

## Signal Detection Rules Across Pregnancy Registries: Do They Make Sense?

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## Introduction

- Pregnancy exposure registries are widely used to monitor drug safety in pregnancy
- Primary objective is to rule out risk of birth defects
  - Overall birth defects
  - Specific birth defect
- Major challenge facing pregnancy registries is how to adequately identify and evaluate signals

## What is a Signal?

- WHO definition: A possible causal association between an adverse event and a drug
- General definition: An increase in numbers or risk of birth defects that warrants further attention
- Statistical definition: A larger than expected number or rate of birth defects (i.e., unlikely to occur by chance alone)

## Purpose

- To assess signal detection methods of various pregnancy exposure registries



## Methods

- Thorough literature review
- Survey of actively enrolling pregnancy registries
  - What signal detection methods are used by the registry?
  - Where are these methods documented?
  - Have any signals been detected?
    - If so, by what method was the signal detected?
    - How was the signal vetted?
    - What was the result?

## Results

- 42 Pregnancy Registries Identified
  - 35 Responses
  - 83% Response Rate
- Registry Enrollment Population
  - 40% US only
  - 40% US and some other countries
  - 20% Global

## What signal detection methods are used?

- Monitoring System
  - Expert evaluation of individual cases 77%
  - Scientific Advisory Committee 77%

## What signal detection methods are used?

### Monitoring Criteria

#### – Individual cases

- Meet criteria for a case
- Timing of exposure (temporality) relative to embryonic organogenesis
- Biologic plausibility
- Etiology
- Unique combination/new syndrome/new drug finding

#### – Aggregate data

- Increase from baseline
- Pattern suggestive of a common etiology



## What signal detection methods are used?

- Overall birth defects
- Frequency observed in exposed cohort evaluated relative to comparator(s)
  - Use at least 1 comparator 100%
  - Use 2 or more comparators 73%
  - Comparators
    - Internal comparator 66%
    - External comparator 60%
- Need 300-500 exposed pregnancies to have sufficient power to identify increased risk

## What signal detection methods are used?

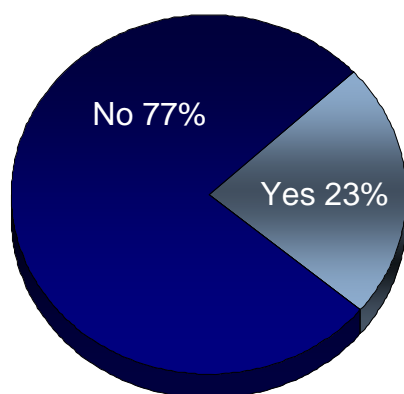
- Specific birth defects
- Rule of Three (54%)
  - 3 exposure-specific cases with the same birth defect requires immediate evaluation
  - Based on statistical principle
    - Likelihood of finding 3 specific defects in a cohort of 600 or fewer by chance alone is less than 5%

## Where are signal detection methods documented?

- Good Question!
- Nowhere
- All over the place  
(e.g., Protocol, Advisory Committee Charter, Monitoring Plan, Interim Report, Publications)
- No consistency
- Often not clearly documented, especially at registry implementation



## Have any signals been detected?



Increase in BD  
Overall BD 8.6%  
Specific BD 5.7%  
Both 8.6%

13

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## North American AED Pregnancy Registry

### Signals

- Increased frequency of major malformations

- Phenobarbital-exposed infants
- Valproate-exposed infants

*Wyszynski DF, et al., Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64:961-965.*

- Increased frequency of specific malformation

- Lamotrigine-exposed infants

*Holmes LB, et al., Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008;70:2152-2158*

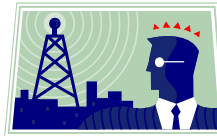
14

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## Antiretroviral Pregnancy Registry

- Monitors pregnancy exposures to 30+ drugs
- Over 12,000 exposed pregnancies
  - Older drugs have 2000+ 1<sup>st</sup> trimester exposures
  - Newer drugs have <200 1<sup>st</sup> trimester exposures
- One size does not fit all

## Conclusion



Signal detection rules – Do they make sense?

YES!

BUT...

- Need to consider each registry separately (e.g., comparator group(s), bias, confounding, etc)
- Need to be documented clearly and completely at registry implementation to provide registry sponsor(s), Advisory Committee, and staff with a good road map for detecting and vetting signals

## Recommendation

- Develop and implement a signal detection plan at registry initiation
- Evaluate effectiveness of signal detection plan periodically as sample size increases and baseline data accumulate
- Update FDA Guidance on Establishing Pregnancy Registries to include a section on Signal Detection

Questions?