



# Using TreeScan as a Signal Identification Approach to Screen for Adverse Maternal Outcomes of Medication Use in Pregnancy

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# Disclaimer

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- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.

# Agenda

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- Overview of TreeScan® analysis

## 02 Study Objective

- Evaluating TreeScan performance to screen for adverse maternal outcomes

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## 05 Conclusions



# Background

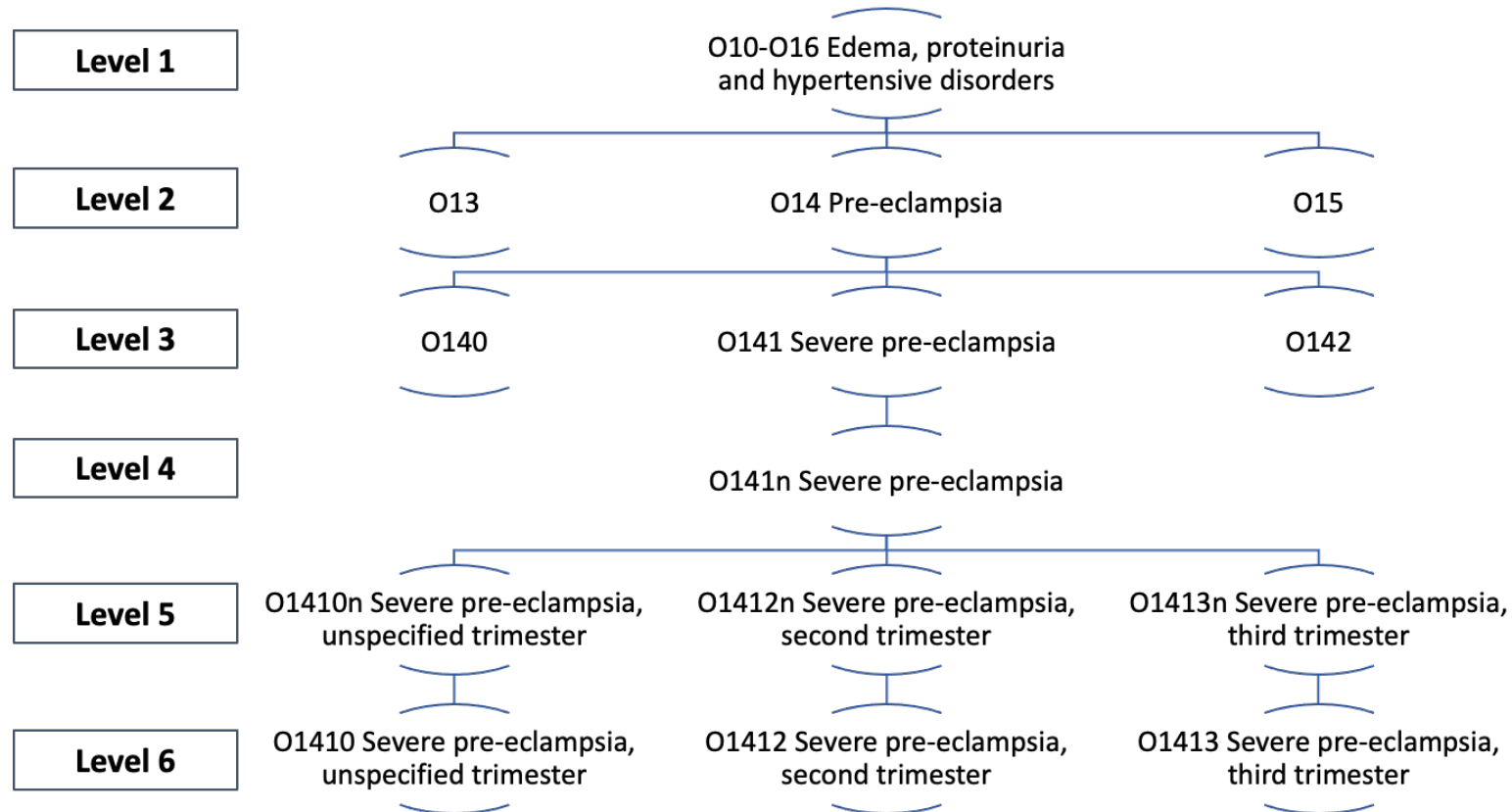
# Lack of Safety Evidence for Medication Use During Pregnancy

- In the US, about 70% of pregnant women use at least one prescription medication during pregnancy and four medications on average.
- Almost 98% of medications approved from 2000 to 2010 have an undetermined teratogenic risk.
- More evidence is needed to guide women and clinicians in making decisions.

# Overview of TreeScan Analysis

- TreeScan™ (<http://www.treescan.org>) is a signal identification method that evaluates thousands of outcomes simultaneously to identify potential adverse events after adjusting for multiple testing.
- Thousands of outcomes are classified into a hierarchical tree structure.

*Figure 1. An example of the maternal tree*

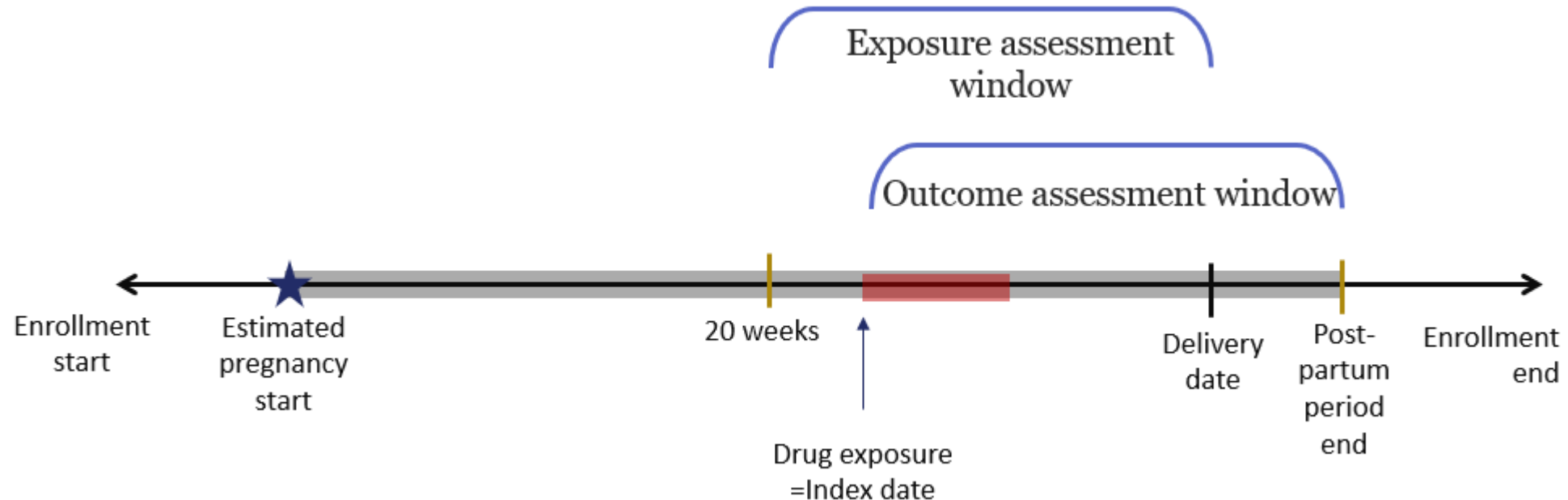




# Study Objective

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- To assess the performance of the TreeScan method to identify signals for **maternal and obstetric adverse outcomes** occurring from **20 weeks of gestation to 30 days** after delivery among women with livebirths exposed to **oral macrolides** compared to **oral penicillins**.
- Macrolides/penicillins were chosen because of their known safety profiles.



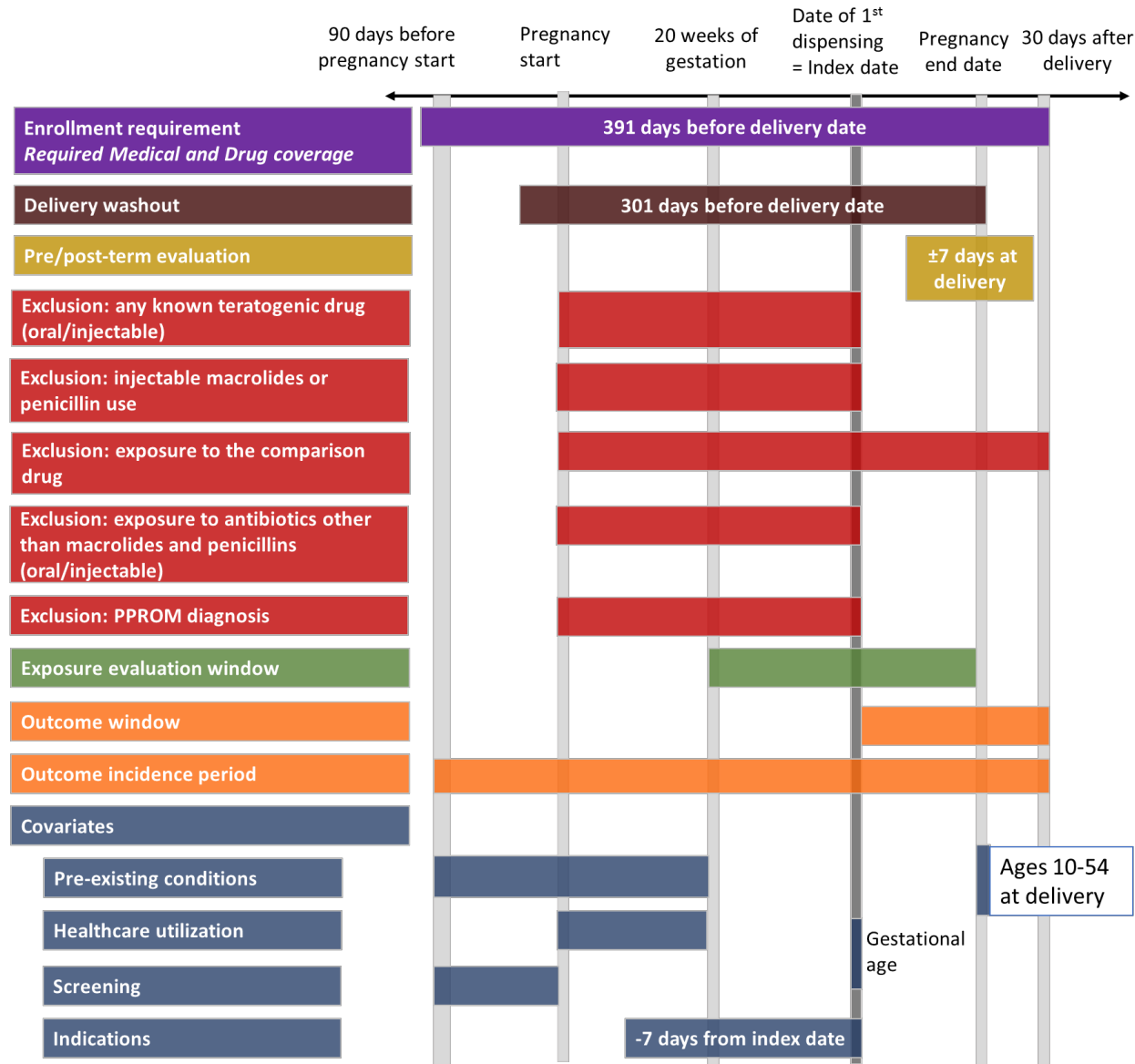




# Methods

# Study Design

Data source:  
MarketScan Commercial  
Claims 2015-2020



**Cohort:** Singleton livebirth deliveries

**Query period:** October 1, 2015 – February 29, 2020

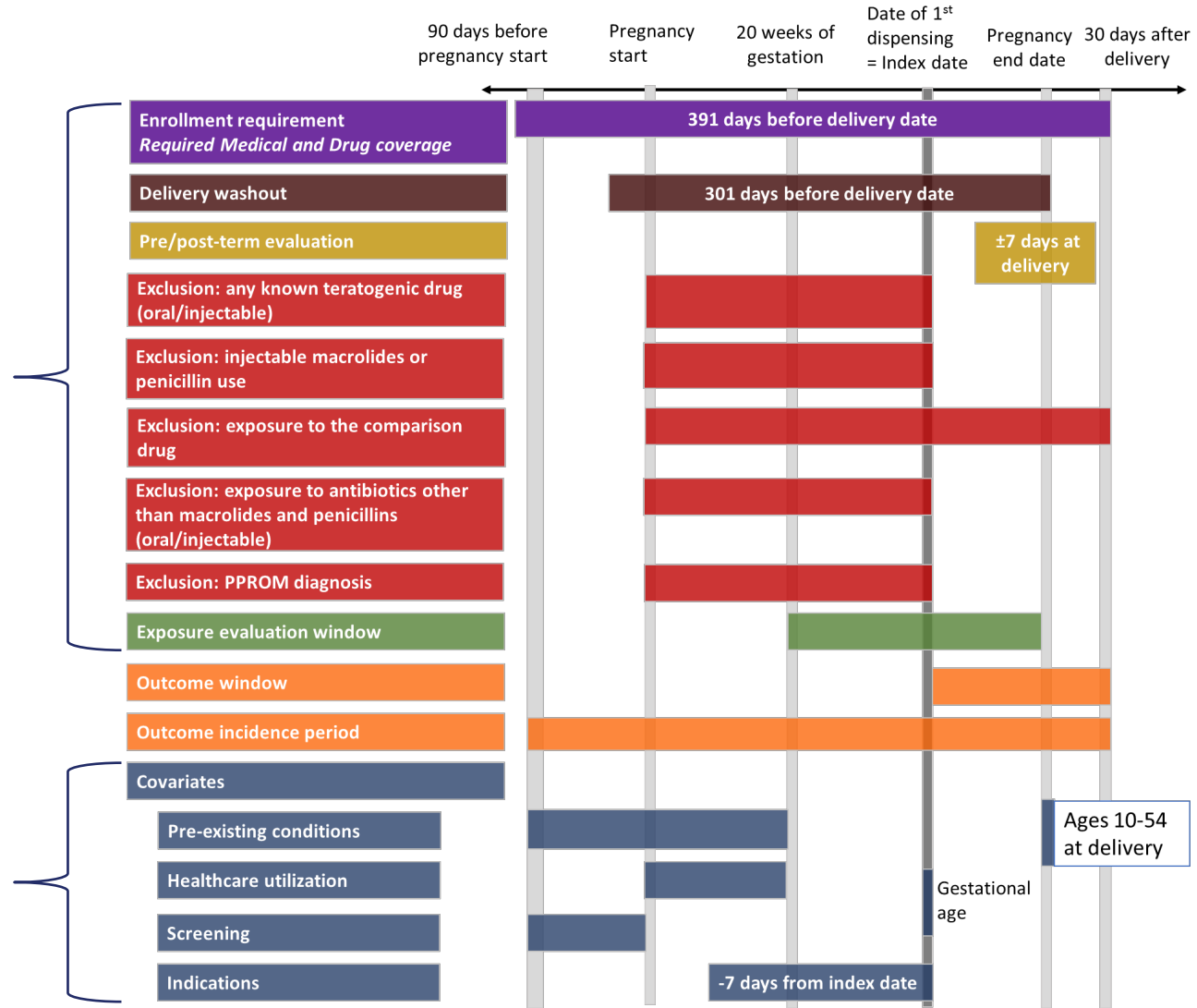
**First valid livebirth delivery date:** October 26, 2016

**Last valid livebirth delivery date:** January 30, 2020

# Study Design

Cohort establishment (inclusion/exclusion criteria) is similar to a traditional observational study

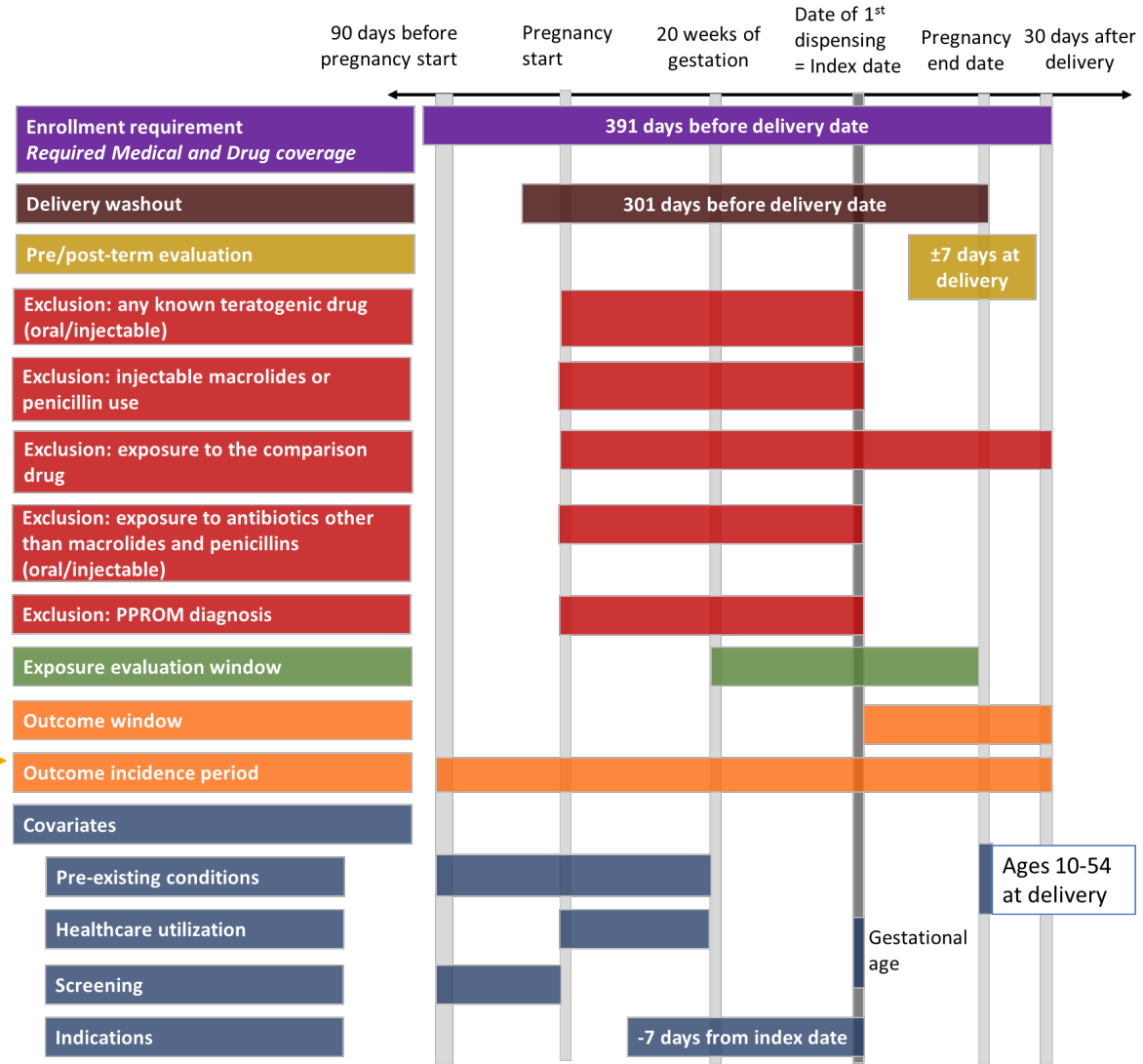
Confounders can be controlled via propensity score method



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# Study Design

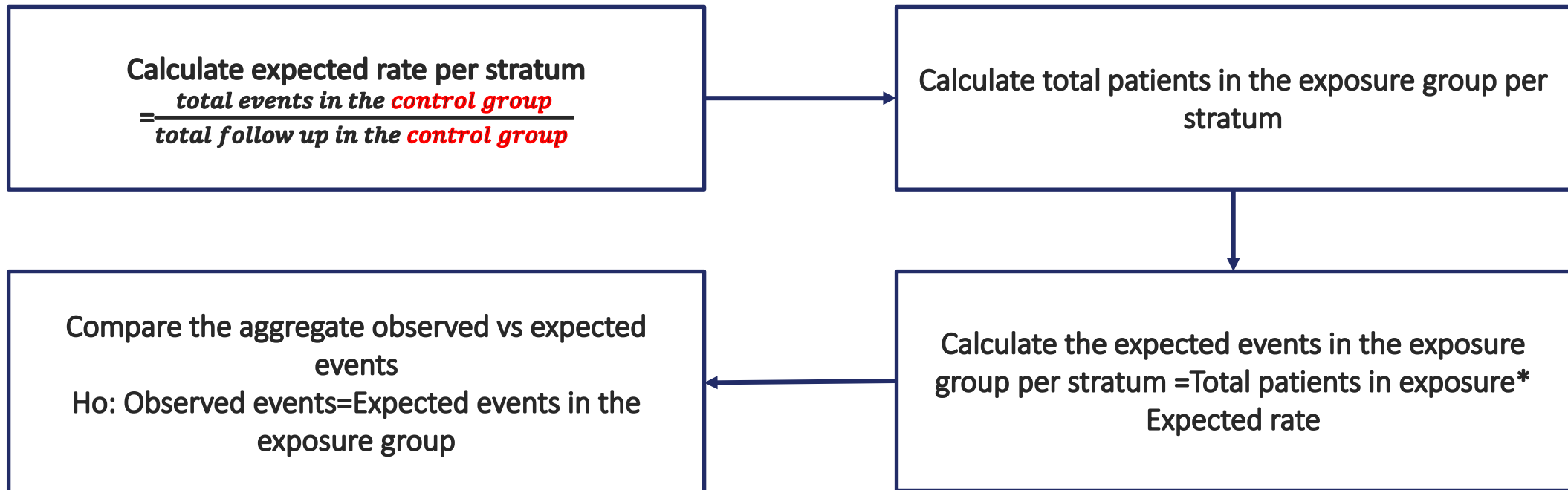
- To identify new-onset conditions emerging after drug exposure
- To prevent repeat counting of the same condition



**Cohort:** Singleton livebirth deliveries  
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# Statistical Analysis

- After trimming non-overlapping regions of the propensity score, the cohort was stratified based on different combinations of propensity score quartiles or deciles and windows of gestational age at treatment initiation to balance on covariates and gestational age of treatment.
- Calculate observed/expected counts per node in the Poisson statistic analysis:



# Statistical Analysis

- The conditional log likelihood ratio (LLR) based test statistic T can be calculated for the Poisson model as follows:

$$LLR(G) = \left[ c_G \ln \left( \frac{c_G}{n_G} \right) + (C - c_G) \ln \left( \frac{C - c_G}{N - n_G} \right) \right] I \left( \frac{c_G}{n_G} > \frac{C - c_G}{N - n_G} \right)$$
$$T = \max_G LLR(G)$$

Where: T = conditional Poisson tree scan statistic  
 $c_G$  = observed cases in the treatment group for a given maternal outcome  
 $n_G$  = expected cases in the treatment group for a given maternal outcome  
C = total number of maternal outcomes in the risk window summed over the tree  
N = total number of expected maternal outcomes summed over the tree  
G = maternal outcome of interest

- Random datasets are generated under the null hypothesis, and the test statistic T is calculated for each random dataset.
- If the statistical significance is set as alpha=0.05, an outcome alert occurs if that outcome's test statistic in the real dataset ranks in the top 5% of all test statistics among the real and replicated datasets.

# Analysis Scenarios

#	Analysis scenarios	Strata of gestation age	Strata of propensity score
1	Vary cut-off of gestational age at treatment initiation	Every 2 weeks	Quartiles
2		Every 4 weeks	
3		Every 6 weeks	
4	Vary cut-off of propensity score	Every 6 weeks	Deciles
5	Restrict to patients with respiratory tract infections (RTI)	Every 6 weeks	Deciles
6	Restrict to patients with RTI and outcomes in inpatient or emergency department visits	Every 6 weeks	Deciles



# Results



# Baseline Characteristics

Mother Characteristics	Pregnant Macrolide Users		Pregnant Penicillin Users		Standardized Difference
	Counts	Percent/ Standard Deviation	Counts	Percent/ Standard Deviation	
Unique patients	13,215		18,554		
<b>Demographic Characteristics</b>					
Age (years)	31.1	5.3	30.9	5.2	0.029
Year					
2016	771	5.80%	875	4.70%	0.05
2017	4,747	35.90%	5,990	32.30%	0.077
2018	3,965	30.00%	5,790	31.20%	-0.026
2019	3,732	28.20%	5,899	31.80%	-0.078
2020	0	0.00%	0	0.00%	NaN
<b>Health Characteristics</b>					
Ear, Nose, and Throat Infections	4,603	34.80%	9,394	50.60%	-0.324
Gastrointestinal Infections	32	0.20%	60	0.30%	-0.015
Lower Respiratory Infections	1,300	9.80%	731	3.90%	0.234
Sexually Transmitted Infections	113	0.90%	31	0.20%	0.097
Other Indications	5	0.00%	97	0.50%	-0.092
Pelvic Inflammatory Disease	105	0.80%	164	0.90%	-0.01
Skin and Subcutaneous Tissue	32	0.20%	208	1.10%	-0.107
Urinary Tract and Kidney Infections	115	0.90%	708	3.80%	-0.196
Other characteristics	Well balanced between the two groups				

# Indication Balance by Analysis Scenarios

Characteristics	Standardized difference					
	Unadjusted	4 weeks GA- quartile PS	2 weeks GA - quartile PS stratification	6 weeks GA - quartile PS stratification	6 weeks GA - decile PS stratification	6 weeks GA - decile PS stratification with RTI restriction
Ear, Nose, and Throat Infections	-0.324	0.011	0.011	0.007	0.007	-0.022
Gastrointestinal Infections	-0.015	0.005	0.004	0.004	0.006	0.005
Lower Respiratory Infections	0.234	0.094	0.093	0.091	0.035	0.015
Sexually Transmitted Infections	0.097	0.064	0.064	0.063	0.049	-0.003
Other Indications	-0.092	-0.057	-0.058	-0.053	-0.046	-0.014
Pelvic Inflammatory Disease	-0.01	0.003	0.002	0.006	0.004	-0.002
Skin and Subcutaneous Tissue	-0.107	-0.065	-0.066	-0.065	-0.048	-0.034
Urinary Tract and Kidney Infections	-0.196	-0.122	-0.122	-0.122	-0.092	-0.019

Note: GA: gestational age; PS: propensity score

Only the decile propensity score stratification could achieve the indications' balance

# Macrolide alert patterns

Node description	Decile PS (Analysis #4)	RTI (Analysis #5)	IP/ED settings (Analysis #6)
<b>Total alerts</b>	<b>10</b>	<b>2</b>	<b>1</b>
Infections related	1		
Maternal care for pelvic problem or excessive fetal growth	5	1	1
Preterm labor without delivery	1	1	
Gestational hypertension	1		
Fetal anemia and thrombocytopenia	1		
Unspecific/non-actionable alert	1		

Note: Shading indicates different clinical groups of alerts; PS: propensity score; RTI: respiratory tract infections; IP/ED: inpatient/emergency department

# Penicillin alert patterns

Node description	Decile PS (Analysis #4)	RTI (Analysis #5)	IP/ED settings (Analysis #6)
<b>Total alerts</b>	<b>23</b>	<b>16</b>	<b>20</b>
Infections related	7	4	3
Antepartum hemorrhage		1	1
Placenta related conditions		2	1
Chorioamnionitis		1	1
Oligohydramnios			1
Pre-eclampsia	1	1	
Premature rupture of membranes		1	1
Gestational diabetes			2
Post-term pregnancy	1		
Obesity complicating pregnancy			1
Obstructed labor due to pelvic abnormality	1	1	1
Third degree perineal laceration		1	1

Note: Shading indicates different clinical groups of alerts; PS: propensity score; RTI: respiratory tract infections; IP/ED: inpatient/emergency department

# Penicillin alert patterns (cont.)

<b>Node description</b>	<b>Decile PS (Analysis #4)</b>	<b>RTI (Analysis #5)</b>	<b>IP/ED settings (Analysis #6)</b>
Vomiting complicating pregnancy	1		
Superficial thrombophlebitis	1	1	1
Nonpurulent mastitis	2		
Cracked nipple/Hypogalactia	2		
Maternal care for abnormal fetal heart rate or other fetal problems			3
Unspecific/non-actionable alerts	7	3	3

Note: Shading indicates different clinical groups of alerts; PS: propensity score; RTI: respiratory tract infections; IP/ED: inpatient/emergency department



# Conclusions

# Conclusion

The alert triage is in process. Alert screening and review of specific cases suggested several pathways for false positive alerts:

- As TreeScan evaluates hypotheses one-sided, exposure group comparisons were repeated with each antibiotic class. Some alerts related to the similar conditions were identified for both macrolide and penicillin users.
- Several alerts appeared to be exacerbations of the initial indication.
- Given the intention-to-treat design, some exposure/outcome pairs were not in close proximity and had limited biological plausibility.

Screening analyses should anticipate and minimize noise but should also tolerate potential false alerts to facilitate full capture of safety issues when prioritizing signals for targeted pharmacoepidemiology studies.

More detail about the project is available on the Sentinel website:

<https://www.sentinelinitiative.org/methods-data-tools/methods/treescan-pregnancy>