Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies

September 18-19, 2023
Day 1
Welcome and Opening Remarks

Marianne Hamilton Lopez
Senior Research Director, Duke-Margolis Center for Health Policy
Workshop Agenda – Day 1

10:00 AM  Welcome and Overview
10:10 AM  FDA Opening Presentation: The Role of Postapproval Pregnancy Safety Studies
10:30 AM  Session 1: Stakeholder Perspectives on the Impact of Postapproval Pregnancy Safety Studies
11:05 AM  Break
11:20 PM  Session 2: Stakeholder Perspectives on Challenges and Opportunities to Optimize Postapproval Pregnancy Safety Study Types and Designs
12:45 PM  Lunch Break
2:00 PM  Session 3: FDA’s Considerations for Constructing a Pregnancy Safety Study Framework
3:15 PM  Break
3:25 PM  Session 4: Design of the Pregnancy Safety Study Framework
4:25 PM  Wrap-up Day 1 - Brief Closing Remarks
4:30 PM  Adjourn
Statement of Independence

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- FDA speakers do not have any financial disclosures to report
- The FDA presentations reflect the views of the speaker and should not be construed to represent FDA's views or policies
Objectives

- Background
- Overview of 2019 Postapproval Pregnancy Safety Studies Draft Guidance
- Efforts to advance safety data collection in pregnant individuals
- PDUFA VII Pregnancy Safety Commitments
Introduction

- FDA’s efforts to advance pregnancy safety data collection
  - 2014 FDA public meeting: Study approaches & methods to evaluate the safety of drugs & biologics during pregnancy in the postapproval setting
  - 2019 Postapproval Pregnancy Safety Studies Draft Guidance published based on input from public meeting
  - National and international collaborations
  - Sentinel Initiative’s expansion of capabilities
  - PDUFA VII commitments
Background

• There are approximately 5.5 million pregnancies in the U.S./year
• Pregnant individuals may need treatment for chronic or acute conditions
• Pregnant individuals have historically been left out of drug development trials
• Most drugs are approved with only nonclinical reproductive toxicology data
• Human safety data are important to inform labeling and clinical care
  – these data are generally collected postapproval
Pregnancy Postmarketing Requirements

- Pregnancy safety studies can be required under section 505(o)(3) of the FD&C Act
- Lack of a safety signal in nonclinical reproductive toxicology data does not indicate that a drug is safe to use in pregnancy
- Lack of human pregnancy safety data is a safety issue
- Congenital malformations due to drug exposure in pregnancy are serious adverse events*
- Historically, pregnancy registries have been issued as postmarketing requirements/commitments (PMRs/PMCs)
- More recently, 2 types of pregnancy PMRs (a pregnancy registry and a complementary database study) have been issued in CDER

*21 CFR 312.32 (a)
A review of pregnancy and lactation postmarketing studies required by the FDA

Jason Krastein, Leyla Sahin, Lynne Yao

First published: 19 November 2022 | https://doi.org/10.1002/pds.5572

Full Text@FDA Library

Prior posting and presentation: Preliminary results from this study were presented as a poster at the FDA Science Forum on May 26th, 2021.

Abstract

Since pregnant and lactating women have historically been excluded from drug development trials, safety studies need to be conducted postapproval. This study evaluated FDA's Post Marketing Requirements for pregnancy and lactation studies from 2007 to 2020, and identified trends and potential future opportunities. The number of...
Note: There are existing disease-based pregnancy registries rather than PMRs in certain therapeutic areas (antiretrovirals, antiepileptics, and psychiatric drugs)
Postapproval Pregnancy Safety Studies
Guidance for Industry

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Denise Johnson-Lyles at 301-796-6169 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical

Published in 2019
Guidance undergoing revision
Highlights of Draft Guidance

PV = Pharmacovigilance

EHD = Electronic healthcare data

PV = Pharmacovigilance

EHD = Electronic healthcare data

Pregnancy Registries

Surveillance Programs/
Descriptive studies
Pregnancy Registries

• Prospective observational cohort study
• Pregnant individuals are enrolled and followed until the outcome occurs (live birth, miscarriage, termination, stillbirth)
• Disease matched comparator cohort (unexposed to the drug of interest) is enrolled
• Infants are followed up to one year of age
• Outcomes that are assessed: major malformations, patterns of malformations, miscarriage, termination, stillbirth, preterm birth, small for gestational age, etc.
Advantages of Pregnancy Registries

• Real time prospective data collection
• Clinical data obtained from the pregnant individual:
  – Can confirm that the drug was taken
  – Can confirm when the drug was taken (gestational timing of exposure), dose, duration
  – Covariates (smoking, alcohol, drugs, etc.), clinical information
• Clinical data from medical records (obstetrical, neonatal/pediatric, medical specialist treating the condition)
• Can capture non live birth outcomes (miscarriage, pregnancy termination (may be for a fetal malformation), and stillbirth)
• Medical records of infants with birth defects are reviewed by experts; allows for clinical judgment
• Some registries have dedicated experts that assess all newborns
Limitations of Pregnancy Registries

• Small sample size due to challenges with enrollment
• Takes a long time to complete
• Selection bias
Database Studies

• Generally, retrospective cohort study with claims data
• Requires mother-infant linkage
• Disease matched cohort(s) (unexposed to the drug of interest)
• Validation needed for:
  – Algorithms that estimate pregnancy start date
  – Positive predictive value of ICD codes
Advantages of Database Studies

- Potential to have a larger sample size/greater power; assessment of specific major malformations
- Potential to complete study faster
- No recruitment/enrollment challenges
Limitations of Database Studies

• Exposure and timing of exposure cannot be confirmed: based on pharmacy dispensing
  – Particularly for drugs used as needed

• Potential exposure misclassification (estimates based on algorithms)

• Potential outcome misclassification (based on ICD codes)

• Non-live birth outcomes are poorly captured

• Some covariates not well captured (e.g., obesity, smoking, alcohol, drugs, etc.)
Considerations for when Exposure in Pregnancy is Expected to be Uncommon

• Adequately powered pregnancy registry or database study may not be feasible
  – E.g., rare disease, labeling contraindicates use in pregnancy based on animal reproductive toxicology study results, pharmacological class

• Potential Role for Descriptive Pregnancy Safety Study
  – Previous terminology was “pregnancy surveillance program”
  – Systematic collection of pregnancy-specific data
  – Includes prospective and retrospective data collection
  – May be part of an existing disease registry (e.g., rare disease registry)
Efforts to Advance Pregnancy Safety Data Collection
Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

- Required under the 21st Century Cures Act of 2016
- Objectives: Identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women
- Reports and recommendations submitted to the Secretary of the Department of Health and Human Services in 2018 and implementation report completed in 2020
- An oversight committee is being formed to monitor implementation
PRGLAC Recommendations (Pregnancy Safety)

- Increase the quantity, quality, and timeliness of research involving therapeutic products used by pregnant women
- Implement a proactive approach to protocol development and study design
  - Develop a systematic plan for timely collection of data (including safety data) in pregnant women
- Optimize pregnancy registries
  - Expand the use of disease-based pregnancy registries
  - Facilitate access to data and transparency of information in registries
- Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women
  - Design health record systems to link mother and infant records
  - Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries
Global Efforts to Advance Pregnancy Safety Data Collection

Pregnancy and Lactation cluster
Efforts to Improve Postapproval Pregnancy Safety Data Collection

• Prescription Drug User Fee Amendment VII (PDUFA VII) Commitments*

• Pregnancy Safety: “FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of postmarket studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects.”

*https://www.fda.gov/media/151712/download
PDUFA VII Pregnancy Safety Commitments

• “The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.”

• 5 demonstration projects and MAPP or guidance to be developed through fiscal year 2027
Summary

• Lack of safety data in pregnant individuals is a public health issue
• Further efforts needed to optimize postapproval pregnancy safety studies
• Stakeholder collaboration is essential
• Purpose of this meeting: seek input from stakeholders on:
  – The development of a framework to optimize postapproval pregnancy safety studies
  – The proposed demonstration projects to fill in the data gaps
Thank You
Session 1: Stakeholder Perspectives on the Impact of Postapproval Pregnancy Safety Studies

Moderator: Megan Clowse, Duke University School of Medicine

Speakers:

Mariah Leach, Mamas Facing Forward
Keele Wurst, GlaxoSmithKline
Katherine Wisner, Asher Center, Feinberg School of Medicine, Northwestern University
Geeta Swamy, Duke University School of Medicine
Break

Workshop will resume at **11:20 a.m. EST**
Session 2: Stakeholder Perspectives on Challenges and Opportunities to Optimize Postapproval Pregnancy Safety Study Types and Designs

Moderator: Geeta Swamy, Duke University School of Medicine

Speakers:

Christina Chambers, University of California San Diego
Jessica Albano, Syneos Health
Christine Olson, Centers for Disease Control and Prevention
Elyse Kharbanda, HealthPartners Institute
MotherToBaby Pregnancy Registries Perspective

Christina Chambers, PhD, MPH
Distinguished Professor, Department of Pediatrics
Herbert Wertheim School of Public Health and Human Longevity Science and Skaggs School of Pharmacy and Pharmaceutical Sciences
UC San Diego School of Medicine, La Jolla CA

FDA Public Workshop
September 18-19, 2023
Is It Safe for Me and My Baby?

Expert, confidential & no-cost information about medications and other exposures during pregnancy and breastfeeding by phone, text, email and chat.

ASK OUR EXPERTS
Mother To Baby Counseling Services

- MotherToBaby is a service provided by the non-profit Organization of Teratology Information Specialists (OTIS) established in 1980’s.
- 14 services currently funded by HRSA, CDC and other State sources.
- MotherToBaby services provide individualized, evidence-based information to pregnant and lactating persons, health care providers, and the public about safety of medications, vaccines, infections, and other exposures they may have had already or are anticipating during pregnancy and lactation.
MotherToBaby Pregnancy Studies

Ongoing Studies: Providing Better Information on Medication Safety in Pregnancy

UC San Diego School of Medicine | MotherToBaby Pregnancy Studies | VAMPSS
The MotherToBaby Pregnancy Registry recruits exposed and unexposed pregnant persons in US and Canada to compare outcomes:

- Major structural birth defects overall and a specific pattern identified up to one year of age
- Pattern of minor structural anomalies among infants who receive a study-related physical examination
- Spontaneous abortion/stillbirth
- Preterm delivery
- Birth weight, length, head circumference
- Postnatal growth
- Serious infections, malignancies in first year of life
- Short and longer-term neurodevelopmental outcomes
Study Schema

- **Interim interviews**
  - 20-22 wks gestational age
  - 32-34 wks gestational age

- **Outcome interview & medical record interview**
  - 0-6 wks post-delivery

- **Delivery/end of pregnancy**

- **Enrollment**
  - <20 wks gestational age

- **Dysmorphological exam for infant aged 6-12 months; Ages and Stages developmental assessment**

- **Pediatric medical record review 12 months; Ages and Stages developmental assessment**

- **cohort I**
  - medication exposed

- **cohort II**
  - diseased matched comparison

- **cohort III**
  - healthy comparison
• Pregnancy registries are typically underpowered to evaluate risk/safety for specific congenital anomalies

• Even if a registry is adequately powered to rule out a 2-3 fold increased risk of major congenital anomalies combined, this is not what we expect of a teratogen – we expect that specific anomalies/clusters of anomalies will be induced

• Goal is to first rule out a thalidomide/isotretinoin/mycophenolate and then maybe a valproic acid

• Requires careful evaluation/accurate classification of congenital anomalies in the context of gestational timing of exposure/biological plausibility, and consistency of patterns

• Teratogens also often associated with a range of adverse outcomes including increased risks for pregnancy loss, growth deficiency, etc.
• Registry focus is on a range of outcomes
• Standard 1 + years of follow-up
• Addition of study-related physical exam for minor anomalies, specifically a pattern
• Source of data on exposure (truth) is directly from the mother
• Internal comparator groups recruited and followed in the same manner for the same follow-up period
• Assessment of a wide range of potential confounders including co-exposures that are unlikely to be obtainable, or obtained reliably, from any other source
Limitations of MotherToBaby Registries

- Time and resources
- Often relatively limited diversity in SES and race/ethnicity of the sample
- Typically small sample sizes
- Statistical power issues exacerbated if the exposure is intermittent
- One study is only one study

Christina D. Chambers a, b, f, x, Diana L. Johnson a, Ronghui Xu b, c, Yunjun J. Luo a, Carol Louik d, f, Allen A. Mitchell d, f, Michael Schatz g, f, Kenneth L. Jones h, f, the OTIS Collaborative Research Group 1

Safety of the 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Preterm delivery and specific malformations, a study from the case-control arm of VAMPSS

Carol Louik h, d, Stephen Kerr h, d, Carla M. Van Bennekom h, d, Christina Chambers b, d, Kenneth L. Jones h, d, Michael Schatz g, d, Allen A. Mitchell h, d, x, x

UC San Diego
School of Medicine
MotherToBaby
PREGNANCY STUDIES
VAMPSS

BARDA
### MotherToBaby Pregnancy Studies – Examples of Registries that “Succeeded”

<table>
<thead>
<tr>
<th>Product</th>
<th>Design</th>
<th>Years of Enrollment</th>
<th>Target Sample Size</th>
<th>Lost to follow-up</th>
<th>Results included in Product Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>3 prospective cohorts</td>
<td>2000-2012</td>
<td>830 (370 exposed)</td>
<td>4%</td>
<td>Yes</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>3 prospective cohorts</td>
<td>2004-2016</td>
<td>602 (257 exposed)</td>
<td>7%</td>
<td>Yes</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>3 prospective cohorts</td>
<td>2015-2020</td>
<td>300 (100 exposed)</td>
<td>6%</td>
<td>Final Analysis Completed</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>3 prospective cohorts</td>
<td>2012-2019</td>
<td>450 (150 exposed)</td>
<td>9%</td>
<td>Final Analysis Completed</td>
</tr>
<tr>
<td>Dupilimab</td>
<td>3 prospective cohorts</td>
<td>2018-date</td>
<td>600 (200 exposed)</td>
<td>3%</td>
<td>Expect completion 2024</td>
</tr>
<tr>
<td>Pfizer-BioNTech Covid-19 Vaccine</td>
<td>2 prospective cohorts</td>
<td>2021-2023</td>
<td>2000 (1100 exposed)</td>
<td>Not yet determined</td>
<td>Enrollment Completed</td>
</tr>
</tbody>
</table>
### MotherToBaby Pregnancy Studies – Examples of Registries that “Failed”

<table>
<thead>
<tr>
<th>Product</th>
<th>Design</th>
<th>Years of Enrollment</th>
<th>Target Sample Size</th>
<th>Sample Size Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab</td>
<td>3 prospective cohorts</td>
<td>2010-2022</td>
<td>300 (100 exposed)</td>
<td>226 (34 exposed)</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>3 prospective cohorts</td>
<td>2013-2022</td>
<td>300 (100 exposed)</td>
<td>211 (11 exposed)</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>3 prospective cohorts</td>
<td>2016-2022</td>
<td>800 (200 exposed)</td>
<td>291 (23 exposed)</td>
</tr>
</tbody>
</table>
When it Works, What are the “Pluses”

• If the prevalence of use in pregnancy is sufficient
  • Having an ongoing open cohort platform that requires no set-up time
  • Engagement with the pregnant woman that leads to high retention rates
  • Ability to classify outcomes using multiple sources of data, including study-related expert assessments for outcome
• Ability to confirm actual exposure, dose and gestational timing
• Ability to acquire data on covariates not typically available through other data sources (substances, OTC, fever, herbal products), as well as measures of disease severity/disease-matched comparators
• Ability to do broad and extended follow-up if needed, including responding to a signal
When it Works: Example of Signal Follow-up

• In etanercept registry, a specific pattern of three or more minor anomalies was identified in 6 children who received the study-related physical examination; one had an associated major congenital anomaly

• In follow-up, these families were recontacted, received a second examination by a different study physician, and examination of the parents for the same anomalies

• Five of the six children received face-to-face neurodevelopmental testing

• The evaluation of the signal led to no further concerns generated
When it Doesn’t Work, What Then?

- If the prevalence of use in pregnancy cannot be reliably predicted to be rare
  - Important to plan for a feasibility period
  - Important to have an additional source of population data to confirm or refute evidence for low use
  - Need an approach to interpretation of small numbers if that’s all that can be obtained – i.e., can the data support the statement that this is not “a thalidomide”
We can build on efficiencies associated with disease-based registries – I would take that one step further and say we would greatly benefit in efficiency and productivity by establishing a single U.S. pregnancy registry to serve as a signal detection system for all new drugs, irrespective of prevalence of use.

Important when pregnancy registries are initiated that they not function in a vacuum – we need coordinated efforts across data sources.
Thank you!

https://mothertobaby.org/pregnancy-studies/

https://www.aaaai.org/about-aaaai/strategic-relationships/vampss

Email: chchambers@health.ucsd.edu
Pregnancy Exposure Registries: multi-product / disease-based example
Jessica Albano, PhD MPH
Disclosures

– I am a salaried employee of Syneos Health, the contract research organization that conducts the Antiretroviral Pregnancy Registry (APR); I own company stock

– The APR is a collaborative study jointly funded by the following manufacturers:

  AbbVie
  Alvogen
  Amneal Pharmaceuticals LLC
  Apotex Inc.
  Boehringer Ingelheim Pharmaceuticals Inc.
  Bristol-Myers Squibb Company
  Celltrion Inc.
  Cipla Ltd.
  Gilead Sciences Inc.
  Hetero Labs Limited
  Hikma Pharmaceuticals USA Inc.
  Janssen Scientific Affairs LLC

  Lannett Company Inc.
  Laurus Labs Limited
  Lupin Pharmaceuticals Inc.
  Macleods Pharmaceuticals Ltd.
  Merck & Company Inc.
  Mylan Laboratories
  Pharmascience Inc.
  Qilu Pharmaceuticals Co. Ltd.
  SigmaPharm Laboratories
  Strides Pharma Science Limited
  Teva Pharmaceuticals USA Inc.
  ViiV Healthcare
Introduction

Multi-product / disease-based pregnancy exposure registry

- Cohort definition:
  - exposure to specific drug(s) regardless of indication; typically all marketed brand and generic versions
  - diagnosis of a specific disease regardless if treated or untreated

Appropriate study design situations:

- Combination products
- Complex multi-drug treatment regimens
- Polytherapy and polypharmacy
- Frequent new product approvals
- Internal comparisons
- Confounding disease or population characteristics
Introduction

- 200 exposures can rule out a 2-fold ↑ in overall birth defects

Introduction

- 2000 exposures can rule out a 3-fold ↑ in more rare birth defects

Neural tube defect
Prevalence 0.1%

Overall defect
Prevalence 3%

The Antiretroviral Pregnancy Registry
Background: Antiretroviral Pregnancy Registry

- Voluntary, international, prospective exposure-registration cohort study
- Designed to assist clinicians and patients in weighing potential risks and benefits of HIV treatment during pregnancy
  - Provide early warning signals of major teratogenicity
  - Estimate prevalence of major birth defects and compare to the general population
  - Supplement animal toxicology, clinical, and epidemiological study data
- Ongoing since 1989; fulfills FDA post-marketing commitments
  - Currently 24 sponsoring manufacturers
  - Monitors prenatal exposures to 164 drugs: 61 brand-name single-entity drugs or fixed-dose combinations; 136 generic versions
    - HIV treatment and prevention (PEP, PrEP)
    - HBV treatment
Methods: Antiretroviral Pregnancy Registry

- Primary outcome is prevalence of major birth defects
  - Infants are not followed after birth
  - Was not designed to formally evaluate premature birth, low birth weight, small for gestational age or developmental delays

- Analysis is multi-tiered
  - Overall prevalence for all drugs being monitored
  - At the drug class level
  - At the individual drug level
  - Common drug combinations or treatment regimens

- Comparison groups
  - External (background) reference group(s) MACDP, TBDR
  - Internal comparison group(s)
Methods: Antiretroviral Pregnancy Registry

- Evaluating potential signals using multiple internal comparison groups

Unexposed to Drug A
- Earliest Exposure to Drug A = 2nd or 3rd Trimester
- Never Exposed to Drug A
- Exposed to Other drugs in 1st Trimester excluding Drug A

Exposed to Drug A
- Earliest Exposure to Drug A = 1st Trimester
Results: Antiretroviral Pregnancy Registry

Prospective Cases with Follow-up Data

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Results: Antiretroviral Pregnancy Registry

- **ARVs with ≥ 200 first trimester exposures**

- **MACDP**
  - 2.72% (2.68, 2.76)

- **TBDR**
  - 4.17% (4.15, 4.19)

**Note:** Confidence intervals are calculated using the Clopper-Pearson exact binomial method.

MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry

Antiretroviral Pregnancy Registry; Interim Report 1 January 1989 through 31 Jan 2023
Governance Structure: Antiretroviral Pregnancy Registry

- Advisory Committee
- Sponsor Representatives
- APR Steering Committee
- Consultants
- Coordinating Center
Advisory Committee Consensus Statement

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no significant increases in frequency of birth defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance for patient counseling. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Given the use of new therapies about which data are still insufficient, healthcare providers are strongly encouraged to report eligible people to the Registry at SM_APR@APRegistry.com via the data forms available at www.APRegistry.com.
THE ANTIRETROVIRAL PREGNANCY REGISTRY INTERIM REPORT
1 JANUARY 2023 TO 30 JUNE 2023

Information Dissemination: Antiretroviral Pregnancy Registry

Syneos Health

Recommnendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States

The information in this report is a snapshot of current trends and guidelines. The report serves as a complement to the national and local recommendations.

Recommendations for the Use of Antiretroviral Drugs During Pregnancy

- Extended antiretroviral therapy (ART) is recommended for all pregnant women with HIV infection.
- ART should be initiated as early as possible in the second trimester or at least before 24 weeks of gestation.
- ART should include at least three drugs from at least two different classes of antiretroviral agents.
- ART should be continued throughout pregnancy and breastfeeding.

Perinatal HIV Transmission

- The risk of perinatal HIV transmission can be reduced to <1% with the use of ART during pregnancy and breastfeeding.
- Cesarean delivery may also reduce the risk of HIV transmission in some cases.
- Antiretroviral prophylaxis for the infant may be considered in certain circumstances.

ADDITIONAL RESOURCES:
- National Institute of Allergy and Infectious Diseases (NIAID)
- Centers for Disease Control and Prevention (CDC)
- World Health Organization (WHO)

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Conclusions
Making the Case for Consolidated Collaborative Registries

Challenges

- **Complexity**
  - Operationally and analytically complex
  - Requires high degree of expertise to implement

- **Collaboration**
  - Marketplace competitors must agree to work together
  - Adopt and adhere to common processes, policies and timelines

- **Communication**
  - Respect established lines of communication
  - Documentation is critical

- **Competition**
  - Innovator companies have onus to set-up and implement

- **Confidentiality**
  - Necessary to be sensitive to proprietary aspects of drug discovery, marketing, life-cycle management

- **Commitment**
  - Various stakeholders may have different priorities and levels of interests

## Making the Case for Consolidated Collaborative Registries

### Advantages

<table>
<thead>
<tr>
<th>Logical</th>
<th>Economical</th>
<th>Efficient</th>
<th>Recruitment</th>
<th>Methodological</th>
<th>Consistency</th>
</tr>
</thead>
</table>
| • Avoid duplicated efforts  
  • Reduces population overlap | • Pool resources and budgets from multiple stakeholders | • Minimize health care provider burden  
  • Consolidated KOL/SME expertise | • Reduced competition  
  • More robust awareness  
  • Increase incentive to participate | • Standardized data collection, assessments and analysis  
  • Increased validity and power | • Coherent assessment of available data  
  • Centralized message safety/risk profile |

Shortening the Distance from Lab to Life®.
CDC COVID-19 Vaccine Pregnancy Registry

Optimizing the Use of Post-approval Pregnancy Safety Studies
September 18, 2023

Christine Olson, MD, MPH
Captain, U.S. Public Health Service
Co-lead, CDC COVID-19 Vaccine Pregnancy Registry
Immunization Safety Office, Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention (CDC)
Objectives

- Describe concept and implementation of the CDC COVID-19 Vaccine Pregnancy Registry

- Operations Overview
  - Enrollment and data collection
  - 2-phase approach
  - Cohort description

- Successes and challenges
CDC vaccine safety monitoring*

*Vaccine Adverse Event Reporting System (VAERS) (co-managed by CDC and FDA); Clinical Immunization Safety Assessment (CISA) Project; Vaccine Safety Datalink (VSD); Data Exploration and Technology (DETECT)
COVID-19 and Pregnancy

- COVID-19 vaccines first available December 2020
- Limited data available about COVID-19 vaccine in pregnant people
  - Excluded from phase 3 clinical trials
  - Only developmental and reproductive toxicity (DART) animal data available at vaccine roll-out

Assumptions
- Pregnant and recently pregnant people more likely to get severely ill from COVID-19 than non-pregnant based on physiology and prior experience with novel respiratory viruses (e.g., H1N1)
- Likely lower uptake of a new vaccine in pregnant population than non-pregnant population
Conception and implementation of the registry

- **Collaborative effort** between CDC’s Immunization Safety Office, Division of Birth Defects and Infant Disorders, and Division of Reproductive Health

- **V-safe After Vaccination Health Checker** - new, voluntary smartphone-based safety surveillance system for adverse events after COVID-19 vaccination (Dec 2020)

- **Used v-safe enrollments** to identify individuals who were pregnant or became pregnant after one of their primary series vaccine doses

- **Readily available convenience sample** of recent vaccinees potentially eligible for pregnancy registry to monitor in real time

- Participant enrollment began January 2021 when vaccines initially available
  - Cohort needs met by volume of individuals who had enrolled in v-safe by June 2021
Goal and framework

- **Goals**
  - Monitor for adverse outcomes of interest in pregnant people receiving COVID-19 vaccines in a systematic and rapid way to identify early safety signals, characterize the safety profiles of COVID-19 vaccines in pregnant people, and supplement existing passive and active surveillance systems.

- **Framework**
  - Up to 5 interviews during and after pregnancy collecting participant-reported data.
  - Medical record acquisition/abstraction for those who consent and have outcomes of interest.
  - Analyze self-reported data initially by chronologically available outcomes; requires clinical review step for some outcomes (e.g., stillbirth, birth defects).
  - More robust analyses later after medical record information available for confirmation of, and more detail about, outcomes of interest.
Outcomes of interest

Obstetric

• Pregnancy outcomes (live birth, stillbirth, SAB*, other)
• Pregnancy complications (hypertensive disorders of pregnancy, gestational diabetes, COVID-19, preterm delivery)
• Maternal ICU admission
• Postpartum complications

Neonatal and Infant

• Birth defects
• Birth weight
• Neonatal ICU admission
• Neonatal/infant death
• Other infant health conditions
• Infant hospitalization

*SAB = spontaneous abortion (fetal loss < 20 weeks' gestational age)

In bold: Outcomes for which medical records requested (for SABs only if ≥ 14 weeks' GA; for birth defects, only if additional information needed after clinical review of interview data)
Enrolled cohort and data flow
CDC COVID-19 Vaccine Pregnancy Registry – enrollment and data collection

**Eligibility Screening**
- Reported a pregnancy into v-safe DEC 14, 2020 – JUN 18, 2021
- 18+ years of age
- Speak English or Spanish
- Pregnant at time of vaccination or during peri-conceptional period

**Consent for registry enrollment and follow-up**
- Survey included:
  - Demographics, health over pregnancy
  - Pregnancy outcome
  - Birth hospitalization, postpartum
  - Infant health to 3 months of age
- Consent obtained for medical records

**Phase 1:** Preconception to 3 months

**Phase 2:** Through 15 months

**Extended follow-up**
- Survey included:
  - Pregnancy outcome (if unknown)
  - Maternal health
  - Infant health through 15 months of age
  - Additional details on possible/probable birth defect from Phase 1
- Consent for medical records

---

*Pregnancy questions in v-safe assessments on first survey after each dose and on post-vaccination days 21 and 42 and months 3, 6, and 12

†Eligibility determined from verbal interviews and responses to 3-question on web-based v-safe follow-up survey received prior to May 31, 2021. Eligible individuals received COVID-19 vaccination during pregnancy or periconceptional period (≤ 30 days before the first day of the last menstrual period before pregnancy).
COVID-19 Vaccine Pregnancy Registry - Enrollment
123,609 pregnancies reported into v-safe, Dec 2020 – Jun 2021

- 53% Called (65,000)
- 47% Not Called
- Unreachable, 32%
- Requested no contact, 6.6%
- Indicated never pregnant in PFUS, 11%
- No response to PFUS survey, 30%
- Assessed for eligibility, 20%
- Language/DOB not confirmed, 0.1%
- Not eligible, 5%
- Declined, 1%
- Enrolled (23k), 94%
- Phase 1
  - 97% Completed Phase 1
  - 2% Lost to Follow-up
  - 1% withdrew/deemed ineligible

PFUS – Pregnancy Follow-up Survey through v-safe platform
Characteristics of enrolled pregnancy registry participants

23,249* total eligible and enrolled participants who reported at least one pregnancy into v-safe Dec 14, 2020 – June 18, 2021

- Mean age at first vaccination 33.5 years old
- 45% healthcare personnel

*16 participants contributed >1 pregnancy
Timing of earliest COVID-19 vaccination during peri-conceptional period or pregnancy among eligible pregnancies (n=23,265)

- Peri-conceptional: N=2,301 (10%)
- First Trimester: N=6,464 (28%)
- Second Trimester: N=9,206 (40%)
- Third Trimester: N=5,293 (23%)

Definitions: Periconceptional: ≤30 days before the first day of the last menstrual period (LMP) before pregnancy; First trimester: 1st day of LMP to <14 weeks gestational age; Second trimester: 14-28 weeks; Third trimester: ≥28 weeks. Timing of earliest dose unknown for 1 pregnancy.
Monovalent booster dose

Among enrolled participants, 8% received a booster during pregnancy; 62% received a booster after pregnancy.

Timing of booster dose by timing of first eligible dose

- Periconceptional (n=2,301)
- First (n=6,464)
- Second (n=9,206)
- Third (n=5,293)

Timing of booster dose:
- No booster at time of last contact
- Postpartum
- Third
- Second
Phase 2 (Extended Follow-up)

- 21,197 of Phase 1 participants eligible for Phase 2
  - Response rate (able to be reached by phone) = 44.2%
  - Completion rate (among those reached) = 96.6%

- Phone interviews conducted November 2022 – September 2023

- Completed Phase 2 interviews for 9,453 Phase 1 participants
Simplified Data Flow – Phase 1

Interview data → Medical records → Preliminary Early Outcomes → Final Outcomes

Clinical Review 1 - based on interview data alone

Clinical Review 2 - based on interview data and available medical record data

Medical records requested & abstracted

Interview data
Birth Defect Identification and Classification

- Classified all reported fetal and infant health conditions as major, minor, possible/probable birth defect or not a birth defect
- Coded all birth defects using the Metropolitan Atlanta Congenital Defects Program
- Included pregnancies with all outcomes (e.g., live birth, stillbirth, induced abortion, spontaneous abortion)
- Included any birth defects identified through 15 months of age
Accomplishments & Challenges
Early Pregnancy Registry Data Use

- **Monitoring** of reported outcomes as pregnancies progressed and interview data accrued for deviations from expected background rates
- **Regular updates** to the Advisory Committee on Immunization Practices' (ACIP) COVID-19 Vaccine Safety Technical Work Group (VaST)
- **Public presentations** at ACIP meetings
  - September 22, 2021
  - October 19, 2022
- **Publications**
- Preliminary data used to **strengthen vaccine recommendations** for COVID-19 vaccination of pregnant persons in any trimester, August 2021
CDC COVID-19 Vaccine Pregnancy Registry: advantages, limitations, and realities

- **Advantages:** flexibility, potential for medical record confirmation of self-reported data for subset of participants who consent, relative speed for earliest outcomes (SAB)

- **Limitations:**
  - Biased toward earliest eligible recipients (and adopters) of vaccine (largely healthcare personnel)
  - Time- and resource-intense, large volumes of data from two sources (interview & medical record)
  - Convenience sample, no control group

- **Real-world experience:**
  - Unknown what pregnancy stage at time of vaccination from v-safe data, so unable to order calls based on gestational age; many participants had delivered by time of first interview
  - Over half of participant-reports of infant birth defects required medical record confirmation for clarification
  - Medical record acquisition/abstraction resource-intense with variable quality
  - Balance between sensitivity and specificity (e.g., possible/probable birth defect inclusion)
Interview data and subsequent clinical review - challenges

- Impact of more open-ended questions to improve feasibility of interview completion
  - Capture broader range of diagnoses
  - Lack of standardization
  - Use of text fields – coding challenges and unusable data

- Participant-report not standard approach for complex medical conditions
  - Iterative process to develop criteria for various conditions from participant-reported data
  - Requires robust protocol for classifications

- Nuanced details needed for clinical adjudication often unavailable

- Inconsistency in reporting during the interview (e.g., birth defects, hypertension)

- Uncertainty if certain conditions noted during pregnancy had resolved in-utero or were still present after birth (impacts birth defect classification)

- Time- and training-intense
  - Interviewers, clinicians, subject matter experts (birth defects, pregnancy), data managers
  - Impacts speed of results
Incorporation of medical record data – challenges

- Records not always obtainable (e.g., no consent, not found, not sent by facility)
  - Variable facility requirements for medical record release of patients
- Incomplete records (e.g., only one of "set" available: prenatal, delivery, outpatient infant)
- Discrepancies within records (dates of diagnoses, diagnostic terms among providers, repetitive procedures with different results, etc.)
- Hand-written records, lack of standardization across multiple platforms (e.g., prenatal flow sheet)
- Certain types of errors may not be detected by quality checks
- Requires robust protocol and training of abstractors
- Time-intense
  - Re-abstractions, data quality checks, comparisons of record abstractions, feedback to abstractors
In retrospect . . .

- Clearly define outcomes of interest – ideally narrow in scope, rather than open ended, particularly for interview questions – requires prior determination of a more limited set of study outcomes
- Minimize number of text fields
- Plan specific analyses, prior to implementation, to guide data collection, including specific definitions of key variables (e.g., pre-existing conditions)
- Recognize, acknowledge, and plan for likely discrepancies within data sources (e.g., hypertension in medical record) that will require decision-making
  - Most challenging participant outcome: hypertension (pre-existing and gestational)
  - Most challenging infant outcome: birth defects
    - Complex outcome of high importance
    - Often requires comprehensive medical records for confirmation
In retrospect (continued) . . .

- Inclusion/exclusion criteria for multiples (including fetal reduction scenarios like vanishing twin)

- Clear and standardized definitions of birth defects
  - Use of participant-report alone, while faster, is highly challenging to standardize and interpret
  - Use of medical records available after first year of life is standard process for routine national birth defect surveillance – challenging to acquire records, delays data collection and results

- Available control group – reliance on background rates, especially when those may be fluctuating (e.g., during pandemic), is limiting
Acknowledgements

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- CDC COVID-19 Vaccine Pregnancy Registry staff and contributors
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  - Erin Stroud
  - Jennita Reefhuis
  - Jan Cragan
  - Cynthia Moore
  - Shana Godfred Cato
  - Sascha Ellington
  - David Shay
**Resources**

- ACIP- COVID-19 Vaccine Safety Technical (VAST) Subgroup Discussion and Interpretation-March 1, 2021 (cdc.gov)
- Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion, NEJM October 2021
- COVID-19 Vaccine Pregnancy Registry
- V-safe After Vaccination Health Checker
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Stakeholder perspective:
Evaluating the safety of vaccines administered during pregnancy in the Vaccine Safety Datalink

Elyse O. Kharbanda, MD, MPH
HealthPartners Institute

Optimizing the Use of Postapproval Pregnancy Safety Studies
National Press Club, Washington, D.C.
9/18/2023
Disclaimer: Dr. Kharbanda’s research on vaccine safety in pregnancy is supported through contracts between HealthPartners Institute and the Centers for Disease Control and Prevention. The findings and views in this presentation are those of Dr. Kharbanda and do not represent the official position of the Centers for Disease Control and Prevention. Mention of a product or company name is for identification purposes only and does not constitute an endorsement.
Overview

- About HealthPartners Institute
- Background on Vaccine Safety Datalink (VSD)
  - Data structure
  - VSD studies on vaccine safety in pregnancy
- Stakeholder perspective on postapproval monitoring of vaccine safety in pregnancy
Largest consumer-governed nonprofit health care organization in the nation, founded in 1957, based in Bloomington, MN

Health Insurance

1.8 million medical and dental health plan members across 6 states in the upper Midwest

Medical and dental care to patients in Minnesota and western Wisconsin

Multispecialty group practice of >1,800 physicians

1.2 million medical and dental patients

8 hospitals, 55 community-based primary care clinics

~12,000 prenatal care patients with live births/year
Nonprofit institute within HealthPartners dedicated to high-quality, public-domain health research

Current or recently completed projects at HealthPartners Institute related to postapproval drug or vaccine safety in pregnancy

- FDA – Sentinel
- NIH – Investigator initiated research on antidepressants in pregnancy and on oral corticosteroids in pregnancy
- CDC – Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS)
- CDC – Vaccine Safety Datalink (VSD)
The Vaccine Safety Datalink (VSD) is a collaborative project between CDC’s Immunization Safety Office, integrated health care organizations, and networks across the U.S. The VSD monitors safety of vaccines in use in the U.S., primarily through observational multisite studies of rare and serious events following vaccination.
Vaccine Safety Datalink (VSD) data structure

• Distributed data model - each VSD site creates standardized data files that can be used in multisite studies
  • Define cohort
  • Inpatient/outpatient/ED diagnoses and procedures
  • Vaccines
  • Birth and death files
• Dynamic pregnancy episode file – validated algorithms for identifying ongoing and completed pregnancies, updated weekly
  • Pregnancy start (LMP)
  • Gestational age
  • Pregnancy outcome (when available)
• Mom-baby linkage
• Ancillary drug or lab files available ad-hoc for specific studies
• Automated data files supplemented with chart review, as needed
Vaccine Safety Datalink (VSD) – expansion to study vaccine safety in pregnancy

• Pregnant women generally not enrolled in clinical trials
  • When trials are conducted in pregnant populations, insufficient power to assess rare post-vaccination safety outcomes

• Vaccines may be recommended for use during pregnancy with limited safety data

• Post-approval observational studies are needed but challenging

• VSD includes >3% of U.S. population, comprehensive data on vaccine exposures, access to medical records as needed

• Increasing number of vaccines recommended in pregnancy
  • Recommendations usually apply to *all* pregnant women
Timeline – vaccines recommended in pregnant populations

1960 – US Public health service recommends pregnant people prioritized for influenza vaccination

1960 – influenza vaccination recommended in any trimester of pregnancy

2004 – influenza vaccination recommended in any trimester of pregnancy

2009 – ACIP prioritizes pregnant women for H1N1 MIV

2010 – California Dept of Health recs Tdap in pregnancy >20 weeks

2011 – ACIP recs Tdap in pregnancy >20 weeks

2012 – ACIP recs Tdap in pregnancy 27-36 weeks, in every pregnancy

2020 – ACIP recs COVID-19 vaccine in pregnancy, any trimester

2023
Maternal Influenza Vaccine and Risks for Preterm or Small for Gestational Age Birth

James D. Nordin, MD, MPH1, Elyse Olshen Kharbanda, MD, MPH1, Gabriela Vazquez Benitez, PhD1, Heather Lipkind, MD, MS2, Claudia Vellozzi, MD, MPH3, and Frank DeStefano, MD, MPH3, on behalf of the Vaccine Safety Datalink*

Objective To study the impact of influenza vaccine administered to pregnant women during all trimesters on the rates of preterm and small for gestational age (SGA) births, evaluating both increased and decreased risk.

Study design This retrospective observational matched cohort study involved 7 Vaccine Safety Datalink sites across the US for the 2004-05 through 2008-09 influenza seasons. Cohort eligibility and outcomes were determined from administrative, claims, medical records, and birth data. In propensity score– and vaccine exposure time–matched analyses, ORs for preterm and SGA births were calculated.

Results Among 57,554 matched vaccinated and unvaccinated pregnant women, including 16,240 women in the first trimester, maternal vaccination was not associated with increased or decreased risk for preterm birth (OR for delivery at <37 weeks gestation, 0.97 [95% CI, 0.93-1.02]; for delivery at ≤32 weeks gestation, 0.98 [95% CI, 0.86-1.12]; and for delivery at ≤34 weeks gestation, 0.96 [95% CI, 0.88-1.04]) or SGA birth (OR for <5th percentile weight for gestational age, 1.02 [95% CI, 0.96-1.09], and for <10th percentile weight for gestational age, 1.00 [95% CI, 0.96-1.04]). Similarly, first trimester vaccination was not associated with increased or decreased risk for preterm or SGA birth.

Conclusion Receipt of trivalent inactivated influenza vaccine during pregnancy was not associated with increased or decreased risk of preterm or SGA birth. These findings support the safety of vaccinating pregnant women against influenza during the first, second, and third trimesters, and suggest that a nonspecific protective effect of the influenza vaccine for these outcomes does not exist. (J Pediatr 2014;164:1051-7).
First Trimester Influenza Vaccination and Risks for Major Structural Birth Defects in Offspring

Elyse Olshen Kharbanda, MD, MPH; Gabriela Vazquez-Beiztey, PhD; Paul A. Romitti, PhD; Allison L. Nealey, PhD; T. Craig Cheatham, PharmD; Heather S. Lipkind, MD, MS; Nicole P. Klein, MD, PhD; Grace Lee, MD, MPH; Michael L. Jackson, PhD, MPH; Simon J. Hambidge, MD, PhD; Natalie McCarthy, MPH; Frank DeStefano, MD, MPH, and James D. Nordin, MD, MPH, for the Vaccine Safety Datalink

Objective To examine risks for major structural birth defects in infants after first trimester inactivated influenza vaccine (IIV) exposures.

Study design In this observational study, we used electronic health data from 7 Vaccine Safety Datalink sites to examine risks for selected major structural defects in infants after maternal IIV exposure. Vaccine exposures for women with continuous insurance enrollment through pregnancy who delivered singleton live births between 2004 and 2013 were identified from standardized files. Infants with continuous enrollment were followed to the age of 1 year of age. We excluded mother–infant pairs with other exposures that potentially increased their background risk.

Results We identified 52,856 infants with maternal first trimester IIV exposure and 373,088 infants whose mothers were unexposed to IIV during first trimester. Prevalence (per 100 live births) for selected major structural birth defects was 1.6 among first trimester IIV exposed versus 1.5 among unexposed mothers. The adjusted PR was 1.02 (95% CI 0.94-1.10). Organ system-specific PRs were similar to the overall PR.

Conclusion First trimester maternal IIV exposure was not associated with an increased risk for selected major structural birth defects in this large cohort of singleton live births. (J Pediatr 2017;187:234-9).

Pregnant women and newborns have long been recognized as being at risk for increased morbidity and mortality from influenza infections. As such, pregnant women are a priority group for prevention through vaccination. Since 2004, the Advisory Committee on Immunization Practices has recommended that women who will be pregnant during the influenza season receive the inactivated influenza vaccine (IIV) in any trimester of pregnancy. Although initial adherence with these guidelines was low, a national survey of women pregnant during the 2014-2015 influenza season noted that about 50% reported receiving IIV before or during pregnancy.
VSD studies of vaccine safety in pregnancy - Tdap

Evaluation of the Association of Maternal Pertussis Vaccination With Obstetric Events and Birth Outcomes

Elyse O. Khartaba, MD, MPH; Gabriela Vosquez-Benitez, PhD; Heather S. Lipkind, MD, MS; Nicola P. Klein, MD, PhD; T. Craig Cheetham, PharmD, MS; Allison Nalley, PhD; Saad B. Omer, PhD; Simon J. Hambridge, MD, PhD; Grace M. Lee, MD, MPH; Michael L. Jackson, PhD; Natalie L. McCarthy, MPH; Frank DeSoefano, MD, MPH; James D. Nordin, MD, MPH

RESULTS
Vaccination was not associated with increased risks of adverse birth outcomes: crude estimates for preterm delivery were 6.3% of vaccinated and 7.8% of unvaccinated women (adjusted RR, 1.03; 95% CI, 0.97-1.09); 8.4% of vaccinated and 8.3% of unvaccinated had an SGA birth (adjusted RR, 1.00; 95% CI, 0.96-1.06). Receipt of Tdap before 20 weeks was not associated with hypertensive disorder of pregnancy (adjusted RR, 1.09; 95% CI, 0.99-1.20); chorioamnionitis was diagnosed in 6.1% of vaccinated and 5.5% of unvaccinated women (adjusted RR, 1.19; 95% CI, 1.13-1.26).
VSD studies of vaccine safety in pregnancy - Tdap

Results: We included 118,211 pregnant people; 103,258 (87%) received Tdap vaccine during pregnancy; 8098 (7%) were diagnosed with chorioamnionitis. The adjusted hazard ratio for chorioamnionitis in the Tdap vaccine-exposed group compared to unexposed was 0.96 (95% CI 0.90–1.03). There was no association between Tdap vaccine and preterm birth or adverse infant outcomes associated with chorioamnionitis. Chart reviews were performed for 528 pregnant people with chorioamnionitis. The PPV for clinical (probable or possible clinical chorioamnionitis) was 48% and 59% for histologic chorioamnionitis. The PPV for the combined outcome of clinical or histologic chorioamnionitis was 81%.

Conclusions and relevance: Tdap vaccine exposure during pregnancy was not associated with chorioamnionitis, preterm birth, or adverse infant outcomes. ICD-10 codes for chorioamnionitis lack specificity for clinical chorioamnionitis and should be a recognized limitation when interpreting results.
VSD studies of vaccine safety in pregnancy – Inadvertent exposures to HPV vaccine

- HPV vaccine is recommended to women of reproductive age, but not during pregnancy
- Data presented to FDA found in 9vHPV trials potential increased risk for spontaneous abortion, as compared to 4vHPV, when vaccination occurred within 30 days of pregnancy
<table>
<thead>
<tr>
<th>Variable</th>
<th>Distal exposure</th>
<th>Peripregnancy exposure</th>
<th>During-pregnancy exposure</th>
<th>Peripregnancy vs distal exposure</th>
<th>During pregnancy vs distal exposure</th>
<th>During pregnancy vs peripregnancy vs distal exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies, No.</td>
<td>552</td>
<td>496</td>
<td>445</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SAB</td>
<td>33 (6.0)</td>
<td>22 (4.4)</td>
<td>25 (5.6)</td>
<td>RR (95% CI): 0.72 (0.42-1.24)</td>
<td>HR (95% CI): 1.12 (0.66-1.93)</td>
<td>HR (95% CI): 1.20 (0.77-1.88)</td>
</tr>
<tr>
<td>Live births with gestational age, No.</td>
<td>518</td>
<td>474</td>
<td>418</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Preterm births(^d)</td>
<td>42 (8.1)</td>
<td>27 (5.7)</td>
<td>26 (6.2)</td>
<td>RR (95% CI): 0.72 (0.45-1.17)</td>
<td>RR (95% CI): 0.73 (0.44-1.20)</td>
<td>RR (95% CI): 0.75 (0.50-1.13)</td>
</tr>
<tr>
<td>Live births with gestational age and birth weight, No.</td>
<td>425</td>
<td>388</td>
<td>341</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SGA births(^e)</td>
<td>27 (6.4)</td>
<td>27 (7.0)</td>
<td>29 (8.5)</td>
<td>RR (95% CI): 1.10 (0.65-1.88)</td>
<td>RR (95% CI): 1.31 (0.78-2.20)</td>
<td>RR (95% CI): 1.18 (0.75-1.85)</td>
</tr>
<tr>
<td>Live births with follow-up, No.(^f)</td>
<td>414</td>
<td>363</td>
<td>320</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Major structural birth defects</td>
<td>4 (1.0)</td>
<td>4 (1.1)</td>
<td>4 (1.3)</td>
<td>PR (95% CI): 1.03 (0.26-4.07)(^a)</td>
<td>PR (95% CI): 1.30 (0.36-4.69)(^a)</td>
<td>PR (95% CI): 1.06 (0.34-3.33)(^a)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; LMP, last menstrual period; NA, not applicable; PR, prevalence ratio; and RR, relative risk.

\(^a\) Exposure windows: distal consisted of 9vHPV or 4vHPV vaccine administered from 22 to 16 weeks before LMP, peripregnancy consisted of 9vHPV vaccine administered from 42 days before LMP until LMP, during pregnancy consisted of 9vHPV vaccine administered from LMP to 19 completed weeks' gestation.

\(^b\) Using 9vHPV or 4vHPV vaccine, with inverse probability weights for age, race/ethnicity, hospitalization before pregnancy, smoking, and site.

\(^c\) Using 9vHPV or 4vHPV vaccine as a time-dependent exposure in a Cox proportional hazards regression model, with inverse probability weights for age, race/ethnicity, hospitalization before pregnancy, smoking, and site.

\(^d\) Preterm birth defined as live birth before 37 weeks' gestation.

\(^e\) SGA birth defined as below 10th percentile, based on Talge et al.\(^{27}\)

\(^f\) For evaluation of birth defect outcomes, infants who survived the first year were required to have at least 1 outpatient visit in the health system, 4 months of insurance in the first year of life, and no diagnosis of a chromosomal anomaly.
## VSD studies of COVID-19 vaccine safety in pregnancy

<table>
<thead>
<tr>
<th>Short title</th>
<th>Exposure</th>
<th>Outcome(s)</th>
<th>Status (as of 9/3/23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion case-control surveillance</td>
<td>Primary vaccine series</td>
<td>Spontaneous abortion – based on automated data</td>
<td>Published JAMA 9/2021&lt;br&gt;Presented at ACIP 9/2021</td>
</tr>
<tr>
<td></td>
<td>Booster vaccination*</td>
<td></td>
<td>Presented at ACIP 10/22&lt;br&gt;Published JAMA Open 5/2023</td>
</tr>
<tr>
<td>Stillbirth and Spontaneous abortion case-control study</td>
<td>Primary vaccine series</td>
<td>Spontaneous abortion and stillbirth – based on chart review and expert adjudication</td>
<td>Analyses ongoing</td>
</tr>
<tr>
<td>Acute maternal outcomes (within 42 days of vaccination)</td>
<td>Primary vaccine series</td>
<td>Fever and other acute local and systemic reactions</td>
<td>Published NEJM 7/2022&lt;br&gt;Published Obstetrics and Gynecology 5/2023</td>
</tr>
<tr>
<td></td>
<td>Booster vaccination*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy complications and birth outcomes</td>
<td>Primary vaccine series</td>
<td>Gestational diabetes, hypertensive disorders of pregnancy</td>
<td>Manuscript in preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small-for-gestational age, preterm birth</td>
<td>Published MMWR 1/2022</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major structural birth defects</td>
<td>Manuscript in preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Growth and developmental outcomes</td>
<td>Finalizing protocol</td>
</tr>
</tbody>
</table>
Stakeholder perspective on postapproval surveillance of vaccine safety in pregnancy

• Outcome selection
  • Biologic plausibility
  • Public health importance
  • Limited availability of data from pre-licensure trials or other surveillance systems to guide outcome selection

• Some vaccine safety outcomes may not be well suited for automated data studies
  • Require chart confirmation and clinical adjudication (stillbirth)
  • Do not result in a care visit (fever)
  • ICD-10-CM codes do not distinguish severity (postpartum hemorrhage)
  • Variation in coding practice (chorioamnionitis)
Stakeholder perspective on postapproval surveillance of vaccine safety in pregnancy

• Defining exposures
  • Need vaccine exposure to be by manufacturer to inform labeling
  • Limited access to results from animal or phase 1 studies to inform exposure windows
    • Outcome risks can vary by gestational week of pregnancy
  • Importance of using accurate data on vaccine exposures
    • At HealthPartners ~25% of COVID-19 vaccine data for VSD population is found through incorporation of state immunization registry data
Challenges with our work in postapproval surveillance of vaccine safety in pregnancy

- Timelines for completing work need to be realistic
  - Time for vaccine data to be available
  - Time for data used in dynamic pregnancy algorithm – to identify and date pregnancies – to mature
  - Time for pregnancy outcomes to occur
    - First trimester exposures and birth defects
Stakeholder perspective on postapproval surveillance of vaccine safety in pregnancy

• Analytic approaches to minimize bias should be used
  • Confounding by indication
  • Healthy vaccinee bias
  • Immortal time bias
  • Risks for outcomes vary by gestational age at vaccination
  • Vaccine availability can vary by gestational age and season
  • Use of optimal analytic approaches is also important when raw data from our studies is incorporated into meta-analyses
This work has been supported by a large team

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- Elyse Kharbanda
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- Victoria Greenberg

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- Allison Naleway
- Stephanie Irving
- Brad Crane

Collaborators at Children’s Minnesota, Gillette Children’s, University of Minnesota, University of Iowa, other VSD sites, and the CDC Immunization Safety Office (ISO)
Optimizing the Use of Postapproval Pregnancy Safety Studies
A Hybrid Public Workshop

Duke MARGOLIS CENTER for Health Policy

September 18 & 19, 2023
Lunch Break

Workshop will resume at 2:00 p.m. EST
Session 3: FDA’s Considerations for Constructing a Pregnancy Safety Study Framework

Moderator: Megan Clowse, Duke University School of Medicine

Speakers:

Wei Hua, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration

Adebola Ajao, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration

Aida Kuzucan, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration

José J. Hernández-Muñoz, Regulatory Science Staff, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration
Session 3: FDA’s Considerations for Constructing a Pregnancy Safety Study Framework

Introduction to Session 3

Wei Hua, MD, PhD, MS, MHS
Deputy Director
Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, FDA

September 18, 2023
General Postapproval Approaches to Assessing Pregnancy Safety

- Routine pharmacovigilance*
  - Spontaneous reports, case reports or case series from medical literature, etc.

- Non-interventional (observational) studies
  - Pregnancy registry studies
    - Prospective cohort studies with primary data collection
  - Healthcare database studies
    - Electronic healthcare data, such as electronic health records (EHR), medical claims
  - Descriptive studies
    - Primary data collection or electronic healthcare data
    - No comparator or sample size requirements

*Draft Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff Available at: https://www.fda.gov/media/130216/download
In parallel with routine pharmacovigilance, non-interventional studies are commonly used to generate postapproval safety data to inform regulatory decision making.

However, when and what non-interventional studies should be used and how they can be used more efficiently remain a question.
PDUFA VII Commitment: Pregnancy Safety Study Framework – Purpose

- To develop a consistent and transparent approach to help decide when and what postapproval pregnancy safety studies might optimally be used to obtain timely evidence of safety for regulatory decision making.
PDUFA VII Commitment: Pregnancy Safety Study Framework – Scope

- **In scope**
  - Postapproval non-interventional studies to assess the safety of maternal exposure to drugs or biological products during pregnancy

- **Out of scope**
  - Routine pharmacovigilance
  - Clinical trials
  - Studies on efficacy, paternal exposure, or lactation
  - Operational issues

The Framework does not address labeling, benefit-risk assessment, or clinical practice; however, safety data generated from studies under this framework, in conjunction with other safety data (e.g., routine pharmacovigilance) may inform regulatory decision making and clinical practice.
 FDA Committed under the PDUFA VII Reauthorization to:

i. Pregnancy Safety

The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner.

(1) FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of post-market studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects. The framework would consider factors such as, but not limited to, purpose of study, types of post-market studies, anticipated exposure in females of reproductive potential (FRP) and pregnant women, potential toxicity of the drug and proposed risk mitigation, benefits of the drug, and magnitude and type of risk to be detected. The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.

(a) FDA will review published literature and conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling.

(b) By September 30, 2023, FDA will hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s), including industry experience and use of Sentinel Initiative and other real-world data resources.

(c) By September 30, 2024, FDA will publish a workshop report describing the proposed framework.

Develop a framework and incorporate knowledge of how different types of post-market safety studies have been used by FDA and industry

Conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling
Understanding the Current State of Using Postapproval Pregnancy Safety Studies for FDA’s Decision-making

<table>
<thead>
<tr>
<th>Analysis #</th>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Analysis of how different types postapproval pregnancy safety studies have been used by FDA</td>
<td>Dr. Adebola Ajao</td>
</tr>
<tr>
<td>2</td>
<td>Review of types of postapproval safety data that have been included in pregnancy labeling</td>
<td>Dr. Aida Kuzucan</td>
</tr>
<tr>
<td>3</td>
<td>Preliminary analysis of drug utilization data to inform the development of the pregnancy safety study framework</td>
<td>Dr. José J. Hernández-Muñoz</td>
</tr>
</tbody>
</table>
Analysis of Postapproval Pregnancy Safety Studies Associated with FDA Approved Products

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Epidemiologist
Division of Epidemiology II, Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology, CDER, FDA

September 18, 2023
FDA Study Team

Center for Drug Evaluation and Research
- Office of Surveillance and Epidemiology: Adebola Ajao, Keewan Kim, Ivone Kim
- Office of New Drugs Division of Pediatric and Maternal Health: Carrie Ceresa, Abigail Melake, Amanda Khan, Sarah Wells
- Office of the Center Director: Ricardo Hernández

Center for Biologics Evaluation and Research
- Office of Biostatistics and Pharmacovigilance: Meghna Alimchandani, Craig Zinderman
Outline

Background
• Prescription Drug User Fee Act VII Commitment
• Post-Marketing Requirements and Commitments

Analysis of Postapproval Pregnancy Safety Studies Associated with FDA Approved Products
• Objective and Design
• Data Sources and Methods
• Variables Collected
• Results
• Summary
• Limitations

www.fda.gov
Postmarketing Requirements/Commitments

PMR/PMC refers to studies and clinical trials that applicants conduct after product approval to gather additional information about product's safety, efficacy, or optimal use.

- **PMRs**: studies and clinical trials that applicants are **required** to conduct under a statutory authority.
- **PMCs**: studies or clinical trials that an applicant agreed upon in writing with FDA and are reportable under 506B of the Food Drug and Cosmetics Act (FDCA).

Under section 505(o)(3) of the FDCA, postmarketing safety studies and clinical trials are required to:

- Assess a known serious risk related to the use of the drug.
- Assess signals of serious risk related to the use of the drug.
- Identify an unexpected serious risk when available data indicate the potential for a serious risk.

---

1. Postmarketing Requirements and Commitments. Introduction: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments#
Analysis of Postmarketing Pregnancy Safety Studies

Study Objective: Understand how different types of postmarketing pregnancy safety studies have been used by FDA;

- Describe characteristics, status, and impact of postmarketing pregnancy safety studies assessing maternal, fetal, and infant outcomes

Study Design

- Cross-sectional descriptive analysis of human postmarketing pregnancy safety studies

1. For the purposes of this protocol, this includes FDA PMR/PMC studies that were released and non-FDA studies that were terminated. FDA PMR/PMC Status Categories: https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-status-and-fulfillment-categories
Data Sources

FDA queried three data sources for pregnancy related postmarketing studies associated with products approved by FDA as of May 31, 2022

<table>
<thead>
<tr>
<th>Data source</th>
<th>Search criteria</th>
</tr>
</thead>
</table>
| FDA PMR/PMC database                             | • Patient population = pregnant  
• Study/trial include pregnant/pregnancy  
• PMR/PMC description mentions pregnant/pregnancy |
| FDA Office of Women's Health (OWH) Pregnancy Registry database | Pregnancy registries                                                            |
| ClinicalTrials.gov                                | • Pregnant, Pregnancy, Observational  
• Limited to studies associated with a drug or biologic                         |

1. Data pulled from FDA’s internal system of record for PMR/PMCs
2. Includes open and closed studies within the past year of data pull
Methods

Studies from the three data sources were combined and deduplicated

Inclusion Criteria

• Studies initiated postapproval to monitor maternal, fetal, and infant outcomes associated with exposure to FDA approved products in pregnancy

Exclusion Criteria

• Animal studies, toxicology studies, pharmacokinetic studies, cross-reactivity studies, lactation studies
Study Variables

- Study Type
- Study Goal
- Therapeutic Class
- Study Status
- Study Establishment Year
- Reasons for Study Termination
- Labeling Update

1. For the purposes of this protocol, this includes FDA PMR/PMC studies that were released and non-PMR/PMC studies that were terminated. FDA PMR/PMC Status Categories: https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-status-and-fulfillment-categories
Study Search Results

- FDA PMR/PMC Database: N=310
- FDA OWH Database: N=50
- Clinical Trials.gov: N=60

Combined and Deduplicated: N=394

Excluded: N=61
Animal, toxicology, pharmacokinetic, cross-reactivity, human factor, lactation, drug-utilization, time to event

Final Pregnancy Dataset: N=333
## Study Type

<table>
<thead>
<tr>
<th>Study Type</th>
<th>N (333)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Exposure Registry (PER) Study</td>
<td>209</td>
<td>63%</td>
</tr>
<tr>
<td>Descriptive Pregnancy Safety Study</td>
<td>69</td>
<td>21%</td>
</tr>
<tr>
<td>Database Study/Pre-specified Outcome</td>
<td>52</td>
<td>15%</td>
</tr>
<tr>
<td>Randomized Clinical Trial</td>
<td>3</td>
<td>1%</td>
</tr>
</tbody>
</table>
Study Goal

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Signal Detection/Identification</td>
<td>330</td>
<td>99%</td>
</tr>
<tr>
<td>Safety Signal Evaluation/Confirmation</td>
<td>3</td>
<td>1%</td>
</tr>
</tbody>
</table>

- **Signal Detection/Identification**: To monitor pregnancies exposed to a medication for possible teratogenic effects of the medication when there is little or no prior human data identifying a specific signal for the purpose of hypothesis generation. Signal detection might test one or multiple pre-specified outcomes at once and might or might not have a pre-specified sample size.

- **Signal Evaluation/Confirmation**: To confirm or quantify an association between pregnancy specific MCM in pregnancies exposed to a medication of interest when there is a specific hypothesis to be tested based on prior human data. Signal evaluation has pre-specified outcomes, sample size, and case adjudication.
# Top Therapeutic Class/Organ Systems

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatry</td>
<td>71</td>
<td>21%</td>
</tr>
<tr>
<td>Neurology</td>
<td>61</td>
<td>18%</td>
</tr>
<tr>
<td>Prophylactic Vaccines and Related Biologic Products</td>
<td>48</td>
<td>14%</td>
</tr>
<tr>
<td>Dermatology</td>
<td>25</td>
<td>8%</td>
</tr>
<tr>
<td>Metabolic</td>
<td>22</td>
<td>7%</td>
</tr>
<tr>
<td>Reproductive</td>
<td>16</td>
<td>5%</td>
</tr>
<tr>
<td>Genetic/Inborn Error</td>
<td>16</td>
<td>5%</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>15</td>
<td>4%</td>
</tr>
<tr>
<td>Others</td>
<td>59</td>
<td>18%</td>
</tr>
</tbody>
</table>
Study Status as of July 2023

<table>
<thead>
<tr>
<th>Status</th>
<th>N (333)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminated$^1$</td>
<td>38</td>
<td>11%</td>
</tr>
<tr>
<td>Completed$^2$</td>
<td>65</td>
<td>20%</td>
</tr>
<tr>
<td>Ongoing</td>
<td>230</td>
<td>69%</td>
</tr>
</tbody>
</table>

1. For the purposes of this protocol, this includes PMR/PMC studies that were released and non-PMR/PMC studies that were terminated.
2. Study completed as of July 2023: For the purposes of this protocol, this includes PMR/PMC studies that are fulfilled and Non-PMR/PMC studies that are completed.
Search Results Limited to PMR/PMC Studies

- FDA PMR/PMC Database: N=310
- FDA OWH Database: N=50
- Clinical Trials.gov: N=60

Combined and Deduplicated: N=394

Excluded: N=61
- Animal, toxicology, pharmacokinetic, cross-reactivity, human factor, lactation, drug-utilization, time to event

Final Pregnancy Dataset: N=333

Non-PMR/PMC Studies: N=91

PMR/PMC Studies: N=242
Study Establishment Year (PMR/PMC)

Total PMR/PMCs Established = 242

169 (~70%) Established in Last 10 Years
Terminated Studies (N=38)

- 24 (63%) of released/terminated studies not feasible due to low enrollment
  - Of these studies, 14 (58%) were replaced by a different study design
- Average time from study establishment to release: 8 years (range 2 – 14 years)
# Completed Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Exposure Registry (PER)</td>
<td>44</td>
<td>68%</td>
</tr>
<tr>
<td>Descriptive Pregnancy Safety Study</td>
<td>12</td>
<td>18%</td>
</tr>
<tr>
<td>Database Study/Pre-specified outcome</td>
<td>7</td>
<td>11%</td>
</tr>
<tr>
<td>Clinical Trial</td>
<td>2</td>
<td>3%</td>
</tr>
</tbody>
</table>

Note: The total number of studies (N) is 65.
Completed Studies (N=65)

- 30 (46%) studies resulted in labeling update
- Average time from study requirement to labeling update: 11 years (range 6 – 18 years), majority of time spent on protocol development and study conduct
- 35 (54%) studies did not result in labeling update
Summary

- Majority of pregnancy safety studies are pregnancy exposure registry (PER). Complementary studies such as database studies are newer FDA requirements. Descriptive pregnancy safety studies are required when exposure in pregnancy is expected to be rare.

- Small proportion of pregnancy safety studies have been completed. Majority of studies were established in the past 5 years and are ongoing. Half of completed studies have resulted in safety labeling update with average time from study requirement to labeling update of 11 years.

- Low utilization in pregnancy is a recurrent factor in some disease areas. A small proportion of pregnancy safety studies have been terminated with majority deemed not feasible due to low enrollment.
Study Limitations

• The three data sources are convenience samples and do not represent the universe of pregnancy safety studies so our results might have limited generalizability

• Majority of the studies reviewed were established in the past 10 years, with peak in the past 5 years
  • Therefore, there has been insufficient time for sample size accrual, study maturity, and completion to inform regulatory action or compare regulatory actions by study type.
Acknowledgement

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Craig Zinderman
Meghna Alimchandani
Aida Kuzucan
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Ricardo Hernandez
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Ivone Kim
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Patricia Bright
Abbreviations

• FDA: Food and Drug Administration
• FDAAA: Food and Drug Administration Amendments Act of 2007
• FDCA: Food Drug and Cosmetics Act
• MCM: Major Congenital Malformations
• PDUFA: Prescription Drug User Fee Act
• PER: Pregnancy Exposure Registry
• PMC: Postmarketing Commitment
• PMR: Postmarketing Requirement
• PREA: Pediatric Research Equity Act
• OWH: Office of Women’s Health
• RCT: Randomized Controlled Trial
Per Protocol Definition of Study Type

- A **descriptive safety study** is a single-arm study of exposed women with no comparator and sample size requirement. Enhanced pharmacovigilance and surveillance programs are classified under descriptive safety studies. Study results are reported descriptively.

- A **pregnancy exposure registry** is a prospective observational study that collects exposure and pregnancy outcomes information from women exposed to a product of interest shortly before or during pregnancy.

- A **database study with pre-specified outcome(s)** is a prospective or retrospective observational study assessing the association between a product exposure during pregnancy and overall or specific MCMs or other adverse pregnancy outcomes.

- A **database study without pre-specified outcome(s)** is a signal generation retrospective observational study designed to assess the risk for MCMs or other adverse pregnancy outcomes in women exposed to a specific product during pregnancy (e.g., TreeScan).

- A **clinical trial** is any prospective investigation in which the investigator determines the method of assigning the product(s) or other interventions to one or more human subjects.
Per Protocol Definition of Study Status

• Not started (Pending): The study has not been initiated (i.e., no subjects have been enrolled but does not meet the criterion for delayed (i.e., the original projected date for initiation of patient accrual or initiation of animal dosing has not passed)

• Ongoing: The study is proceeding according to or is ahead of original schedule. The FDA considers a study to be ongoing until a final study report is submitted to the FDA. Delayed studies are placed here as long as the study has started.

• Released: FDA has informed the applicant that it has been released from its obligation to conduct the postmarketing study because the study is either no longer feasible or would no longer provide useful information.

• Terminated: The study or clinical trial was ended before completion, but a final report has not yet submitted to the FDA.

• Completed/Fulfilled: Final report for the study or clinical trial was submitted to the FDA and FDA notified the applicant that the requirement or commitment, was fulfilled through a written correspondence

Note: Definition of study status was modified from Postmarketing Requirements and Commitments: Status and Fulfillment Categories | FDA
https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-status-and-fulfillment-categories
Sources and Characteristics of Quantitative Human Pregnancy Data in PLLR Product Labeling, 2015-2021

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September 18, 2023
PLLR Study Team Members

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Division of Pediatrics and Maternal Health (DPMH), Office of New Drugs (OND): Jane Liedtka, Abigail Melake, Amanda Harrilal Khan, Sarah Wells

Acknowledgment - the current study is based on previous work identifying quantitative / qualitative human safety data in PLLR labeling which was conducted by DPMH: Carrie Ceresa, Ashley Dao, Katherine Kratz, Miriam Dinatale, Tamara Johnson, Leyla Sahin
Outline

• Background - PDUFA VII Pregnancy Safety Commitments
• Study - sources and characteristics of quantitative human pregnancy safety data in PLLR product labeling from 2015 through 2021
  • Methods
  • Describe studies included in PLLR labeling with quantitative human data
  • Examples of commonly used data sources
  • Summary
Objectives

• To examine the sources and characteristics of quantitative human pregnancy safety data included in the "Human Data" subheading in the Pregnancy subsection of the PLLR labeling of products during the period June 30, 2015-December 31, 2021
pregnancy categories (A, B, C, D, and X)

PLLR format

Narrative summaries of products’ risks during pregnancy and discussions of the data supporting those summaries
Design Overview

• Cross-sectional, descriptive study of a convenience sample of PLLR labeling.

• Used standardized extraction sheets and Microsoft Excel Workbooks to capture detailed characteristics.

• Multiple quality checkpoints to ensure accurate and consistent capture of characteristics.
METHODS
Methods – Criteria for Inclusion

• PLLR labeling from July 2015 to December 2021 with “quantitative” human safety data in the Pregnancy subsection of the labeling
  
  – Quantitative data was defined as measured numeric values describing exposures or results. These numbers were usually doses, percentages, or ratios.
  
  – Qualitative human data labeling statements were not included in the current study.

• Pharmacokinetic (PK) studies were only included in analysis if they provided specific safety information in addition to the PK data.

• Products with multiple formulations and containing the same active moiety are counted only once. The latest product labeling was extracted.
Methods- Sample Labelings for Analysis

- 1,795 PLLR labeling from 2015-2021
  - 811 PLLR labeling with human pregnancy data in the Pregnancy subsection
    - 216 quantitative PLLR labeling
    - 145 unique labeling
  - 595 labeling without quantitative human safety pregnancy or PK pregnancy data in the Pregnancy subsection
- 71 duplicate active moieties in Product labelings with different tradenames
Methods- Outcomes

Product Labeling and Study Characteristics

– Study Type
– Product Therapeutic/ Organ Class
– Postmarketing requirement of commitment (PMR or PMC) associated with Product Labeling
– Study Goal
– Geographic Location of Study
– Publication Status of Study
Methods - Data extraction

**Step 1: Characterize Product Labelings and Identify Study**
- Standardized extraction sheets used to identify product labeling characteristics and studies reflected in labeling.

**Step 2: Extract Study Characteristics**
- Three epidemiologists used standardized definitions to identify study characteristics.

**Quality Control**
- Weekly discussions for every extraction among larger team. Team included epidemiologists and clinicians.
- Each extraction was checked by another epidemiologist. Discrepancies in assessments were resolved through consensus.
Methods- Analysis

• Descriptive statistics were used to describe key features and characteristics of studies in product labeling:
  – Frequency (counts) and proportion (%) by product labeling and study characteristics

• All analyses were performed using Microsoft EXCEL
RESULTS
Product Labelings and Studies Evaluated in Analysis

PLLRR Labeling- years included: 2015-2021

- 145 product labelings
- 177 unique studies
Product Labeling Characteristics: Frequency of Data from Different Study Types (N=145 labelings)*

- Pregnancy Exposure Registry: 66 (46%)
- Database Study with prespecified outcome: 51 (35%)
- Clinical Trial: 37 (26%)
- Case Report/Case Series: 15 (10%)
- Other: 29 (20%)

*Product labelings could have one or more “quantitative” human safety statements supported by one or more studies, so these proportions do not equal 100.
Product Labeling Characteristics: Other Study Types

29 “Other” Study Types

- 3 Pooled Analyses
- 16 Systematic Literature Reviews
- 4 Meta-analyses
- 6 Guidelines or Expert Opinions
Product Labeling Characteristics: Top Therapeutic Class/ Organ System (N=145 labelings)

<table>
<thead>
<tr>
<th>Therapeutic class/ organ system</th>
<th>Count</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral Agents</td>
<td>40</td>
<td>27.6%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>10</td>
<td>6.9%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12</td>
<td>8.3%</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>12</td>
<td>8.3%</td>
</tr>
<tr>
<td>Reproductive and Urologic Agents</td>
<td>9</td>
<td>6.2%</td>
</tr>
<tr>
<td>Other</td>
<td>62</td>
<td>42.8%</td>
</tr>
</tbody>
</table>
Study Characteristics: Geographic Location of Study Population (N=177 studies)

- From U.S. only: 57 (32%)
- From outside of the U.S. only: 41 (23%)
- From U.S. and outside of the U.S.: 73 (41%)
Study Characteristics: Publication (N=177 Studies)

- Published or publicly available report: 152 (86%)
- Not published or publicly available: 25 (14%)
Study Characteristics: Study Goal (N=177 Studies)

- Signal detection: 144 (81%)
- Signal evaluation/confirmation: 33 (19%)
EXAMPLES: COMMONLY USED DATA SOURCES
Antiretroviral Pregnancy Registry (APR)  
(N=38 Product Labelings)

Example: EPIVIR-HBV (lamivudine)

Excerpt from the Human Data subheading in the Pregnancy subsection of labeling:

Based on prospective reports from the APR of over **11,000 exposures** to lamivudine (including over 4,600 exposed in the first trimester) during pregnancy resulting in live births, less than 1% of which were patients with HBV, there was **no substantial difference in birth defects** with lamivudine compared with the birth defect rate of 2.7% observed in the comparator population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to lamivudine containing regimens.

*The Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based tracking system for birth defects.
Clinical Trial (N=37 Product labelings)

Example: METRONIDAZOLE

Excerpt from the Human Data subheading in the Pregnancy subsection of labeling:

“In addition, more than ten randomized placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy.”

Scandinavian Birth Register (N=21 Product labelings)

Example: Sertraline Hydrochloride Capsule (sertraline)

Excerpt from the Human Data subheading in the Pregnancy subsection of labeling:

“A study of 831,324 infants born in Sweden in 1997 to 2005 found a PPHN risk ratio of 2.4 (95% CI 1.2 to 4.3) associated with patient-reported maternal use of SSRIs “in early pregnancy” and a PPHN risk ratio of 3.6 (95% CI 1.2 to 8.3) associated with a combination of patient-reported maternal use of SSRIs “in early pregnancy” and an antenatal SSRI prescription “in later pregnancy”.”

Example: RISPERDAL CONSTA (risperidone)

Excerpt from the Human Data subheading in the Pregnancy subsection of labeling:

A retrospective cohort study from a Medicaid database of **9258** women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a **small increase in the risk major of birth defects** (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Summary

• Many different study types and data sources have supported quantitative human data statements in the Pregnancy subsection in PLLR labeling.

• Study types identified in this analysis included:
  – Pregnancy Exposure Registries (46%)
  – Database studies with prespecified outcomes (35%)
  – Clinical trials (26%)
  – Case reports / Case series (10%)

• The Antiretroviral Pregnancy Registry was the most common source of quantitative human data (26%) in this analysis.
Backup slides
Background: PDUFA VII Commitment Letter

FDA will develop a framework and incorporate knowledge of how different types of post-market safety studies have been used by FDA and industry.

FDA will conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling.
Data extraction worksheets – all available for review in SharePoint

### EXTRATION SHEET DRAFT Version 3 (5/10/2023)

1. Save extraction sheet as "<productname>_NOA/BLA number extraction" in the following folder: Study ID Extraction Sheets

2. Application numbers (list multiple if more than one brand has same generic):
   - NOA
   - BLA

3. Tradename (application number) of product used to answer questions 4 through 13:

4. Generic Name:

5. Applicant:

6. Label line:

7. Label year (year label converted to PLE in DARITLS. Data can be found in column F in the "Copy of PLEE approvals worksheet"):

8. Indication for use (copy and paste from label):

9. Year of approval:

10. Does the label have the following pregnancy-related statements or front page of label?

   - Pregnancy category (if applicable)

11. Section 8.1 text (copy and paste entire section 8.1 directly from label):

### Data Sources

#### Quantitative Information

- **Data**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

#### Quantitative Information

- **Quantitative Information**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 1

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 2

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 3

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 4

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 5

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 6

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 7

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 8

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 9

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 10

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 11

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 12

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No

### Study 13

#### Data

- **Data #**
  - Title 1
  - Title 2
  - Title 3
  - Title 4

#### Literature Search

- Were we able to identify published literature to support quantitative data in label:
  - Yes
  - No

#### References

- Were any references identified:
  - Yes
  - No
Methods- defining study type

- **Case reports / Case series**: detailed reports of the diagnosis, treatment, and follow-up of an individual patient. A case series is a collection of case reports involving patients who were exposed to the product of interest.
- **Pregnancy exposure registry**: an observational and voluntary study that collects exposure and pregnancy outcomes information from women exposed to a product of interest shortly before or during pregnancy.
- **Database study with pre-specified outcome(s)**: a prospective or retrospective observational study assessing the association between a product exposure during pregnancy and overall or specific major congenital malformations (MCM) or other adverse pregnancy outcomes.
- **Database study without pre-specified outcome(s)**: a signal generation retrospective observational study designed to assess the risk for MCMs or other adverse pregnancy outcomes in women exposed to a specific product during pregnancy (e.g., TreeScan)
- **Clinical trial**: any prospective investigation in which the investigator determines the method of assigning the drug or drugs or other interventions to one or more human subjects.
- **Other** study types are those that are not described above (e.g., systematic review).
Methods- defining study purpose

• **Signal detection**: to monitor pregnancies exposed to a medication for possible teratogenic effects of the medication when there is little or no prior human data identifying a specific signal for the purpose of hypothesis generation

• **Signal evaluation/confirmation**: to evaluate or confirm an association between pregnancy adverse events or specific MCM in pregnancies exposed to a medication of interest when there is a specific hypothesis to be tested based on prior human data
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary

The limited available data with ACTEMRA in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as tocilizumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero exposed infant [see Clinical Considerations]. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at doses 1.25 times and higher than the maximum recommended human dose by the intravenous route of 8 mg per kg every 2 to 4 weeks. The literature in animals suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition [see Data]. Based on the animal data, there may be a potential risk to the fetus.
Study Characteristics: Study Types Supporting Quantitative Data in Product Labeling (N=177 studies)

- Case Report/Case Series: 24 (14%)
- Pregnancy exposure registry: 28 (16%)
- Database Study with prespecified outcome: 53 (30%)
- Clinical Trial: 47 (27%)
- Other: 24 (13%)
Preliminary Analysis of Product Utilization Data to Inform the Development of the Pregnancy Safety Study Framework

José J. Hernández-Muñoz, RPh, MPH, MS, PhD
Sentinel Core Team, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, FDA

September 18, 2023
Agenda

• Study objectives
• Product selection
• Study design
• Characterization of utilization during pregnancy
• Conclusions
Study Objectives

• Describe the product selection to understand exposure levels for assessing feasibility of using electronic healthcare claims data for pregnancy safety studies

• Characterize product utilization during pregnancy among pregnancies that ended in live births

• Explore product characteristics that may be used to estimate exposure during pregnancy
Product Selection

• Inclusion: A total of 249 products associated with studies in the analysis of postapproval pregnancy safety were identified for this preliminary analysis.

• Exclusion: Products with pregnancy exposures ranging from 0 and 2,500 during the 15-year query period were not included in this analysis.
  • The emphasis of this preliminary analysis is on products with medium and high exposure since low exposure products are not likely to be suitable for comparative studies in administrative healthcare data systems which are the focus of the demonstration projects.

• A convenience sample of 28 products with pregnancy exposure <2,500 was included for representation of low exposure products to inform the framework development.

• This preliminary analysis is limited to 72 products.
  • 44 products with pregnancy exposure ≥2,500
  • 28 products with pregnancy exposure <2,500
Study Design

• **Data**: Six data partners from the Sentinel Distributed Data (SDD)
  - 4 National Health Insurers
  - Medicaid and Medicare

• **Population**: Female members with evidence of live birth delivery during query period

• **Query Period**: January 1, 2008 – January 31, 2023
  - Data contribution varied by data partner
Study Design

Data Availability* by Data Partner

- CMS Medicare
- CMS Medicaid
- Commercial DP 1
- Commercial DP 2
- Commercial DP 3
- Commercial DP 4

* Data prior to January 1, 2008, not utilized; dates are current as of August 4, 2023, query distribution
CMS: Centers for Medicare and Medicaid Services; DP: Data Partner; FFS: Fee-for-service
Characterization of Live Birth Deliveries in the Sentinel Distributed Database: January 1, 2008 – January 31, 2023

6,165,744 unique patients
7,299,350 live birth deliveries

Maternal Age Distribution

- 25-34 years: 4,126,201 (56.5%)
- 35-44 years: 1,309,303 (17.9%)
- 18-24 years: 1,679,861 (22.0%)
- 10-17 years: 145,976 (2.0%)

Live Birth Deliveries, by Year
Characterization of utilization during pregnancy

- Time each product is contributing utilization data to the analysis
  - 0-6 years (approved on or after 01/01/2016)
    - Total of 11 products
  - 7-13 years (approved from 02/01/2009 to 12/31/2015)
    - Total of 11 products
  - 14-15 years (approved on or before 01/31/2009)
    - Total of 50 products
Total Number of Exposed Pregnancies for Products Contributing 0 to 6 Years of Utilization Data to the Analysis from the Convenience Sample

- Rem des i mivir (Veklury only) *
- Duloxetine (except Cymbalta and equivalents)
- Varenicline-containing products (except Chantix and equivalents)
- Varenicline (Chantix equivalents only)
- Semaglutide (Wegovy only)
- Semaglutide (except Vegovy and Ozempic)
- Emtricitabine and tenofovir disoproxil fumarate (Truvada equivalents only)
- Dupilumab (Dupixent only) *
- Enemab-aooe (Aimovig only) *
- Semaglutide (Ozempic only)
- Etonogestrel and ethinyl estradiol (Nuvista equivalents only)
Total Number of Exposed Pregnancies for Products Contributing 14 to 15 Years of Utilization Data to the Analysis from the Convenience Sample
Average Number of Exposed Pregnancies by Therapeutic Class during the Query Period

Therapeutic Class | Average # of exposed pregnancies
--- | ---
Antidiabetic | 37
Antibiotic | 38
Musculoskeletal | 247
Adrenal | 457
Anticholinergic | 556
Antihistaminic | 560
Antimicrobial | 818
Anxiolytic | 1,523
Depressant | 1,649
Anticoagulant | 2,166
Contraceptives | 4,987
Antineoplastic | 8,871
Antipsychotics | 10,114
Antihypertensive | 20,287
Antiepileptic | 23,692
Antiviral | 24,441
Antidiabetic | 25,009
Antidepressants | 28,792
Sedative | 56,800
Hypnotics | 84,850

Average cumulative pregnancy exposure
Average Number of Years of Contribution to the Analysis by Products in each Therapeutic Class (1-15 years)

Therapeutic Class

- Average Number of Years of Contribution to the Query
- Number of Products in Therapeutic Class
Conclusions

• Utilization of the 72 products from the convenience sample during pregnancy was low, especially among those approved after 2008.

• 80% of the products included in this preliminary analysis had 10 or more years of utilization data in Sentinel to characterize their use during pregnancy.

• Sedative/hypnotic and antidepressant products showed the highest exposure during pregnancy.
  • The oldest sedative/hypnotic included in this query was approved in 1992 and the oldest antidepressant was approved in 1961.
Next steps

• The product exposure characterization during pregnancy among live birth deliveries will be updated to include products that were excluded from this convenience sample

  • These updates will be used to inform framework development and implementation of the demonstration projects

• Year of approval, disease, and product related factors will be further explored to inform observed patterns of utilization

• Product exposure by trimester of pregnancy will be described
Acknowledgements

This Sentinel activity is a public health surveillance activity conducted under the authority of the Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight. This activity leveraged Sentinel's Cohort Identification and Descriptive Analysis (CIDA) module, version 12.1.0, with custom programming.

FDA Query Team

Sentinel Operations Center

Participating Sentinel Data Partners

- CVS Health, Aetna, part of the CVS Health Family of companies
- Carelon Research, part of the Carelon Family of Companies under Elevance Health
- Duke University School of Medicine, through the Centers for Medicare and Medicaid Services
- Humana Healthcare Research, Inc.
- OptumInsight Life Sciences, Inc.
Session 3: FDA’s Considerations for Constructing a Pregnancy Safety Study Framework

Introduction to Session 3

Wei Hua, MD, PhD, MS, MHS
Deputy Director
Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, FDA

September 18, 2023
General Postapproval Approaches to Assessing Pregnancy Safety

- Routine pharmacovigilance*
  - Spontaneous reports, case reports or case series from medical literature, etc.

- Non-interventional (observational) studies
  - Pregnancy registry studies
    - Prospective cohort studies with primary data collection
  - Healthcare database studies
    - Electronic healthcare data, such as electronic health records (EHR), medical claims
  - Descriptive studies
    - Primary data collection or electronic healthcare data
    - No comparator or sample size requirements

*Draft Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff Available at: https://www.fda.gov/media/130216/download
General Postapproval Approaches to Assessing Pregnancy Safety (cont’d)

- In parallel with routine pharmacovigilance, non-interventional studies are commonly used to generate postapproval safety data to inform regulatory decision making.

- However, when and what non-interventional studies should be used and how they can be used more efficiently remain a question.
PDUFA VII Commitment: Pregnancy Safety Study Framework – Purpose

- To develop a consistent and transparent approach to help decide when and what postapproval pregnancy safety studies might optimally be used to obtain timely evidence of safety for regulatory decision making
PDUFA VII Commitment: Pregnancy Safety Study Framework – Scope

- In scope
  - Postapproval non-interventional studies to assess the safety of maternal exposure to drugs or biological products during pregnancy

- Out of scope
  - Routine pharmacovigilance
  - Clinical trials
  - Studies on efficacy, paternal exposure, or lactation
  - Operational issues

- The Framework does not address labeling, benefit-risk assessment, or clinical practice. However, safety data generated from studies under this framework, in conjunction with other safety data (e.g., routine pharmacovigilance) may inform regulatory decision making and clinical practice
i. Pregnancy Safety

The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner.

(1) FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of post-market studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects. The framework would consider factors such as, but not limited to, purpose of study, types of post-market studies, anticipated exposure in females of reproductive potential (FRP) and pregnant women, potential toxicity of the drug and proposed risk mitigation, benefits of the drug, and magnitude and type of risk to be detected. The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.

(a) FDA will review published literature and conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling.

(b) By September 30, 2023, FDA will hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s), including industry experience and use of Sentinel Initiative and other real-world data resources.

(c) By September 30, 2024, FDA will publish a workshop report describing the proposed framework.

Develop a framework and incorporate knowledge of how different types of post-market safety studies have been used by FDA and industry

Conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling
Understanding the Current State of Using Postapproval Pregnancy Safety Studies for FDA’s Decision-making

<table>
<thead>
<tr>
<th>Analysis #</th>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Analysis of how different types postapproval pregnancy safety studies have been used by FDA</td>
<td>Dr. Adebola Ajao</td>
</tr>
<tr>
<td>2</td>
<td>Review of types of postapproval safety data that have been included in pregnancy labeling</td>
<td>Dr. Aida Kuzucan</td>
</tr>
<tr>
<td>3</td>
<td>Preliminary analysis of drug utilization data to inform the development of the pregnancy safety study framework</td>
<td>Dr. José J. Hernández-Muñoz</td>
</tr>
</tbody>
</table>
Three Presentations
Session 3: FDA’s Considerations for Constructing a Pregnancy Safety Study Framework

Overview of Considerations to Optimize the Use of Postapproval Non-Interventional Pregnancy Safety Studies

Wei Hua, MD, PhD, MS, MHS
Deputy Director
Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, FDA

September 18, 2023
Reminder
Pregnancy Safety Study Framework – Purpose

- To develop a consistent and transparent approach to help decide when and what **postapproval pregnancy safety studies** might optimally be used to obtain timely evidence of safety for regulatory decision making
Examples of Source(s) of Safety Concern

- Biological plausibility, theoretical concern
- Animal data
- Clinical trials
- Pharmacovigilance, spontaneous reports, e.g., FAERS, VAERS
- Medical literature
- Similar drugs on the market
- Others
What Informs Selection of Non-interventional Studies for Postapproval Pregnancy Safety

- Is the study able to detect (or evaluate) a signal?
- How early can the signal be detected (or evaluated)?

Factors informing selection of study
- Outcome of interest
- Study goal
- Study’s technical capability
- Magnitude of drug exposure
Factors informing selection of study

- **Outcome of interest**
- **Study goal**
- **Study’s technical capability**
- **Magnitude of drug exposure**
Pregnancy-Related Outcomes of Interest

Maternal/Fetal/Infant Outcome, for example:

- Major congenital malformation (MCM): any
- Specific malformations, e.g., cardiac defects
- Miscarriage
- Stillbirth
- Elective termination
- Preterm birth
- Small for gestational age
- Low birth weight
- Developmental and growth delays in infancy
- Maternal complications (e.g., preeclampsia)
- Others

What outcomes are relevant to drug toxicity?

How much do we know about the risk based on available information?
### Data Gaps about Risk Determines Study Goal

<table>
<thead>
<tr>
<th>How much do we know about the risk based on available information?</th>
<th>Study Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Adequate evidence of an association</td>
<td>Signal evaluation</td>
</tr>
<tr>
<td>☐ Some basis for suspicion of an association</td>
<td>Signal detection or signal evaluation</td>
</tr>
<tr>
<td>☐ Critical gap in knowledge for specific safety issue or population</td>
<td>Signal detection</td>
</tr>
</tbody>
</table>
Study Goal

- **Signal Detection**
  - Hypothesis generation to identify a risk
  - Prespecified outcomes (one or range) or non-prespecified outcomes
  - More uncertainty accepted (less accuracy or precision due to potential bias)

- **Signal Evaluation**
  - Hypothesis testing to confirm a risk or quantify a risk
  - Prespecified, signaled outcomes
  - Higher level of certainty needed, strong internal validity
What Constitutes a Meaningful Signal in Non-interventional Studies?

- Trade-off between missing a true signal and identifying too many false signals
- Scientific and clinical decision, depending on study scenario
  - Observed vs. expected
  - Exposed vs. unexposed
  - May or may not require statistical testing (e.g., Type I error 5% vs. numerical imbalance)
  - May consider a less strict Type I error to avoid missing a signal (e.g., 20%)
  - Based on one analysis or a series of analyses (e.g., sequential monitoring)
- Others
Factors informing selection of study

- Outcome of interest
- Study goal
- **Study’s technical capability**
- Magnitude of drug exposure
Study Technical Capability Considerations

- Suboptimal study design, data, and methods may impact study's internal validity (e.g., selection bias, misclassification, confounding, etc.)
  - Identification of pregnancy population and episodes
  - Mother-infant linkages
  - Estimate of gestational age and pregnancy start
  - Exposure definition and ascertainment for critical periods
  - Outcome definition and ascertainment
  - Ability to capture key covariates and competing risks
  - Length of follow-up required for outcome of interest
  - Need for linkage to external vital records (e.g., birth certificates, death certificates)
  - Need for comprehensive data collection (e.g., chart review, primary data collection)
  - Others

Accuracy of outcome ascertainment (and the corresponding outcome misclassification) is used as an example in Session 4 Framework.
Study Technical Capability Considerations (cont’d)

- A wealth of methods development and validation studies in medical literature
- However, concerns remain for the validated methods given suboptimal validation approach and results
  - In addition, comparisons across study types (e.g., registry vs. database) are incomplete
- Data and methodological challenges differ by study goal, study question, type of medication, nature of outcome of interest, characteristics of data source, etc.
- Need adequate evidence to support regulatory decision making
- There is no perfect study; necessary level of evidence depends on study goal (signal detection vs. evaluation) on a case-by-case basis
Study Technical Capability Considerations (cont’d)

- Tolerance of uncertainty

<table>
<thead>
<tr>
<th></th>
<th>Signal Detection</th>
<th>Signal Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large effect</td>
<td>High</td>
<td>Low to Medium</td>
</tr>
<tr>
<td>Small effect</td>
<td>Medium to High</td>
<td>Low</td>
</tr>
</tbody>
</table>

- For example, if we are concerned about missing a **small effect in signal evaluation**, we might have less tolerance for uncertainty around bias.
- In contrast, if we are concerned about confirming a **large effect in signal evaluation**, or detecting a **signal**, we may be able to tolerate more uncertainty around bias in favor of a less controlled study that may be completed more quickly.
**Non-interventional Studies Can be Considered* for Postapproval Pregnancy Safety**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Signal Detection</th>
<th>Signal Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy registry study</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• Primary data collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• With comparator and sample size requirements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare database study with prespecified outcomes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• EHR and/or medical claims data, additional data collection, medical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>record review, as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prespecified one outcome or a range of outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare database study without prespecified outcomes, e.g., TreeScan™</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>• EHR and/or medical claims data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-prespecified outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descriptive study</td>
<td>Yes</td>
<td>Maybe**</td>
</tr>
<tr>
<td>• Primary data collection, EHR with medical record review, or other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>data sources or data collection methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No comparator or sample size requirements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Depending on study’s technical capabilities

** Possible strong evidence from case series
Factors informing selection of study

- Outcome of interest
- Study goal
- Study’s technical capability
- Magnitude of drug exposure
Magnitude of Drug Exposure

### Conceptual Categories

<table>
<thead>
<tr>
<th>Very rare exposure in pregnancy</th>
<th>Uncertain exposure in pregnancy</th>
<th>Very common exposure in pregnancy</th>
</tr>
</thead>
</table>

### Categorization informed by patient, product, and treatment Factors

- Signal detection is feasible using descriptive pregnancy safety study
- Signal evaluation is unlikely
- The likelihood of using electronic healthcare data increases
- Outcome of interest affects sample size requirement, a particular issue in conjunction with the rarity of exposure
- An adequately large exposed population can be quickly accrued postapproval
- Both signal detection and evaluation may be conducted in electronic health care data
- In this scenario, registry study enrollment may also be more efficient
Linking FDA’s analysis of postapproval pregnancy safety studies, labeling, and drug utilization to proposed factors informing study selection

<table>
<thead>
<tr>
<th>Analysis #1: A convenience sample of studies used by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study types used by FDA</strong></td>
</tr>
<tr>
<td>- Pregnancy registry 63%</td>
</tr>
<tr>
<td>- Descriptive study 21%</td>
</tr>
<tr>
<td>- Database study with prespecified outcome 15%</td>
</tr>
<tr>
<td>- Clinical trial 1%</td>
</tr>
<tr>
<td><strong>Study goal</strong></td>
</tr>
<tr>
<td>- Signal detection 99.1%</td>
</tr>
<tr>
<td>- Signal evaluation 0.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis #2: A sample of PLLR labeling with quantitative human data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study types informed PLLR</strong></td>
</tr>
<tr>
<td>- Pregnancy registry 46%</td>
</tr>
<tr>
<td>- Database study with prespecified outcome 35%</td>
</tr>
<tr>
<td>- Clinical trial 26%</td>
</tr>
<tr>
<td>- Case report/case series 10%</td>
</tr>
<tr>
<td>- Other 20%</td>
</tr>
<tr>
<td><strong>Study goal</strong></td>
</tr>
<tr>
<td>- Signal detection 81.4%</td>
</tr>
<tr>
<td>- Signal evaluation 18.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis #3: Drug utilization of a convenience sample of products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Magnitude of exposure</strong></td>
</tr>
<tr>
<td>- Drug utilization in pregnancy was low, especially among products approved after 2008</td>
</tr>
<tr>
<td>- Sedative/hypnotic and antidepressant products showed the highest exposure during pregnancy</td>
</tr>
<tr>
<td>- Utilization pattern cannot be explained by years on the market; other disease, patient, and product related factors will be explored</td>
</tr>
</tbody>
</table>
Observations

- A wide variety of approaches have been used to assess the safety of medications during pregnancy and have informed drug labeling
  - Pregnancy registry studies are used the most and have primarily contributed to signal detection and informing labeling (particularly from a disease-based pregnancy registry)
  - In the PLLR analysis, 10% of product labeling came from case reports and case series
- Slow patient enrollment and data accrual seems a common occurrence and can lead to long lag to labeling or study termination/release
- Drug utilization in pregnant individuals for newly approved drugs in the current analyses is low and pattern is not predictable based on the number of years marketed alone
- These observations emphasize the need for
  - A consistent approach to help determine optimal use of postapproval pregnancy safety studies
  - Better understanding of potential gaps in decision making of use of postapproval pregnancy safety studies through demonstration projects
Thank You
Break

Workshop will resume at 3:25 p.m. EST
Session 4: Design of the Pregnancy Safety Study Framework

Moderator: Geeta Swamy, Duke University School of Medicine

Speakers:

Wei Hua, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration

Clara Kim, Office of Biostatistics/Office of Translational Sciences, U.S. Food and Drug Administration

Leyla Sahin, Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine, Office of New Drugs, CDER, U.S. Food and Drug Administration

Sara Eggers, Decision Support and Analysis Staff, CDER, U.S. Food and Drug Administration
Session 4: Design of the Pregnancy Safety Study Framework

FDA’s Current Thinking on the Pregnancy Safety Study Framework

Wei Hua, MD, PhD, MS, MHS
Deputy Director
Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology, CDER, FDA

September 18, 2023
Why Develop a Pregnancy Safety Study Framework?

• Approximately 5.5 million pregnancies occur each year in the U.S.; half of pregnant individuals use at least one drug or biological product to treat medical conditions.

• Typically, at the time of approval, there are limited or no human data on the safety of product used during pregnancy; as a result, for most products, human pregnancy safety data are collected postapproval.
Why Develop a Pregnancy Safety Study Framework? (cont’d)

- The purpose of the framework is to develop a consistent and transparent approach to help decide when and what postapproval pregnancy safety studies might optimally be used to obtain timely evidence of safety for regulatory decision making
  - Focuses on non-interventional (observational) studies, under PDUFA VII commitment
  - In parallel with other safety surveillance approaches, e.g., routine pharmacovigilance (spontaneous reports, case reports or case series from medical literature, etc.)
  - Combined, all sources of safety data may inform product labeling, benefit-risk assessment, clinical practice, etc.
## Non-interventional Studies Can be Considered* for Postapproval Pregnancy Safety

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Signal Detection</th>
<th>Signal Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy registry study</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• Primary data collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• With comparator and sample size requirements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare database study with prespecified outcomes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• EHR and/or medical claims data, additional data collection, medical record review, as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prespecified one outcome or a range of outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare database study without prespecified outcomes, e.g., TreeScan™</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>• EHR and/or medical claims data</td>
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<td></td>
</tr>
<tr>
<td>• Non-prespecified outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descriptive study</td>
<td>Yes</td>
<td>Maybe**</td>
</tr>
<tr>
<td>• Primary data collection, EHR with medical record review, or other data sources or data collection methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No comparator or sample size requirements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Depending on study’s technical capabilities

** Possible strong evidence from case series
Study Goal

• Signal Detection
  • Hypothesis generation to identify a risk
  • Prespecified outcomes (one or range) or non-prespecified outcomes
  • More uncertainty accepted (less accuracy or precision due to potential bias)

• Signal Evaluation
  • Hypothesis testing to confirm a risk or quantify a risk
  • Prespecified, signaled outcomes
  • Higher level of certainty needed, strong internal validity
### Defining Key Terms

<table>
<thead>
<tr>
<th>Factor</th>
<th>Definition and Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome of interest</td>
<td>Pregnancy-related maternal, fetal, and infant outcomes, prespecified or non-prespecified, determined by available information (or lack of information)</td>
</tr>
<tr>
<td>Study goal</td>
<td>Signal detection or signal evaluation</td>
</tr>
<tr>
<td>Technical capability</td>
<td>The ability of a study to achieve necessary level of certainty, accounting for potential sources of bias</td>
</tr>
<tr>
<td>Magnitude of drug exposure</td>
<td>Expected utilization of this drug by pregnant individuals, over time</td>
</tr>
<tr>
<td>▪ Study exposure capture</td>
<td>Fraction of magnitude of drug exposure that a given study expects to capture by year, depending on data source and data collection methods</td>
</tr>
</tbody>
</table>
Preliminary Framework
Determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data

Regulatory Gap/Question
- What pregnancy safety information is needed?
- What are the outcomes of interest(s)?

Study Goal:
- What is the purpose (signal detection, signal evaluation)?
- What is the desired timeframe?

Available information
- What studies have been done?
- What do we know about the potential risk(s)?
- What do we know about the patient population, the product, and utilization of similar drugs (if any) on the market?

Potential Study: Technical Capabilities
For a given study, what are the potential sources of bias? In what direction and to what extent?

Magnitude of drug exposure
What is the expected utilization of this drug by pregnant individuals in U.S., over time?

Internal validity
Does the study have too much bias to detect (or evaluate) a signal regardless of sample size?

Minimum Sample Size
What sample size is required for a given study, dependent on study goal and the study’s technical capability?

Viable studies
Which study(ies) can meet the study goal with necessary level of evidence and within a desired timeframe?

Optimal study
Which of the viable study(ies) is optimal, considering timeliness, resource requirements, patient burden, etc.?

The optimal may be a combination of studies, combining different strengths.

Potential Study: Exposure Capture
How much pregnancy exposure does the study expect to capture by year?
Preliminary Framework
Determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data

Step 1: Determine Outcome of Interest and Study Goal
- Regulatory Gap/Question
  - What pregnancy safety information is needed?
  - What are the outcomes of interest(s)?

- Available information
  - What studies have been done?
  - What do we know about the potential risk(s)?
  - What do we know about the patient population, and utilization of similar drugs (if any) on the market?

Step 2: Assess Technical Capabilities
- Study Goal:
  - What is the purpose (signal detection, signal evaluation)?
  - What is the desired timeframe?

- Potential Study:
  - Technical Capabilities
  - For a given study, what are the potential sources of bias? In what direction and to what extent?

- Internal validity
  - Does the study have too much bias to detect a signal regardless of sample size?

Step 3: Assess Magnitude of Drug Exposure and Study Exposure Capture
- Magnitude of drug exposure
  - What is the expected utilization of this drug by pregnant individuals, over time?

- Potential Study:
  - Exposure Capture
  - How much pregnancy exposure does the study expect to capture by year?

Step 4: Determine Study viability
- Minimum Sample Size
  - What sample size is required for a given study, dependent on study goal and the study's technical capability?

- Viable studies
  - Which study(ies) can meet the study goal with necessary level of evidence and timeframe?

Step 5: Select optimal study
- Optimal study
  - Which of the viable study(ies) is optimal, considering how fast and what cost, etc.

  The optimal may be a combination of study designs, combining different strengths.
Preliminary Framework
Determining the viable and optimal non-interventional pregnancy studies to meet regulatory decision-making needs

Step 1: Determine Outcome of Interest and Study Goal

Regulatory Gap/Question
- What pregnancy safety information is needed?
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The optimal may be a combination of studies, combining different strengths.

Magnitude of drug exposure
What is the expected utilization of this drug by pregnant individuals, over time?

Potential Study: Exposure Capture
How much pregnancy exposure does the study expect to capture by year?
Determining Outcome of Interest and Study Goal

- Pregnancy safety involves a broad list of maternal, fetal, and infant outcomes, with varying relevance to toxicity of a particular drug.
- Outcome of interest can be pre-specified or non-prespecified.
- Available information (e.g., animal data, clinical trials, routine pharmacovigilance, similar products on the market, lack of information) informs regulatory question which determines outcome of interest of a study.
- Data gap (e.g., known risk, some suspicion of risk, unknown or unexpected) determines whether the study is for signal detection or evaluation.
Preliminary Framework

Determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data

**Step 1: Determine Outcome of Interest and Study Goal**

**Regulatory Gap/Question**
- What pregnancy safety information is needed?
- What are the outcomes of interest(s)?

**Study Goal:**
- What is the purpose (signal detection, signal evaluation)?
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**Available information**
- What studies have been done?
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- What do we know about the patient population, the product, and utilization of similar drugs (if any) on the market?

**Step 2: Assess Technical Capabilities**

**Potential Study:**

**Technical Capabilities**
- For a given study, what are the potential sources of bias? In what direction and to what extent?

**Internal validity**
- Does the study have too much bias to detect (or evaluate) a signal regardless of sample size?

**Minimum Sample Size**
- What sample size is required for a given study, dependent on study goal and the study’s technical capability?

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- Which of the viable study(ies) is optimal, considering timeliness, resource requirements, patient burden, etc.?

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**Magnitude of drug exposure**
- What is the expected utilization of this drug by pregnant individuals, over time?

**Potential Study:**

**Exposure Capture**
- How much pregnancy exposure does the study expect to capture by year?
Importance of Study Technical Capabilities

• Study internal validity
  • Priority in epidemiologic studies
  • Suboptimal study design, data, and methods can introduce bias*
  • There is no perfect study, so it is important to understand the impact of potential bias on study findings and interpretation of results
  • Necessary level of evidence depends on study goal (e.g., quantifying a known risk vs. signal detection) on a case-by-case basis

• Minimum sample size
  • Required sample size may vary depending on the direction and extent of bias

*Bias: Systematic error in an epidemiologic study that results in an inaccurate estimate of the association between exposure and outcome
What do we need to specify to estimate minimum sample size, depending on study’s goal and technical capabilities?

<table>
<thead>
<tr>
<th>Key Parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumed true risk (product-outcome specific)</td>
<td></td>
</tr>
<tr>
<td>Prevalence (outcome specific)</td>
<td></td>
</tr>
<tr>
<td>Desired power</td>
<td></td>
</tr>
<tr>
<td>Exposed vs. unexposed ratio</td>
<td></td>
</tr>
<tr>
<td>Type I Error</td>
<td>When appropriate, may be less strict for signal detection to avoid missing a signal</td>
</tr>
<tr>
<td>Bias parameters, e.g., sensitivity and specificity of outcome ascertainment</td>
<td>Adjusted to estimate the projected RR and its sample size under various scenarios of bias</td>
</tr>
</tbody>
</table>
Illustration of Impact of Bias on Internal Validity and Minimum Sample Size

Assuming RR=2, Prevalence=3%, power=80%, 1:1 ratio (exposed vs. unexposed)

<table>
<thead>
<tr>
<th>Technical Capability</th>
<th>Type I Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Sample Size Exposed</td>
</tr>
<tr>
<td>Outcome ascertainment</td>
<td>Projected RR</td>
</tr>
<tr>
<td>Sensitivity (fixed)</td>
<td>Specificity in Exposed</td>
</tr>
<tr>
<td>No bias</td>
<td>1.0</td>
</tr>
<tr>
<td>Examples of</td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td></td>
</tr>
<tr>
<td>misclassification</td>
<td></td>
</tr>
<tr>
<td>scenarios</td>
<td></td>
</tr>
</tbody>
</table>

- Sensitivity (fixed) values: 0.8, 0.9, 0.6
- Specificity in Exposed values: 0.8, 0.9, 0.6
- Specificity in Unexposed values: 0.8, 0.9, 0.8

Projected RR and Sample Size calculations are based on assuming RR=2, Prevalence=3%, power=80%, 1:1 ratio (exposed vs. unexposed).
Illustration of Impact of Bias on Internal Validity and Minimum Sample Size

Assuming RR=2, Prevalence=3%, power=80%, 1:1 ratio (exposed vs. unexposed)

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<tr>
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<td>1.0</td>
<td>2.000</td>
</tr>
<tr>
<td>Examples of outcome</td>
<td>0.8</td>
<td>0.9</td>
<td>0.6</td>
<td>0.345</td>
</tr>
<tr>
<td>misclassification</td>
<td>0.8</td>
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<td>0.6</td>
<td>0.573</td>
</tr>
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<td></td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
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<td></td>
<td>0.8</td>
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1) Suboptimal outcome ascertainment introduces outcome misclassification
### Illustration of Impact of Bias on Internal Validity and Minimum Sample Size

Assuming RR=2, Prevalence=3%, power=80%, 1:1 ratio (exposed vs. unexposed)

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2) Risk estimate is biased in different directions to varying extents depending on the interplay of bias parameters.
**Illustration of Impact of Bias on Internal Validity and Minimum Sample Size**

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<td>No bias</td>
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<td>748</td>
</tr>
<tr>
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<td>0.8</td>
<td>808</td>
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<tr>
<td></td>
<td>0.9</td>
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<tr>
<td></td>
<td>0.6</td>
<td>3826</td>
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<tr>
<td></td>
<td>0.8</td>
<td>842</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>793</td>
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<td></td>
<td>0.9</td>
<td>175</td>
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</tbody>
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3) Minimum sample size could be larger (or smaller) than the true sample size in the presence of bias
Illustration of Impact of Bias on Internal Validity and Minimum Sample Size

Assuming RR=2, Prevalence=3%, power=80%, 1:1 ratio (exposed vs. unexposed)

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4) Missing a signal even with large sample size
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4) Missing a signal even with large sample size
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3) Minimum sample size could be larger (or smaller) than the true sample size in the presence of bias
4) Missing a signal even with large sample size
5) Inaccuracy acceptable for signal detection but concerning for signal evaluation if bias not accounted
Potential Bias Impacts Both Signal Detection and Signal Evaluation

• In general, more bias is tolerable for signal detection, and a more rigorous study is required for signal evaluation (e.g., chart review of outcome events)

• However, in the presence of bias, minimum sample size to detect a signal may be larger (or smaller) than the true sample size

• More importantly, even if there is a large enough sample size, the signal may still be missed in certain scenarios, e.g., where the direction of association is biased to less than 1

• Hence, study internal validity is still important even for signal detection
Determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data

Step 1: Determine Outcome of Interest and Study Goal

Regulatory Gap/Question
- What pregnancy safety information is needed?
- What are the outcomes of interest(s)?

Study Goal:
- What is the purpose (signal detection, signal evaluation)?
- What is the desired timeframe?

Available information
- What studies have been done?
- What do we know about the potential risk(s)?
- What do we know about the patient population, the product, and utilization of similar drugs (if any) on the market?

Step 2: Assess Technical Capabilities

Potential Study:
- Technical Capabilities
  - For a given study, what are the potential sources of bias? In what direction and to what extent?

Internal validity
- Does the study have too much bias to detect (or evaluate) a signal regardless of sample size?

Minimum Sample Size
- What sample size is required for a given study, dependent on study goal and the study’s technical capability?

Viable studies
- Which study(ies) can meet the study goal with necessary level of evidence within a desired timeframe?

Step 3: Assess Magnitude of Drug Exposure and Study Exposure Capture

Magnitude of drug exposure
- What is the expected utilization of this drug by pregnant individuals, over time?

Potential Study: Exposure Capture
- How much pregnancy exposure does the study expect to capture by year?

Optimal study
- Which of the viable study(ies) is optimal, considering timeliness, resource requirements, patient burden, etc.?

The optimal may be a combination of studies, combining different strengths.
Magnitude of Drug Exposure among Pregnant Individuals Has an Impact on Study Suitability

- Even ranges can be informative, if precise estimates aren’t possible

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of pregnant individuals exposed to drug, annual (range)*</th>
<th>Impact on study suitability in the Framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Very rare)</td>
<td>&lt;10</td>
<td>Descriptive study may be the only option in this framework for signal detection; signal evaluation is likely not possible</td>
</tr>
<tr>
<td>2</td>
<td>10 - 100</td>
<td>Registry and database studies are likely possible options for signal detection and/or evaluation, depending on outcome of interest, study technical capabilities, and study’s capture of exposure</td>
</tr>
<tr>
<td>3</td>
<td>100 – 1,000</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1,000 – 10,000</td>
<td></td>
</tr>
<tr>
<td>5 (Very common)</td>
<td>10,000+</td>
<td>Many possible study options for signal detection and evaluation</td>
</tr>
</tbody>
</table>

*May not apply to first few years of approval considering slow market uptake
Estimating Magnitude of Drug Exposure by Year Integrates Multiple Patient and Treatment Factors

- Patient Population (1)
- Who becomes pregnant (2)
- Who takes the drug (3)

Image: Venn diagram with overlapping circles labeled as described.
Estimating Magnitude of Drug Exposure by Year Integrates Multiple Patient and Treatment Factors

(1) Patient Factors
- Prevalence of disease or condition
Estimating Magnitude of Drug Exposure by Year Integrates Multiple Patient and Treatment Factors

(1) Patient Factors
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(2) Patient Factors
- Characteristics of patient population, in particular: age, sex, and whether condition is common in pregnancy

Patient Population (1)

Who becomes pregnant (2)

Who takes the drug (3)
Estimating Magnitude of Drug Exposure by Year
Integrates Multiple Patient and Treatment Factors

(1) Patient Factors
- Prevalence of disease or condition

(2) Patient Factors
- Characteristics of patient population, in particular: age, sex, and whether condition is common in pregnancy

(3) Product and Treatment Factors
- Potential market share of product (e.g., 1<sup>st</sup> vs. 9<sup>th</sup> in class) and utilization of similar drugs on market
- Indicated for a pregnancy-related condition
- Toxicity risk (e.g., pregnancy-related warning or contraindication labeling or Risk Evaluation and Mitigation Strategy (REMS))
- Individual treatment decision making, considering:
  - Benefits to patient during pregnancy
  - What is currently known about drug toxicity
  - Other available options
  - Potential for inadvertent exposure in pregnancy
Estimating Magnitude of Drug Exposure by Year Integrates Multiple Patient and Treatment Factors

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- Individual treatment decision making, considering:
  - Benefits to patient during pregnancy
  - What is currently known about drug toxicity
  - Other available options
  - Potential for inadvertent exposure in pregnancy

(4) Time factors
- Time since approval/Years on market
Magnitude of Drug Exposure - Example of Hypothetical Scenario

**Scenario: Newly approved drug for serious condition, 5th in class**

**Patient factors**
- 800,000 patients in U.S.
- Predominately affects females;
- age of onset common in 20s and 30s;
- condition can flare during pregnancy

**Treatment factors**
- No pregnancy-related warnings or contraindication labeling or REMS
- Relatively small market share expected
- Likely to be prescribed among pregnant individuals, considering need for treatment, drug benefit, lack of evidence of teratogenicity

This may be enough to assume exposure will be **common** (category 4, i.e., 1,000 – 10,000 annual)
A Study’s Exposure Capture Can Be Thought of as a Fraction of the Magnitude of Drug Exposure

- This fraction primarily depends on how patients are enrolled or accrued in a potential study, for example,
  - Pregnancy registry study scope, recruitment and retention strategies, patient’s willingness, etc.
  - EHR/claims database size and relevance to pregnancy
- Time factors also influence the fraction a study can capture, especially in the initial years of approval, for example,
  - Time needed to establish a registry
  - Potential data lag
Integrating the Magnitude of Drug Exposure and the Study’s Capture of Exposure

Hypothetical example

- Overall magnitude of drug exposure is estimated in Category 4 (1,000 – 10,000, annual)
  - A nationwide pregnancy registry study with successful recruitment and retention -> study capture estimated at 10%, i.e., 100 – 1,000 annual
  - A large-scale EHR/claims database covering 40% of U.S. population -> study capture estimated at 40%, i.e., 400 – 4,000 annual
Preliminary Framework

Determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data

Step 1: Determine Outcome of Interest and Study Goal
- Regulatory Gap/Question
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  - What are the outcomes of interest(s)?

- Study Goal:
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- Potential Study:
  - Technical Capabilities
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- Magnitude of drug exposure
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Available information
- What studies have been done?
- What do we know about the potential risk(s)?
- What do we know about the patient population, the product, and utilization of similar drugs (if any) on the market?
# Hypothetical Look-up Table of Projected Risk Estimates and Possible Sample Sizes Based on Various Parameters

<table>
<thead>
<tr>
<th>Assumed True Relative Risk (RR)</th>
<th>Outcome Ascertainment (Assuming outcome misclassification the only bias)</th>
<th>Projected Relative Risk (RR)</th>
<th>Sample size for Exposed (1:1 Exposed to Unexposed ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Desired power</td>
</tr>
<tr>
<td></td>
<td>Exposed</td>
<td>Unexposed</td>
<td>Exposed</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
## Integrating Internal Validity, Minimum Sample Size, and Expected Exposure for a Given Signal Detection Study

### Study Goal: Signal Detection for Outcome X *(Hypothetical example)*

<table>
<thead>
<tr>
<th>Study Option 1</th>
<th>Study Option 2</th>
<th>Study Option 3</th>
<th>Study Option 4</th>
<th>Study Option 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential Study</td>
<td>Pregnancy Registry</td>
<td>Pregnancy Registry</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>Healthcare Database Pre-specified outcome</td>
</tr>
<tr>
<td>Chart review</td>
<td>Claims-based algorithm</td>
<td>Non-Prespecified outcome</td>
<td>Singular codes, untargeted</td>
<td></td>
</tr>
</tbody>
</table>

- **Internal validity**

- **Minimum sample size**

- **Expected exposure**

---

Likelihood of detecting a signal within 10 years of approval
## Integrating Internal Validity, Minimum Sample Size, and Expected Exposure for a Given Signal Detection Study

### Study Goal: Signal Detection for Outcome X (Hypothetical example)

<table>
<thead>
<tr>
<th>Study Option</th>
<th>Potential Study</th>
<th>Internal validity</th>
<th>Minimum sample size</th>
<th>Expected exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case Report Form</td>
<td>Non-differential Outcome misclassification</td>
<td>90% sensitivity</td>
<td>Likelihood of detecting a signal within 10 years of approval</td>
</tr>
<tr>
<td>Study Option 1</td>
<td>Pregnancy Registry</td>
<td>100% specificity</td>
<td>90% specificity</td>
<td>*Despite bias, interpretation of results not changed for signal detection</td>
</tr>
<tr>
<td>Study Option 2</td>
<td>Pregnancy Registry</td>
<td>90% sensitivity</td>
<td>90% specificity</td>
<td></td>
</tr>
<tr>
<td>Study Option 3</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>80% sensitivity</td>
<td>90% specificity</td>
<td></td>
</tr>
<tr>
<td>Study Option 4</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>80% sensitivity</td>
<td>80% specificity</td>
<td></td>
</tr>
<tr>
<td>Study Option 5</td>
<td>Healthcare Database Non-Prespecified outcome</td>
<td>Singular codes, untargeted</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

- **Internal validity**
  - Non-differential Outcome misclassification: 90% sensitivity, 100% specificity
  - Assumed True RR: 3.0
  - Projected RR in the presence of bias: 3.0 *

- **Minimum sample size**
  - N/A

- **Expected exposure**

---

*Despite bias, interpretation of results not changed for signal detection*
## Integrating Internal Validity, Minimum Sample Size, and Expected Exposure for a Given Signal Detection Study

### Study Goal: Signal Detection for Outcome X (Hypothetical example)

<table>
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<tr>
<td><strong>Potential Study</strong></td>
<td>Pregnancy Registry</td>
<td>Pregnancy Registry</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>Healthcare Database Pre-specified outcome</td>
</tr>
<tr>
<td><strong>Case Report Form</strong></td>
<td>perfectly designed</td>
<td>Case Report Form with less accuracy</td>
<td>Chart review</td>
<td>Claims-based algorithm</td>
</tr>
</tbody>
</table>

### Internal validity

<table>
<thead>
<tr>
<th>Non-differential Outcome misclassification</th>
<th>90% sensitivity</th>
<th>90% sensitivity</th>
<th>80% sensitivity</th>
<th>80% sensitivity</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% specificity</td>
<td>90% specificity 3.0</td>
<td>90% specificity 3.0</td>
<td>90% specificity 3.0</td>
<td>90% specificity 3.0</td>
<td></td>
</tr>
<tr>
<td>Assumed True RR</td>
<td>3.0 *</td>
<td>1.39 *</td>
<td>1.39 *</td>
<td>1.17 *</td>
<td></td>
</tr>
<tr>
<td>Projected RR in the presence of bias</td>
<td>3.0 *</td>
<td>1.39 *</td>
<td>1.39 *</td>
<td>1.17 *</td>
<td></td>
</tr>
</tbody>
</table>

### Minimum sample size

<table>
<thead>
<tr>
<th>Type I Error 20%</th>
<th>140</th>
<th>2,308</th>
<th>2,308</th>
<th>11,506</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I Error 5%</td>
<td>245</td>
<td>4,019</td>
<td>4,019</td>
<td>20,219</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4,000 (hypothetical)</td>
</tr>
</tbody>
</table>

### Expected exposure

- **Likelihood of detecting a signal within 10 years of approval**

*Despite bias, interpretation of results not changed for signal detection*
Integrating Internal Validity, Minimum Sample Size, and Expected Exposure for a Given Signal Detection Study

**Study Goal: Signal Detection for Outcome X** *(Hypothetical example)*

<table>
<thead>
<tr>
<th>Potential Study</th>
<th>Study Option 1</th>
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<th>Study Option 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Report Form</td>
<td>Pregnancy Registry</td>
<td>Pregnancy Registry</td>
<td>Healthcare Database</td>
<td>Healthcare Database</td>
<td>Healthcare Database</td>
</tr>
<tr>
<td>Case Report Form perfectly designed</td>
<td></td>
<td></td>
<td>Pre-specified outcome</td>
<td>Pre-specified outcome</td>
<td>Non-Prespecified outcome</td>
</tr>
<tr>
<td>Case Report Form with less accuracy</td>
<td></td>
<td></td>
<td>Chart review</td>
<td>Claims-based algorithm</td>
<td>Singular codes, untargeted</td>
</tr>
</tbody>
</table>

**Internal validity**

- Non-differential Outcome misclassification
  - 90% sensitivity
  - 90% sensitivity
  - 80% sensitivity
  - 80% sensitivity
  - N/A
- 100% specificity
- 90% specificity
- 90% specificity
- 80% specificity
- 80% specificity

- Assumed True RR
  - 3.0
  - 3.0
  - 3.0
  - 3.0

- Projected RR in the presence of bias
  - 3.0 *
  - 1.39 *
  - 1.39 *
  - 1.17 *

**Minimum sample size**

- Type I Error 20%
  - 140
  - 2,308
  - 2,308
  - 11,506
  - 4,019
  - 4,019
  - 4,019
  - 4,019

- Type I Error 5%
  - 245
  - 4,019
  - 4,019
  - 4,019
  - 20,219
  - 20,219
  - 20,219
  - 4,000 (hypothetical)

**Expected exposure**

- Nationwide registry
  - Capture at 10%
  - 100 – 1,000 annual
  - Expected 10-year capture**
    - 700 – 7,000
  - 70 – 700
  - 2,800 – 28,000
  - 2,800 – 28,000
  - 2,800 – 28,000

- Regional registry
  - Capture at 1%
  - 10 – 100 annual
  - Expected 10-year capture**
    - 700 – 7,000
  - 70 – 700
  - 2,800 – 28,000
  - 2,800 – 28,000
  - 2,800 – 28,000

- Large database
  - Capture at 40%
  - 400 – 4,000 annual
  - Expected 10-year capture**
    - 700 – 7,000
  - 70 – 700
  - 2,800 – 28,000
  - 2,800 – 28,000
  - 2,800 – 28,000

- Large database
  - Capture at 40%
  - 400 – 4,000 annual
  - Expected 10-year capture**
    - 700 – 7,000
  - 70 – 700
  - 2,800 – 28,000
  - 2,800 – 28,000
  - 2,800 – 28,000

**Likelihood of detecting a signal within 10 years of approval**

*Despite bias, interpretation of results not changed for signal detection; **Considering slow market penetration in the initial years of approval, potential data lag, etc.*
Integrating Internal Validity, Minimum Sample Size, and Expected Exposure for a Given Signal Detection Study

Study Goal: Signal Detection for Outcome X *(Hypothetical example)*

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<td>Case Report Form</td>
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<td>Pre-specified outcome</td>
<td>Pre-specified outcome</td>
</tr>
<tr>
<td></td>
<td>perfectly designed</td>
<td>less accuracy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internal validity</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Non-differential outcome misclassification</td>
<td>90% sensitivity</td>
<td>90% sensitivity</td>
<td>80% sensitivity</td>
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<td></td>
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</tr>
<tr>
<td>Assumed True RR</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
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</tr>
<tr>
<td>Projected RR in the presence of bias</td>
<td>3.0*</td>
<td>1.39*</td>
<td>1.39*</td>
<td>1.17*</td>
</tr>
<tr>
<td><strong>Minimum sample size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>140</td>
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<td>4,019</td>
<td>4,019</td>
<td>20,219</td>
</tr>
<tr>
<td><strong>Expected exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nationwide registry</td>
<td>Regional registry</td>
<td>Large database</td>
<td>Large database</td>
<td>Large database</td>
</tr>
<tr>
<td>Capture at 10%</td>
<td>Capture at 1%</td>
<td>Capture at 40%</td>
<td>Capture at 40%</td>
<td>Capture at 40%</td>
</tr>
<tr>
<td>In U.S., 1,000-10,000 annual</td>
<td>100 – 1,000 annual</td>
<td>10 – 100 annual</td>
<td>400 – 4,000 annual</td>
<td>400 – 4,000 annual</td>
</tr>
<tr>
<td>Expected 10-year capture**</td>
<td>700 - 7,000</td>
<td>70 – 700</td>
<td>2,800 – 28,000</td>
<td>2,800 – 28,000</td>
</tr>
</tbody>
</table>

Likelihood of detecting a signal within 10 years of approval

- More likely viable study
- Not viable
- Likely viable study
- Possibly not viable
- Likely viable study

*Despite bias, interpretation of results not changed for signal detection; **Considering slow market penetration in the initial years of approval, potential data lag, etc.*
Informing Viable Study Options

• The hypothetical example is a simple illustration of concepts. Real study scenarios involve a more complex interplay of outcome of interest, various sources of bias, necessary level of evidence, and the expected exposure.

• Direction and magnitude of bias affects the accuracy of risk estimate and the minimum sample size:
  • In the presence of bias, larger than expected sample size may be required for a viable study.
  • Even with adequately large sample size, risk estimate remains inaccurate, and a signal may still be missed due to the direction of bias.
  • Enhanced technical capabilities should be considered, depending on the impact of bias on study results and inference.
Informing Viable Study Options (cont’d)

• If the expected exposure is very rare, descriptive study may be the only viable option in this framework for signal detection, and signal evaluation is likely not feasible; if the expected exposure is not very rare, multiple viable study options might be considered
  • Threshold for “very rare” may differ by scenario. Precise estimation of expected exposure will be difficult. Refined categories are desired.

• Viable studies may be used alone or in combination (sequentially or simultaneously) to improve efficiency
Preliminary Framework
Determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data

Step 1: Determine Outcome of Interest and Study Goal
Regulatory Gap/Question
- What pregnancy safety information is needed?
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Magnitude of drug exposure
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Potential Study: Exposure Capture
How much pregnancy exposure does the study expect to capture by year?

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Minimum Sample Size
What sample size is required for a given study, dependent on study goal and the study's technical capability?

Step 5: Select optimal study
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Does the study have too much bias to detect (or evaluate) a signal regardless of sample size?

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Which study(ies) can meet the study goal with necessary level of evidence within a desired timeframe?

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Which of the viable study(ies) is optimal, considering timeliness, resource requirements, patient burden, etc.?

The optimal may be a combination of studies, combining different strengths.
# How Early Can a Signal be Detected?

## Study Goal: Signal Detection for Outcome X (Hypothetical example)

<table>
<thead>
<tr>
<th>Study Option</th>
<th>Potential Study</th>
<th>Likelihood of detecting a signal within 10 years of approval</th>
<th>Minimum sample size Type 1 Error 20%</th>
<th>Minimum sample size Type 1 Error 5%</th>
<th>Year since approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pregnancy Registry Nationwide</td>
<td>More likely viable study</td>
<td>140</td>
<td>245</td>
<td>1-3</td>
</tr>
<tr>
<td>2</td>
<td>Pregnancy Registry Regional</td>
<td>Not viable</td>
<td>2,308</td>
<td>4,019</td>
<td>4-100</td>
</tr>
<tr>
<td>3</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>Likely viable study</td>
<td>2,308</td>
<td>4,019</td>
<td>4-4,000</td>
</tr>
<tr>
<td>4</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>Possibly not viable</td>
<td>11,506</td>
<td>20,219</td>
<td>5-400-4,000</td>
</tr>
<tr>
<td>5</td>
<td>Healthcare Database Non-Prespecified outcome</td>
<td>Likely viable study</td>
<td>4,000 (hypothetical)</td>
<td>4,000 (hypothetical)</td>
<td>6-1,200-12,000</td>
</tr>
</tbody>
</table>

- **Likelihood of detecting a signal within 10 years of approval**
  - More likely viable study
  - Not viable
  - Likely viable study
  - Possibly not viable
  - Likely viable study

- **Minimum sample size Type 1 Error 20%**
  - 140
  - 2,308
  - 2,308
  - 11,506
  - 4,000 (hypothetical)

- **Minimum sample size Type 1 Error 5%**
  - 245
  - 4,019
  - 4,019
  - 20,219
  - 4,000 (hypothetical)

- **Year since approval**
  - 1-3
  - 4-100
  - 4-4,000
  - 5-800-8,000
  - 6-1,200-12,000
  - 7
  - 8
  - 9-2,400-24,000

- **Timely signal detection**
  - Yes
  - Yes
  - Yes
## Selection of Optimal Study – Timeliness, Resource requirement, and Other Trade-offs

<table>
<thead>
<tr>
<th>Study Goal: Signal Detection for Outcome X <em>(Hypothetical example)</em></th>
<th>Study Option 1</th>
<th>Study Option 2</th>
<th>Study Option 3</th>
<th>Study Option 4</th>
<th>Study Option 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential Study</td>
<td>Pregnancy Registry Nationwide</td>
<td>Pregnancy Registry Reginal</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>Healthcare Database Pre-specified outcome</td>
<td>Healthcare Database Non-Prespecified outcome, singular codes, untargeted</td>
</tr>
<tr>
<td>Case Report Form</td>
<td>Perfectly designed</td>
<td>Case Report Form with less accuracy</td>
<td>Chart review</td>
<td>Code-based algorithms</td>
<td></td>
</tr>
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<td>Likelihood of detecting a signal within 10 years of approval</td>
<td>More likely viable study</td>
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<td>Likely viable study</td>
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</tr>
<tr>
<td>Timely signal detection</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resource requirement</td>
<td>High, need to establish and maintain a large-scale registry</td>
<td>Medium, existing data system with access to medical records</td>
<td>Low, existing data system and tool, no chart review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other trade-offs</td>
<td>Not efficient for prespecified outcome X, concerns of false signals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal study in this hypothetical example</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Hypothetical Example Walk-through

Regulatory Gap/Question
Is there an increased risk of outcome X associated with drug A during pregnancy?

Study Goal:
Signal detection; if detected, followed by signal evaluation, within 10 years of approval

Potential Study: Technical Capabilities
A study using database Z may be subject to non-differential outcome misclassification with 80% sensitivity and 90% specificity according to a prior validation study.

Internal validity
The direction and magnitude of bias is acceptable for signal detection. For signal evaluation to quantify the risk, technical capabilities need to be improved to account for bias.

Available information: Drug A
- Animal data suggested some risk for Outcome X; no safety concern for any other outcomes from any sources.
- Indicated for a common condition that affects women of reproductive potential, 5th in class, no pregnancy-related warning or contraindication labeling or REMS.

Minimum Sample Size
Assuming RR=3, with prevalence=3% and 80% desired power, 2,308 exposed are required for signal detection (α=20%) and 4,019 (α=5%).

Viable studies
Signal detection is anticipated in Year 4. With improved technical capabilities for more accuracy, signal evaluation may be achieved in Year 5. The study is a viable option.

Optimal study
Comparing with other viable study options, this study is able to detect and evaluate the signal for outcome X with required level of evidence in a timely manner. The study can be efficiently operationalized using the existing resources.

Magnitude of drug exposure
- Estimated 1,000 – 10,000 exposure annual, based on patient and treatment factors and drug utilization of similar drugs on market.

Potential Study: Exposure Capture
- Database Z anticipates to capture 40% of overall exposure in U.S.
Further Development

• Identify gaps in the preliminary thinking of the framework
• Determine how to estimate the magnitude of drug exposure (e.g., at the time of approval) and the fraction that a potential study can capture
• Evaluate how these studies perform (similarly or differently) in different scenarios
• Other areas?
Acknowledgments

FDA PDUFA VII Pregnancy Safety Workgroup

FDA Center for Drug Evaluation and Research

- Office of the Center Director
  Drug Safety Operations
- Office of New Drugs
- Office of Strategic Programs
  Decision Support and Analysis Staff
- Office of Surveillance and Epidemiology
  Divisions of Epidemiology, Drug Use Team, Sentinel Core Team
- Office of Translational Sciences
  Division of Biometrics VII

FDA Center for Biologics Evaluation and Research

- Office of Biostatistics and Pharmacovigilance
- Office of Vaccines Research and Review
Questions
Closing Remarks

Marianne Hamilton Lopez
Senior Research Director, Duke-Margolis Center for Health Policy
Thank You!

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Duke Margolis
Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies

September 18-19, 2023
Day 2
Welcome and Opening Remarks

Gerrit Hamre
Research Director, Duke-Margolis Center for Health Policy
Workshop Agenda – Day 2

10:00 AM Welcome and Overview
10:10 AM Open Public Comment
10:40 AM Session 5: Filling the Known Gaps for a Comprehensive Pregnancy Safety Study Framework
11:50 AM Lunch
01:05 PM Session 6: Stakeholder Perspectives on the FDA’s Proposed Pregnancy Safety Study Framework
02:25 PM Wrap-up and Closing Remarks
02:30 PM Adjourn
Statement of Independence

The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

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Join at slido.com #PregSafe
Open Public Comment
Session 5: Filling the Known Gaps for a Comprehensive Pregnancy Safety Study Framework

Moderator: Evan Myers, Duke University

Speakers:

Patricia Bright, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration

Judith Maro, Harvard Pilgrim Health Care Institute and Harvard Medical School

Joann Gruber, Office of Biostatistics and Pharmacovigilance, CBER, U.S. Food and Drug Administration
PDUFA VII Pregnancy Safety Demonstration Projects:
Informing the Pregnancy Safety Framework by Addressing Knowledge Gaps

Patricia (“Trish”) Bright, MSPH, PhD
Associate Director for the Sentinel, Epidemiologist
Sentinel Core Team | Regulatory Science Staff
Office of Surveillance & Epidemiology
Center for Drug Evaluation and Research
Outline

- PDUFA VII Pregnancy Safety Commitments
- Gaps in knowledge
  - Overview of what we know
  - How demonstration projects “a” through “d” can inform the Pregnancy Safety Framework
- FDA’s Active Risk Identification and Analysis System (ARIA)
Pregnancy Safety

The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner.

1) FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of post-market studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects. The framework would consider factors such as, but not limited to, purpose of study, types of post-market studies, anticipated exposure in females of reproductive potential (FRP) and pregnant women, potential toxicity of the drug and proposed risk mitigation, benefits of the drug, and magnitude and type of risk to be detected. The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.

a) FDA will review published literature and conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling.

b) By September 30, 2023, FDA will hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s), including industry experience and use of Sentinel Initiative and other real-world data resources.

c) By September 30, 2024, FDA will publish a workshop report describing the proposed framework.

2) Incorporating feedback from (1), conduct 5 demonstration projects to address gaps in knowledge about performance characteristics of different study designs. FDA will initiate the following demonstration projects which may be modified as needed, before September 30, 2024:

a) Assess the performance of pregnancy registries versus electronic healthcare database studies to detect a signal when the exposure to medication in pregnancy is relatively common.

b) Assess the performance of single arm safety studies versus signal identification methods using electronic healthcare data to detect a signal when the exposure to medication in pregnancy is anticipated to be low.

c) Assess the performance of pregnancy registries versus electronic healthcare database studies to evaluate a signal when the exposure to medication in pregnancy is relatively common.

d) Assess the performance of major congenital malformations (MCM) as a composite outcome in signal detection and evaluation when there is true risk for some but not all specific malformations.

3) By September 30, 2027, based on the results of demonstration projects in (2) update the proposed framework and develop a guidance or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.
2) Incorporating feedback from (1), conduct 5 demonstration projects to address gaps in knowledge about performance characteristics of different study designs. FDA will initiate the following demonstration projects which may be modified as needed, before September 30, 2024:

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e) Assess the performance of an algorithm using electronic health record (EHR) and claims-linked healthcare data for a pregnancy-related outcome, or composite of outcomes (e.g., spontaneous abortion, stillbirth, congenital malformations), after use of vaccines in pregnant women. The parameters of the pregnancy-outcome algorithm will be developed to have general usability with therapeutic products.

3) By September 30, 2027, based on the results of demonstration projects in (2) update the proposed framework and develop a guidance…

3) By September 30, 2027, based on the results of demonstration projects in (2) update the proposed framework and develop a guidance or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.
Gaps in Knowledge

• What are the “gaps in knowledge about performance characteristics of different study designs?”
  ○ We already know a few things about the data generated by different study designs
## What Does Each Design Provide?

<table>
<thead>
<tr>
<th>Study design: Non-database studies</th>
<th>What do we know about the data this study design will provide?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registries</td>
<td>• Systematic collection of pregnancy-specific data in real time</td>
</tr>
<tr>
<td></td>
<td>• Offers a comparator</td>
</tr>
<tr>
<td></td>
<td>• Requires patient to enroll</td>
</tr>
<tr>
<td>Descriptive safety studies without comparator or predefined sample-size</td>
<td>• Systematic collection of pregnancy-specific data in real time</td>
</tr>
<tr>
<td></td>
<td>• Requires patient to enroll</td>
</tr>
</tbody>
</table>

**Question:** Traditionally pregnancy registries have been the primary design/method to fulfill post-approval pregnancy studies – Why?

**Answer:**

Reading clinical narratives that include temporal sequences of events in the context of comparators helps clinicians to evaluate causality when there is a limitation imposed by small sample size.

• Data becomes available with each enrolled participant and may be available sooner

**Question:** Could database studies also help inform safety assessments?
<table>
<thead>
<tr>
<th>Study design: Database studies</th>
<th>What do we know about the data this study design will provide?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signal Detection</strong></td>
<td></td>
</tr>
<tr>
<td>No prespecified outcome (like TreeScan)</td>
<td>Broad coverage, non-specific confounding control</td>
</tr>
<tr>
<td></td>
<td>• Can be conducted at intervals as data accrues</td>
</tr>
<tr>
<td>Prespecified outcomes (for example, sequential surveillance)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rather than “all outcomes,” this approach involves a set of targeted outcomes</td>
</tr>
<tr>
<td></td>
<td>• Power to detect is higher for targeted outcome than for all outcomes</td>
</tr>
<tr>
<td></td>
<td>• Has targeted confounding control</td>
</tr>
<tr>
<td></td>
<td>• Can be conducted at intervals as data accrues</td>
</tr>
<tr>
<td><strong>Signal Evaluation</strong></td>
<td></td>
</tr>
<tr>
<td>Prespecified outcome, active comparator, new users design</td>
<td>• High internal validity</td>
</tr>
<tr>
<td></td>
<td>• Using real world data to conduct longitudinal studies of medication safety, leveraging biostatistics techniques to mitigate bias and conduct statistical testing of hypotheses, and can be used to quantify rare events</td>
</tr>
</tbody>
</table>
Gaps in Knowledge

• What are we hoping to gain from the demonstration projects?
  o The use-case demonstration projects will provide data to both inform and challenge our collective view of the strengths and limitations of the study designs for assessing pregnancy-related outcomes in different context
  o Insights provided by the use-cases can help us to update the proposed framework

Let’s take a look at what gaps the studies will address
## Study Designs Being Compared

<table>
<thead>
<tr>
<th>Project “a”</th>
<th>Pregnancy registries versus electronic healthcare database studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project “c”</td>
<td>Pregnancy registries versus electronic healthcare database studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approach</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal Detection</td>
<td>Common</td>
</tr>
<tr>
<td>Signal Evaluation</td>
<td></td>
</tr>
</tbody>
</table>

This will help us to understand the strengths and limitations of 1) these two study designs and 2) the study approach.
# Pregnancy Safety Demonstration Projects

<table>
<thead>
<tr>
<th>Study Designs Being Compared</th>
<th>Approach</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project “b”</td>
<td>Single arm safety study versus electronic healthcare database study</td>
<td>Signal Detection</td>
</tr>
</tbody>
</table>

This will help us to understand the strengths and limitations of these two study designs when the outcome is rare.
Pregnancy Safety Demonstration Projects

<table>
<thead>
<tr>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project “d”</td>
</tr>
<tr>
<td>Assess the performance and usefulness of major congenital malformations (MCM) as a composite outcome using Signal Detection and Signal Evaluation when there is true risk for some but not all specific malformations</td>
</tr>
</tbody>
</table>

This will help us to understand whether using MCM as the pregnancy-related outcome of interest is appropriate or compromises assessments in some context (potential for dilution of effect)

- Assessing MCM is required in most pregnancy-related PMRs
- MCM is relatively straightforward to study in claims, but understanding the performance characteristics of different methods and MCM algorithms is important to know
2) Incorporating feedback from (1), conduct 5 demonstration projects to address gaps in knowledge about performance characteristics of different study designs. FDA will initiate the following demonstration projects which may be modified as needed, before September 30, 2024:

a) Assess the performance of pregnancy registries versus electronic healthcare database studies to detect a signal when the exposure to medication in pregnancy is relatively common.

b) Assess the performance of single arm safety studies versus signal identification methods using electronic healthcare data to detect a signal when the exposure to medication in pregnancy is anticipated to be low.

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3) By September 30, 2027, based on the results of demonstration projects in (2) update the proposed framework and develop a guidance or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.
Gaps in Knowledge

- How might the findings of these four demonstration projects inform the proposed Pregnancy Safety Framework?
### How Will the Demonstration Projects Inform the Proposed Framework?

#### Context

<table>
<thead>
<tr>
<th>Likely sample size</th>
<th>Potential market share of the exposure (e.g., nth product in class)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Likely patterns of use during pregnancy (e.g., prevalence of disease, frequency of use, timing in gestation)</td>
</tr>
<tr>
<td>Toxicity Risk (e.g., requiring pregnancy-related warning or REMS)</td>
<td></td>
</tr>
<tr>
<td>Severity of disease being treated</td>
<td></td>
</tr>
<tr>
<td>Is outcome known (prespecified) or not?</td>
<td></td>
</tr>
<tr>
<td>Likely capture: exposure, pregnancy-related outcome, covariates</td>
<td></td>
</tr>
</tbody>
</table>

#### Study Approach

<table>
<thead>
<tr>
<th>Study Approach</th>
<th>Non-database study</th>
<th>Database study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registry</td>
<td>Registry</td>
<td>Database study</td>
</tr>
<tr>
<td>Safety study without comparator or sample-size</td>
<td>Safety study without comparator or sample-size</td>
<td>Database study</td>
</tr>
<tr>
<td>Signal detection</td>
<td>Signal detection</td>
<td>Database study</td>
</tr>
<tr>
<td>No prespecified outcome (like TreeScan)</td>
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</tr>
<tr>
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<td>Signal Evaluation</td>
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</tr>
<tr>
<td>Inferential study</td>
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<td>Database study</td>
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</tbody>
</table>

**In what context should a registry study, a database study or both studies be required at approval?**
### How Will the Demonstration Projects Inform the Proposed Framework?

<table>
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<tr>
<th>Context</th>
<th>Study Approach</th>
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<tbody>
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<td><strong>Likely sample size</strong></td>
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<tr>
<td><strong>Demonstration projects will consider Signal Detection vs Signal Evaluation</strong></td>
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<td></td>
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Demonstration projects will consider whether MCM is an appropriate outcomes
Gaps in Knowledge

• What else are we doing to address knowledge gaps?
  o Drug utilization information is still coming in and will include data on products not included in the current analysis.
  o Data may also include further analyses, such as based on year of approval and number of drugs in class.
  o We will be developing approaches to estimate the magnitude of exposure
The Sentinel System
FDA’s Active Risk Identification and Analysis System (ARIA)
Sentinel Initiative

- Launched in 2008 in response to the FDA Amendments Act (FDAAA) 2007, which mandated FDA to:
  - Develop a postmarket Active Risk Identification and Analysis (ARIA) system for medical products
  - Incorporate data on at least 100 million patients by July 2012 from both public and private sources of healthcare data
  - Have the capacity to both identify and evaluate safety concerns for medical products
FDAAA also requires the FDA to determine whether ARIA is sufficient to assess a serious safety risk prior to requiring a sponsor to conduct a postmarket observational study of their medical product.
Guidance for Industry

Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk
Signal evaluation consists of the implementation of a full epidemiological analysis to more thoroughly evaluate the causal relationship between exposure to the medical product and the adverse outcome of interest.

Signal refinement is a process by which an identified potential safety signal is further investigated to determine whether evidence exists to support a relationship between the medical product exposure and the outcome.

Signal generation is an approach that uses statistical methods to identify medical product–adverse outcome associations that may be safety signals; no particular medical product exposure or adverse outcome is prespecified.

The system being created under the auspices of the Sentinel Initiative (the Sentinel System) will help FDA identify and investigate postmarket safety signals, a concern about an excess of adverse events compared with what is expected to be associated with a product’s use, through the processes of signal generation, signal refinement, and signal evaluation.

Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk
### Guidance for Industry

Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

#### Study Goal

- **Adequate evidence of an association exists**
  - Signal evaluation

- **Some basis for suspicion of an association**
  - Signal detection or signal evaluation

- **Critical gap in knowledge for specific safety issue or population**
  - Signal detection

---

**Data Gaps about Risk Determines Study Goal**

How much do we know about the risk based on available information?  

<table>
<thead>
<tr>
<th>How much do we know about the risk</th>
<th>Study Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate evidence of an association exists</td>
<td>Signal evaluation</td>
</tr>
<tr>
<td>Some basis for suspicion of an association</td>
<td>Signal detection or signal evaluation</td>
</tr>
<tr>
<td>Critical gap in knowledge for specific safety issue or population</td>
<td>Signal detection</td>
</tr>
</tbody>
</table>
Defining ARIA

Active Risk Identification and Analysis (ARIA) System

ARIA uses a subset of Sentinel System’s full capabilities to fulfill the FDAAA mandate to conduct active safety surveillance

* Pre-defined, parameterized, and re-usable to enable faster safety surveillance in Sentinel (in contrast to protocol-based assessments with customized programming)

† Electronic claims data, without manual medical record review
### Distribution of Safety Concerns Insufficient for Assessment in ARIA Attributed to Capture of Health Outcome

<table>
<thead>
<tr>
<th>Health Outcome (MedDRA System Organ Class)</th>
<th>Safety Concerns Identified Pre-Approval</th>
<th>Safety Concerns Identified Post-Approval</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>42</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts)</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other$^1$</td>
<td>12</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>112</strong></td>
<td><strong>20</strong></td>
<td><strong>132</strong></td>
</tr>
</tbody>
</table>

$^1$ A recording of “Other” indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.

Part of the concern is whether ARIA can appropriately capture MCM.
Gaps in Knowledge

Summary:
1. The demonstration projects
2. Other ongoing work (such as drug utilization data)
3. Feedback from this workshop

will provide insights to inform the proposed Pregnancy Safety Framework
Gaps in Knowledge

Summary (continued):

• The demonstration projects will also help us to consider:
  
  o In what context a registry study, a database study, or both studies should be required at approval?
    ▪ We don’t expect one size to fit all
Gaps in Knowledge

Summary (continued):

• The demonstration projects will also help us to consider:
  o Whether using MCM as a composite pregnancy-related outcome of interest is appropriate
The next presentation will provide more information about CDER’s Sentinel System capabilities can support the demonstration projects

Thank you for listening
Using the Sentinel System to Respond to FDA Regulatory Needs in Monitoring Medication Safety in Pregnancy

Judith C. Maro, PhD

Sentinel Operations Center
Sentinel Analytic Tools were developed to respond to FDA needs, including for monitoring the safety of medications in pregnant individuals.
Inability to Adequately Measure “Adverse Pregnancy and Fetal Outcomes” is the Top Reason for ARIA Insufficiency

Trends in ARIA Insufficiency by Year (N = 197)

ARIA = Reusable and Parameterizable Tools + Electronic Data

* Pre-defined, parameterized, and re-usable to enable faster safety surveillance in Sentinel (in contrast to protocol-based assessments with customized programming)
† Electronic claims data, without manual medical record review

https://pubmed.ncbi.nlm.nih.gov/37391385/; ARIA = Active Risk Identification and Analysis
Enhancements to Sentinel Common Data Model (SCDM)

1.0: Sentinel Common Data Model (SCDM) published

2.0: Added Laboratory and Vitals Tables

3.0: Added State Vaccine Table*; Converted Laboratory Table into Laboratory Results Table

4.0: Expanded Enrollment, Demographic, and Laboratory Results Table

5.0: Expanded Laboratory Results Table; Shifted Laboratory Results Guidance into Separate Documentation

6.0: Added Inpatient Pharmacy and Inpatient Transfusion Tables

7.0: Added Mother-Infant Linkage Table

7.1.0: Expanded Laboratory Results Table: COVID-19 Diagnostic Test Results

8.0: Added Prescribing, Facility, and Provider Tables

8.1.0: Added Patient-Reported Measures Tables, Multi-Racial classification, COVID-19 Antibody Test Results, expanded Procedure table to capture CDC CVX codes

*The State Vaccine table has not been in use since SCDM v6.0.
Live Birth Deliveries Available in Sentinel

Identified 13.5 million pregnancies with a live birth delivery, Jan 2008 – Jan 2023

• Applying standard enrollment requirements (medical and drug coverage during entire pregnancy): ~7.3 million total pregnancies

There are currently 10.8 million linked deliveries.

This slide is an updated version of a slide previously shown here: https://www.sentinelinitiative.org/news-events/meetings-workshops-trainings/2023-sentinel-public-training-innovation-day-april-11-12. It is from a query executed in August 2023 to include Medicaid data from years 2014-2020.
Enhancements to Sentinel’s Routine Querying System

2014
1.0: Query Request Package (QRP) Published
2.0: Self-Controlled Risk Interval Design

2015
2.2: Medical Product Use During Pregnancy
3.0: Propensity Score Analysis (PSA) Expansion

2016
4.0: QRP Redesign

2017
5.0: Medical Product Utilization, Most Frequent Utilization

2018
6.0: Medical Product Switching, Multiple Events, Treatment Overlap, Concomitant Use
7.0: Mother-Infant Linkage with PSA

2019
8.0: Signal Identification

2020
9.0: Interrupted Time Series
10.0: PSA Expansion, Program Efficiency Redesign

2021
11.0: Dose Analysis, Automated Report Expansion
12.0: PSA Enhancements, Laboratory Baseline Characteristics Reporting

2022
13.0: QRP Reporting Tool Published

Routine Querying System, also known as Query Request Package (QRP) and QRP Reporting Tool
Sentinel Analytic Tools Were Built to Address FDA’s Signal Management Needs

Template computer programs with standardized questions
Parameterized at program execution
Pre-tested and quality-checked
Standard output
Validation of the Signal Validation Tools Against Existing Studies

ORIGINAL ARTICLE

Assessing medical product safety during pregnancy using parameterizable tools in the sentinel distributed database

Jennifer G. Lyons ✉️ Elizabeth A. Suarez, Elnara Fazio-Eynullayeva, Judith C. Maro, Catherine Corey, Jie Li, Sengwee Toh, Mayura U. Shinde

First published: 09 November 2022 | https://doi.org/10.1002/pds.5568

Disclaimer: The views expressed in this paper reflect those of the authors and should not be construed to represent U.S. Food and Drug Administration's views or policies.

Funding information: US Food and Drug Administration, Grant/Award Number: HHSF223201400030I

Read the full text 🈸

Public Training on Signal Validation Studies in Pregnancy

Sentinel Public Training on Maternal Health and Pregnancy

Date: Monday, November 2, 2020
Time: 9:00am - 12:00pm EST
Event Type: Training

Description:
The 2020 Sentinel Public Training consisted of presentations on the Sentinel System's distributed database and broad analytic capabilities. We discussed pregnancy-related analyses including how Sentinel links and uses mother and infant data, cohort identification approaches.

https://www.youtube.com/watch?v=BpdrFTXco2g
Signal Identification – Use of Untargeted Methods

We can test for increases in risk in the composite outcomes at any level simultaneously.

Individual ICD-10-CM codes

ICD-10-CM = International Classification of Diseases, Clinical Medication, 10th Edition
Sentinel Analytic Tools Already Have Been Developed for Both Targeted Outcome Studies AND Untargeted Outcome Studies

Steps for an observational single outcome study in EHR data:

1. Identify a cohort
2. Classify exposure based on records of medication dispensings
3. Identify the outcome using a validated algorithm
4. Control for confounding using propensity score methods
5. Calculate a point estimate for the exposure-outcome association

Steps for an observational multiple outcome study in EHR data:

1. Identify a cohort
2. Classify exposure based on records of medication dispensings
3. Create an outcome tree with multiple outcomes of interest
4. Control for confounding using propensity score methods
5. Calculate test statistics for each outcome using TreeScan

EHR = Electronic Health Record
Validation of Signal Identification in Pregnancy Using Empirical and Simulated Data

Noël methods for pregnancy drug safety surveillance using the FDA Sentinel System

Elizabeth A. Suarez, Michael Nguyen, Di Zhang, Yueqin Zhao, Danijela Stojanovic, Jane Liedtka, Abby Anderson, Wei Liu, Inna Dashovsky, David Cole, Sandra Menzin, Jennifer Noble, Monica Munoz, Judith Maro

First published: 24 July 2022 | https://doi.org/10.1002/pds.5512

This work was presented at the International Conference of Pharmacoepidemiology (virtual event).

Funding information: US Food and Drug Administration (FDA), Grant/Award Numbers HHSF223201400030I, HHSF223201012T

Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs

Epidemiology 34(1):90-98, January 2023. | DOI: 10.1097/EDE.0000000000001561

Author Information

Public Training on Signal Identification Studies in Pregnancy

Leveraging the Sentinel System for Signal Identification Among Infants Following Maternal Medication Use During Pregnancy

Sentinel Public Training
April 11, 2023
Sentinel Operations Center | Harvard Pilgrim Health Care Institute

2023 Sentinel Public Training Day | 11th April, 2023

https://www.youtube.com/watch?v=A35DMjF4wms
Back to ARIA Insufficiency...

• A key issue that contributed to ARIA insufficiency for adverse pregnancy and fetal outcomes related to lack of medical record review.

• There are multiple current validation studies of adverse pregnancy outcomes:

• There are not many validation studies of adverse infant outcomes in the current (ICD-10-CM) coding era.
How can the Sentinel Analytic Tools meet the needs of the FDA’s Pregnancy Framework?
### PDUFA VII Commitments Timeline

<table>
<thead>
<tr>
<th>FY 23</th>
<th>FY 24</th>
<th>FY 25</th>
<th>FY 26</th>
<th>FY 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 1, 2022</td>
<td>Sep 30, 2023</td>
<td>Oct 1, 2023</td>
<td>Sep 30, 2024</td>
<td>Oct 1, 2025</td>
</tr>
<tr>
<td><strong>By September 30, 2023, FDA will hold a public workshop postapproval safety studies in pregnant individuals</strong></td>
<td><strong>By September 30, 2024, FDA will publish a pregnancy workshop report describing the proposed framework</strong></td>
<td><strong>By September 30, 2025, FDA will publish on its website an update on facilitation of public and sponsor access to Sentinel’s distributed data network</strong></td>
<td><strong>By September 30, 2027, FDA will publish a report on the results of the negative control and pregnancy development projects</strong></td>
<td></td>
</tr>
<tr>
<td><strong>By September 30, 2023, FDA will hold a public workshop on the use of negative controls</strong></td>
<td><strong>By September 30, 2024, FDA will initiate 5 pregnancy demonstration projects (may be modified as needed):</strong> 1. Pregnancy registries vs. EHR for signal detection 2. Single arm safety study vs. EHR for signal detection 3. Pregnancy registries vs. EHR for signal evaluation 4. Performance of MCM as a composite outcome 5. EHR algorithm for pregnancy outcomes following vaccines</td>
<td><strong>By September 30, 2025, FDA will analyze, and report on the use of Sentinel for regulatory purposes (e.g., labeling changes, PMRs, PMCs)</strong></td>
<td><strong>By September 30, 2027, FDA will publish a report on the results of the negative control and pregnancy development projects</strong></td>
<td></td>
</tr>
<tr>
<td>For FY23-27, FDA will report its obligations for updated PDUFA VI commitments in PDUFA Financial Report with detail for spending categories (e.g., data infrastructure, analytical capabilities, safety issue analyses, etc.)</td>
<td><strong>By September 30, 2024, FDA will initiate methods projects:</strong> 1. Negative control automation in Sentinel tools 2. Double negative control adjustment</td>
<td><strong>PDUFA = Prescription Drug User Fee Act, PMRs = Postmarket Requirements, PMCs = Postmarket Commitments, MCM = Major Congenital Malformations, EHR = Electronic Health Record</strong></td>
<td><strong>PDUFA = Prescription Drug User Fee Act, PMRs = Postmarket Requirements, PMCs = Postmarket Commitments, MCM = Major Congenital Malformations, EHR = Electronic Health Record</strong></td>
<td></td>
</tr>
</tbody>
</table>
Key Questions for Pregnancy Demonstration Projects

• The goal is to generate Real World Data that is accurate and timely and can be quickly converted (via analytic methods) into Real World Evidence.

• **Key Words: Accurate**
  - Registry-based data use *primary* research collection methods and so algorithms may be inherently more accurate than *secondary* research data collection methods.
  - Additional review may be required for electronic health data to ensure accuracy.

• **Key Words: Timely**
  - Registry-based data are expected to enroll only consented individuals (often *after* they are aware they are pregnant) whereas secondary research data collection methods automatically generate larger sample size populations available for analysis and do not require individual consent.
Key Factors Contributing to Accuracy and Timeliness

• **Exposure Sensitivity**
  • How capable are our data collection systems for covering/following 100% of pregnant individuals that take a given medication?

• **Exposure Specificity**
  • How capable are our data collection and analytic systems of minimizing the impact of exposure misclassification, particularly for unexposed pregnant individuals?

• **Outcome Sensitivity (assumes targeted outcomes)**
  • How capable are our data collection systems of collecting evidence of important outcomes, some of which are known to be frequently medically unattended (e.g., spontaneous abortion)?

• **Outcome Specificity (assumes targeted outcomes)**
  • How capable are our data collection and analytic systems of minimizing the impact of outcome misclassification arising from differential diagnosis lists or other ways that an outcome may be unconfirmed?
Important to First Agree to Outcome Definitions in Targeted Analyses

Levetiracetam Pregnancy Registry: Final results and a review of the impact of registry methodology and definitions on the prevalence of major congenital malformations

Angela E. Scheuerle, Lewis B. Holmes, Jessica D. Albano, Vincent Badalamentí, Dina Battino, Deborah Covington, Cynthia Harden, David Miller, Georgia D. Montouris ... See all authors

First published: 23 May 2019 | https://doi.org/10.1002/bdr2.1526 | Citations: 9

Funding information UCB Pharma

- LEV-Registry: 46/144 had MCMs
- EURAP Registry review of same cases: 22/144 had MCMs.
- North American AED Pregnancy Registry review: 7/144 had MCMs.

- We observe similarly substantial disagreement depending on how MCMs are defined in electronic data with preliminary estimates that can range from 2-20% depending on inclusion of particular conditions (e.g., ankyloglossia, patent ductus arteriosus).

Is *A Priori* Chart Validation Needed for Monitoring Major Congenital Malformations in a Signal Detection Framework?

- **Back to Accuracy Considerations....**
  
  - Perhaps the tolerance for false negative v. false positive error is different in *signal identification* v. *signal evaluation* studies such that quasi-chart validation mechanisms (claims profiles) can be reviewed in near real-time during a signal identification phase to be followed by full chart adjudication for unvalidated algorithms in a signal evaluation phase.

---

**Validation of an electronic algorithm for Hodgkin and non-Hodgkin lymphoma in ICD-10-CM**

Mara M. Epstein, Sarah K. Dutcher, Judith C. Maro, Cassandra Saphirak, Sandra DeUccia, Muthalagu Ramanathan, Tejaswini Dhawale, Sonali Harchandani ... *See all authors*  

First published: 26 April 2021 | [https://doi.org/10.1002/pds.5256](https://doi.org/10.1002/pds.5256) | Citations: 2

An abstract was presented at the 2020 Society for Epidemiologic Annual Meeting (virtual) as a poster.  
**Funding information:** National Center for Advancing Translational Sciences, Grant/Award Number: KL2TR001454; U.S. Food and Drug Administration, Grant/Award Number: HHSF223201400030I

“We examined the ability of the clinician adjudicators to classify lymphoma case status for algorithm-identified cases based on these de-identified, patient-level claims profiles, and ultimately compared these results to the chart review results.”

“Adjudicators correctly categorized 87% of lymphoma cases (92/106 cases identified by claim profile adjudication). Fourteen patients (13%) categorized as likely cases based on summary claims data were not confirmed by chart review.”
Explore Treating Major Congenital Malformations as a Composite or as Specific Outcomes in Signal Identification Analyses

- Say we agree that Major Congenital Malformations (MCMs) comprise 30-40 underlying conditions that are created from more than 100+ individual diagnostic codes when using electronic data resources
  - What are the power and time-to-detection tradeoffs in using a single composite outcome or a “tree” that is composed solely of MCM diagnostic codes?
- When is statistical hypothesis testing necessary and when is descriptive monitoring enough?
- These are some of the questions that we hope to answer in the demonstration projects.

MCM = Major Congenital Malformation, Power = probability of identifying a signal if a true signal exists
Takeaways

• Sentinel has the data and analytic tools available to perform these demonstration projects.

• We are trying to explore and quantify material differences in best approach, paying particular attention to the accuracy and timeliness in multiple approaches.

• These demonstration projects are part of a framework that is designed to be generally useful but it is impossible to expect that findings will generalize to every situation.

• The goal is to find conditions under which different approaches may be preferred. There is no expectation that a single approach is always and uniformly preferable.
Questions?
CBER’s Biologics Effectiveness and Safety (BEST) Initiative: Safety Surveillance of Biologics in Pregnancy

Joann F. Gruber, PhD
Epidemiologist
Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance

September 19, 2023
Outline

- Background: PDUFA VII Commitment Letter
- Introduction to the Biologics Effectiveness and Safety (BEST) Initiative
- Capabilities of BEST to Study Safety of Biologics in Pregnancy
  - Validating Claims-based Algorithms to Identify Pregnancy Outcomes
  - Linkage of Mothers and Infants in Claims Databases
Background: PDUFA VII Commitment Letter
Demonstration Projects

(2) Incorporating feedback from (1), conduct 5 demonstration projects to address gaps in knowledge about performance characteristics of different study designs, statistical methods, and software tools. Demonstration projects will be completed by September 30.

(a) Assess electronic health records when there is limited common denominator.

(b) Assess signal data to pregnancy registries.

(c) Assess the performance of pregnancy registries versus electronic healthcare database studies to evaluate a signal.

(d) Assess the performance of major congenital malformations (MCM) as a composite outcome in signal detection and but not all

(e) Assess the performance of an algorithm using electronic health record (EHR) and claims-linked healthcare data for a pregnancy-related outcome, or composite of outcomes (e.g., spontaneous abortion, stillbirth, congenital malformations), after use of vaccines in pregnant women. The parameters of the pregnancy-outcome algorithm will be developed to have general usability with therapeutic products.
Introduction to the Biologics Effectiveness and Safety (BEST) Initiative
Sentinel Initiative

- FDA Amendments Act of 2007 (FDAAA 2007) mandated FDA build an active post-marketing safety surveillance system for FDA-regulated products

- FDA established the Sentinel Initiative
  - CDER: **Sentinel System** to monitor drug safety
  - CBER: **Biologics Effectiveness and Safety (BEST) System** to monitor safety of biologics

September 19, 2023
Biologics Effectiveness and Safety (BEST) Infrastructure

- EHR Network
- Access to Medical Charts
- Short Data Lag
- Expandable Common Data Model
- Analytic Capabilities On-Demand
- Large Claims Databases Linked to IIS

September 19, 2023
# BEST Data Sources

<table>
<thead>
<tr>
<th>Data Source*</th>
<th>Database Type</th>
<th>No. Patients Covered (Millions)</th>
<th>Time Period Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS–Medicare</td>
<td>Claims</td>
<td>105</td>
<td>2005 - present</td>
</tr>
<tr>
<td>MarketScan Commercial and Medicare Supplemental</td>
<td>Claims</td>
<td>254</td>
<td>1999 - 2019</td>
</tr>
<tr>
<td>MarketScan Medicaid</td>
<td>Claims</td>
<td>48</td>
<td>1999 - 2019</td>
</tr>
<tr>
<td>Blue Health Intelligence</td>
<td>Claims</td>
<td>33.6</td>
<td>2012 - present</td>
</tr>
<tr>
<td>Optum–Adjudicated</td>
<td>Claims</td>
<td>66</td>
<td>1993 - present</td>
</tr>
<tr>
<td>Optum–Pre adjudicated</td>
<td>Claims</td>
<td>22</td>
<td>2017 - present</td>
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<tr>
<td>Carelon Research</td>
<td>Claims</td>
<td>76</td>
<td>2006 - present</td>
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<tr>
<td>CVS Health</td>
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<td>26</td>
<td>2018 - present</td>
</tr>
<tr>
<td>OneFlorida Clinical Research Consortium–Medicaid</td>
<td>Claims</td>
<td>6.7</td>
<td>2012 - present</td>
</tr>
<tr>
<td>OneFlorida Clinical Research Consortium–EHR</td>
<td>EHR</td>
<td>5.6</td>
<td>2012 – present</td>
</tr>
<tr>
<td>Optum EHR</td>
<td>EHR</td>
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<td>2007 - 2020</td>
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<tr>
<td>MedStar Health Research Institute</td>
<td>EHR</td>
<td>6.0</td>
<td>2009 - present</td>
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<tr>
<td>PEDSnet</td>
<td>EHR</td>
<td>6.2</td>
<td>2009 - present</td>
</tr>
<tr>
<td>IBM CED</td>
<td>Linked EHR Claims</td>
<td>5.4</td>
<td>2000 - present</td>
</tr>
<tr>
<td>OneFlorida Clinical Research Consortium–Linked EHR Claims</td>
<td>Linked EHR Claims</td>
<td>1.5</td>
<td>2012 - present</td>
</tr>
</tbody>
</table>

*Data lag varies for different databases from a few days to a few months.
Validating Claims-based Algorithms to Identify Pregnancy Outcomes
Background and Motivation

To conduct safety surveillance of biologics in pregnancy, BEST needs the capability to:

- Identify pregnancy outcomes using standard coding systems (ICD-10 era)
- Determine gestational age
Study Aims

- **Aim 1**: Develop claims-based algorithms to identify pregnancy outcomes and estimate gestational age in administrative claims data.

- **Aim 2**: Evaluate the performance of the claims-based algorithms by physician adjudication of linked EHR charts.
**Study Database & Population**

**Database:**
IBM Linked Claims-EMR Data Set (CED)

- **250M+ Claims Patients** (MarketScan)
- **70M+ EMR Patients** (Explorys)
- **5.6M** (CED) Patients
- **3M+ Lab Pats**

2000 – 2019

**Population:**
Female persons aged 12–55 years at the time of the outcomes of interest who
- were continuously enrolled with medical benefit during the pregnancy episode and
- had the pregnancy outcome on or after August 1, 2016
Methods

Algorithms: Outcomes of Interest (Aim 1)

- Pregnancy Outcomes
  - Live births
    - Full term (≥37 weeks)
    - Preterm (<37 weeks)
  - Stillbirth
  - Spontaneous abortion
- Gestational age

Validation: Use of Structured EHR to Evaluate Algorithms (Aim 2)

- Sample identified pregnancy outcomes
- Use structured EHR data and the Global Alignment of Immunization safety Assessment (GAIA) in pregnancy case definitions to evaluate the performance of claim-based algorithms
- Estimate Percent Agreement and 95% Confidence Intervals
Algorithm Performance: Pregnancy Outcomes

Pregnancy Outcome | Percent Agreement (95% CI)
--- | ---
Live birth (full term) | 62.4 (52.0–71.7)
Live birth (preterm) | 97.8 (91.8–99.9)
Spontaneous abortion | 100.0 (93.9–100.0)
Stillbirth | 70.8 (50.2–85.5)
Algorithm Performance: Gestational Age by Pregnancy Outcome

![Graph showing percent agreement by pregnancy outcome.](image)

- **Live birth (full term)**
  - Within 7 days: 85.9% (77.0–91.8)
  - Within 14 days: 98.9% (93.3–100.0)

- **Live birth (preterm)**
  - Within 7 days: 81.7% (72.4–88.5)
  - Within 14 days: 92.5% (84.8–96.6)

- **Spontaneous abortion**
  - Within 7 days: 61.3% (49.8–71.7)
  - Within 14 days: 81.3% (70.7–88.8)

- **Stillbirth**
  - Within 7 days: 66.7% (46.2–82.4)
  - Within 14 days: 79.2% (58.6–91.4)
For Additional Information

Protocol: Validating Pregnancy Outcomes and Gestational Age in a Claims-EMR Linked Database

Report: Validating Pregnancy Outcomes and Gestational Age in a Claims-EMR Linked Database
Additional Information: Vaccine Exposures in Pregnancy

Vaccine exposure during pregnancy among privately and publicly insured women in the United States, 2016–2018

Keran Moll a, b, Hui-Lee Wong b, Kathryn Fingar a, Cindy Ke Zhou a, Michael Lu c, Mao Hu c, Shayan Hobbi a, Timothy Burrell a, Bethany Baer b, Julia Simard c, Joyce Obidi b, Yoganand Chillarige c, Thomas Macurdy c, f, Steve Anderson b, Azadeh Shoai b

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September 19, 2023

Center for Biologics Evaluation and Research
Linkage of Mothers and Infants in Claims Databases
Background and Motivation

To conduct safety surveillance of biologics in pregnancy and on the health of infants, BEST needs the capability to:

- Link pregnant individuals to infants
Study Aim

- Aim 1: Link pregnant individuals with live deliveries to live born infants in claims databases
Methods

Claim Databases
(Carelon Research, CVS Health, Optum)

1. Live Delivery
2. Liveborn Infant

3. Linkage
Mother’s Subscriber ID == Infant’s Subscriber ID
AND
Mother’s Delivery Date = Infant’s Date of Birth
(Exact, +/- 3 Days, +/- 7 days)
Mother-Infant Linkage
Total Live Deliveries by Data Source

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Data Start (Year)</th>
<th>Data End (Year)</th>
<th>Total Live Deliveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carelon Research</td>
<td>2016</td>
<td>2022</td>
<td>1,269,762</td>
</tr>
<tr>
<td>CVS Health</td>
<td>2019</td>
<td>2023</td>
<td>646,573</td>
</tr>
<tr>
<td>Optum</td>
<td>2020</td>
<td>2023</td>
<td>347,583</td>
</tr>
</tbody>
</table>
Mother-Infant Linkage Rates

Data Source
- Carelon Research
- CVS Health
- Optum

Percent
100
75
50
25

Delivery and Infant Birth Dates
Same Day
Within 3 Days
Within 7 Days

48.4
44.3
40.5
81.1
70.5
70.3
81.9
71.4
71.2

September 19, 2023
Summary

- BEST Initiative is used by CBER to conduct postapproval non-interventional safety studies of biologics, including vaccines

- Capabilities of BEST to Study Safety of Biologics in Pregnancy
  - Ability to identify pregnancy outcomes and gestational ages using claims-based algorithms
  - Ability to link live deliveries and infants in claims databases

- Next Steps
  - Potential study evaluating a safety of a vaccine with respect to pregnancy outcomes
Acknowledgments

- CBER Surveillance Program Team
- CBER OBPV Colleagues
- FDA BEST Partners:
  - Acumen
  - Carelon Research and IQVIA
  - CVS Health
  - IBM
  - Optum

www.bestinitiative.org
Session 5: Filling the Known Gaps for a Comprehensive Pregnancy Safety Study Framework

Moderator: Evan Myers, Duke University

Speakers:

Patricia Bright, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration

Judith Maro, Harvard Pilgrim Health Care Institute and Harvard Medical School

Joann Gruber, Office of Biostatistics and Pharmacovigilance, CBER, U.S. Food and Drug Administration
Lunch Break

Workshop will resume at 01:05 p.m. EST
Session 6: Stakeholder Perspectives on the FDA’s Proposed Pregnancy Safety Study Framework

Moderator: Evan Myers, Duke University

Speakers:

- Marie Teil, UCB BioPharma SRL
- Lynne Yao, Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine, Office of New Drugs, CDER, U.S. Food and Drug Administration
- Robert Ball, Office of Surveillance and Epidemiology, CDER, U.S. Food and Drug Administration
- Sonia Hernandez-Diaz, Harvard TH Chan School of Public Health
- Krista Huybrechts, Brigham and Women’s Hospital, Harvard Medical School
- Janet R Hardy, Independent Consultant
Preliminary Framework
Determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data

Regulatory Gap/Question
- What pregnancy safety information is needed?
- What are the outcomes of interest(s)?

Study Goal:
- What is the purpose (signal detection, signal evaluation)?
- What is the desired timeframe?

Potential Study: Technical Capabilities
For a given study, what are the potential sources of bias? In what direction and to what extent?

Internal validity
Does the study have too much bias to detect (or evaluate) a signal regardless of sample size?

Viable studies
Which study(ies) can meet the study goal with necessary level of evidence and within a desired timeframe?

Optimal study
Which of the viable study(ies) is optimal, considering timeliness, resource requirements, patient burden, etc.?

The optimal may be a combination of studies, combining different strengths.

Available information
- What studies have been done?
- What do we know about the potential risk(s)?
- What do we know about the patient population, the product, and utilization of similar drugs (if any) on the market?

Magnitude of drug exposure
What is the expected utilization of this drug by pregnant individuals in U.S., over time?

Minimum Sample Size
What sample size is required for a given study, dependent on study goal and the study’s technical capability?

Potential Study: Exposure Capture
How much pregnancy exposure does the study expect to capture by year?
Closing Remarks

Gerrit Hamre

Research Director, Duke-Margolis Center for Health Policy
Thank You!

Contact Us

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