

Signal Detection using TreeScan with Drug Classes: Pilot Projects in Sentinel

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- This presentation reflects the views of the authors and not necessarily those of the U.S. FDA.

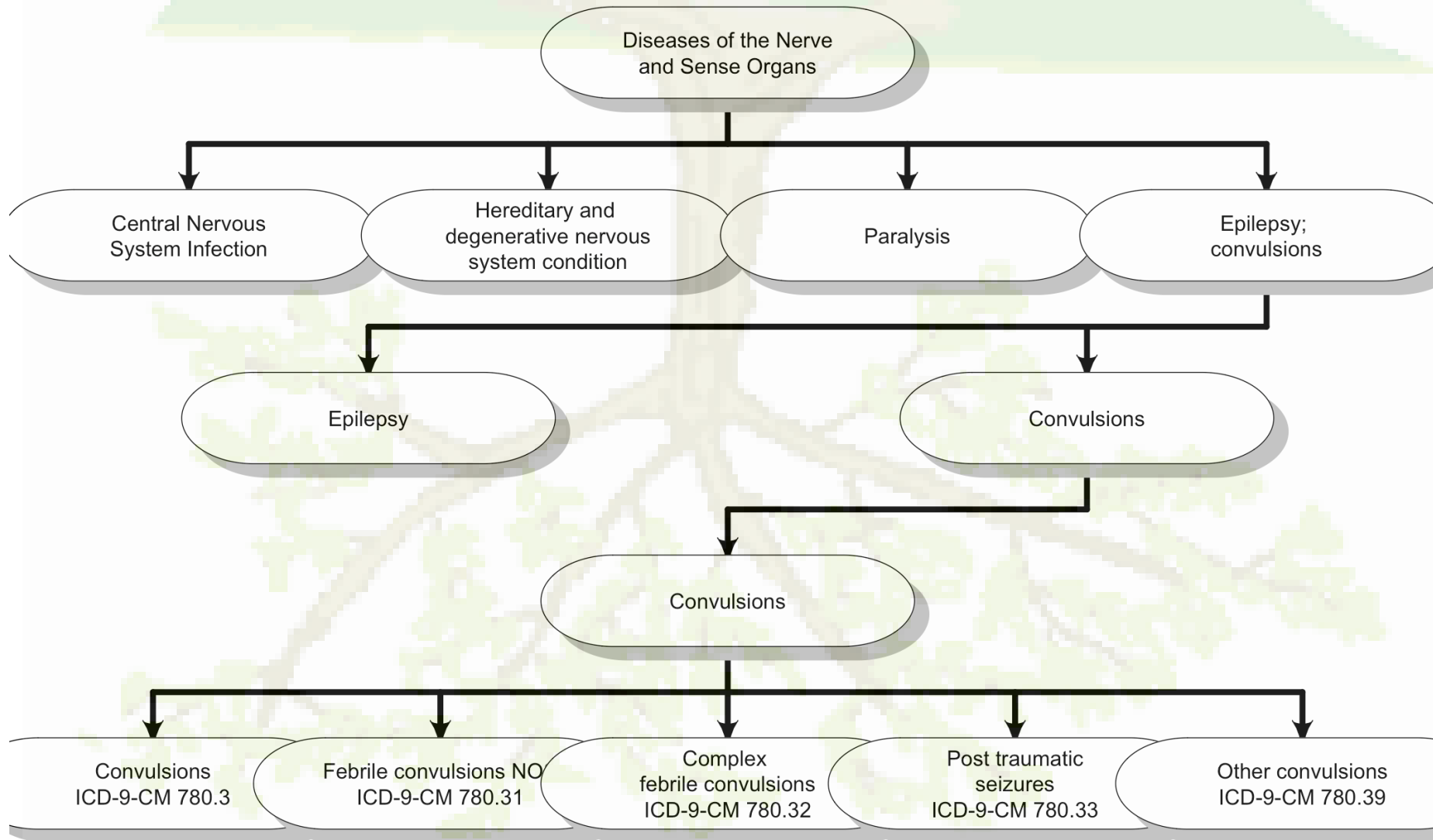
Tree-Based Scan Statistics are Enabled by:

- A signal detection / data-mining method
- Scans electronic health outcome data that are grouped into hierarchical tree structures
- Automatically adjusts for multiple hypothesis testing



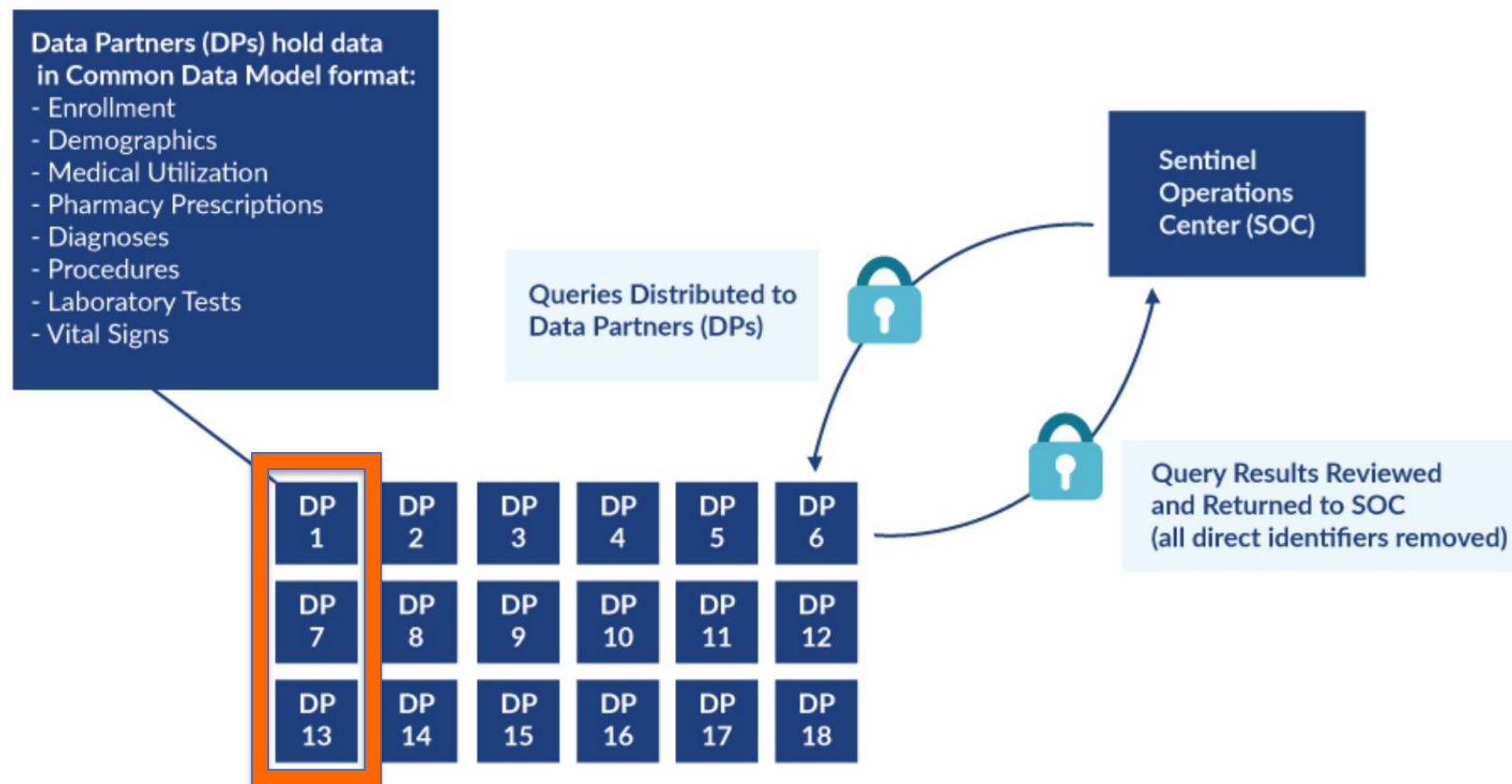
<http://www.treescan.org>

Multi-Level Clinical Classification System Tree



Data Source

- 3 Data Partners in Sentinel Distributed Database
 - Represents ~35% of the Overall Sentinel Distributed Database
 - Data from 2000 to Latest Available (between 2016-2017)



Three Medical Product Study Classes (Test Cases)



- Long-Acting Reversible Contraceptives
 - Small Sample Size
 - Medically-attended procedures present as point exposures
- Statins
 - Large Sample Size
 - Established Safety Record
- Selected Antibiotics
 - Very Large Sample Size
 - Therapeutic administered in an urgent treatment situation

Universal Self-Controlled Study Design Diagram

No Prior Outcomes in the 4th Level of the MLCCS Tree in 183 days

No Study Drug in [-183,-1]

Study-Specific Exclusions with varying Time Periods

TreeScan Observation Window [1,56]

Query Start Date

New Study Drug Use

ED or IP Outcome

Query End Date

Pre-Exposure Enrollment Requirements [-183,0]

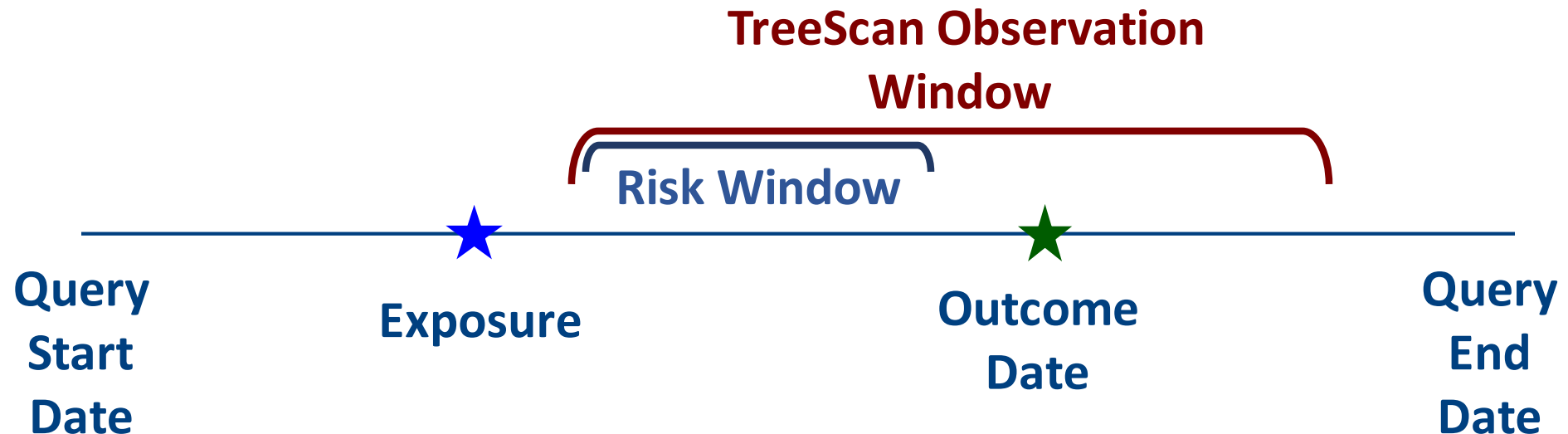
Post-Exposure Enrollment Requirements [1,56]

Continuous Enrollment Requirements (w/45-d gaps)

Conditional Tree-Temporal Scan Statistic

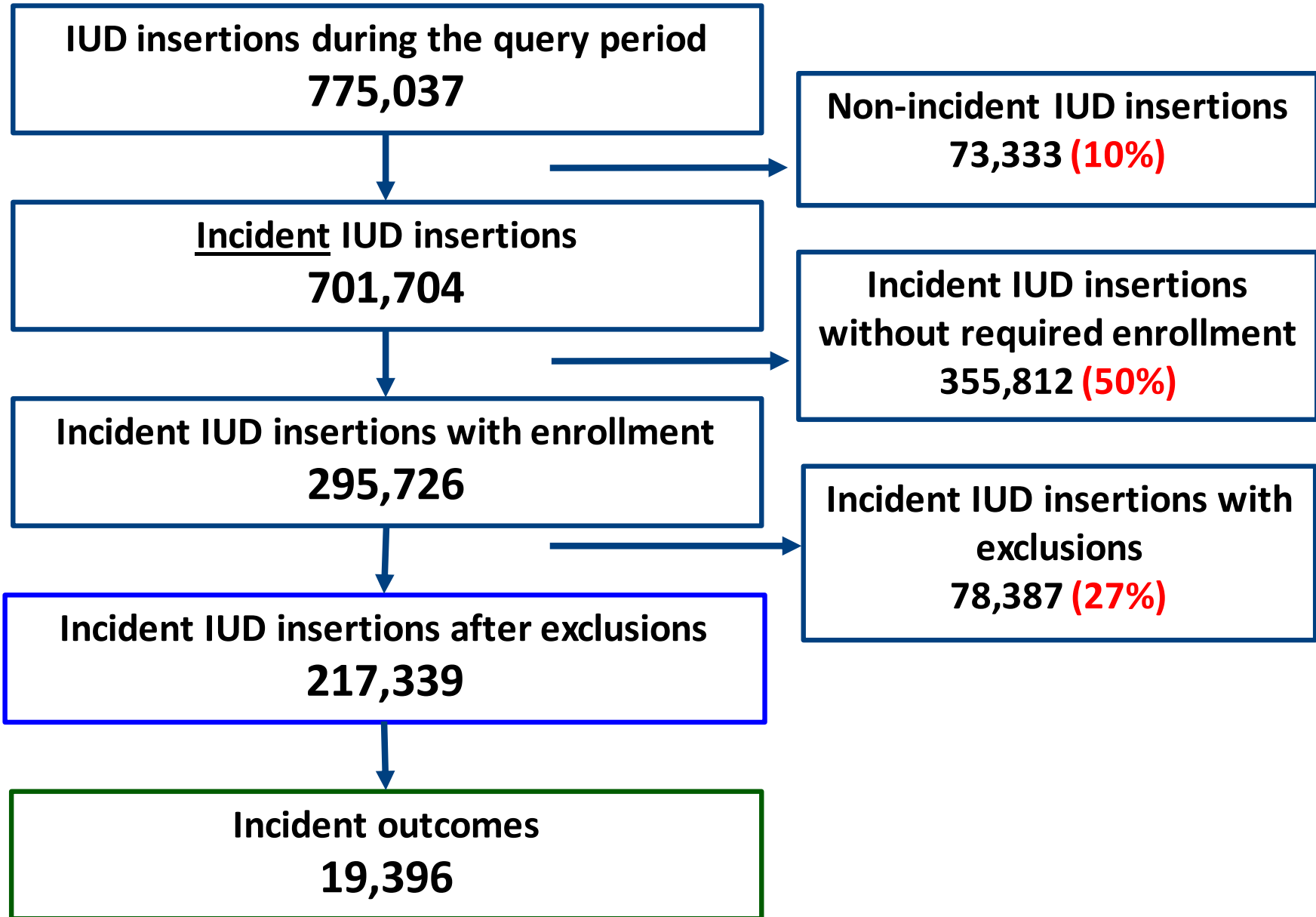
Under the **null hypothesis**, there is no unusual clustering of events within any node or clinically-related group during any time interval.

Under the **alternative hypothesis**, there is at least one node or clinically-related group of the tree for which there is a temporal cluster of events during some time interval.



Results

Intrauterine Device (IUD) Cohort Attrition



Exposed Cohort

Analytic Cohort

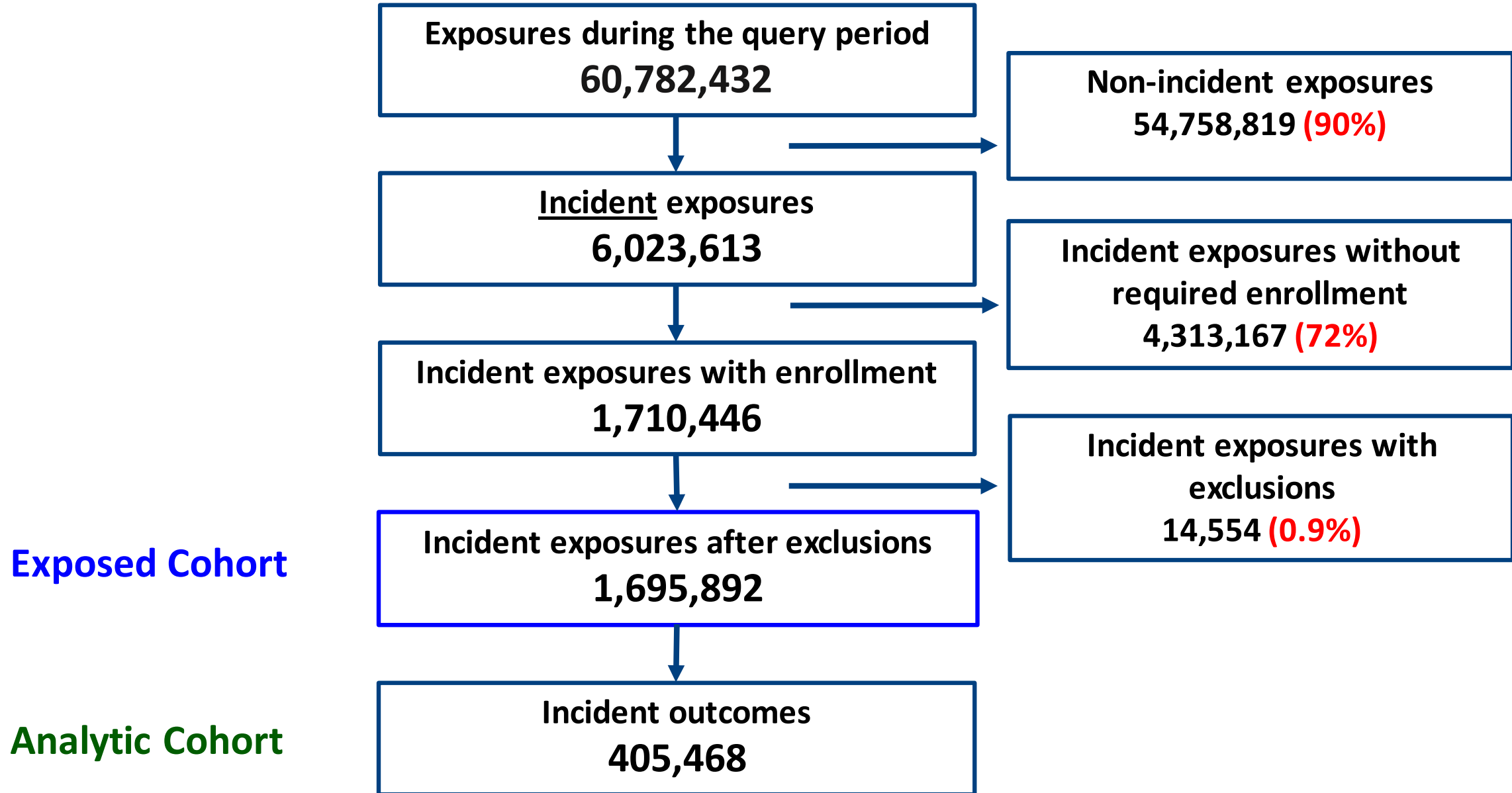
All Intrauterine Device Primary Results



Node Name	Node ID	Node Outcomes	Node Outcomes in Risk Window	RW Start	RW End	Relative Risk	P Value
Female genital pain and other symptoms	10030901	612	115	1	4	2.74	0.0001
....Female genital symptoms NOS	6259	576	112	1	4	2.85	0.0001
Other complications of internal prosthetic device; implant; and graft	16100103	114	30	1	4	4.09	0.0003
....Complication NEC due to GU device	99676	106	29	1	4	4.31	0.0002
Other specified non-inflammatory disorders of vagina	6238	254	200	2	29	3.21	0.0016

These “alerts” are not unexpected and reflect routine but rare complications of IUD insertions.

Simvastatin Cohort Attrition



Simvastatin Primary Results



Node Name	Node ID	Node Outcomes	Node Outcomes in Risk Window	RW Start	RW End	Relative Risk	P Value
Unstable angina (intermediate coronary syndrome)	07020402	2269	523	1	7	1.68	0.0001
...Intermediate Coronary Syndrome	4111	2269	523	1	7	1.68	0.0001
Angina Pectoris	07020401	1408	377	1	8	1.77	0.0001
...Angina Pectoris NEC & NOS	4139	1353	360	1	8	1.76	0.0001
Cardiac arrest and ventricular fibrillation	07021000	459	160	44	56	1.95	0.0006
...Cardiac Arrest	4275	307	106	47	56	2.61	0.0001
Disorders of lipid metabolism	03060000	7449	2269	1	13	1.22	0.0001
Other forms of chronic heart disease	07020405	5447	1676	1	13	1.24	0.0001
Hemorrhage or hematoma complicating a procedure	16100205	990	227	1	7	1.67	0.0002
...Hematoma Complicating a Procedure	99812	451	113	1	6	2.25	0.0001
Conditions associated with dizziness or vertigo	06080200	4633	628	1	5	1.3	0.0011
...Dizziness & Giddiness	7804	4210	578	1	5	1.32	0.0006
Respiratory failure	08060100	3063	804	42	54	1.29	0.0031
Surgical Complication-Peripheral Vascular	9972	121	40	1	6	3.32	0.0099
Coronary atherosclerosis	07020404	6247	1243	1	8	1.2	0.0100
Lower extremity aneurysm	4423	82	28	1	5	4.29	0.0100

Antibiotic Results

Name	Exposure Cohort	Analytic Dataset	Alerts at 0.01
Azithromycin	7,500,871 episodes	1,412,160 events	174 alerts
Ciprofloxacin	3,706,774 episodes	1,206,543 events	209 alerts
Levofloxacin	1,506,530 episodes	638,717 events	72 alerts

- Overwhelmed by signs and symptoms followed by individuals with profiles for acute organ failure, septic shock, and other acute traumatic events.

Limitations

- Self Controlled Design:
 - Depends on onset times in the data model
 - May capture alerts due to signs and symptoms related to drug indications
 - Cannot distinguish sustained elevated risk of outcome
 - Is vulnerable to time-varying confounding
- Analytic Limitations:
 - Acute outcome events only with fixed follow-up

- We empirically tested tree-temporal scan statistics in 3 different drug classes.
- Self-controlled TreeScan methods performed as expected:
 - Best when applied to stable patients (eg, contraceptives, vaccines)
 - Moderate performance for statins; Better performance possible with more careful exclusion criteria for recently hospitalized / unstable patients
 - Poor performance for acutely ill, unstable patients
- New propensity score based TreeScan may better account for these conditions (more unstable patient populations)
 - Next Up: Shirley Wang presents **“Data mining for adverse drug events with a propensity score matched tree-based scan statistic”**

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