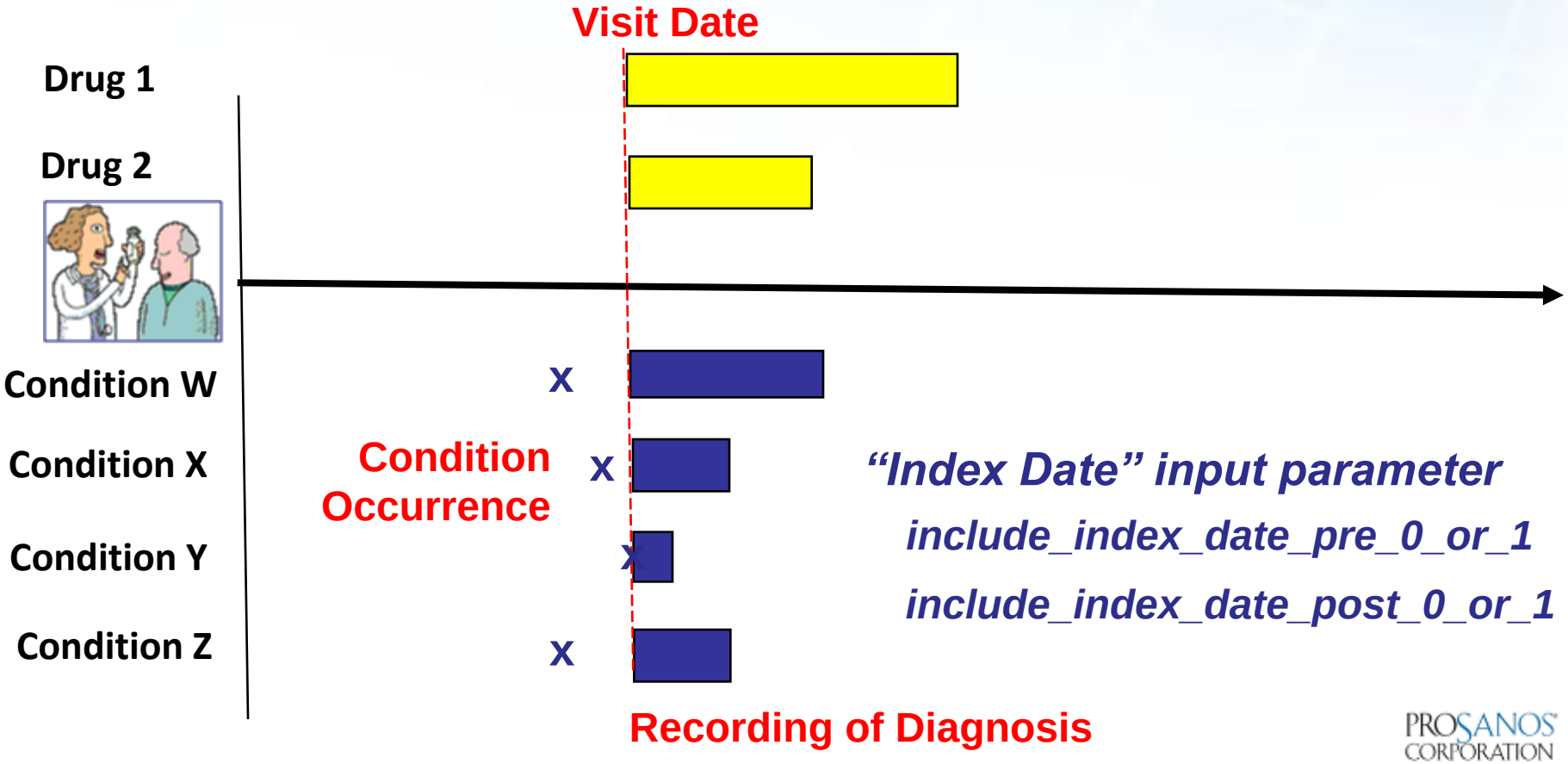
Include Day of Initiation?

- Conditions tend to be recorded in "clumps" based on visit dates
- Consider when to include DoI, particularly with self controlled designs (anaphylaxis? MI?)



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Background Comparator Design

Screening Rate 1

Drug Exposure

Screening Rate 2

SRR = Screening Rate 1 / Screening Rate 2

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Time at Risk for Background Design

Total time in database:
Enrollment end – Enrollment Start

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Summary of Observational Screening

- **Unspecified Outcomes & Outcomes of Interest**
- **Screening Rate Metric**
  - Number of Events per 1,000 years of Exposure
- **Screening Rates Parameters**
  - Varying “at risk” periods (surveillance window)
  - First or all exposures
  - First, all or incident outcome
  - Day of initiation
- **Screening Rate Ratio for Signal Detection**
  - UB and LB metrics also calculated
- **Three designs (two implemented for this research)**
  - Self Controlled (pre ←→ post exposure)
  - Background (exposed vs background)
  - *Target vs. comparator cohort*

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Summary of Observational Screening Parameters

Parameter	Description
name_of_database	Selection of DB for Screening
comparator_group_1_to_3	1=Self Controlled, 2=Background
define_screening_metric_list	1=Screening Rate Ratio, 2=Lower Bound CI, 3=Upper Bound CI
surveillance_window_post_in_days_list_0_to_99999	0=during exposure, positive number=post exposure, negative number =post initiation
surveillance_window_pre_in_days_list_0_to_99999	0=exposure length, positive number=added to exposure length, negative number=prior to initiation (self controlled design)
drug_first_exposure_only_0_or_1	0=All, 1=First
outcome_first_occurrence_only_0_to_2	0 = All, 1=First, 2=Incident
include_index_date_post_0_or_1	Include the index date when counting outcomes
include_index_date_pre_0_or_1	Include the index date when counting outcomes for self controlled design
Drugs_of_interest.txt, conditions_of_interest.txt	Required for Screening Health Outcomes of interest

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4 Preliminary Research Goals

1. **Detect 8 <u>known</u> Health Outcomes of Interest**
2. **Compare results for various combinations of parameters**
   - Are specific combinations better at detecting different types of outcomes?
3. **Compare detection capability when using different definitions of same outcome**
4. **Compare performance of alternative study designs (self controlled, background comparator design)**

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8 Known Health Outcomes of Interest

Drug	Outcome of Interest	Alternative Event Definitions
Erythromycin	Liver Failure	6
Tricyclic Antidepressants	Acute Myocardial Infarctions	3
Atypical Antipsychotics	Acute Myocardial Infarctions	3
Amphotericin B	Acute Renal Failure	3
Carbamazapine	Aplastic Anemia	5
Warfarin	Bleeding	2
Benzodiazepine	Hip Fracture	4
Bisphosphonate	Upper GI Ulcer Hospitalization	2

Alternative Definitions:

- **Diagnosis codes only**
- **Diagnosis codes plus associated procedures**
- **Lab Results (+/- diagnoses, procedures)**

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Aplastic Anemia Alternative Definitions*

#1

Occurrence of at least 1 **Broad Diagnosis** Code:

284.0*

284.8*

284.9

#2

Occurrence of at least 1 **Broad Diagnosis Code** AND at least one **Procedure Code** for bone marrow aspiration or biopsy w/in 60 days prior to diagnosis

#3

Occurrence of at least one **Narrow Diagnosis Code** – 284.8*, AND at least one **Procedure Code** for bone marrow aspiration or biopsy w/in 60 days prior to diagnosis

#4

Occurrence of at least two or three of the following **Lab Values:**

WBC <= 3.5x10^9L

Platelet Count<= 50x10^L

Hemoglobin<=100 g/L

#5

3 OR #4

*Source: omop.fnih.org

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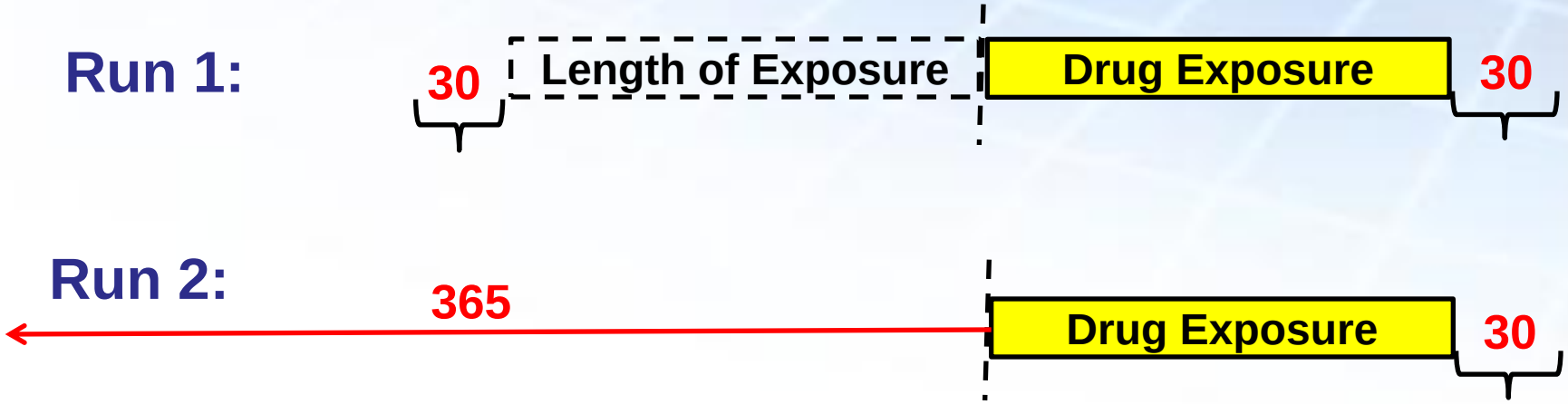
Analysis 1: Self Controlled Design varying Surveillance Windows



Run 1:

- All Drug Exposures
- First Outcome
- Exposure + 30 day length for comparator

Run 2:

- All Drug Exposures
- First Outcome
- 365 day fixed length for comparator

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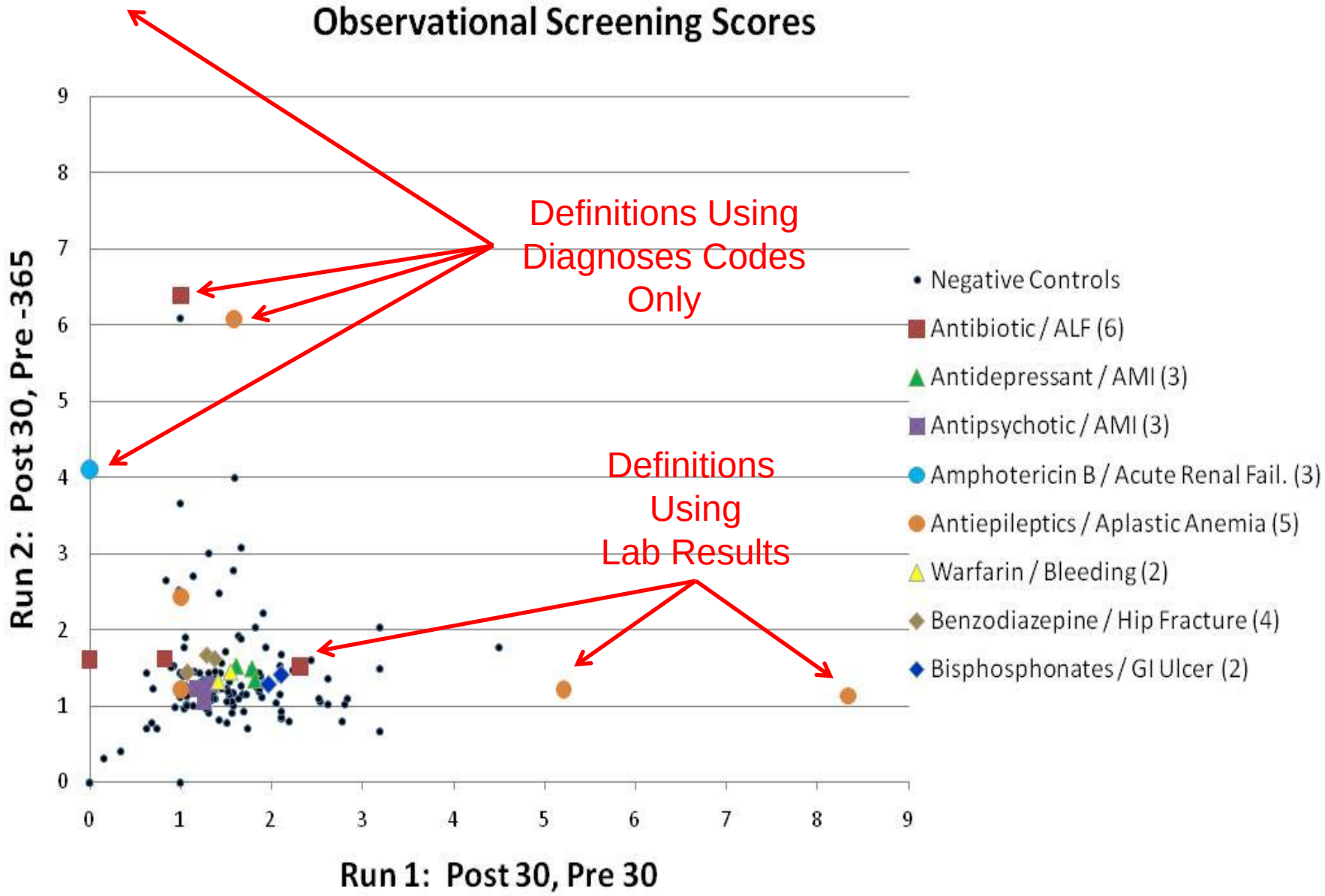
Antibiotic / ALF (34.08)



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Analysis 2: Self Controlled Design varying Exposure & Outcome Parms

Run 1:

- All Drug Exposures
- All Outcomes

Run 2:

- First Drug Exposure
- First Outcome

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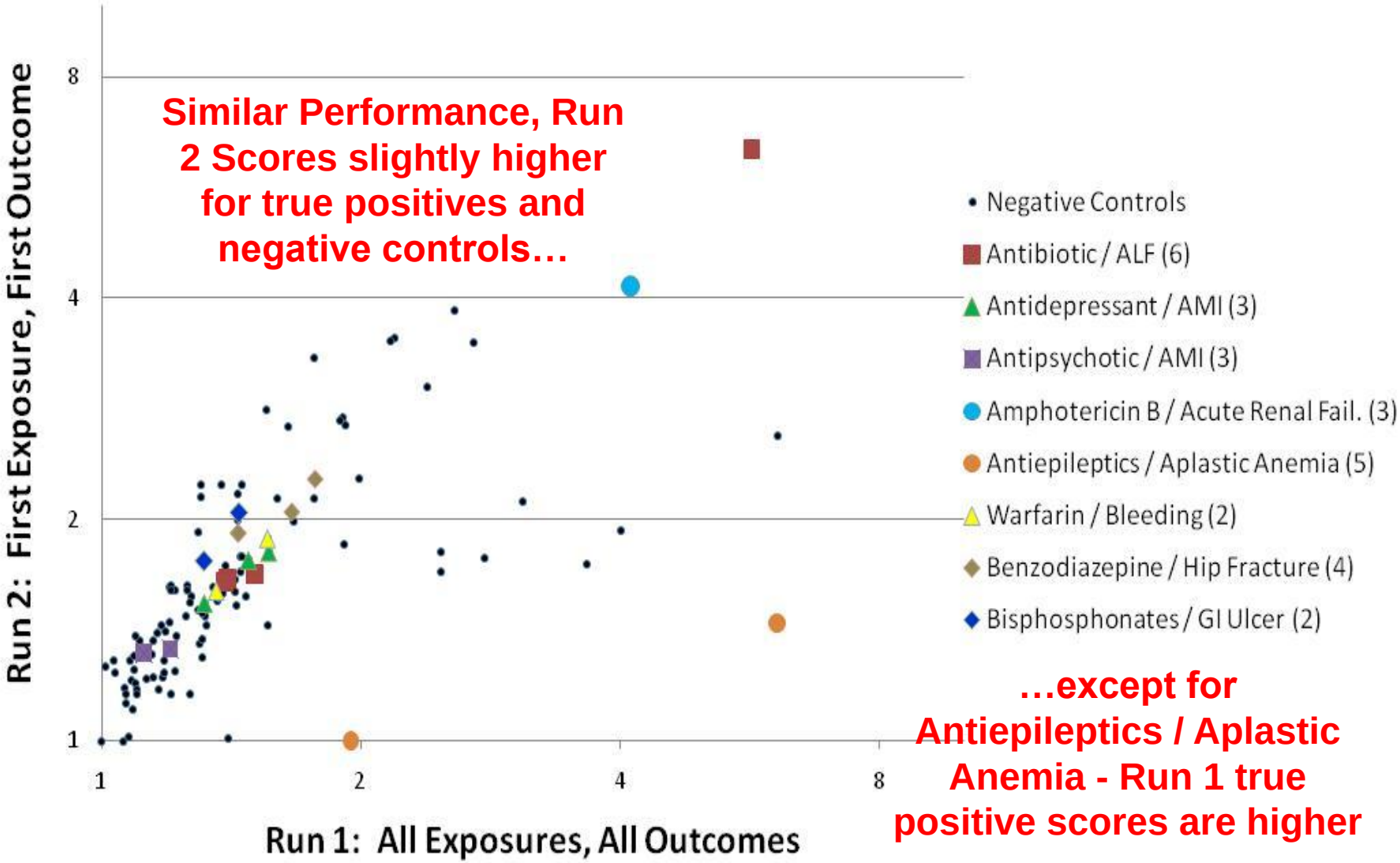
Observational Screening Scores



Similar Performance, Run 2 Scores slightly higher for true positives and negative controls…

…except for Antiepileptics / Aplastic Anemia - Run 1 true positive scores are higher

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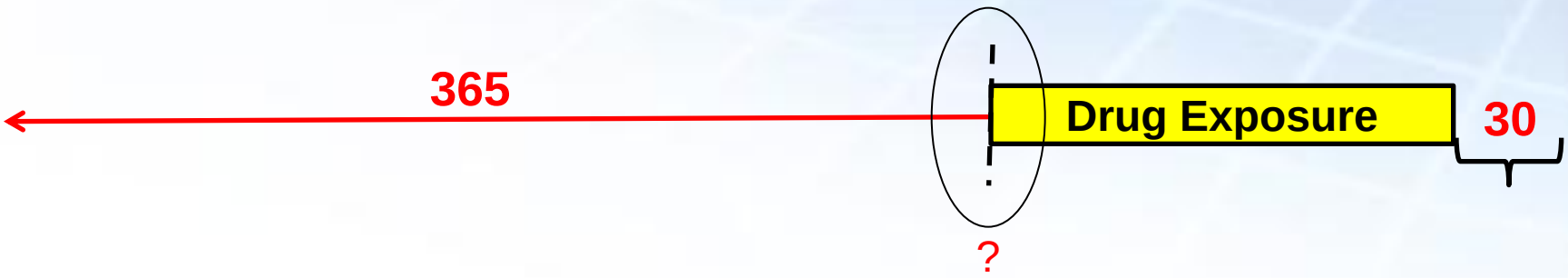
Analysis 3: Self Controlled Design varying Day of Initiation Parms



Run 1:

- All Drug Exposures
- All Outcomes
- Don't include DoI before or after

Run 2:

- All Drug Exposures
- All Outcomes
- Include DoI after, but not before

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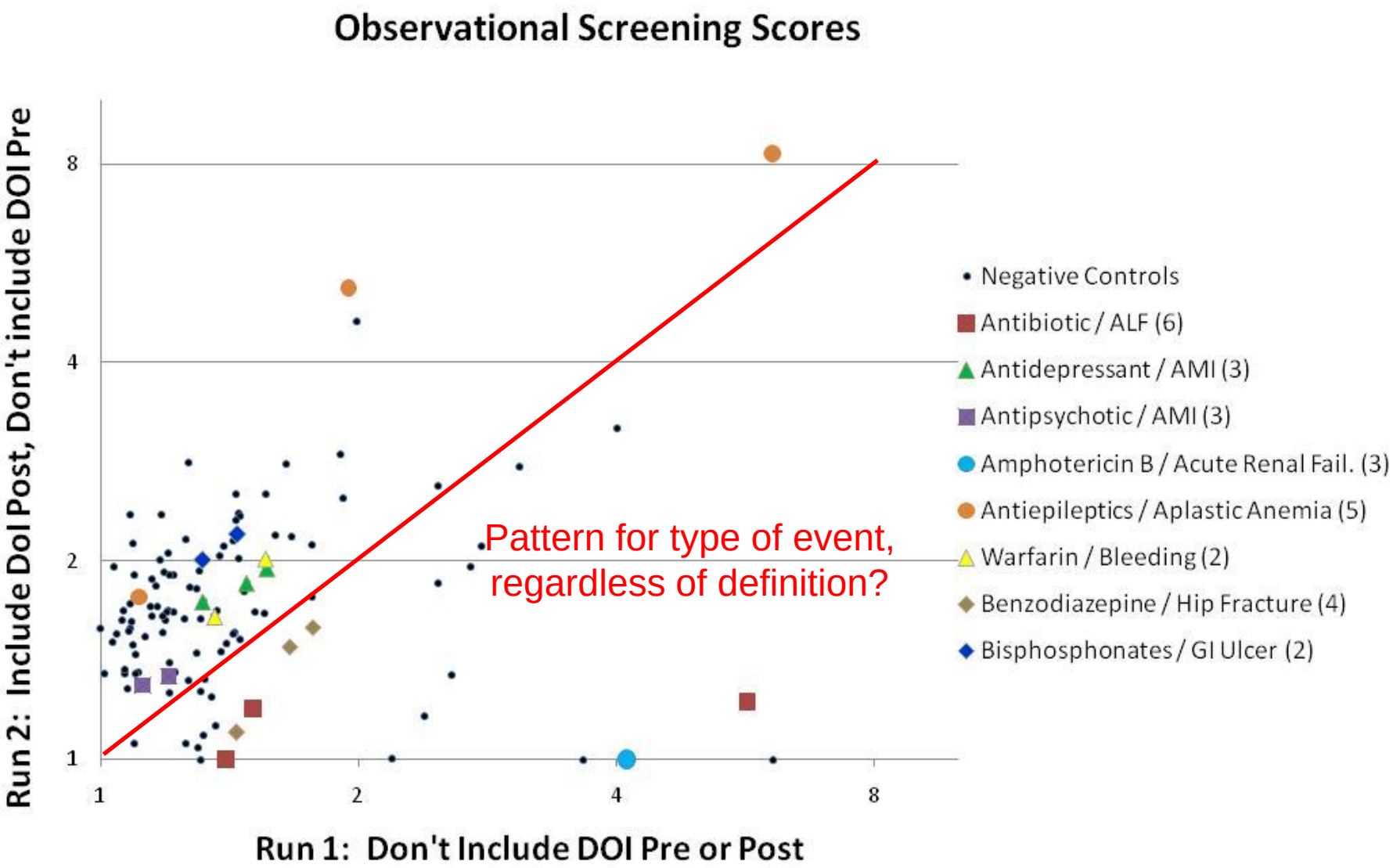

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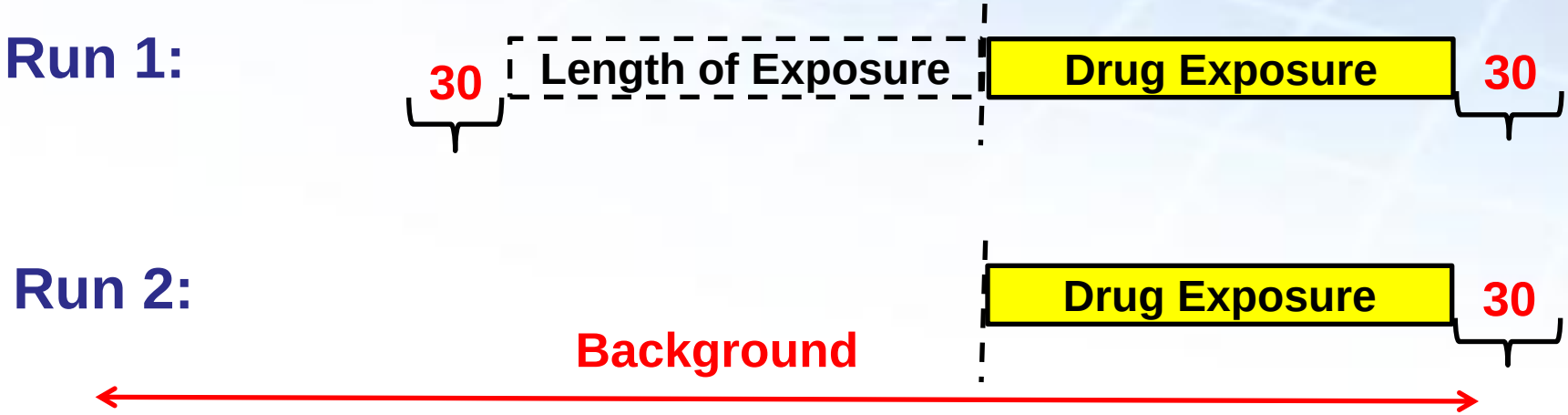
Analysis 4: Self Controlled Design vs Background Comparison



Run 1:

- Background Comparator
- All Exposures
- All Outcomes, not including DoI

Run 2:

- Self Controlled
- All Exposures
- All Outcomes

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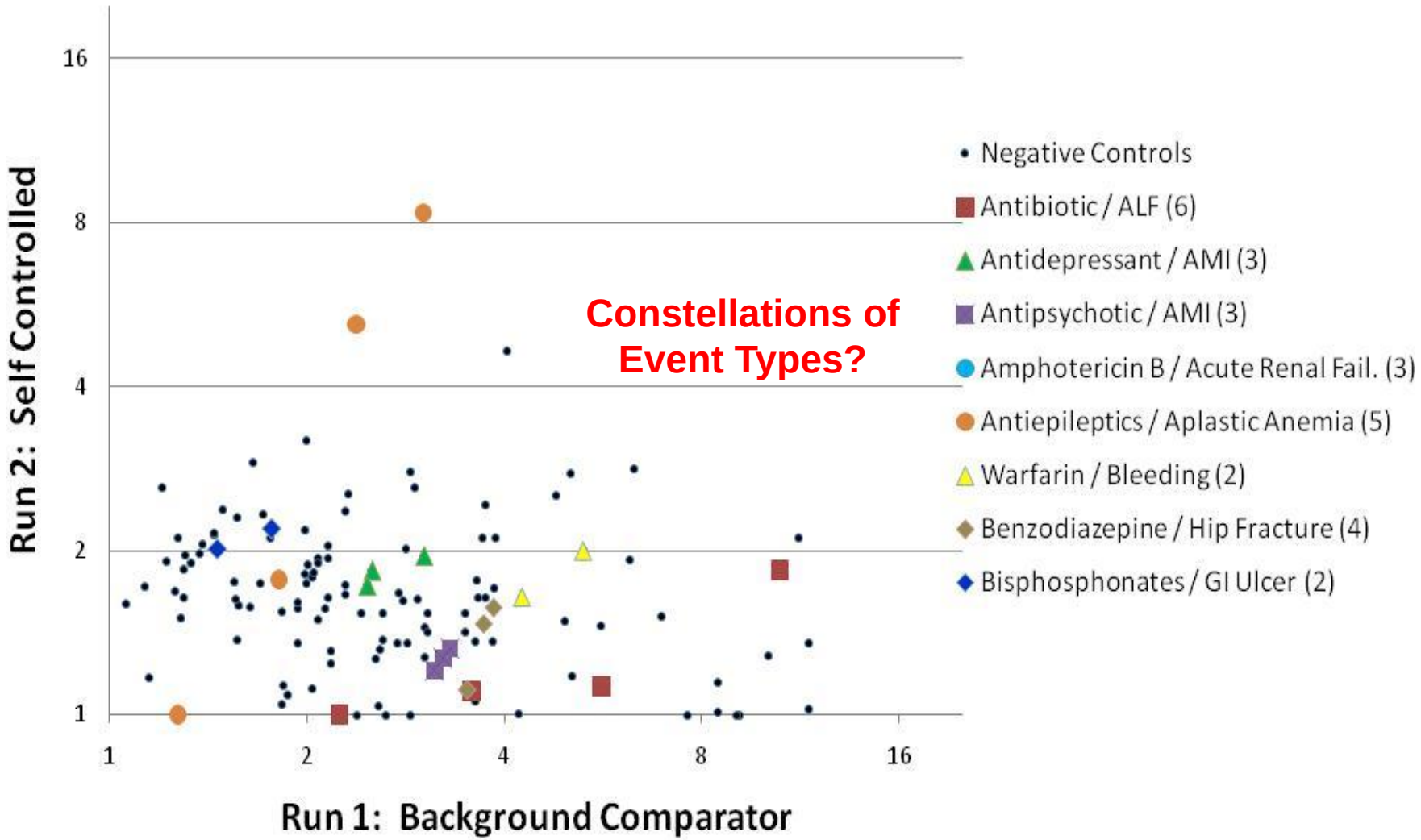
Observational Screening Scores



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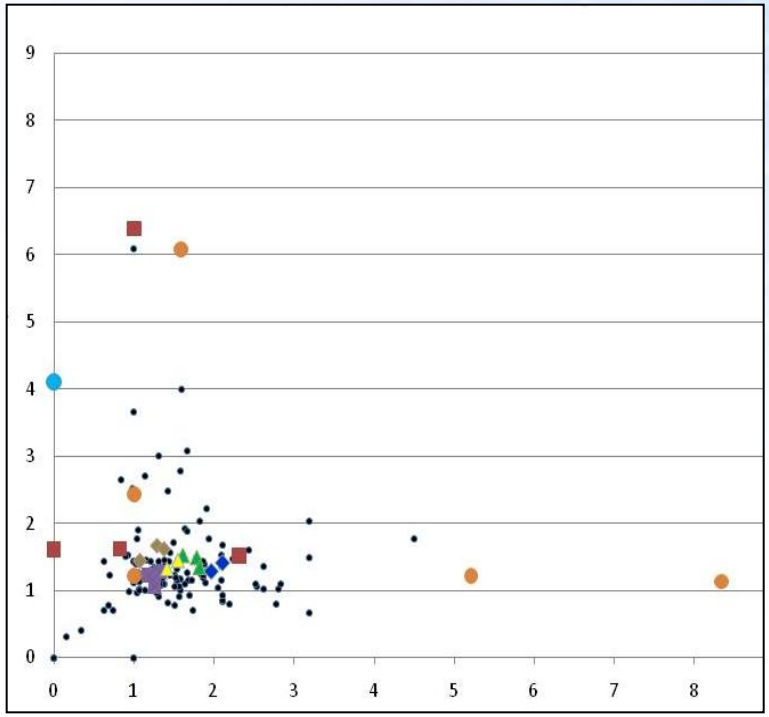
9
8
7
6
5
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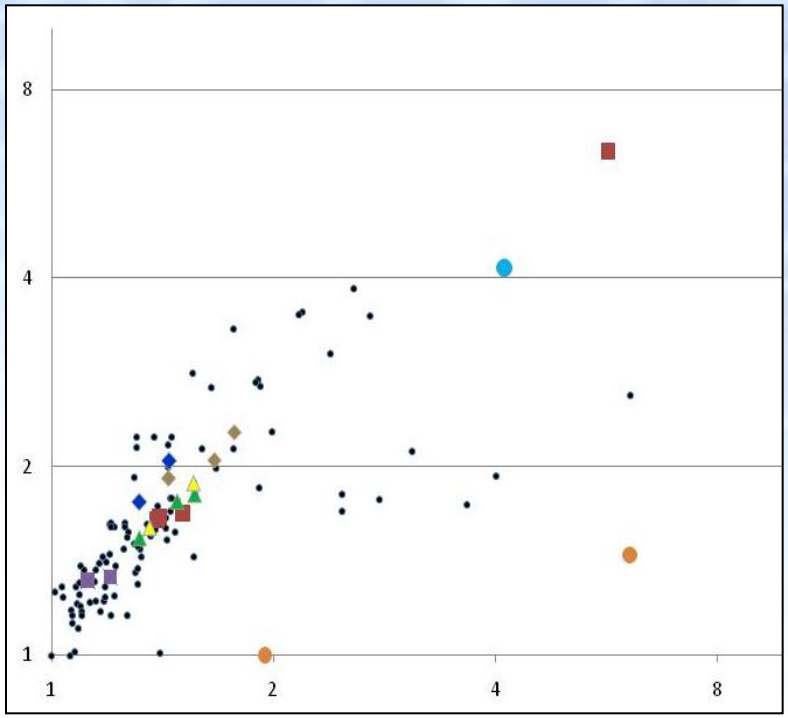
0 1 2 3 4 5 6 7 8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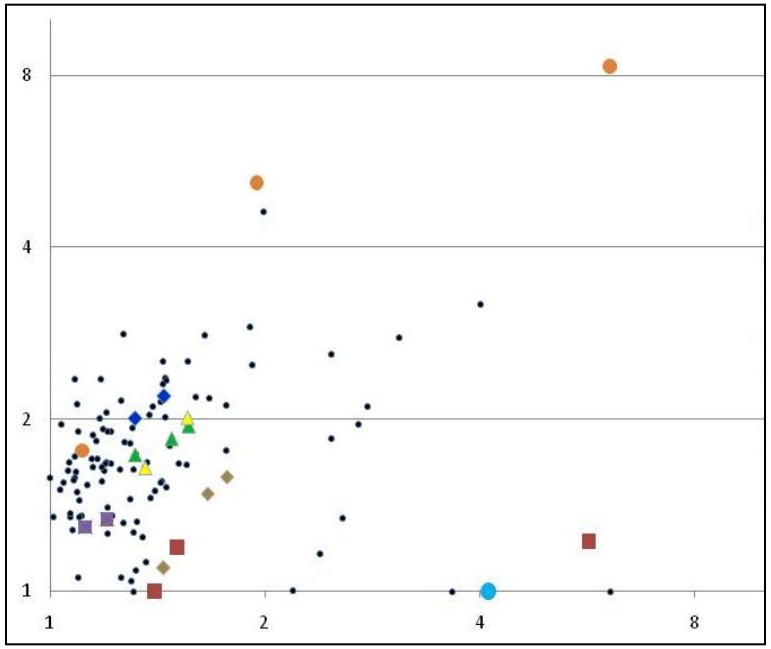
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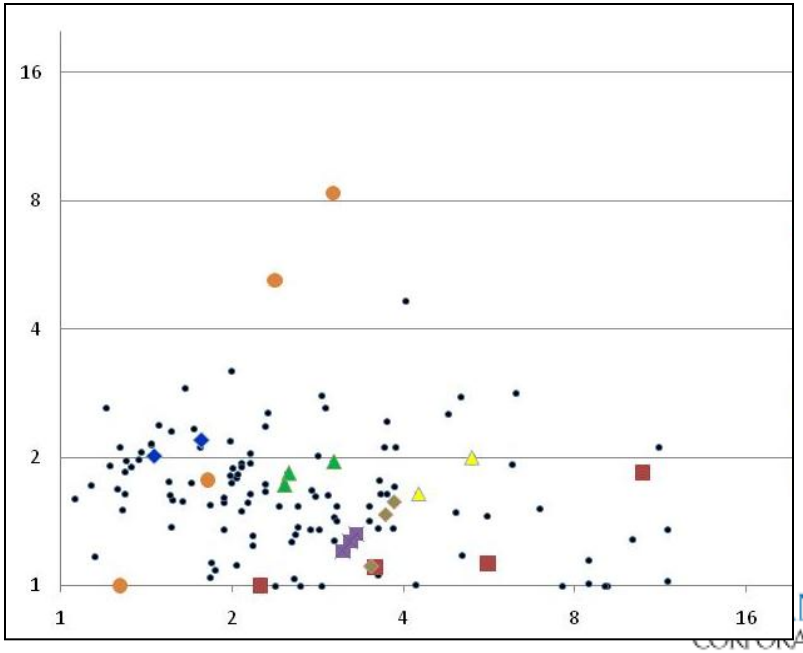
16
8
4
2
1
1 2 4 8 16

Future Research

- **Identify parameter combinations with best performance for:**
  - Different types of outcomes
  - Different outcome definitions
  - Different types of observational data (Claims, EMR…)
- **Performance of Observational Screening versus other OMOP signal identification methods**

Thank You!!

Questions?

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