Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Primer on Sentinel Inferential Queries

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Sentinel Data Queries: Routine Querying Tools

Query Parameterization

Design:

Identify patients with a ___ dispensing for . To be eligible, patients must have met the following criteria in the ____ days before the index dispensing: (1) continuous enrollment with _____ benefits, (2) be between ages of_____ on index date of exposure, and (3) have not received a dispensing for _____ in the prior __ days.

From Question to Query…

Design:

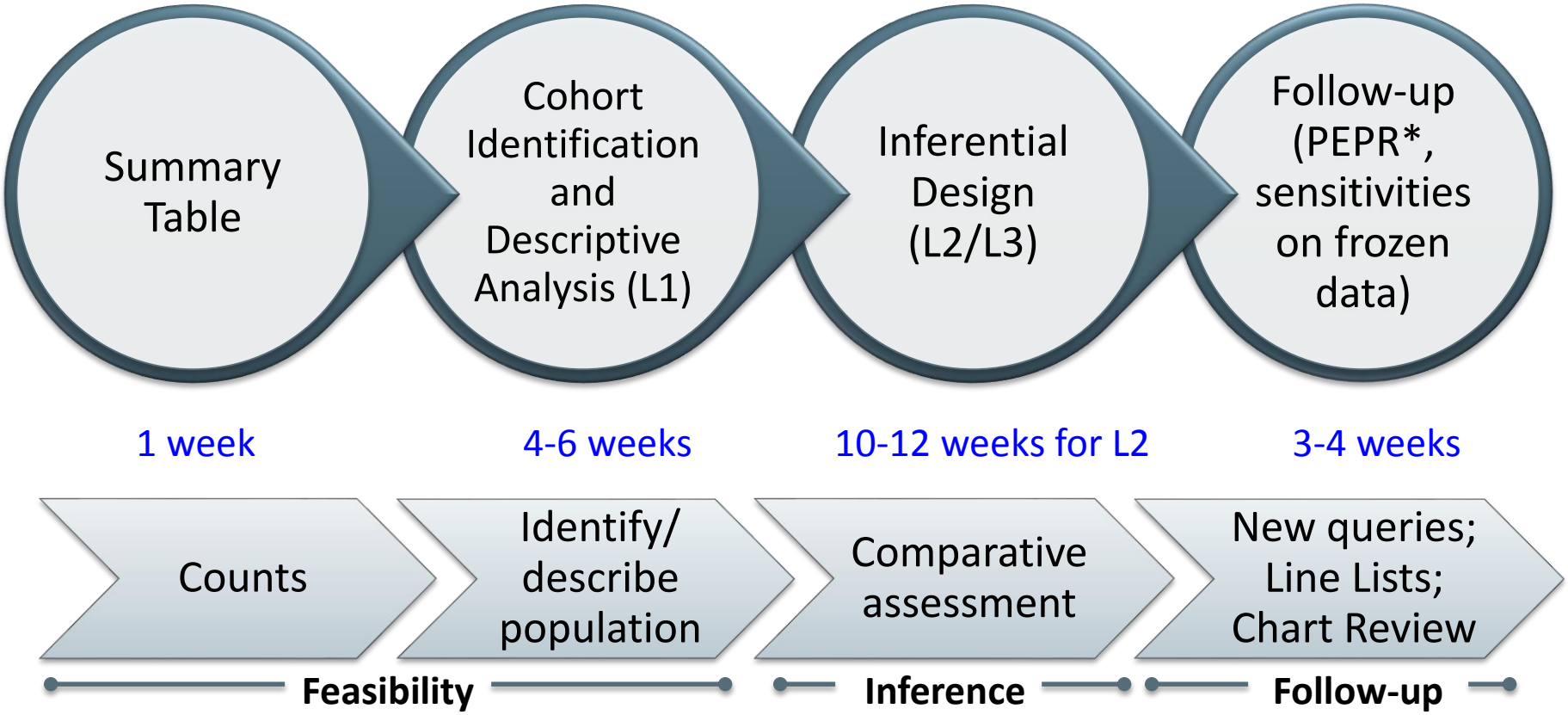
Identify patients with a **new** dispensing for an **ACE Inhibitor.** To be eligible, patients must have met the following criteria in the **183** days before the index dispensing: (1) continuous enrollment in **medical and pharmacy** benefits, (2) be between ages of **18-100** on index date of exposure, and (3) have not received a dispensing for **any ACE inhibitor, beta-blocker, ARB, or aliskerin** in the prior **183** days.

How Are Routine Queries Implemented?

- Query “templates” target common needs
  - Example: Identify cohorts, execute statistical analysis
- Parameterized at program execution
  - Example medical product exposure: ACE inhibitors
- Pre-tested and validated with minimal custom programming
  - Significantly shortens response time

Main Advantages: Speed, Transparency, Reproducibility

Typical Query Sequence



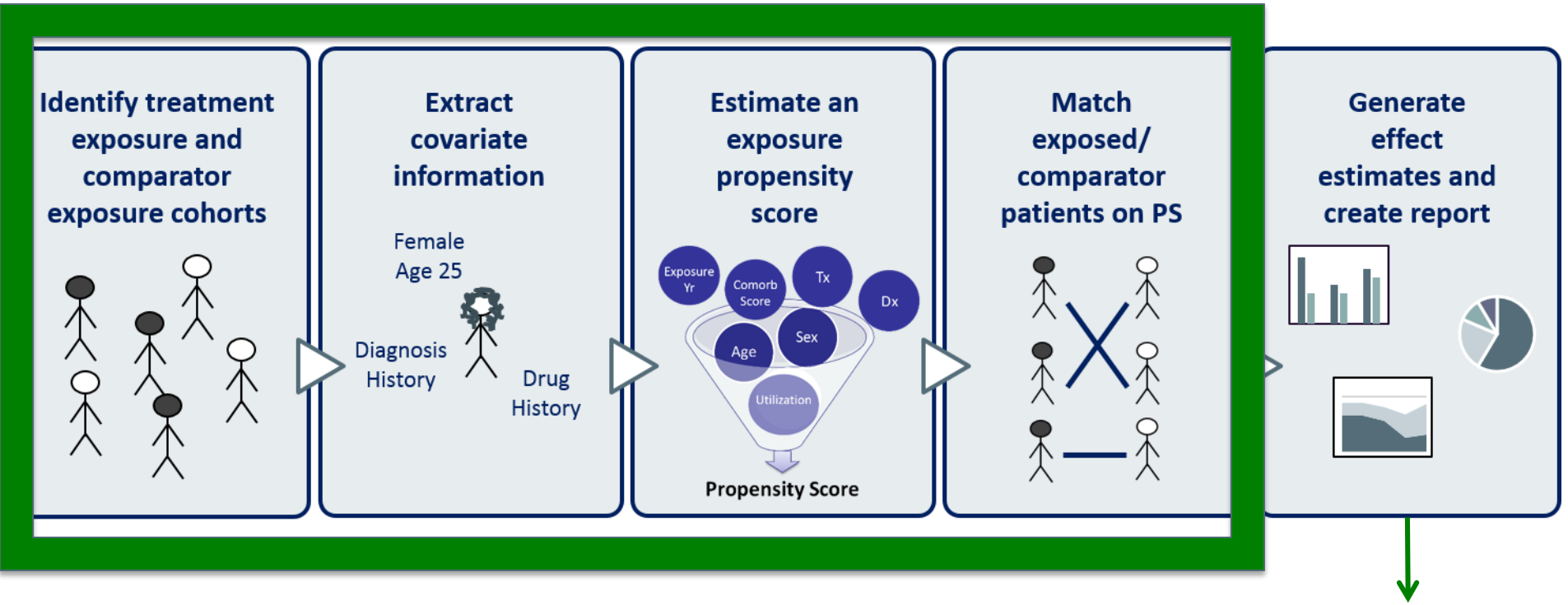
*Patient Episode Profile Retrieval

Types of Queries

1. Count-based queries (presence or absence)
2. Descriptive/feasibility queries (rates)
3. Inferential queries (effect estimates)
   - Level 2 Propensity Score Matching or Stratification Query
   - Level 2 Self Controlled Risk Interval Design Query
4. Follow-up queries (line lists)

Propensity Score Adjustment Tool: Matching or Stratification

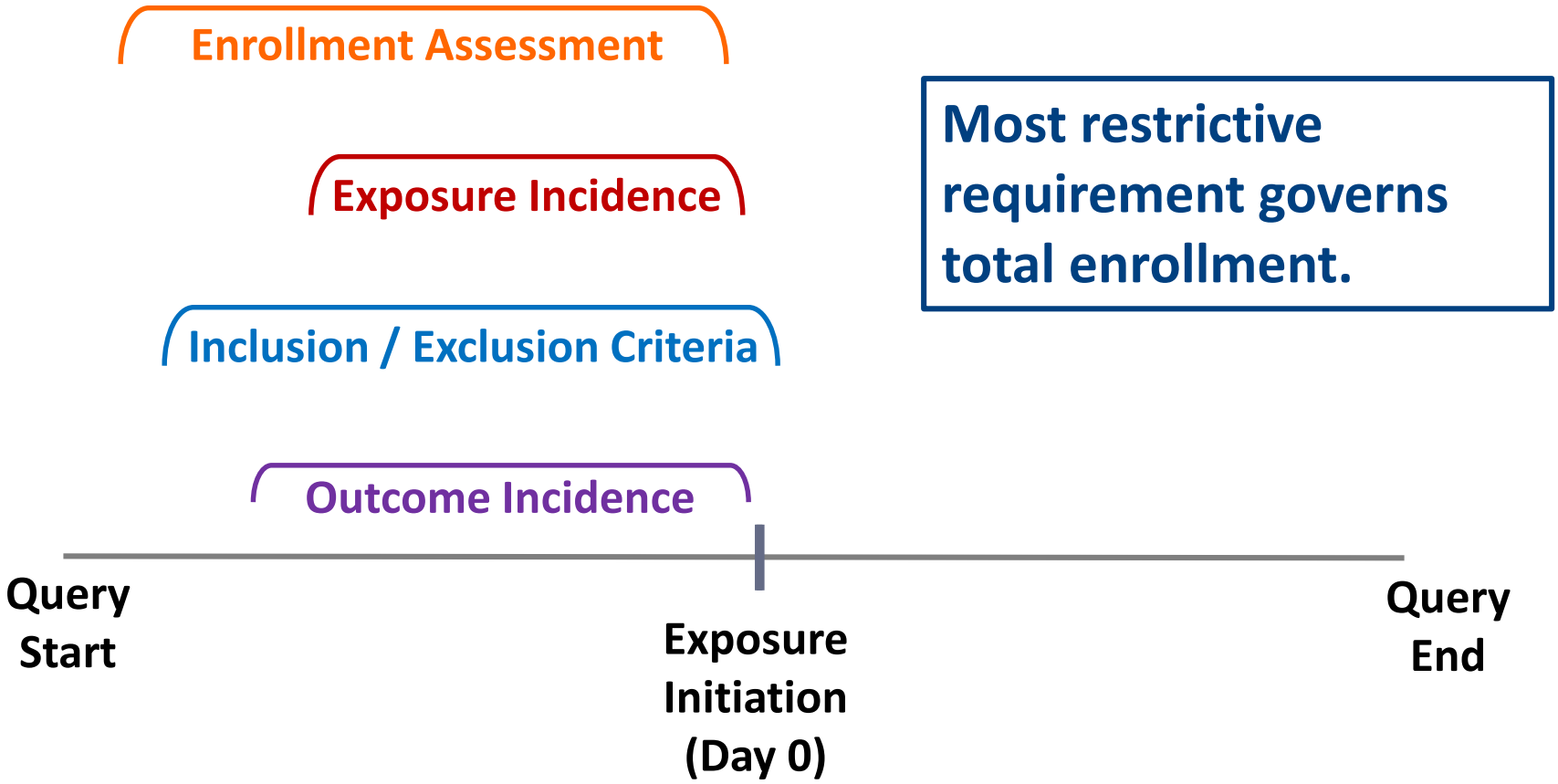
Propensity Score Adjustment in a Distributed Network



Performed at Data Partner Site

Performed at SOC

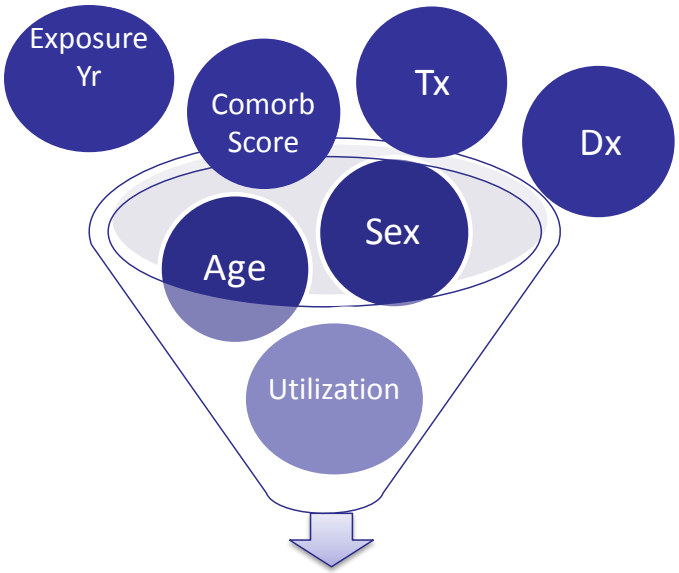
Step 1: Identify the Two Cohorts



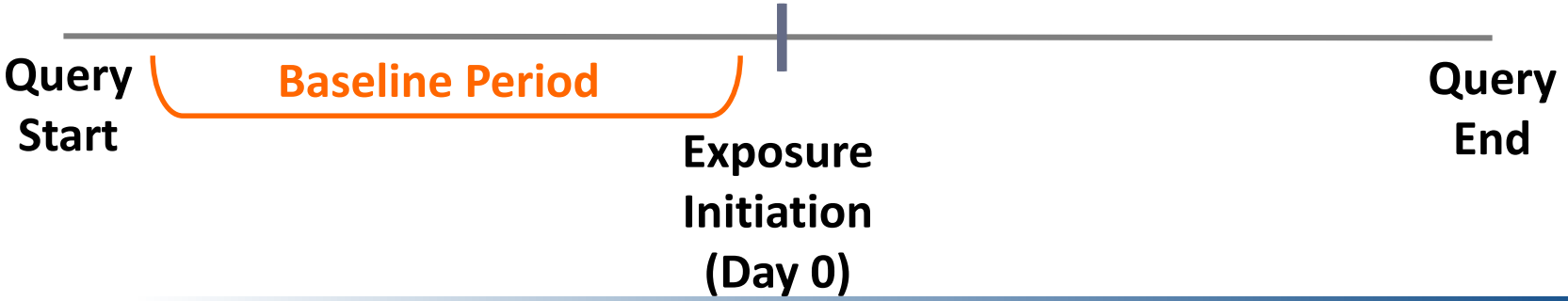
Most restrictive requirement governs total enrollment.

All require setting a universal enrollment membership gap parameter.

Step 2-4: Estimate the Propensity Score Model



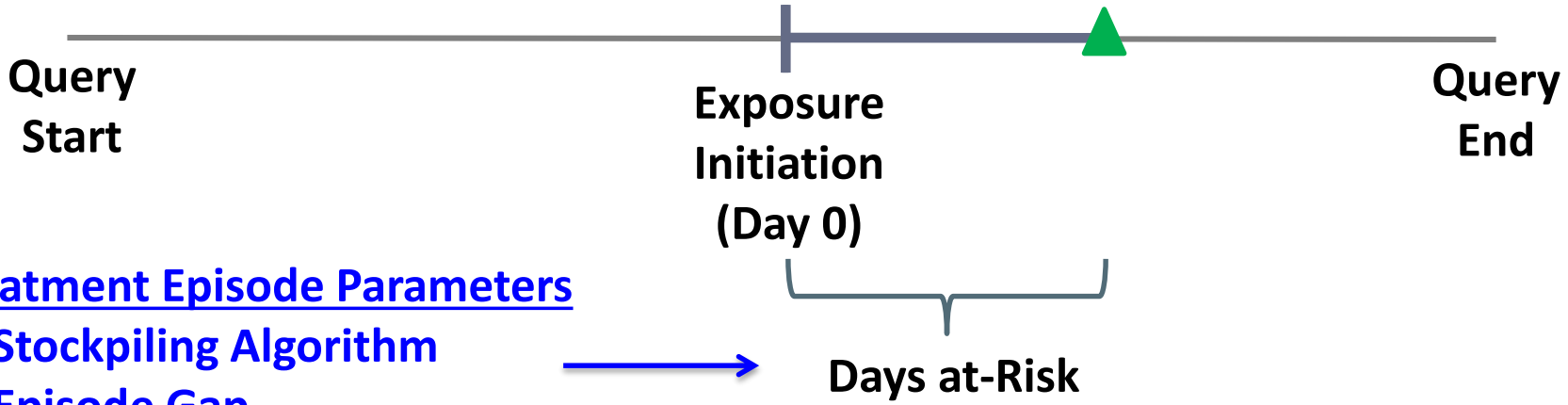
If matching, choose a matching strategy (1:1 or 1:n) within a caliper.



Step 5: Follow the Patient and Return Data

Censoring Event

1. Outcome
2. Disenrollment
3. End of Data
4. End of Study Period
5. User-Defined Truncation
6. Evidence of Death



Treatment Episode Parameters

1. Stockpiling Algorithm
2. Episode Gap
3. Episode Extension

Analysis at Sentinel Operations Center

- Site-stratified Cox Proportional Hazards Model or Case-centered Logistic Regression (mathematically equivalent) Produce Hazard Ratios (HRs)
  - Can condition on matched set or stratification n-tile
- Can perform subgroup analyses

PS Outputs

Table 1b. Cohort of New Initiators of Continuous or Extended Combined Oral Contraceptives and Cyclic Combined Oral Contraceptives (Matched, Aggregated), Ratio = 1:1, Caliper = 0.01

	Medical Product				Covariate Balance	
Characteristic[2]	Continuous or Extended Combined Oral Contraceptives		Cyclic Combined Oral Contraceptives			
	N/Mean	%/Std Dev[1]	N/Mean	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients (N)	203,402	96.5%	203,402	38.9%	-	-
Demographics:						
Mean age	30.2	8.5	30.3	8.7	-0.113	-0.013
Age: 18-24	69,501	34.2%	69,236	34.0%		
Age: 25-34	73,480	36.1%	73,965	36.4%		
Age: 35-50	60,421	29.7%	60,201	29.6%		
Gender (Female)	203,402	100.0%	203,402	100.0%		
History of use:						
Other Study Combined Hormonal Contraceptive	4,241	2.1%	3,740	1.8%		
Any Non-study Combined Hormonal Contraceptive	70,521	34.7%	71,700	35.3%		
Recorded history of:						
Prior Combined Comorbidity Raw Score	0.1	0.5	0.1	0.5		
Cardiac Conditions	832	0.4%	824	0.4%		
Cardiovascular and Metabolic Conditions	13,827	6.8%	13,876	6.8%		
Cerebral Palsy	*186*	*0.1%*	*62*	*0.0%*		
Cystic Fibrosis	*35*	*0.0%*	*64*	*0.0%*		
Gynecological Conditions	78,910	38.8%	79,509	39.1%		
Hypercoagulable States	87	0.0%	89	0.0%		
Immobility Conditions	1,095	0.5%	1,077	0.5%		
Infection Diseases	*93*	*0.0%*	*98*	*0.0%*		
Inflammatory Conditions	5,107	2.5%	4,995	2.5%		
Obesity and Overweight	6,099	3.0%	6,025	3.0%		

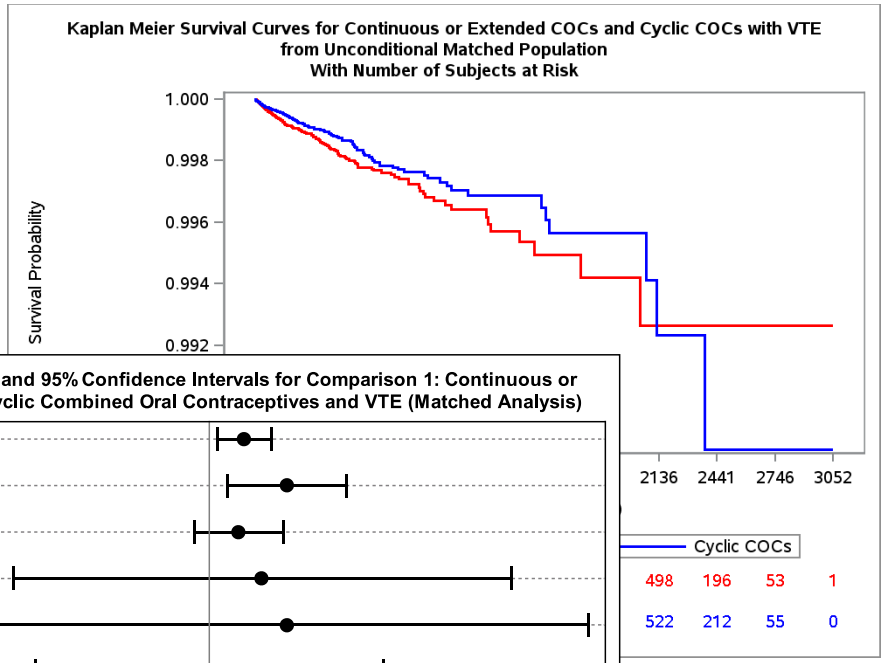


Table 2: Effect Estimates for Typical Antipsychotics and Atypical Antipsychotics by Analysis Type

Medical Product	Number of New Users	Person Years at Risk	Average Person Days at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1000 Person Years	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person Years	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Typical Antipsychotics	45,576	10,125.82	81.15	0.22	25	2.47	0.55	1.30	0.06	1.75 (1.17, 2.63)	0.0067
Atypical Antipsychotics	806,003	338,706.27	153.49	0.42	396	1.17	0.49				
1:1 Matched Unconditional Predefined Analysis; Caliper=0.05											
Typical Antipsychotics	45,495	10,113.92	81.20	0.22	25	2.47	0.55	-0.10	-0.62	0.87 (0.54, 1.41)	0.5657
Atypical Antipsychotics	45,489	20,634.52	165.68	0.45	53	2.57	1.17				
Predefined Percentile Analysis											
Typical Antipsychotics	45,576	10,125.82	81.15	0.22	25	2.47	0.55	1.30	0.06	1.25 (0.83, 1.89)	0.2801
Atypical Antipsychotics	806,003	338,706.27	153.49	0.42	396	1.17	0.49				

Self-Controlled Risk Interval Design

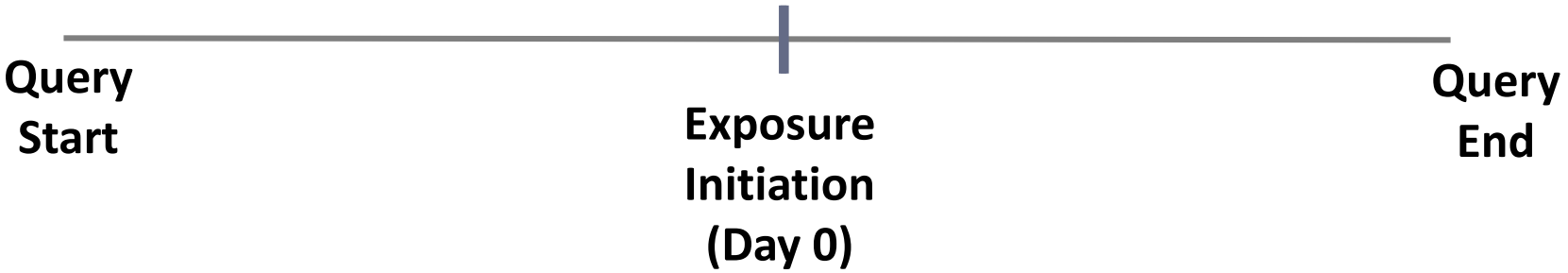
Step 1: Identify the Self-Controlled Cohort

Enrollment Assessment

Exposure Incidence

Inclusion / Exclusion Criteria

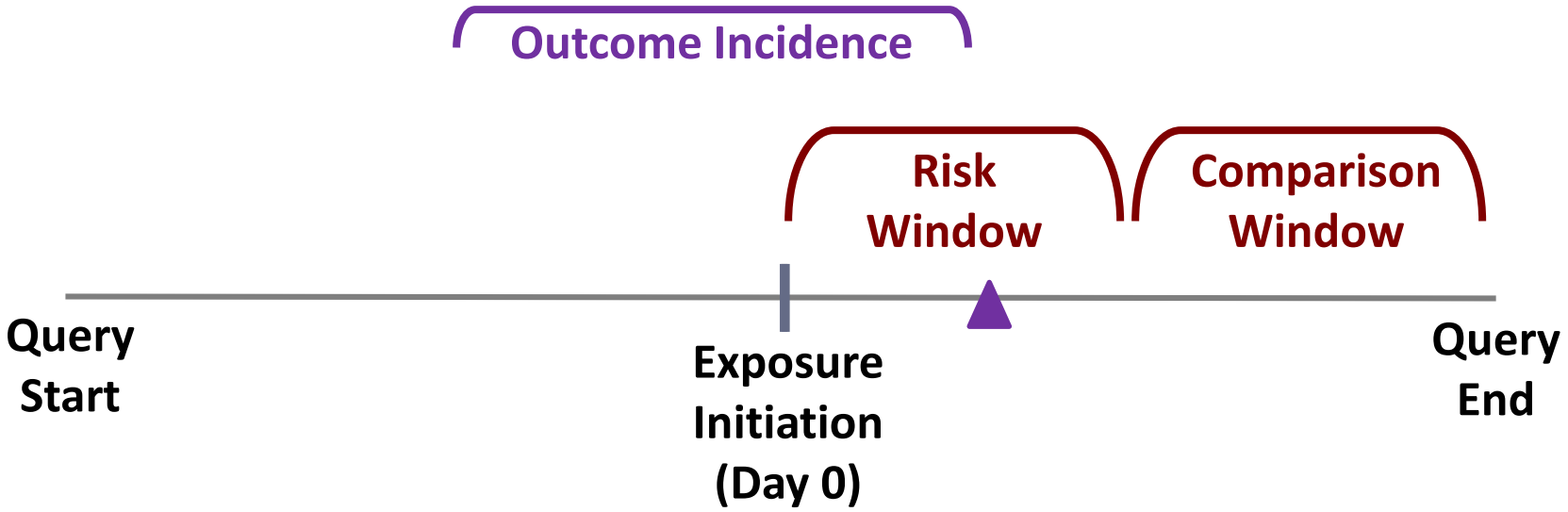
Most restrictive requirement governs total enrollment.



All require setting a universal enrollment membership gap parameter.

Step 2: Follow the Patient and Return Data

Patients that experience events and contribute time in both windows are informative to the test statistic.



Analysis at Sentinel Operations Center

- Case-centered Logistic Regression produces Relative Risk

Table 1c. Baseline Characteristics of Patients with a Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA) with Contrast Agent Compared to MRI or MRA without Contrast Agent from January 1, 2008 to November 30, 2016

Characteristic[1]	Contrast MRI or MRA		Non-Contrast MRI or MRA	
	N/Mean	%/Std Dev[2]	N/Mean	%/Std Dev[2]
Number of Unique Patients	1,708,779	100.0%	6,714,901	100.0%
Patient Characteristics				
Mean Age	49.5	16	47.3	16.7
Age: 2-17 years	89,429	5.2%	521,959	7.8%
Age: 18-44 years	527,870	30.9%	2,247,636	33.5%
Age: 45-64 years	794,012	46.5%	2,947,174	43.9%
Age: 65+ years	297,468	17.4%	998,132	14.9%
Gender (Ambiguous)	1	0.0%	1	0.0%
Gender (Female)	1,030,234	60.3%	3,479,031	51.8%
Gender (Male)	678,446	39.7%	3,235,486	48.2%
Gender (Unknown)	98	0.0%	383	0.0%
Recorded History of:				
Prior Combined Comorbidity Raw Score	0.5	1.3	0.1	0.8
Advanced Liver Disease	9,802	0.6%	4,343	0.1%
Allergy	225,542	13.2%	813,083	12.1%
Chronic Heart Failure	45,094	2.6%	91,113	1.4%
Coronary Artery Bypass Surgery	10,000	0.6%	28,122	0.4%
Diabetes Mellitus	175,123	10.2%	609,846	9.1%
Hospitalized Intracranial Bleed	36	0.0%	33	0.0%
Hyperlipidemia	210,256	12.3%	744,789	11.1%
Hypertension				
Major Surgery				
Metastatic Cancer				
Peripheral Vascular Disease				
Trauma with Likely Immob				
History of Use:				
Antiarrhythmic Medication				
Antihypertensive Medicati				
Diuretics				
Oral Antidiabetic Medicati				
Proton Pump Inhibitors				
SSRI or SNRI				
Statins				
Health Service Utilization Inter				
Mean number of ambulato				
Mean number of emergen				
Mean number of inpatient				
Mean number of non-acut				
Mean number of other am				
Mean number of filled RX				
Mean number of generics				
Mean number of unique				

[1] All metrics are reb based on total
[2] Value represents standard dev

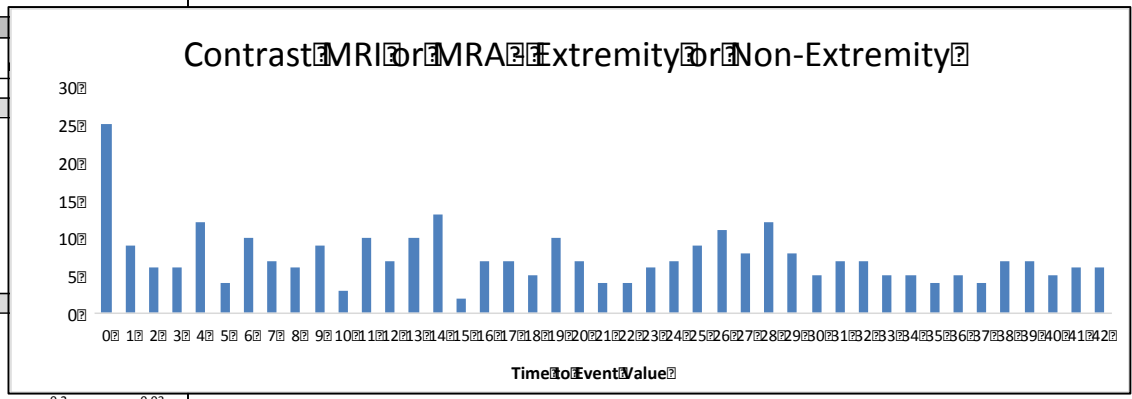


Table 2: Summary of Incident Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA) Exposures and Seizures in the Sentinel Distributed Database between January 1, 2008 and November 30, 2016, by MRI or MRA Location and Exclusion Criteria

	Exposure Cohort		*Analysis Cohort*		*Number of Events*		
	Number of Patients	Number of Index Dates	Number of Patients	Number of Index Dates	Risk Window	Control Window	Estimate (95% CI)
Contrast MRI/MRA Extremity or Non-Extremity							
	1,708,779	1,991,158	316	317	25	292	3.49 (2.32, 5.25)
Contrast MRI/MRA Non-Extremity							
	1,210,037	1,445,364	245	246	21	225	3.85 (2.46, 6.03)
Contrast MRI/MRA Extremity							
	507,944	535,838	70	70	4	66	2.35 (0.86, 6.47)
Contrast MRA Extremity or Non-Extremity							
	57,705	63,919	13	13	3	10	12.60 (3.47, 45.78)
Non-Contrast MRI/MRA Extremity or Non-Extremity							
	6,714,901	7,955,932	1,150	1,152	87	1,065	3.35 (2.69, 4.16)

Takehome Messages

- Parameterized and semi-automated programs enable speed, transparency, and reproducibility.
  - Generate effect estimates and confidence intervals quickly.
  - Compare to a fully customized protocol, programmed *de novo.*
- They do not enable push-button epidemiology.
- Usual limitations of observational data apply.