Sentinel

ICPE 2022 Symposium

Methods and Considerations for Hypothesis-Free Signal Detection Studies Accommodating Various Types of Medications, Populations and Regions

Presented at the 38th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

Sentinel

Surveillance of Adverse Infant and Maternal Outcomes Following Maternal Medication Use During Pregnancy Using Tree-Based Scan Statistics

Judith C. Maro, PhD

On behalf on the Sentinel TreeScan in Pregnancy Workgroup

judy_maro@harvardpilgrim.org

Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School

38th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

August 2022, Copenhagen, Denmark

Disclosures and Acknowledgements

- This project was supported by Task Order HHSF22301012T under Master Agreement HHSF223201400030I from the US Food and Drug Administration (FDA).

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

TreeScan in Pregnancy workgroup members:

Sentinel Operations Center
- Judy Maro
- Elizabeth Suarez
- Sandra DeLuccia
- Jennifer Noble
- Inna Dashevsky
- Talia Menzin
- David Cole

FDA
- Michael Nguyen
- Danijela Stojanovic
- Monica Munoz
- Abby Anderson
- Yueqin Zhao
- Di Zhang
- Jane Liedtka
- Wei Liu

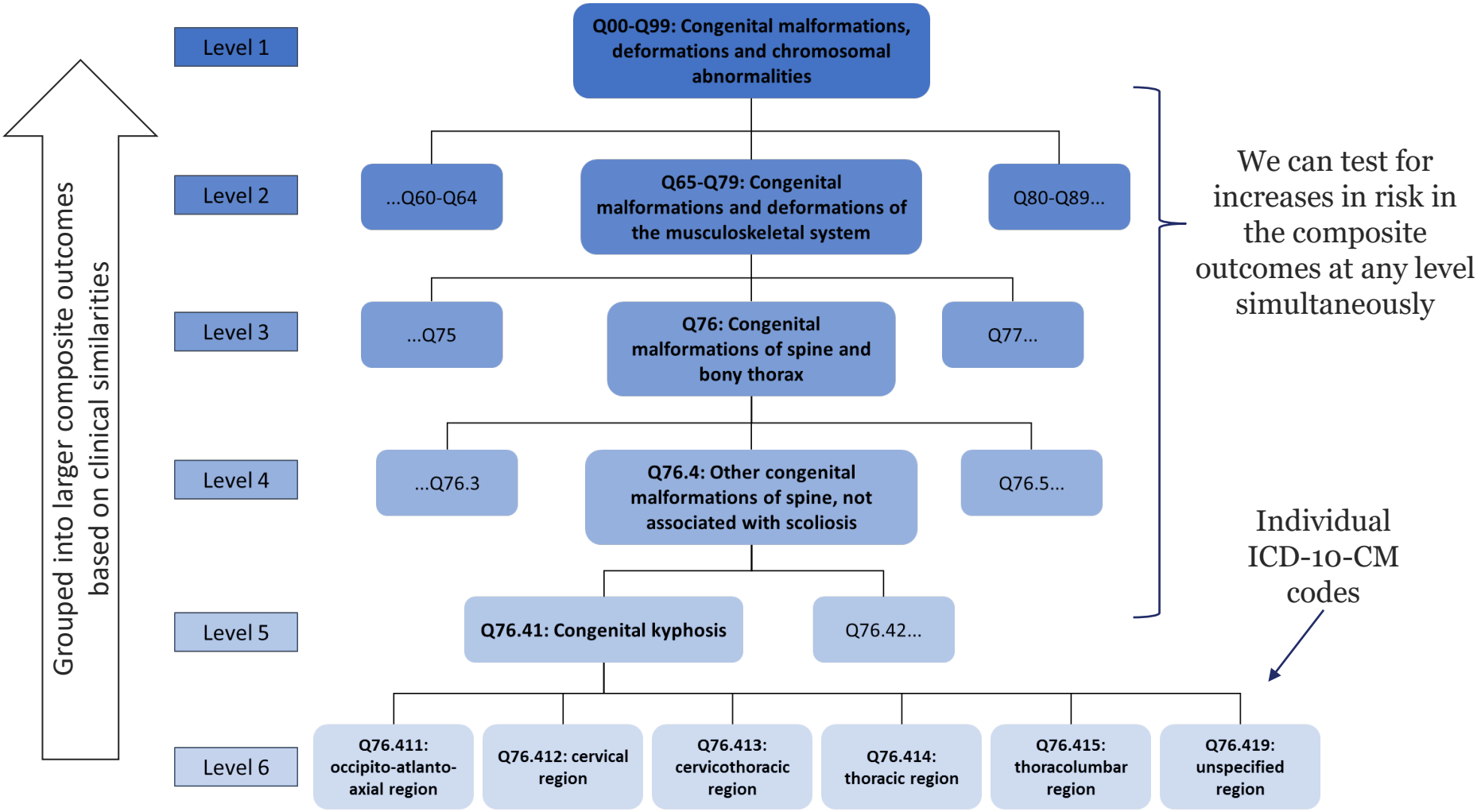
TreeScan™

- TreeScan is a statistical data mining tool that can be used for signal identification in pharmacovigilance/pharmacoepidemiologic analyses
  - Simultaneously scans for increased risk across multiple outcomes and allows for testing of very specific outcomes (e.g., atrial septal defect) or in groupings of concepts (e.g., congenital malformations of the circulatory system)
  - Formally adjust for multiple scenarios with composite null hypothesis testing to hold type I error due to chance alone at a user-specified threshold
  - Compatible with multiple epidemiologic study designs and confounding control methods

Design: Single Outcome Study → Multiple Outcomes Study

Steps for an observational single outcome study in claims data:		Steps for an observational multiple outcome study in claims data:	
Identify a cohort of pregnancies and infants	→	Identify a cohort of pregnancies and infants	✓
Classify exposure based on records of medication dispensings	→	Classify exposure based on records of medication dispensings	✓
Identify the outcome using a validated algorithm	→	**Create an outcome tree with multiple outcomes of interest**	
Control for confounding using propensity score methods	→	Control for confounding using propensity score methods	✓
Calculate a point estimate for the exposure-outcome association	→	**Calculate test statistics for each outcome using TreeScan**	

How the Outcome Tree Works



Two Outcome Trees

Infant Tree

- Major congenital malformations
  - Excluded minor malformations using guidance from the WHO
- Conditions related to gestational length and birth weight
  - Preterm birth, low birth weight, small for gestational age, etc

Maternal Tree

- Complications of pregnancy, childbirth and the postpartum period

WHO/CDC/ICBDSR. Birth defects surveillance: a manual for programme managers. Geneva: World Health Organization; 2014

TreeScan Statistics and p-values for Alerting

- Hypothesis testing:
  - Null: there is no increase in risk across any outcome in the tree in the exposed group
  - Alternative: there is an increase in risk for at least 1 outcome in the exposed group
- Formal adjustment for multiple scenarios to limit false positives
- Two probability models: Bernoulli and Poisson
  - These models use the referent population in different ways to calculate the expected outcome count in the exposed group
  - The Poisson version has greater power
- A statistical alert occurs when an outcome meets a pre-specified p-value threshold, e.g., <0.05

Infant Study Aims

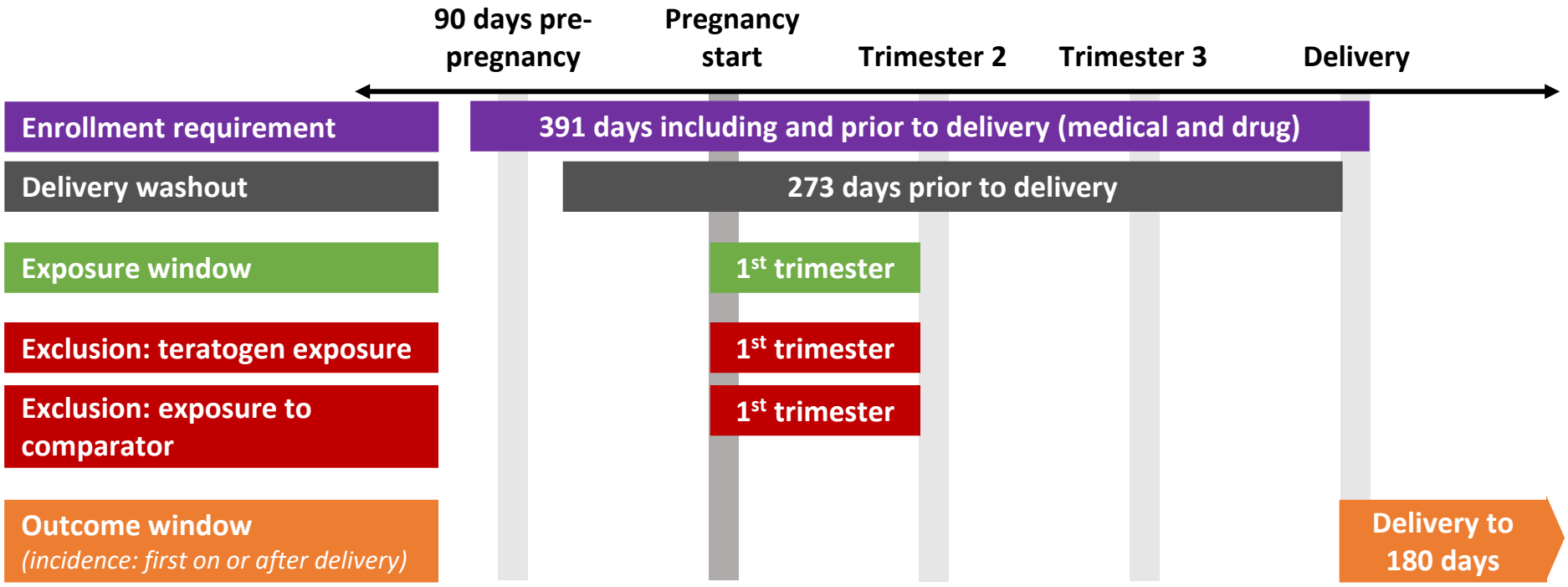
1. **Simulation study: Assess the performance of TreeScan under known conditions**
   - Can TreeScan identify an increase in risk for a specific malformation in our tree, given a certain sample size?
   - We can simulate a cohort with a known increase in risk to determine if TreeScan is powered to detect pre-specified increases in risk
2. **Case study: Demonstrate the use of TreeScan in real data, in a cohort of pregnant women linked to their live-born infants**
   - How do results look in real data?
   - How do results compare when we use different propensity score methods/TreeScan models?

Mother Study Aims

1. **Simulation study: Assess the performance of TreeScan under known conditions**
   - What is the impact of high numbers of strata on bias and power?
2. **Case study: Demonstrate the use of TreeScan in real data, in a cohort of pregnant women with active and unexposed comparators**
   - How do results look in real data?
   - How do results compare when we use different propensity score methods/TreeScan models?

Infant Outcomes Study Design

Data source	Merative MarketScan® Research Database
Eligible population	Women with live birth deliveries between October 1, 2015, and December 31, 2018, aged 10-55 years at delivery



https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Protocol_TreeScan_Pregnancy_V3.pdf

Infant Simulation Study Findings

- We recommend using the Poisson model to increase power to observe alerts
- A potential disadvantage of using the Poisson model is that matching is expected to result in better confounding control than stratification
  - We attempted to improve power using the Bernoulli method by using N:1 fixed ratio matching, but this proved unreliable as a general strategy
- For our purposes, power is more important than confounding control
  - An observed alert can be investigated in a targeted study, where uncontrolled confounding can be mitigated
- Our outcome misclassification bias analysis suggests a highly sensitive outcome definition is useful for maintaining power, regardless of TreeScan model used

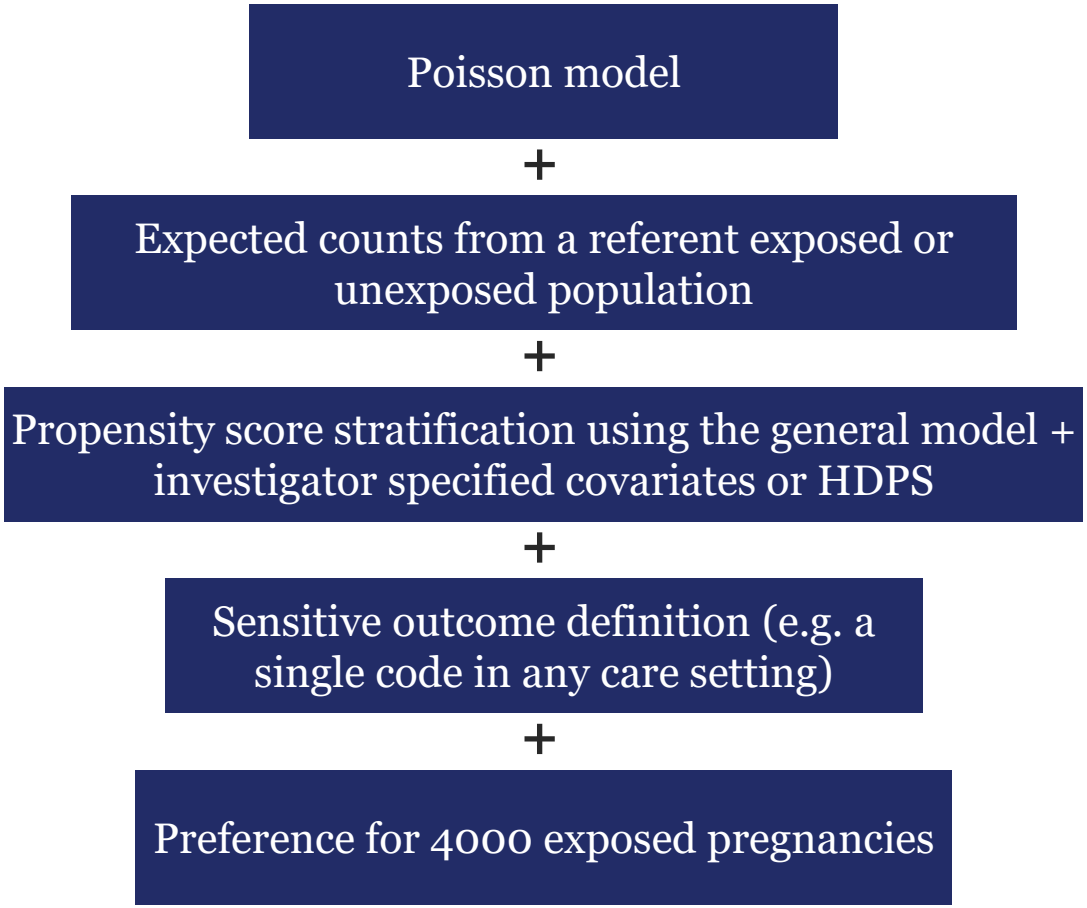
Suarez EA, Nguyen MD, Zhang D, Zhao Y, Stojanovic D, Munoz M, Liedtka J, Anderson A, Liu W, Dashevsky I, Cole, D, DeLuccia S, Menzin T, Noble J, Maro JC. Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs. Epidemiology. In Press.

Infant Case Study Findings

- We did not observe evidence that fluoroquinolone use in first trimester increases the risk of adverse infant outcomes when compared to cephalosporin use in first trimester
- Two alerts were observed that can be explained without a targeted follow-up studies:
  - Q31grp (Congenital malformations of larynx): only observed in analysis with lowest level of confounding control, and considered a minor malformation
  - Q513grp (bicornate uterus): observed across Poisson scenarios, but we can be confident this is a condition of the mother, not the infant
- At 1791 fluoroquinolone exposed, we are underpowered to see smaller increases in risk (this is supported by the simulation results)
- Use of propensity score stratification did not result in many spurious alerts
  - In this active comparator setting, a slight decrease in confounding control is likely worth the increase in power attained by using Poisson vs Bernoulli

Suarez EA, Nguyen MD, Zhang D, Zhao Y, Stojanovic D, Munoz M, Liedtka J, Anderson A, Liu W, Dashevsky I, Cole, D, DeLuccia S, Menzin T, Noble J, Maro JC : Novel Methods for Pregnancy Drug Safety Surveillance in the FDA Sentinel System. Pharmacoepidemiology and Drug Safety. In Press

Recommendations for Future Investigations

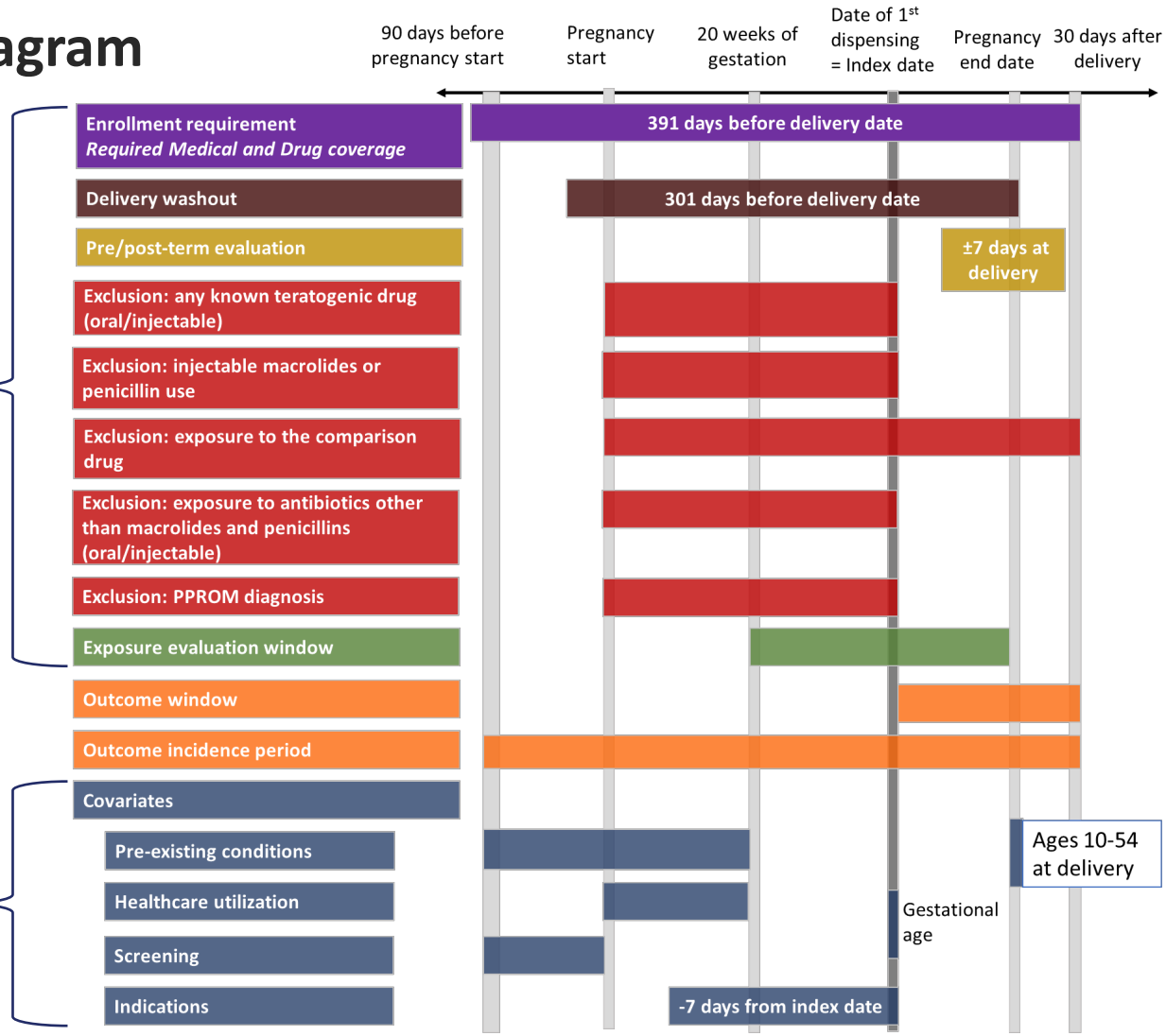


Suarez EA, Nguyen MD, Zhang D, Zhao Y, Stojanovic D, Munoz M, Liedtka J, Anderson A, Liu W, Dashevsky I, Cole, D, DeLuccia S, Menzin T, Noble J, Maro JC. Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs. Epidemiology. In Press.

Mother Design Diagram

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

Confounders can be controlled via PS method



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

https://www.sentinelinitiative.org/sites/default/files/documents/Sentinel_Protocol_TreeScan_Pregnancy_Maternal-Outcomes_v2.1.pdf

Conclusions

- TreeScan is a promising method for use in surveillance of potential adverse infant events and adverse maternal outcomes following maternal medication exposure during pregnancy
- Using TreeScan in administrative data within Sentinel offers notable advantages:
  - Utilize the large sample sizes available in administrative data, and build off previous methods to identify pregnancies and pregnancy exposures
  - Not limited to major congenital malformations as a primary outcome – can scan for all types of outcomes individually and in clinically relevant groupings (e.g., atrial septal defect, any cardiac malformation)
- Alerts that are identified are able to be quickly triaged by reviewing claim profiles among patients with those alerts
- Signal detection (as opposed to signal validation) favors sensitivity over specificity when looking at adverse outcomes of interest

Questions?

Contact: judy_maro@harvardpilgrim.org